Relationships between psychological factors and immune dysregulation in context: A life-course approach

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Summary

The thesis provides evidence about relationships between adverse exposures, psychological responses to them and immune dysregulation. The approach taken is informed by theories about the life-course, the stress process, the stress response and the inflammatory theory of depression.

The first two empirical chapters provide evidence about the contribution of psychosocial factors to immune dysregulation. Immune dysregulation is measured by onsets of asthma and rheumatoid arthritis during adulthood. Comprehensive life-course data are used to provide valuable evidence about the epidemiology of each disease. More specifically, new evidence is provided about the psychosocial pathways that lead to disease onset. After adjustment for material adversities, social adversities predict onsets of each disease. Chronic as opposed to acute adversities are salient for rheumatoid arthritis onset, which is consistent with existing theory that chronic stress contributes to immune dysregulation. Depressive symptoms mediate an association between childhood adversity and asthma onset decades later. A small but consistent association between depressive symptoms and asthma onset soon afterwards may reflect psychological consequences of chronic inflammation preceding asthma diagnosis. The third empirical chapter tests prospective associations between chronic inflammation and depressive symptoms. It finds that chronic inflammation predicts depressive symptoms and provides new evidence that these associations are mediated by factors associated with sickness behaviours.

Findings indicate the relevance of psychosocial pathways to the development of immune-mediated diseases and the potential involvement of immune behaviours in psychological symptoms. Practitioners and policy makers working with people who have conditions characterised by immune dysregulation should consider the psychological predictors and

consequences of immune dysregulation. More research in this area is needed and this would be facilitated by the development and inclusion in surveys of well-validated measures of psychological and biological stress and of the psychological and behavioural correlates of sickness behaviours thought to be induced by inflammation.

Chapter 1: Introduction

This PhD is motivated by an interest in how social and economic exposures and psychological responses to them combine over the life-course to affect health outcomes. Its aim is to explore how psychological factors interact with immune dysregulation within a life-course context.

This first chapter introduces the research topic, describes the life-course approach and presents a model of relationships between negative exposures (adversities) and health outcomes. In the model, health impacts of adversities are buffered by resources and transmitted through interlinked pathways classified as material, behavioural and psychosocial. Psychosocial pathways involve psychological responses to social exposures. Two theories are introduced that draw on biological evidence to provide understanding about how relationships may develop between psychological factors (specifically, psychological stress and depressive symptoms) and immune dysregulation. Finally, the research aims and three empirical chapters are summarised.

1. Rationale

Recognition of socio-economic inequalities in health (Black 1980, Acheson 1998) focused attention on how inequalities develop over the life-course; how life gets under the skin (Bartley 2012) or how the social becomes biological (Blane et al. 2013). A theoretical review of relevant evidence describes the interlinked processes that link money with health, classifying them into three pathways, referred to as material, behavioural and psychosocial (Benzeval et al. 2014). The focus here is on the psychosocial pathway, that is, social exposures and psychological responses to them, but its relationship with health is understood within the context of the other two.

The area of physical health examined is dysregulation of the immune system. The immune system provides defence against external agents that might cause damage. Dysregulation of the immune system can lead to the development of allergic, autoimmune and autoinflammatory diseases, chronic low-grade inflammation and immune-deficiency. Allergic, autoimmune and autoinflammatory diseases are sometimes referred to as immune-mediated diseases. Allergic diseases involve immune responses to substances that are not necessarily harmful (Henderson 2015), whilst autoimmune diseases involve "an immune response by the body against one of its own tissues, cells, or molecules" (American Heritage Medical Dictionary 2007). Autoinflammatory diseases are a relatively new classification of (rare) diseases characterised by unprovoked inflammation (McDermott et al. 1999) and include Still's disease and Crohn's disease. Allergies include asthma and autoimmune diseases include rheumatoid arthritis (RA).

Immune dysregulation is chosen for two reasons. First, immune dysregulation is important for public health. This is because conditions involving and arising from immune dysregulation are common and costly to individuals and the state. According to patient.co.uk, allergies affect about one in four people at some point in their lives (Henderson 2015). Although less common than allergies, prevalence and incidence rates of autoimmune diseases have risen substantially over the last 30 years, especially in Northern and Western countries (Lerner et al. 2015). The British Society for Immunology states that eighty autoimmune diseases have been identified, affecting hundreds of thousands of individuals in the United Kingdom (UK, Lowry 2016) and prevalence rates have been estimated at just under one in ten in Denmark and the United Stated (US) (Cooper et al. 2009, Shurin & Smolkin 2007, respectively). The National Institutes of Health (NIH 2005) estimated that the number of Americans with an autoimmune disease was similar to the number with heart disease. In addition, there is growing interest in immune-mediated

diseases and especially auto-inflammatory diseases because the physiological mechanisms that underlie them may contribute to the chronic inflammation that characterizes better known diseases such as artherosclerosis, diabetes and osteoporosis (Ciccarelli et al. 2014).

Symptoms of immune-mediated diseases are often inadequately controlled by existing medications and they are disabling and involve suffering (Lowry 2016). They are chronic diseases with lasting impacts, which increases their burdens to the individual and state (Lowry 2016). In illustration, the World Health Organisation (WHO) estimates that the number of disability adjusted life years lost due to asthma is similar to numbers for diabetes, liver cirrhosis and schizophrenia (Bosquet et al. 2005). The quality of life associated with RA has been described as one of the poorest among all diseases (Furneri et al. 2012) and the (British) National Institute for Health and Care Excellence (NICE) states that approximately one third of people with RA stop work within two years of its onset in the UK (NICE 2009). Further, autoimmune diseases are a leading cause of death, especially among females. Thomas et al. (2010) estimate that among females, autoimmune diseases were the sixth or seventh leading cause of death between 1995 and 2003, depending upon age group. More evidence is needed about the common determinants of this group of diseases (Thomas et al. 2010). They are not currently classified as a group either in the International Classification of Diseases or by the WHO, which presents challenges for researchers, practitioners and policy makers interested in their common risk factors and causes (Thomas et al. 2010).

As is the case for many health conditions, most immune-mediated conditions are more common and their consequences are more severe for those who suffer socio-economic disadvantages (Lerner et al. 2015). This adds to the public health importance of these

conditions because those affected tend to have fewest resources to manage symptoms and their impacts.

The second reason for the focus on immune dysregulation is that immune-mediated diseases appear to have a psychological component as many are exacerbated by psychological stress (Straub & Besedovsky 2003, Cutulo & Straub 2007) and many are linked to symptoms of depression and anxiety (Chida et al. 2008, Loerbroks et al. 2010, Scott et al. 2008, Covic et al. 2012). This may be because the immune system is closely integrated with the endocrine and nervous systems, which connect with psychological experience. In an overview of relationships between behaviour and immunity, Irwin writes:

> The immune system "is sensitive to virtually every hormone, and sympathetic, parasympathetic, and sensory nerves innervate the organs of the immune system. In turn, the nervous, endocrine, and immune systems communicate bi-directionally through common hormones, neuropeptides, and cytokines" (Irwin 2007:450).

Physiological links between immune behaviours and psychological symptoms do not exist in isolation. They are affected by and contribute to psychological and behavioural responses to social and economic exposures, within contexts of culture, history, politics and life stage. That is why the aim of the PhD is to examine prospective relationships between psychological factors and immune dysregulation within a life-course perspective, drawing on multiple disciplines.

2. The immune system and immune dysregulation

As mentioned above, the immune system provides defence against external agents that might cause damage. This involves three stages; (1) recognition of the potentially harmful

external agent or pathogen, (2) an acute inflammatory response, and (3) suppression of this response once the threat has been resolved.

Most immune-mediated diseases develop because of errors in the first stage. As explained above, in allergic diseases, the immune system recognises as potentially harmful an external agent, such as pollen, referred to as an allergen. The allergen does not stimulate an immune response among healthy individuals, but among those with an allergic condition, a specific allergen or group of allergens stimulates an acute inflammatory response, which is often unpleasant and disabling and can be fatal. In individuals with autoimmune diseases, the body recognises as potentially harmful one of its own molecules, cells or tissues.

The acute inflammatory response involves the production of white blood cells called T-lymphocytes. There are many different types of T-lymphocytes, and they have been classified according to whether they act to defend the body against intracellular or extracellular pathogens. T-helper 1 (Th1) cells act against viruses and other intracellular pathogens and eliminate cancer cells. Th2 cells act against pathogens external to cells, such as parasitic infections. Th1 and Th2 responses involve the production of specific arrays of signalling molecules (cytokines) that promote and suppress particular immune pathways, and the production of specific white blood cells. For example, the Th2 response is usually associated with a white blood cell called immunoglobulin E (IgE) and cytokines called interleukins 4, 5, 13 and 10 (Berger 2000).

Acute allergic responses are associated with a Th2-type immune response as the allergen is external to the cells. In contrast, autoimmune responses are mostly associated with a Th1-type immune response, since the body is responding to its own tissues or cells (Jeong et al. 2018).

As an aside, the immune pathways typically involved in most allergic responses are stimulated in response to a group of parasites (worm infections). In countries and households with high levels of hygiene, infants and children are rarely exposed to these parasites and it has been argued that this lack of exposure is a risk factor for the development of allergic conditions. It has been argued that the increase in hygiene is a reason why prevalence rates of allergic conditions are increasing in industrialised countries (Hellman et al. 2017).

Allergic conditions cause an inflammatory response that is unpleasant, disabling and can be fatal. Autoimmune diseases cause damage for two reasons. First, the immune system attempts to destroy the part of the body that it mistakenly recognises as a pathogen. In RA, this is connective tissue. Second, a untreated continuining acute inflammatory response leads to extreme fatigue, malaise, anaemia, weight loss, and, over time, wasting away and death.

Auto-inflammatory diseases involve an uncontrolled acute inflammatory response for no identified reason. The immune pathways stimulated are similar to those involved in autoimmune diseases. Untreated, these diseases would lead to wasting away and death.

Chronic inflammation is a sub-clinical condition that results from incomplete suppression of an immune response that is usually stimulated by genuine pathogens. The level of inflammation is much lower than in immune-mediated diseases, but it predicts cardiovascular disease, type II diabetes, and mortality (Maes et al. 2011, Liu et al. 2016, Padayachee et al. 2009, Zhang 2011).

The immune system is complex and immune dysregulation takes various forms. I have chosen to adopt a comprehensive approach and so I examine relationships between psychological factors and an allergic condition (asthma), an autoimmune condition (RA), and chronic inflammation.

3. The life-course approach

Elder & Johnson (2002) describe life-course ideas as a "focus on the changing contexts of lives and their consequences for human development" (p.54). The approach provides a conceptual framework that aids understanding of how exposures and experiences during earlier years link to outcomes later in life. Human lives are seen in their entirety, which directs attention to the causal pathways across the life-course. In addition, individuals are placed in their historical context. The life-course approach is necessarily interdisciplinary because human lives combine historical, geographical, political, economic, sociological, psychological and biological influences.

The life-course can be divided into life stages constructed on the basis of age-graded biological events and social institutions (Elder & Johnson 2002). Familiarly named life stages include childhood, youth, transition to adulthood, adulthood, early adulthood, middle age and late adulthood.

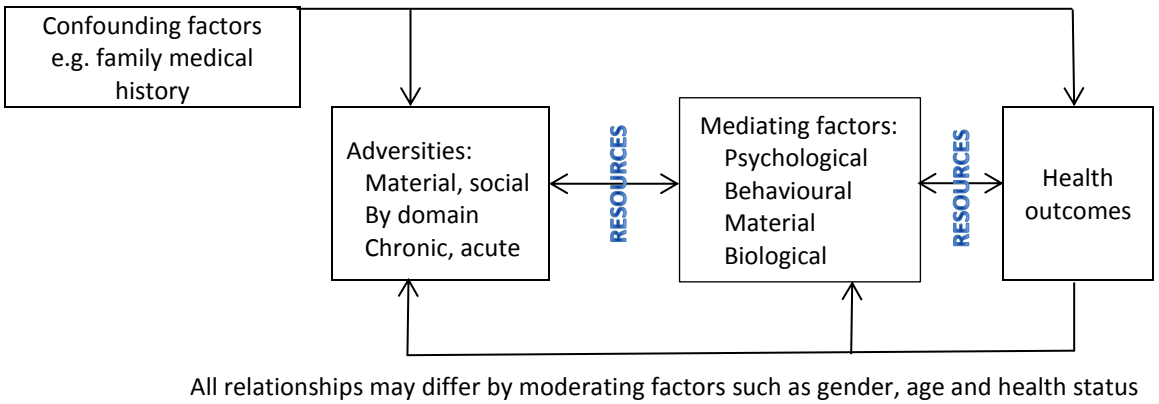
Research in social determinants of health and social epidemiology examines (among other things) the ways in which biological and psychosocial factors combine throughout the life-course to affect health in later life. Kuh et al. (2003) describe life-course models that have been used to describe these relationships. The model of accumulation of risk posits that life-course exposures independently predict an outcome. The model of social pathways or chains of risk describes, "A sequence of linked exposures that raise disease risk because one

bad experience or exposure tends to lead to another and then another" (Kuh et al. 2003: 779). Effects are not independent or cumulative because earlier exposures only matter because they predict later ones, which are more proximal to the outcome. A third model refers to sensitive periods, "When an exposure has stronger effects on development and subsequent disease risk than it would at other times" (Kuh et al. 2003: 781). Any combination of these models can describe the ways in which interlinked factors combine over the life-course to predict health outcomes later in life.

4. Relationships between psychological factors and health in context

Figure 1.1 illustrates relationships between psychological factors and health in the context of adversities and the factors that may affect relationships between adversities and health, by buffering, confounding, mediating and moderating them. The relationships illustrated in Figure 1.1 are repeated over the life-course.

Figure 1.1: Relationships between adversity and health



4.1 Adversities

Adversities, on the left-hand side of Figure 1.1, are events and circumstances that are usually appraised negatively and that one would expect to have negative consequences.

4.1.1 Material and social adversities

Gustafsson et al. (2012) classified adversities as material and social. These authors define material adversities are defined as, "exposures to unfavourable circumstances mainly related to the immediate physical environment or the financial situation" (p.120) and they classify as material adversities low income, unemployment and financial strain. Social adversities are defined as, "exposures which hypothetically would impact on health mainly by directly threatening salient relationships" (p.119) and include relationship breakdown and social isolation.

4.1.2 Adversities experienced in various domains

Gallo et al. (2011) classify chronic stress based on the domain in which it is experienced. Drawing on this approach, adversities (that may contribute to chronic stress) are classified by domain as financial, occupation-related, relationship-related, child loss related and traumatic. Broadly speaking, financial and occupation-related adversities would be classified as material, and adversities relating to relationships, child loss and trauma would be classified as social.

4.1.3 Chronic and acute adversities

Pearlin (1989) discusses the distinction between life events and "more enduring or recurrent life problems", which he refers to as chronic strains (p.243). He argues that chronic strains are often rooted in institutionalised social roles that involve interpersonal relationships, such as being a spouse or parent, and gives as examples difficulties in marriage and

parenthood. In contrast to chronic strains, life events are usually discrete and observable with a clear onset and offset. However, Pearlin notes that life events are rarely free-standing; frequently, they are indicators of ongoing conditions. For example, divorce (a life event) may be closely associated with the chronic strain of relationship difficulty. More contemporary authors continue to classify adversities as chronic stressors and life events, whilst noting that the distinction between the two is blurred (Theorell 2012).

Physiological evidence and evidence from animal studies suggests that chronic and acute psychological stress have different impacts on health (McEwen 2004, Eisenmann et al. 2016). A handful of small-scale epidemiological studies provide evidence about the different relationships between chronic and acute adversities and health outcomes (Lepore et al. 1997, Vreshek-Schallhorn et al. 2015, Bryan et al. 2015), but large-scale epidemiological evidence remains scarce.

4.1.4 Examples of adversities

Which events and circumstances are appraised negatively depends upon period and culture (Seeman et al. 2004, Bolger et al. 2003, Hobfoll 2001). Appraisals also depend on life stage; individuals can be exposed to the same event or circumstance at any life stage, but its meanings and impacts may differ (Pearlin 2010, Elder & Shanahan 2006).

With this in mind, exposures are more likely to be appraised negatively, reported as stressful and classified as adversities if the event and its consequences are in fact or perceived to be out of one's control (Fairbank & Hough 1979, Averill 1973, Fusilier et al. 1987, Glass & Singer 1972), unpredicted (Glass & Singer 1972), not normative (Pearlin 2010), associated with negative emotional affect (Semmer et al. 2005), or unresolved (Turner & Avison 1992, Thoits 1994).

Childhood adversities include early parental loss (through death, divorce, or other reasons), neglect, psychological, physical and sexual abuse, exposure to violence, conflict and tension in the family and living with a household member who is mentally ill, has substance use issues, or has been imprisoned, and family poverty (Felitti et al. 1998, Rosenman & Rodgers 2004).

Moving house can also be stressful, especially for children, who have little control over decisions about moving (Jelleyman & Spencer 2008). Childhood moves are particularly difficult if the move involves a change of school (Herbers et al. 2013), as this disrupts the child's social networks and education (Brown et al. 2012, Duncan & Zuberi 2006). Furthermore, the circumstances or events that precipitate the move may be difficult for the child (Dong et al. 2005).

During adulthood, material adversities include financial hardship and occupation-related adversities such as long term unemployment (Gustafsson et al. 2012, Gerston 1974) and involuntary job loss (Wahrendorf et al. 2013). Dohrenwend et al. (1978) included as a negative life event failing at school or college, which would be more common during youth or the transition to adulthood, and would be classified as an occupation-related adversity. Work stress (Siegrist 1996, Karasek et al. 1998) might be classified as social or material.

Family and relationship-related adversities, classified as social, include relationship difficulties (Loving & Slatcher 2013) and broken partnerships (Holmes & Rahe 1967, Dohrenwend 1978). Lone parenthood, a role more frequently occupied by women, can involve an unshared burden of financial responsibility, work overload, insufficient time for rest and sleep, difficulties with social life, isolation and difficult relationships with ex-partners (Richards 1989, Richards & Schmiege 1993, Sanik & Mauldin 1986, Richards &

Schiete 1993). Caring for sick relatives and friends has also been conceptualised as a stressor (Pearlin et al. 1997). Cousino & Hazen (2013) report that caring for a child with a longstanding illness often involves anxiety for the child's wellbeing, watching the child suffer, managing hospital admissions and treatments, school issues and explaining the child's health problems to strangers. Death of one's child and stillbirth are ranked as highly stressful life events by Dohrenwend and colleagues (1978). Infertility has been described as a "chronically stressful" situation (Schmidt et al. 2005).

Traumatic events are an additional group of adversities that pose a significant risk of death or serious injury and evoke fear, helplessness or horror (American Psychological Association 2000). They include active combat, large scale disasters, serious assault and rape.

4.1.5 Combinations of adversities

Adversities tend to cluster, often among the most vulnerable sections of the population (Bolte et al. 2009, Evans 2003, Evans et al. 2007), a phenomenon referred to as stress proliferation (Pearlin et al. 1997, 2005) and cumulative disadvantage (Sampson & Laub 1997, Ross & Wu 1996). While single adversities have impacts, individuals are often exposed to multiple adversities (Garmezy 1991, Rutter 1981, 2009), and studies have found that exposures to multiple adversities incrementally predict poorer health outcomes (Felitti et al. 1998, Evans 2003, Evans et al. 2007, Larson et al. 2008, Power et al. 2012, Schilling et al. 2008). For these reasons, researchers create indices of multiple adversities or of adversities in multiple domains in order to examine their cumulative impact. A limitation of this type of index is that it assumes that different types of adversity are interchangeable and can be added together to represent the total load experienced by the individual (Lepore 1995, Evans et al. 2007).

4.1.6 Bi-directional relationships between adversities and health

Whilst adversities predict health outcomes, health status also predicts negative exposures such as poverty, unemployment and stress in relationships and at work.

4.2 Resources

Resources are illustrated in Figure 1.1 as buffers of the impacts of adversity. They include money (Benzeval et al. 2014), education (Bartley 2006) and social support (Bartley 2006, Ozbay et al. 2007, Wahrendorf et al. 2013). Resources contribute to resilience (Schoon & Bartley 2008), and individual differences in access to resources partly explains individual differences in the health outcomes associated with a particular adversity, even when exposure occurs within the same life stage and context.

Hobfoll (2001) argues that adversity is sometimes equivalent to a lack or loss of resources. For example, poverty (an adversity) is a lack of wealth (a resource). However, this argument does not apply to some adversities, for example, work stress. Therefore, the distinction between adversities and resources is retained.

4.3 Confounding and mediating factors

Factors that confound and mediate associations between adversity and health outcomes are, by definition, correlated independently with both. Confounding factors occur earlier than both adversity and the health outcome in causal pathways. Mediating factors occur after adversity but before the health outcome. Mediation is consistent with but does not necessarily imply a causal pathway.

In Figure 1.1, confounding factors include family medical history. For example, if the health outcome were asthma onset, parental experiences of asthma could independently lead to

family difficulties that impact on the child, and reflect a genetic vulnerability to asthma and related conditions. Another example is difficulties during pregnancy or birth, which could affect a child's early family circumstances and independently have lasting effects on health.

Mediating factors affect and are affected by health status. They are classified as behavioural, material, biological and psychological. Behavioural factors include smoking, drinking patterns, physical activity and diet. Material factors include living in poor housing conditions and working in occupations that are associated with high risk of exposure to toxins. These could be classified as material adversities in the model but are not because of where they are hypothesised to occur in causal pathways.

Biological mediators are specific to the health outcome. They include biological factors, such as obesity, which predicts various diseases, and atopic history and early respiratory infections, which predict asthma onset. Biological mediators also include sub-clinical changes, such as the development of low-grade chronic inflammation, which might predict onsets of asthma and RA..

Psychological factors include psychological stress and related psychological factors such as distress, low self-efficacy and isolation. Physiological evidence suggests that psychological stress can lead to immune dysregulation.

Sections 4 and 5 describe two hypotheses about links between psychological factors and immune dysregulation. Each hypothesis applies to part but not all of the model illustrated in Figure 1.1. The first hypothesis is that psychological stress, which is a response to adversity, leads to immune dysregulation. The second hypothesis is that immune dysregulation leads

to chronic inflammation, which has psychological and behavioural correlates that lead to the development of depressive symptoms.

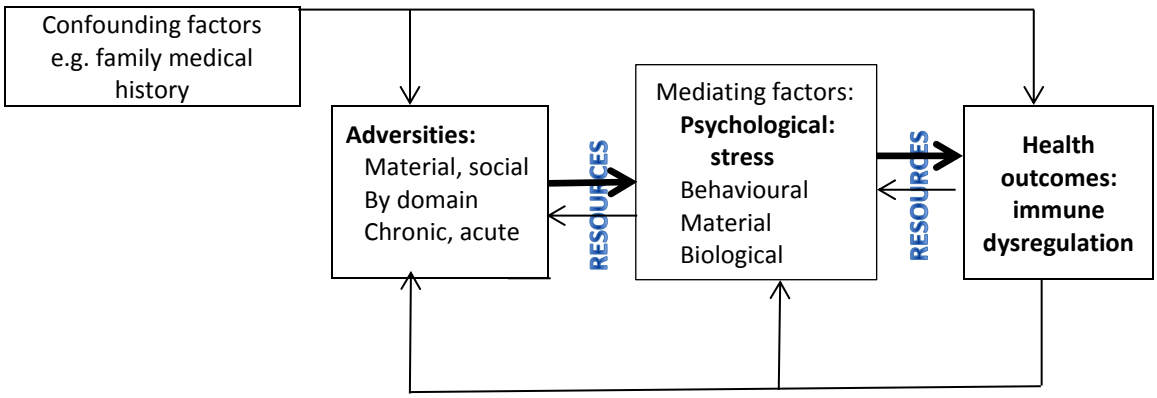
4.4 Moderators

All relationships in Figure 1.1 may differ by factors referred to as moderators, such as gender, age and health status.

5. Psychological stress and immune dysregulation

Figure 1.2 presents the same model as the one illustrated in Figure 1.1, but the parts of the model that this section relates to are in bold font.

Figure 1.2: Relationships between adversity and health with relevant parts in bold font



Psychological experiences of stress are believed to evoke and reflect a set of common physiological responses (Selye 1956). These responses appear to vary little between mammals (Brunner & Marmot 2006).

The physiological response is a form of crisis management in which the 'fight or flight' response is prepared for whilst other systems are put on hold. This is achieved through the activation of two separate but inter-related systems; the sympathoadrenal medullary (SAM) and the hypothalamic-pituitary-adrenal (HPA) axis. When the SAM is stimulated, it activates the fight or flight response by increasing the heart rate and blood supply to the skeletal muscles, the brain and other parts of the body that are involved in the response. This happens within milliseconds, lasts for only a few minutes, and is experienced as a 'rush'. The HPA axis response, on the other hand, takes minutes to become activated and continues for hours. It involves a chain of reactions, resulting in elevated levels of cortisol in the blood. High levels of cortisol act together with other signalling molecules (called catecholamines) to change the balance of activity in distinct but inter-related physiological systems. For example, the cardiovascular and respiratory systems are upregulated and stores of energy are mobilized in preparation for fight or flight, while other functions that use energy but are not necessary during a crisis are inhibited, for example, digestion, reproduction and immune activity.

These responses are important for saving life and they cause the body no harm if the threat is acute with a well-defined ending, especially when exercise is part of the response. On the other hand, if the stimulus is chronic, a continued stress response can lead to adverse physiological changes (Sapolsky 1993), such as wear and tear on systems that are continuously activated and dysregulation of systems that are chronically activated or suppressed.

An important physiological consequence of prolonged stress responses is dysregulation of the stress response itself. For example, adults who experienced traumatic events as children appear to have chronically elevated cortisol levels (Luecken and Appelhaus 2006) and

unusually large cortisol responses to acute stress (Luecken 1998). It is argued that early experiences of intense or prolonged stress can lead to increased responsiveness to stressful events and circumstances for many years afterwards, on both psychological and physiological levels.

The stress response inhibits immune activity, indicated by associations between chronic stress responses and raised levels of a latent virus (Chida & Mao 2009) and slower wound healing (Kiecolt-Glaser et al. 1995). In addition, chronic stress responses can lead to dysregulation of the immune system resulting in increased levels of inflammation. More specifically, elevated levels of cortisol, associated with the stress response, act on proteins called cytokines that regulate inflammatory activities. Continued exposure to cortisol resulting from chronic stress results in these cytokines becoming less sensitive to cortisol, a phenomenon referred to as glucocorticoid resistance (Miller et al. 2002, Chrousos et al. 1996). Glucocorticoid resistance is associated with higher levels of pro-inflammatory cytokines in the blood leading to inflammation. Some of these pro-inflammatory cytokines are associated with specific autoimmune diseases, such as RA (Noack & Miossec 2017) and asthma (Wright et al. 1998). In addition, prolonged stress responses, especially during early life, has been linked to increased levels of IgE (Wright et al. 2005), which is often raised in allergic conditions.

In order to test whether stress is involved in psychosocial pathways linking adversity with immune dysregulation, it is necessary to consider how best to define and measure stress. Stress involves psychological and biological responses to events and circumstances. It is a construct that has been described as a model (Selye 1956), a process (Pearlin 1981, 1999) and a transaction between individuals and situations (Lazarus 1966). Cohen (1997) describes stress as,

> "A process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk of disease" (p.3).

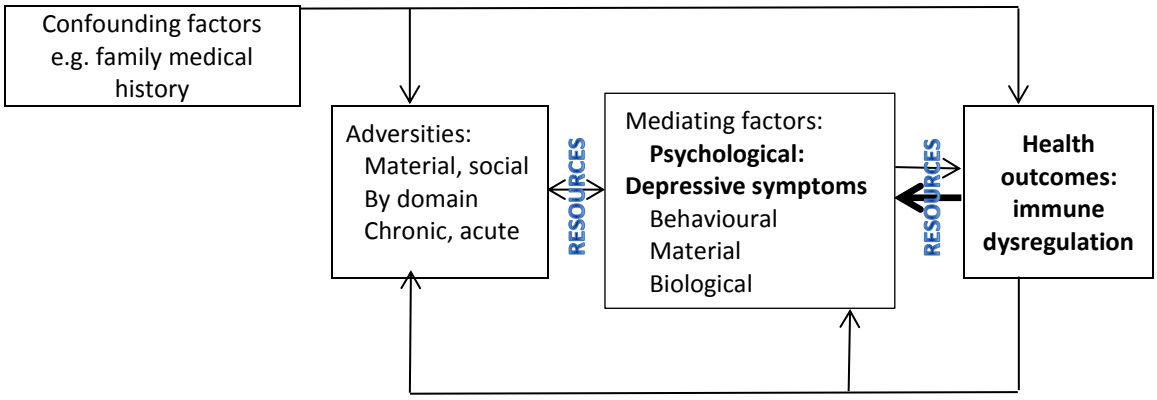
Stress is measured in various ways. Cortisol, sometimes referred to as a stress hormone, is used as a physiological marker of stress (Ryan et al. 2016, Chen et al. 2015, Hostinar et al. 2015, Wosu et al. 2013). Psychological stress is measured using self-report. Well-developed theories and measures of work stress involve the balance between perceived effort and reward (Siegrist 1996), and a combination of perceived demands, control, social support, and job insecurity at work (Karasek et al. 1998). Instruments have also been developed to measure relationship stress and distress (Locke & Wallace 1959, Schuster et al. 1990), loneliness (Hughes et al. 2004), and community stress (Stafford et al. 2003). However, it is the combination of pressures that act on the individual to make them feel stressed, and there is no well tested or validated measure of global stress that combines perceived stress in multiple domains.

Adversities can also be used to indicate stress (Holmes & Rahe 1967, Pearlin et al. 2005) because they are likely to be experienced as stressful. They are a step removed from psychological and physiological experiences of stress as these experiences arise not only from exposure to adversity but also how the individual responds to it (Lazarus 1966).

6. The inflammatory theory of depression

Figure 1.3 presents the same model as the one illustrated in Figure 1.1, but the parts of the model that this section relates to are in bold font.

Figure 1.3 Relationships between adversity and health with relevant parts in bold font



As explained above, the healthy immune system responds to injuries or infection in a process that involves three stages; (1) recognition of the potentially harmful external agent or pathogen, (2) a series of inter-related responses that stimulate a cascade of defensive behaviours, referred to as the acute inflammatory response, and (3) suppression of this response once the threat has been resolved. In healthy individuals, suppression is complete. When it is not complete, this is manifested as chronic low-grade inflammation, a phenomenon that reflects immune dysregulation and predicts cardiovascular disease, type II diabetes, and mortality (Maes et al. 2011, Liu et al. 2016, Padayachee et al. 2009, Zhang 2011).

Symptoms of acute inflammation are familiar and unpleasant. They include redness, swelling, heat, pain (Calder et al. 2013), and also sickness behaviours that have psychological features, such as fatigue, social withdrawal, negative mood, loss of appetite, sleep disturbance, arousal and anxiety (Miller & Raison 2016, Dantzer & Kelly 2007). Sickness behaviours may have been selected for in the past because they promote withdrawal into a place of safety during periods of sickness and convalescence, away from predators (Miller & Raison 2016), as well as conservation of energy to fight infections. The inflammatory theory of depression (Smith 1991) is that these sickness behaviours contribute

to the development of depression as well as to other psychiatric disorders including anxiety and schizophrenia.

Sickness behaviours resemble symptoms of depression (Byrne et al. 2016, Capuron & Miller 2011). For example, the 8 item version of the Centre for Epidemiologic Studies Depression Scale (CESD) includes items relating to motivation and fatigue; “Much of the time during the last week, you could not get going” and, “Much of the time during the last week, everything you did was an effort”. A cross-sectional study found that these items and two others, referring to sleep disturbance and feeling depressed, were associated with chronic inflammation (White et al. 2017).

Evidence from various research perspectives is consistent with the inflammatory theory of depression. Substantial progress is being made in understanding the physiological mechanisms that link inflammatory processes with the psychological changes that characterise sickness behaviours and heightened arousal (Byrne et al. 2016, Miller & Raison 2016). In addition, injecting pro-inflammatory cytokines induces both an acute inflammatory response and depressive-like behaviours in animals and depressive symptoms in humans (Byrne et al. 2016, Dantzer & Kelly 2007), and some studies report that anti-inflammatory drugs reduce depressive symptoms (Kohler et al. 2014, Kohler et al. 2016).

Dantzer et al. (2011) discuss the relative timings of the acute inflammatory response, sickness behaviours and the development of depressive symptoms. They cite evidence that whilst sickness behaviours are concurrent with the acute inflammatory response, there is a delay before these develop into depressive symptoms. Clinical studies found that among cancer patients treated with high doses of cytokines, most reported fatigue, pain, decreased appetite and sleep disturbance immediately after administration of the cytokines, and

during subsequent weeks, some reported depressed mood and feelings of worthlessness and guilt (Capuron et al. 2000). Equivalent studies conducted in mice report that cytokine administration provokes immediate sickness behaviours such as reduced activity and decreased food intake that last for a few hours, followed 24 hours later by depressive-like behaviours (Frenois et al. 2007, O'Connor et al. 2009). This evidence is consistent with hypotheses that (1) prolonged periods of inflammation lead to greater increases in depressive symptoms, and (2) other factors are involved in the development of depressive symptoms.

Prospective epidemiological studies provide evidence about relationships between chronic inflammation and depressive symptoms years later. These studies make an implicit assumption that symptoms of chronic inflammation include the same sickness behaviours as those that are associated with acute inflammation, albeit to a lesser degree. Most studies report prospective associations between chronic low-grade inflammation and subsequent depression or depressive symptoms (Valkanova et al. 2013). Inconsistent results may reflect differences between samples and in the timing between measures of inflammation and depressive symptoms.

7. Research aims

The broad research aim is to explore how psychological factors interact with immune dysregulation within the context of the life-course. Each empirical chapter addresses a different type of immune dysregulation.

In Chapters 2 and 3, immune dysregulation is measured using onsets of immune-mediated diseases; adult onset asthma in Chapter 2 and RA in Chapter 3. Probably because incidence

rates of these conditions are low, there is a lack of epidemiological evidence about the psychosocial factors that contribute to them.

In relation to adult onset asthma, I have found three large-scale epidemiological studies that examine relationships between adversities and asthma onset during adulthood. Two examine adversities shortly before asthma diagnosis (Lietzen et al. 2011, Loerbroks et al. 2009, Loerbroks et al. 2010) and the other uses retrospective information about childhood adversities (Scott et al. 2008), but no study provides comprehensive life-course evidence about adversity as a predictor of asthma onset.

While there is clear evidence that symptoms of anxiety and depression are associated with asthma activity, and some evidence that depressive symptoms predict asthma onset, evidence from prospective studies remains sparse (Chida et al. 2008, Loerborks et al. 2010), and none examine when during the life-course depressive symptoms are salient for asthma onset. Neither am I aware of any studies that examine whether psychological factors mediate associations between adversity and asthma onset, as illustrated in Figure 1.1.

In relation to RA, a recent study states that evidence about psychosocial predictors of RA is sparse and inconclusive (Wesley et al. 2014). Large scale epidemiological studies include Wesley's, which measures a wide range of adversities shortly before RA onset and others that examine the contributions of job stress and child death to RA onset (Bengtsson et al. 2009, Li et al. 2005, respectively). A small study examines life-course adversities as predictors of RA onset but numbers are low, with just 55 respondents reporting RA onset (Carette & Surtees 2000).

The aims of chapters 2 and 3 are to provide evidence about the contributions of a wide range of adversities over the life-course to onsets of asthma and RA in the context of the framework set out in Figure 1.1. They will compare the importance for disease onset of social adversities of different types, after adjustment for material adversities. Further objectives are to estimate the extent to which associations between adversity and disease onset are mediated by behavioural and psychological factors, and when during the life-course psychosocial factors are particularly salient for disease onset. This approach will provide more comprehensive evidence than presently exists about the psychosocial factors that contribute to onsets of each immune-mediated condition.

Because adult onset asthma and RA have importance for public health, subsidiary aims of chapters 2 and 3 are to provide evidence about additional factors that predict them.

In chapter 4, immune dysregulation is measured using a biomarker; C-reactive protein (CRP). Biomarkers are relatively new to longitudinal surveys and there is potential for novel research using them. One aim of this chapter is to contribute to existing evidence about prospective associations between chronic low-grade inflammation and depressive symptoms. Another aim is to provide new evidence about the biological, behavioural and psychological factors that mediate any prospective association found, and to test whether associations are moderated by gender, age group or health condition.

8. Empirical chapters in more detail

Chapter 2: Does adversity predict onset of asthma during mid-adulthood? Do psychosocial pathways play a role?

Asthma is disabling, frightening, costly to the nation, and is the most common chronic disease among children (WHO 2011). Asthma develops during all life stages and compared against childhood asthma, relatively little is known about the determinants of adult onset asthma. Chapter 2 provides evidence that contributes to this area with a focus on psychosocial factors.

The importance of life-course adversity for adult onset asthma is estimated. As mentioned above, evidence about life-course adversity is lacking and chapter 2 contributes by including more comprehensive measures of life-course adversities than in previous studies, and examining relationships within the context of a model similar to that set out in Figure 1.1. It provides new evidence about whether associations differ by gender, atopic history and childhood temperament, how adversities during different life stages combine to predict asthma onset, and the relative importance for asthma onset of different types of adversity, including social and material adversities.

Associations between social adversities and adult onset asthma after adjustment for material adversities suggest the importance of psychosocial pathways in the development of asthma during adulthood. This hypothesis is further tested by examining whether depressive symptoms mediate associations between childhood adversity and asthma onset decades later.

Epidemiological studies provide evidence about other factors that predict asthma. The chapter tests whether these factors predict asthma onset during mid-adulthood, as much of the existing evidence relates to asthma with onsets during other life stages. Using a novel approach, life-course adversity is included in models as a summary measure of social and material exposures so that the specific contributions of psychological and behavioural factors can be assessed. These factors are measured in multiple life stages so that comparisons can be made between their salience at different life stages for asthma onset later.

Chapter 3: Does adversity predict onset of rheumatoid arthritis? Do psychosocial pathways play a role?

This chapter addresses the importance of psychosocial pathways in the development of RA. RA is a relatively common chronic inflammatory disorder that is a concern for public health because it is associated with very poor quality of life (Furneri et al. 2012) and is costly to the state (NICE 2009). It is also thought to be exacerbated by psychological stress (National Rheumatoid Arthritis Society 2017), although evidence about whether adversities that are likely to be stressful predict RA onset is sparse and inconsistent (Wesley et al. 2014).

The chapter addresses this gap in the literature by estimating associations between adversity and RA onset, including a range of adversities measured over the life-course that is much more comprehensive than measures used in previous studies. New evidence is provided about whether relationships between life-course adversity and RA onset vary by gender. Further, comparisons are made between different types of adversity. Adjustment for material adversity and health behaviours means that new evidence is provided about the importance for RA onset of social adversities likely to affect health through psychological

pathways. Finally, a new research question is addressed that concerns the relative importance for RA onset of acute and chronic social adversity.

Chapter 4: Prospective associations between low-grade inflammation and depressive symptoms and the factors that confound and mediate them.

A growing body of epidemiological evidence suggests that chronic low-grade inflammation predicts depressive symptoms several years later (Valkanova et al. 2013). Epidemiological evidence about prospective associations between depressive symptoms and subsequent inflammation is less consistent (Das 2016, Engler et al. 2016).

This chapter contributes to existing evidence by estimating prospective associations in both directions using a large-scale dataset with measures of CRP and depressive symptoms on multiple occasions. This provides useful evidence because few studies include multiple measures of CRP as it has not yet been measured on more than two occasions in many longitudinal surveys. In addition, new evidence is provided about the factors that mediate prospective associations, and differences by gender, age group and health status. Three health statuses are included; at least one longstanding health condition and two immune-mediated conditions, asthma and RA.

Methods and data

The thesis uses exclusively quantitative methods. This approach was chosen because quantitative methods allow the generalisability of findings to be tested. In addition, individuals have limited insight into the causes of disease onset, low-grade inflammation and depressive symptoms, and so in-depth interviews and focus groups would not have yielded much useful information.

It was not necessary to collect quantitative data as large-scale longitudinal datasets are publicly available for researchers and these contain comprehensive information collected to the highest standards. Data are analysed using sophisticated software and statistical methods.

Chapter 2 uses data from the National Child Development Study (NCDS). This was originally a perinatal mortality survey of all babies born during one week in mainland Britain in March 1958. The original sample of over 17,400 babies has been followed up on multiple occasions with collections of comprehensive information. Data are used from every wave up to 2000, when the sample was aged 42. Asthma onset is measured during mid-adulthood and using prospective data, a wide range of material and social adversities are measured throughout the life-course, as well as other factors thought to predict adult onset asthma.

Chapters 3 and 4 use data from the English Longitudinal Study of Ageing (ELSA), a representative sample of over 10,000 adults living in private households in England, mostly aged 50 and over. Comprehensive data have been collected every two years since 2001-2002.

This dataset is appropriate for Chapter 3 because good measures of RA are available and RA onset typically occurs between ages 40 and 60, so the ageing sample maximizes numbers reporting the condition. Life-course adversities are measured using retrospective information collected during an interview in which a temporal referencing system was used to aid full and accurate recall (Berney & Blane 1997, Means et al. 1991). RA was measured using contemporaneous information and a wide range of adversities were measured using the retrospective data.

ELSA was appropriate for chapter 4 because depressive symptoms were measured during all waves and biomarkers of inflammation were measured during three nurse interviews. Comprehensive contemporaneous information is also available so that it was possible to test whether a range of factors mediated prospective associations between inflammation and depressive symptoms. Furthermore, because of its age, the sample includes relatively high levels of baseline inflammation, as well as high proportions with longstanding illness, asthma and RA.

9. Final remarks

The PhD combines evidence and theory from Sociology, Psychology and Biology to investigate links between psychological factors and immune dysregulation using a life-course approach. Evidence and theory inform the choice of research questions and interpretation of findings.

The approach taken is to examine the psychosocial factors that predict onsets of two immune-mediated diseases, adult onset asthma and RA, about which existing evidence is sparse. In addition, prospective associations are estimated between chronic low-grade inflammation and depressive symptoms, and new evidence is provided about the factors that moderate and mediate these associations. New findings raise questions about generalisability and should be tested in other datasets. They also contribute to the development of hypotheses to explain links between psychological factors and immune dysregulation in the context of the life-course.

This PhD and the papers published from it will direct attention to the links between psychological factors and immune dysregulation within a real life (life-course) context because understanding about these links may be integral to understanding the psychosocial

pathways through which health inequalities develop over the life-course. I hope that the findings prompt further research about these links and greater consideration of them by policy makers and practitioners.

Chapter 2: Does adversity predict onset of asthma during mid-adulthood? Do psychosocial pathways play a role?

The aim of this chapter is to investigate the psychosocial factors that contribute to asthma onset during mid-adulthood. It does so by examining the contributions of life-course adversities of various types to asthma onset during mid-adulthood, and the factors that moderate, confound and mediate associations that are identified.

1. Introduction

1.1 Rationale

Asthma onset is the health outcome examined in this chapter because it is a major concern for public health. Furthermore, while the disease is diagnosed by physical symptoms such as respiratory problems, it appears to be closely linked to psychological symptoms. For example, asthma prevalence, severity, and progression are associated with psychological stress (Chida et al. 2008, Wainwright et al. 2007, Kilpelainen et al. 2002) and its prevalence is correlated with symptoms of anxiety and depression (Loerbroks et al. 2010).

Asthma with adult onset is of particular interest for several reasons. One is that while an interaction between genetic and environmental factors contributes to asthma onset during all life stages, environmental factors are probably more important contributors to asthma with onset later in life. Adult onset asthma has received scant attention from researchers compared with childhood asthma and adult asthma with no specified age of onset, and many key questions have hardly been addressed. For example, it is not clear that adult onset asthma reflects the same pattern of aetiologies as asthma with childhood onset, or

why onset is delayed until adulthood for some individuals. Indeed, it may be that asthma with onsets during different stages of adulthood has different determinants.

Asthma onset is therefore measured during a relatively short period of adult life; mid-adulthood. This is late enough to be distinct from childhood and early enough to precede decades of working life. Findings will contribute to understanding about the causes of adult onset asthma generally, but with a focus on psychosocial pathways. This understanding will inform public health decision-making about preventive strategies to reduce risk of adult onset asthma. Findings about the psychosocial predictors of adult onset asthma may also be relevant to childhood asthma, and to other immune-mediated conditions with adult onset, for example, late onset hay fever, urticaria and many autoimmune diseases.

1.2 Asthma

Asthma is a major concern for public health. The WHO (2011) estimates that 235 million people worldwide suffer from asthma, and that it is the most common chronic disease among children. Prevalence rates of asthma are almost as high among adults as they are among children. Asthma UK (2013) reported that 5.4 million people in the UK were currently receiving treatment for asthma, and of these, 1.1 million were children (1 in 11) and 4.3 million were adults (one in twelve). The Centers for Disease Control and Prevention (CDC 2012) reports similar rates of asthma prevalence in the US.

Rates of asthma vary widely between countries, and according to the Department of Health (DoH 2012), the UK has the highest prevalence in the world, with rates estimated between 11% and 17% (Simpson & Shiekh 2010, Hall & Mindell 2011). Although asthma is more common in higher income countries, it is the low income and minority groups within them that experience the highest levels of morbidity and mortality associated with it (NIH 2002,

Basagana et al. 2004). Specifically, Simpson & Sheikh (2010) report a graded relationship between socio-economic deprivation and risk of asthma onset in England.

Although asthma onset is most common during childhood, substantial numbers develop asthma for the first time during adulthood. In a large study using English medical records, Simpson & Shiekh (2010) estimated that of the 50 million individuals living in England in 2005, 0.45% (5,459) persons aged 15 to 44 and 0.38% (2,892) aged 45 to 64 developed asthma during that year. In addition, whilst incident rates of asthma between 2001 and 2005 had fallen by around one third among children, declines in incidence during adulthood were more modest (by around one sixth for the 15-44 age group, and by one fifth for those aged 45-64).

In a report published by the WHO, Bosquet et al. (2005) state that prevalence rates of asthma are rising in countries where prevalence is relatively low, and suggest that this occurs as communities adopt modern lifestyles and become more urbanised. In contrast, prevalence rates have plateaued in countries where rates were already high (Bosquet et al. 2005), and may even be decreasing (Simpson & Shiekh 2010). Simpson & Shiekh suggest that changes in incidence rates of asthma may reflect real changes in asthma incidence and/or changes in diagnosis.

Asthma is frightening and disabling and can result in death. For example, in 2010, there were 1,143 recorded deaths from asthma in the UK, almost all of them among adults (Asthma UK, 2013). Adult asthma is also costly to the state. The WHO estimates that the number of disability adjusted life years (DALYs) lost due to asthma are similar to numbers for diabetes, liver cirrhosis, and schizophrenia (Bousquet et al. 2005). Although some of these DALYs are lost due to care of children with asthma, others may result from asthma

among adults. In the UK, the DoH recently reported that asthma costs the National Health Service (NHS) around one billion pounds each year (DoH 2012), and a substantial proportion of this money is spent on adult asthma.

Asthma is a chronic condition that affects the airways in the lungs (DoH 2012). Unlike chronic obstructive pulmonary disease, obstruction of the airways is periodic or variable (Hall & Mindell 2011). Attacks can be triggered by allergens, exercise, occupational exposures, tobacco smoke, air pollution, and airway infections (CDC 2012). During attacks, airways become inflamed, making it hard to breathe (CDC 2012). Because the process of inflammation is a symptom critical to the diagnosis of asthma, it is classified as an immune as well as a respiratory disorder (Newson 2015). However, the causes of asthma are not well understood; it is a syndrome diagnosed on the basis of symptoms, triggered by a variety of circumstances.

A high proportion of individuals with asthma have other atopic conditions such as eczema and hay fever and/or raised levels of the immunoglobulins (total and specific IgEs) associated with atopy (Pearce et al. 1999). Preliminary evidence suggests that individuals with asthma are at increased risk of some autoimmune conditions (Hemminki et al. 2010) and at reduced risk of others (Tirosh et al. 2006). These comorbidities suggest that the development of asthma and other immune-mediated conditions may share common pathways (Rottem & Shoenfeld 2003, Lee et al. 2014).

1.3 A model of adversities over the life-course and the development of adult onset asthma

The model illustrated in Figure 2.1 illustrates how adversities experienced during the life-course may contribute to onset of asthma during mid-adulthood. It is similar to the model

set out in Figure 1.1 in Chapter 1. As with the model illustrated in Chapter 1, relationships may differ by gender and other characteristics. For asthma onset, these include atopic vulnerability and internalising temperament.

As explained in Chapter 1, adversities are events and circumstances that are usually appraised negatively and that one would expect to have negative consequences. They are exposures, conceptually distinct from responses and appraisals, and include life events and stressors. Evidence of associations between a range of adversities and negative health outcomes is summarised in Appendix 1.

In Figure 2.1, adversities are classified by domain, but it is the combination of adversities that act on an individual and it is relatively rare that a single risk factor is associated with serious consequences (Garmezy 1991, Rutter 2009).

Figure 2.1 includes mediating factors, classified as material, behavioural, psychological and biological. It also includes confounding factors, such as very early experiences and temperament. No direct effects of adversities on health are included. Some material mediating factors could be (but are not) classified as adversities. For example, occupational exposures to airborne pollutants are negative exposures but they are classified as a hypothesised mediator because they are a risk factor specific to asthma and may not be involved in the development of other health conditions, or other negative outcomes.

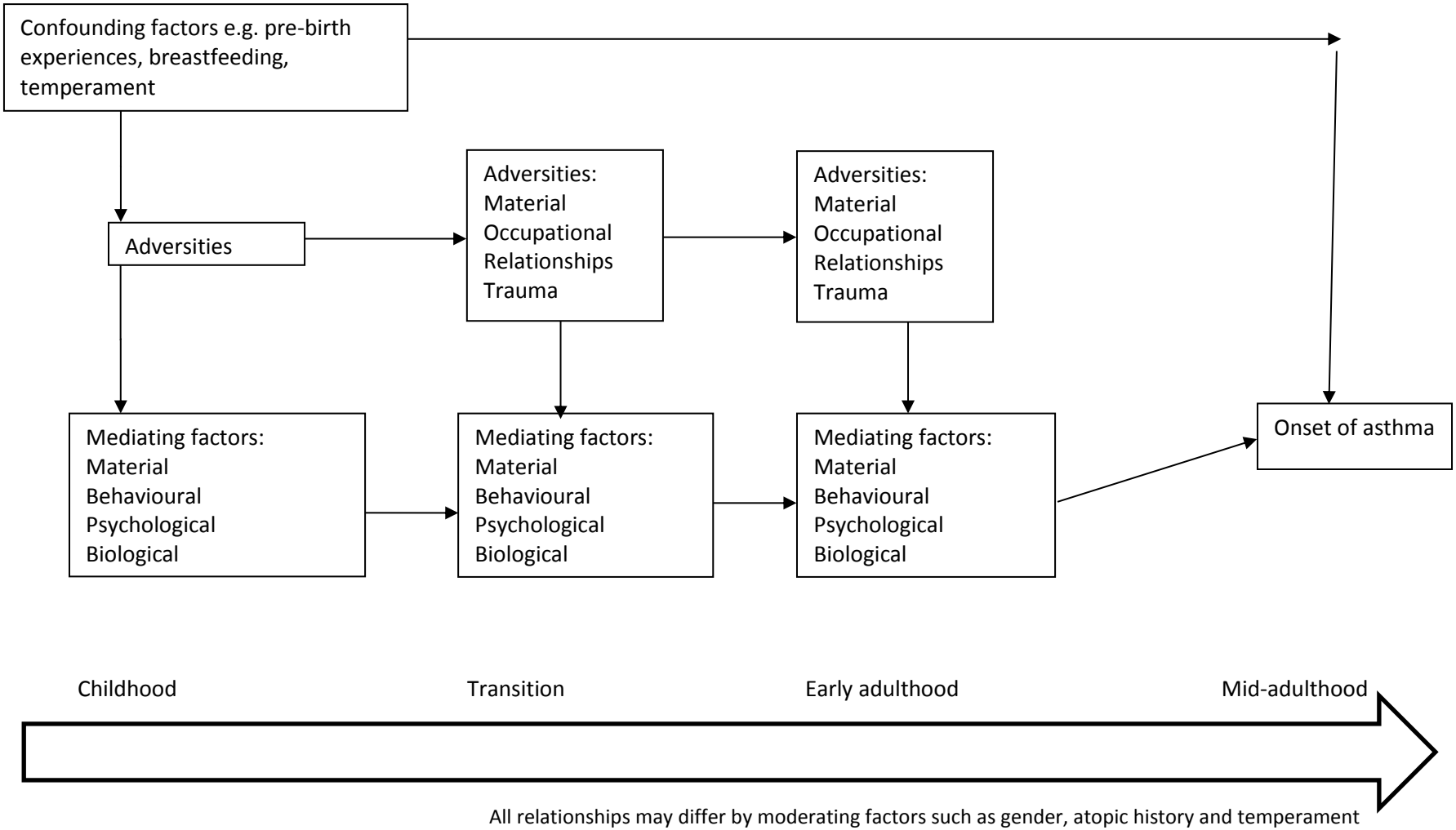
The arrow at the bottom of Figure 1 includes four life stages; childhood, transition to adulthood (referred to as transition), early and mid-adulthood. Adversity is measured during the first three life stages and asthma onset during the fourth. As explained in Chapter 1, theories of cumulative disadvantage (Ross & Wu 1996) and stress proliferation (Pearlin et al.

1997) suggest that exposure to adversity during earlier life stages predicts adversity during later life stages.

Adversities over the life-course combine in various ways to predict an outcome (Kuh et al. 2003). Models of cumulative exposure refer to the cumulative impact of exposures regardless of life stage. 'Chains of risk' refers to earlier exposures that have relevance for an outcome only because they predict later exposures that are more proximal to it. In contrast, exposures during critical or sensitive periods are not proximal to the outcome and have particular relevance for the outcome, regardless of subsequent exposures.

In relation to the sensitive period, Martinez (2009) argues that early life is a "developmental window of susceptibility", during which functional and structural characteristics of the respiratory system are established that affect asthma risk subsequently. For example, early respiratory infections are associated with the development of childhood asthma, probably through damage to the airways combined with over-stimulation of specific pathways in the developing immune system that are associated with atopy (Busse 1990).

Figure 2.1 Model of the contribution of the stress process to adult onset asthma



1.4 Summary of existing evidence about factors that predict adult onset asthma

1.4.1 Adversity

A few studies provide evidence consistent with prospective associations between adversity and asthma onset among adults. None examine how adversities combine over the life-course to predict asthma onset.

A large prospective study in Finland found that cumulative exposure to negative life events during a five year period predicted asthma onset during the following two years among adults aged 20-54 at baseline (Lietzen et al. 2011). Life events included death and severe illness of a family member, divorce or separation, marital problems, severe conflicts with a supervisor, and emotional, sexual, or physical violence. One hundred and ninety-two respondents developed asthma, and those who reported high as opposed to low levels of exposure had twice the risk of incident asthma, an association not explained by age, gender, education, marital status, pets, smoking status, and baseline allergic rhinitis.

Loerbroks and colleagues (2009) used data from over 4,000 German residents aged 40-65 at baseline, who were followed up for eight and a half years, with 63 developing asthma. Exposure to three specific adversities during the five years prior to baseline was reported retrospectively. Breaking a relationship with a partner or parent predicted asthma onset for women, but job loss and death of a partner, family member, or friend did not. The association found with breaking a partnership among women was not explained by age, education, family history of asthma, smoking status, alcohol consumption, body mass index, or physical activity. Using the same dataset, an association was found between work stress and asthma onset during the following 8.5 years, with slightly fewer (41) participants reporting new diagnoses of asthma (Loerbroks et al. 2010).

Using data from national cross-sectional surveys in ten countries worldwide, Scott and colleagues (2008) report a graded relationship between childhood adversities reported retrospectively and asthma with onset after age 20. Compared to adults exposed to no childhood adversities, those exposed to two and three adversities had increased odds of adult onset asthma by 49% and 71%, respectively. This study included almost 650 respondents with adult onset asthma.

Two smaller scale clinical studies used retrospective data collected from asthma patients, who were more likely than non-asthmatic control groups to report divorce, marital separation or family illness prior to onset (Teiramaa 1979, Salminen 1985).

This evidence is limited because it provides no information about how adversities combine over the life-course to predict asthma onset, and little insight into the types of adversity that matter most.

1.4.2 Moderators

As mentioned above, the relationships illustrated in Figure 2.1 may differ by gender and other variables. These variables would moderate relationships, because the magnitudes and consistencies of the associations would depend upon them. Factors that I consider as moderators of the association between adversity and asthma onset are gender, atopic history, and internalising temperament during childhood.

More boys than girls develop childhood asthma (Peckham & Butler 1978), and it has been suggested that this is because boys up to age 10 have narrower airways and increased airway tone than girls, which may predispose them to asthma (NIH 2002). In contrast, adult onset asthma is more common among women than men (Simpson & Shiekh 2010). This may

reflect gender differences in exposure to adversities and responses to them, in terms of self-reported stress (Gersten 2008, Gustafsson et al. 2012), and behavioural and physiological responses (Gersten 2008, Stroud et al. 2002). Moderation by gender is suggested by Loerbroks' finding that breaking a life partnership predicted asthma onset for women but not men (Loerbroks et al. 2009). However, other studies found no evidence of moderation by gender, although this may reflect power as numbers developing asthma (especially of men) were low (Lietzen et al. 2011, Rod et al. 2012).

Asthma is sometimes classified as atopic and non-atopic. Atopic asthma is identified by raised levels of specific IgEs and a history of atopic conditions other than asthma. If atopy reflects a genetic vulnerability, then one would predict adversity to be more strongly associated with non-atopic than atopic asthma. In order to examine the relative importance of adversity for atopic and non-atopic individuals, Lietzen and colleagues (2011) identified asthmatics with and without allergic rhinitis. They found no evidence that associations between adversity and subsequent asthma onset differed by atopic status.

Temperament refers to "consistencies in emotional and motivational responses" that begin to stabilize during childhood (Friedman 2011, p.220). It could affect responses to adversities in systematic ways. However, styles of appraisal and coping are not stable over time and context (Watson et al. 1999), and authors emphasise the specificity of coping responses to each stressor (or adversity) and context (Lazarus 1991, Eckenrode 1991).

1.4.3 Confounding factors

A factor confounds an association between two variables if it predicts both variables independently and if adjustment for the factor attenuates the association. In addition, a confounding factor occurs in causal pathways earlier than each variable. The association

here is between childhood adversity and asthma onset decades later, and factors considered as confounders are conditions during pregnancy, low birthweight, breastfeeding, and temperament. Temperament is also hypothesised as a moderator.

Conditions during pregnancy include maternal smoking and complications such as bleeding. Studies provide evidence that maternal smoking during pregnancy predicts life-course adversities (Jarvis & Wardle 2006, Phung et al. 2003), and childhood asthma (NIH 2002, Burke et al. 2012). I am aware of no direct evidence that complications during pregnancy predict life-course adversities, but Norbeen & Tilden (1983) report that earlier adversities predict complications during pregnancy. Based on theories of stress proliferation (Pearlin et al. 1997) and cumulative disadvantage (Ross & Wu 1996), complications during pregnancy should predict subsequent adversities because they are markers of earlier adversity. A large scale study using the NCDS found that bleeding during pregnancy predicted childhood asthma and protein in the urine during pregnancy (albuminaria) predicted adult onset asthma (Strachan et al. 1996).

Low birth weight predicts life-course adversity (Roland et al. 2014, Lechtig et al. 1975) and childhood asthma (Jaakkola & Gissler 2004).

A large population study in Gateshead, UK, concludes that affluent women are particularly likely to breastfeed their babies (Wright et al. 2006). Assuming that compared against women who are less affluent, more affluent women live in families with fewer circumstances that are classified as childhood adversities, it follows that breastfed babies tend to come from backgrounds with little adversity. Evidence that breastfeeding is negatively associated with childhood asthma is marginal (Gdalevich et al. 2001, Schmitz et al. 2012), possibly because associations between breastfeeding and asthma depend upon

atopic characteristics of the child and mother. I am aware of no evidence about associations between breastfeeding and adult onset asthma.

Temperament has been conceptualised as a moderator, but could also confound associations between adversity and asthma onset. The idea that temperament predicts ill health dates back to Hippocrates, and in 1950, Alexander suggested that asthma is associated with separation anxiety (Alexander 1950). Friedman & Booth-Kewley (1987) found evidence of associations with trait anxiety. It also appears that asthma is associated with internalising behaviours, which encompass level of mal-adaption, but also response type. Temperament is of particular interest in this chapter because it is likely to be associated with psychological factors that predict asthma onset.

Internalising behaviours during childhood encompass anxiety, fearfulness, withdrawal, and depression (Fanti and Henrich 2010). Consistently high levels during childhood predict outcomes during adolescence and adulthood that include depressive symptoms (Toumbourou et al. 2011, Dingle et al. 2011, Gander & Buchheim 2013) and anxiety (Dingle et al. 2011, Gander & Buchheim 2013). With few exceptions, studies consistently find positive cross-sectional correlations between internalising behaviours and childhood asthma (Annesi-Maesano et al. 2013). One large prospective study found that asthma at age 5 predicted high levels of internalizing behaviour at 14, but high levels of internalizing behaviour at age 5 did not predict onset of asthma between ages 5 and 14 (Alati et al. 2005).

1.4.4 Mediating factors

Mediating factors are predicted by adversity and predict asthma onset. They are classified as material, behavioural, biological, and psychological.

The material mediating factors referred to in Figure 2.1 are exposures to airborne pollutants and toxins that result from area of residence and occupation.

Material adversities, such as low income, predict exposures to airborne pollutants. In a recent study of socio-economic differentials in exposure to air pollution in England, Malojevic et al. (2017:2) state that there is a "significant body of evidence" from developed countries including the UK demonstrating that individuals on low incomes tend to be exposed to higher levels of air pollution. High prevalence of childhood asthma is associated with living in urban as opposed to rural areas, where air pollution is relatively high (Schmitz et al. 2012). Further, emergency admissions for asthma among adults and children have been linked to air pollution in European cities including London (Sunyer et al. 1997).

In addition, those working in poorly (as opposed to well) paid occupations are relatively likely to be exposed to pollutants and toxins at work. Kennedy et al. (2000) developed a job exposure matrix specific to asthma, and found that high risk occupations tended to fall into skilled and unskilled manual categories associated with low rates of pay. Adult asthma onset and prevalence are predicted by occupational exposures (Lillienberg et al. 2013, Ghosh et al. 2013, respectively).

Smoking is a behavioural mediator. Those who smoke tend to be exposed to more as opposed to less adversity (Kouvonon et al. 2005, Jarvis & Wardle 2006), and the NIH (2002) reports that smoking contributes to the progression of asthma, although it may not contribute to its onset. It has been suggested that smoking may increase the risk of asthma onset because smokers have elevated levels of serum IgE, which is raised in atopic conditions (Gerrard et al. 1980, Tsukioka et al. 2010), as well as increased bronchiole hyper-responsivity (Nadel & Comroe 1961).

Biological mediators include early respiratory infections, growing up in a family with older siblings, exposure to parental smoking, obesity, and the development of other atopic conditions. Referring back to the model described in Chapter 1, these are biological factors as opposed to the sub-clinical changes.

Children exposed to adversity are more likely to develop respiratory infections early in life (Cohen 2005, Trueba & Ritz 2013). Large scale studies report evidence of associations between early respiratory infections and asthma onset and prevalence (Montgomery et al. 2013, Strachan et al. 1996). Wright et al. (1998) suggest that early respiratory infections lead to asthma onset through damage to epithelium cells that line the airways, causing local inflammation.

Evidence from the NCDS led to the development of the hygiene hypothesis (Strachan 1989). Childhood asthma was less common among children who grew up in households with older children, and Strachan suggested that these children were exposed to more immune challenges from bacteria and viruses than children without older siblings, which protected them from the development of allergic conditions.

There is a socio-economic gradient in smoking among parents of young children (Kuntz et al. 2016). Tobacco smoke appears to increase risk of asthma onset during childhood, and also to exacerbate existing asthma (Karimi et al. 2015), although I am aware of no evidence about parental smoking and subsequent asthma onset during adulthood.

Whilst there is insufficient evidence to draw conclusions about whether or not childhood adversity predicts obesity (Tamayo et al. 2010), obesity predicts asthma with onsets during childhood, youth, and old age (Chen et al. 2013, Leone et al. 2012).

Eczema and hay fever predict asthma onset (Burgess et al. 2008, Dharmage et al. 2014), a phenomenon sometimes described as the atopic march (Zheng et al. 2011, Han et al. 2017). Bosquet et al. (2008) suggest that hay fever predicts asthma onset because it is characterised by hyper-reactivity of the upper respiratory airways (Cirillo et al. 2009), which may lead to more widespread bronchial hyper-reactivity and asthma. Childhood adversity may predict the development of allergic conditions other than asthma, such as eczema and hay fever, through a similar group of factors to those described in this section.

The hypothesised psychological mediator of an association between childhood adversity and asthma onset decades later is symptoms of depression. Depressive symptoms are predicted by childhood adversity (Felitti et al. 1998), and by stressful life events (Cohen et al. 2007), and they predict asthma onset (Chida et al. 2008, Loerbroks et al. 2010, Scott et al. 2008). The mechanisms underlying associations between asthma and depressive symptoms (and internalising behaviours among children) are unclear. One possibility is that immune dysregulation associated with not-yet-diagnosed asthma has psychological symptoms that resemble and lead to the development of depressive symptoms (Smith 1991, Miller & Raison 2016). Another is that psychological stress leads to (1) the development and recurrence of depressive symptoms (Hammen 2005, Leggett et al. 2016) and (2) lasting changes in the immune and respiratory systems. Wright and colleagues (2005) discuss the physiological mechanisms through which psychological stress may lead to biological hypersensitivity to environmental stimuli, and the development of asthma and other atopic conditions. In relation to respiration, the immediate physiological response to stress that is co-ordinated by the sympathoadrenal medullary results in narrowing of the airways. Frequent and prolonged activation, especially during infancy, may lead to lasting changes in the structure and functioning of these airways (Martinez 2009, Chen et al. 2006, Joachim et al. 2003, Hasler et al. 2005, Rietveld et al. 2000).

1.5 Research questions

The research questions (RQs) are designed to elicit information that will contribute to limited existing evidence about the psychosocial pathways that contribute to the development of asthma during mid-adulthood. They ask about the importance for adult onset asthma of adversities over the whole life-course, which is a question that has not been addressed before. Questions are also asked about the factors that moderate associations between adversities and asthma onset, as very little evidence exists about gender differences or differences by atopic history, and the question has never before been asked before in relation to temperament. Other studies have compared the importance for asthma onset of different types of adversity, but they have not classified them as social and material or by domain, or examined the factors that mediate associations between adversity and asthma onset. These questions are addressed to provide evidence about psychosocial pathways. The final RQ, which addresses the life-course factors that predict asthma onset, will provide new evidence because salient psychological and biological factors will be identified after adjustment for a comprehensive range of social and material adversities measured over the life-course.

The RQs are set out below.

1. Do life-course adversities predict asthma onset during mid-adulthood?
    a. Does total life-course adversity predict asthma onset?
    b. Do associations between adversity and adult onset asthma vary by gender, atopic history or temperament?
    c. Do adversities at any particular life stage matter, and if so, which life stage matters most?

   d. Do social adversities predict asthma onset after adjustment for material and occupation-related adversities?

2. What confounding and mediating factors explain the association between childhood adversity and adult onset asthma? Are psychological factors important?
3. What combination of factors best predicts asthma onset during mid-adulthood?

2. Data and measures

The dataset used is from the National Child Development Study (NCDS), a perinatal mortality survey of every baby born in England, Scotland and Wales during a week in March 1958 with over 17,400 babies. Follow-up occurred at ages 7, 11, 16, 23, 33, 42, 46, 50, and 55, and data are used from all the sweeps up to and including age 42. During cohort members' childhoods, information was collected by health visitors from parents and children through educational and medical assessments. Teachers also supplied information. Since adulthood, data have been collected directly from cohort members using structured interviews. Power & Elliott (2006) provide a full description of the study.

2.1 Onset of asthma during mid-adulthood

Onset of asthma is measured for all cohort members with no history of asthma at age 33. The variable takes a value of one if the cohort member reports asthma onset between ages 33 and 42. Questions used to code asthma onset are presented in Table 2.1.

Measures for asthma onset up to age 23 include wheezy bronchitis. This is partly because at ages 16 and 23 questions did not discriminate between the two outcomes. In addition, until the 1980s when cohort members were in their twenties, asthma and wheezy bronchitis were often used interchangeably as diagnoses (Koopman et al. 2001), and authors argue that conditions diagnosed as asthma and wheezy bronchitis were clinically and

pathologically equivalent (Williams & McNicol 1969, Sibbald et al. 1980). For these reasons, other studies using the same dataset have combined asthma with wheezy bronchitis during childhood and up to age 23 (Power & Manor 1995, Butland & Strachan 2007). I do the same.

For many cohort members, reports of asthma history are inconsistent, with history reported in earlier sweeps combined with later reports of never having had asthma. In these cases, I assume that information provided earlier is correct. At age 42, cohort members who reported ever having had asthma were asked about age of onset. This information was used only if information about asthma was not available in earlier sweeps.

Table 2.1: Questions used to code asthma or asthma and/or wheezy bronchitis

Age 7	"Has the child ever had attacks of asthma?"	(parental and medical questionnaires)
	"Has the child ever had bronchitis with wheezing?"	(parental and medical questionnaires)
Age 11	"Has the child ever had attacks of: asthma, wheezy bronchitis, both, neither?"	(parental questionnaire)
	"Has the child ever had wheezy bronchitis or asthma (other than mild attacks in infancy)?"	(medical questionnaire)
Age 16	"Has the child ever had an attack of asthma or wheezy bronchitis?"	(parental questionnaire)
Age 23	"Since your sixteenth birthday have you had an attack of asthma or wheezy bronchitis?"	
Age 33	"Have you ever been told that you have asthma?"	
Age 42	"Have you ever had or been told you had:	
	"migraine or severe headaches associated with vomiting or dizziness	
	"hay fever	
	"bronchitis	
	"asthma	
	"allergic rhinitis (persistent runny nose when you haven't got a cold)	
	"none of these?"	
	"How old were you when you first became aware that you had this condition?"	

2.2 Adversities

Adversities at each life stage are listed in Tables 2.2 and 2.3 with the domain in which they are classified and the questions used to measure them. Childhood is birth to 16, transition is 17-23, early adulthood is 24-33, and mid-adulthood is 34-42. Each measure of adversity takes two values to indicate exposure or no exposure.

The measure for cumulative exposure during childhood is the total number of adversities reported. Measures of cumulative exposure during transition and early adulthood were created in two stages. First, variables were created to indicate whether the cohort member was exposed to any adversities within each domain. Second, these were summed to create variables taking values between 0 and 4 domains in which adversity was reported during transition, and 0 and 5 domains in which adversity was reported during early young adulthood.

Table 2.2: Questions asked about childhood adversity

Variable	Age	Questions used
Early parental loss (up to 16)	0	Mother's marital status at birth (only used if other information is missing)
	7	Health visitor reports family difficulties due to death of mother, death of father, divorce, separation or desertion. "Please ascertain, or state to your knowledge, whether the child is normally cared for by his/her: …" "Please ascertain, or state to your knowledge, whether the child's father is his/her : …" Parental situation of illegitimate children
	11	"The actual relationship to the Study child of the persons acting as the child's parents is: (Please ring as appropriate):"
	16	"The relationship to the study child of the person acting as the child's mother is:…" "The relationship to the study child of the person acting as the child's father is:…"
	33	Cohort member's parents ever permanently separated or divorced, and if so, age when parents last lived together (only used to code a positive value and if other information is missing)
	50	Age of cohort member when mother died, age of cohort member when father died (only used to code a positive value and if otherwise missing)
Any time in care	7	"Has the child been in the care of the local authority?"
	11	"Has the child ever been in the care of a Local Authority Children's Committee?" "Has the child ever been in the care of a Voluntary Society?"
	16	"Has this child ever been in the care of a Local Authority?" "Has this child ever been in the care of a Voluntary Society?"
	23	"Were you ever, to your knowledge, "in care" as a child?" "Note: "in care" of a local authority social services / children's department or voluntary children's society. Children can be "in care" but live at home or with relatives."
Neglect at either age	7	Teacher rating of child's appearance as "looks underfed"/"scruffy and dirty"
	11	Teacher rating of child's appearance as "looks underfed"/"scruffy and dirty"
Parental mental illness reported at any age	7	Health visitor reports family difficulties "due to mental illness or neurosis"
	11	"Since the child's 7th birthday has either parent (or parent substitute) suffered from chronic or serious disability or ill-health, including any hospital in-patient admission of two weeks or longer?" "What is/was the condition?.../psychiatric/…"
	16	"Chronic ill health or disability in the household. In answering this question: "Include conditions which have been present since the study child's 11th birthday, irrespective of when they commenced "Include only the most severe condition if more than one is affecting the same person "Include parent substitute under mother or father "Has the study child since his/her 11th birthday lived in the same household as anyone suffering from chronic physical or mental ill health or disability?" Diagnosis for mother and father: "…psychiatric…"
Residential and school moves: at least one move of home and school between 5 and 16	7	"Number of times family has moved since child's birth (applicable only where the child has been with this family since birth). Please state number of moves" "Since the age of five, how many schools has the child attended? (Count the present school as one)"
	11	"How many times has the family moved home since the child was born. State number of moves, e.g. 6 moves=6. If 9 or more, enter 9. If the answer is not straight-forward give brief details" "How many schools has the child attended since the age of 5 years, not

		counting moves from one department to another of the same school."
	16	"How many schools has the study child attended since his/her 11th birthday?"
		"How many times has the family moved since the study child was born?"
Poverty: Free school meals at 11 and/or 16	11	"Does any child of the family receive free school meals at present?"
		"Is the child at present receiving free school meals?"
	16	"Does any child of the family receive free school meals at present?"

Con-current information about parental loss up to age 16 was provided by 12,052 cohort members, and this was supplemented by retrospective information provided by 2,540 cohort members at age 33 and by 20 cohort members at age 50. Con-current information about whether the cohort member had spent time in care up to age 16 was provided by 9,280 cohort members, and this was supplemented by retrospective information provided by 4,885 cohort members at age 23. The variable used to measure neglect was also used by Kelly-Irving et al. (2013a,b).

Table 2.3: Exposures to adversities during transition and early adulthood

Variable	Age	Questions asked
Material adversities		
Financial hardship		
Currently on means tested benefits[1] and savings of no more than £1,000.	23	"I now want to talk to you about income from sources other than work. At present are you (or your husband/wife/partner) receiving any of the state benefits or payments shown on this card?" "Which of these are (or your husband/wife/partner) receiving?" "Do you get any rebates on your rent or rates?" "Do you (or your husband/wife/partner) get a rent allowance or a rate rebate from the local council?" "At the moment do you (or your husband/wife/partner) have any money saved in any of the places mentioned on this card? At the present time, how much do you (or your husband/wife/partner) have saved in..."
Currently on means tested benefits[2] and not a part or full owner occupier.	33	"I now want to talk about income from sources other than work. At present, are you (or your husband/wife/partner) receiving any of the state benefits or payment shown on this card?" Details of benefits received, period covered, and whether it was respondent or spouse who received it. Household tenure at age 33.
Ever been homeless		
Time spent homeless or in a refuge.	23 33	"Have you ever had to move out of a place and had nowhere to go?" "Have you ever over the last 10 years become homeless, I mean having to move out of a place and having nowhere permanent to live? (NOTE: LIVING WITH PARENTS = 'NO')" Normal address hostel for homeless/women's refuge/night shelter.
Occupation-related adversities		
Unemployment		
Ever unemployed for at least 12 months[3].	23	Activity histories with start and end dates for each period of activity. One of the activities is unemployment.
Unemployed for at least 12 months since age 24.	33	Activity histories with start and end dates for each period of activity. One of the activities is unemployment.
Involuntary job loss		
Involuntary job loss, ever	23	"I would like to ask you how your first job came to an end. Did it come to an end because: it was a temporary job, the firm closed down, you were made redundant, you were sacked, or did you leave of your own accord?" Also asked about last job.
Involuntary job loss since age 24	33	"If not currently in paid work: (About most recent job) "What was the main reason you left this job? Please show me on this card. It was a fixed term or temporary job / you were made redundant / you were dismissed / you were pregnant / for other health reasons / you decided to leave yourself / other". Asked about most recent job, and two previous jobs since March 1981.
Failed a course		
No qualifications from year+ full-time accredited	23	"Did you pass all the qualifications you were studying for on this course?" "Which of these types of course was it? Full-time course / …"
Relationship adversities		
Caring for sick child		
Current care of biological child	23	"Does any child born to you have any longstanding illness, disability or infirmity?" "Does the child normally live with you?"
Poor quality relationship		
With current partner	33	Items from the Locke-Wallace Marital Adjustment Test. See

		Appendix 2.
Overcrowded housing		
Overcrowded housing[4]	33	"(Apart from the bathroom and kitchen) how many rooms does this accommodation have? Include shared rooms. Exclude kitchen, bathroom, toilets, halls, garages, etc." Household composition from household grid.
Broken partnerships		
One+ broken partnerships since 16	23	"Apart from anyone you subsequently married, how many people have you lived with as married for six months or more? (Include current partner if lived with for 6 months or more)" "When did you first start living together?" "Are you living with someone as married at present?" Age 33 information used only if age 23 information was missing.
…… since 24	33	Couple separated or partner died (with dates).
Lone parenthood		
Spent any time as a lone parent since 16	23	"Now I want to ask you about lone parenthood – I mean having to bring up a child on your own because a relationship with a husband/wife or partner has broken down or ended. Have you ever been a lone parent for a continuous period of one month or more?"
Spent any time as a lone parent since 24	33	"Could you tell me when each of these periods of lone parenthood started and ended? If 4 or more take first three and most recent"
Separation from child		
Current separation	23	"Is the child living with you now", asked of up to four biological children.
Currently not living with biological child under 16[5]	33	Age of child "Child is: living with respondent/living elsewhere/not living or not born" "Who is this child living with now?" Options include special school, boarding school
Loss of child		
Death of child, stillbirth		
Death of own child Stillbirth	23	"Is the child still alive?" "How old was the child when he/she died?" Options include stillborn. Age 33 information used only if age 23 information was missing.
Death of own child	33	"Please give details of each child by answering questions (a) – (e) opposite. You should start with your first child. If you have had any more than four children continue on pages 10 and 11. If you had twins, or a multiple birth, please fill in a separate column for each child" "Where is the child now? Living with you/living elsewhere/stillborn /died (please give date below)"
Stillbirth since age 24	33	"I would like to ask about any pregnancies you may have conceived / fathered, whether or not the pregnancy was carried to full term. Can I first check, have you ever conceived / fathered a pregnancy?" "It is important to know in what order things have happened, so I would like to ask a few questions about each pregnancy in turn. Let's start with the first pregnancy. Did this pregnancy end in a live birth, or a miscarriage, or a still birth, or what? Live birth, single / twins identical / twins fraternal / twins, no sure / multiple / still birth / miscarriage / abortion / still pregnant"
Infertility		
Infertility	23	"Can we talk about the future now. As far as you know, are you personally able to have (more) children of your own?" Age 33 information used only if age 23 information was missing.
Infertility	33	"As well as pregnancy, we are interested in any problems couples may have in getting pregnant when they want to. Has there ever been a time of six months or more when you and your partner were

		having sex regularly without using any method of birth control? Yes / no / never use birth control" "When was this? Approximate duration" "Do any of these apply to you or your partner? You have been sterilized or had a vasectomy or hysterectomy / you have been told by a doctor that you are unable to have children / you have been told by a doctor that you should not have children for health reasons / none of these"
Traumatic events		
Assault or rape	33	"Which of the things on this card best describes why you had to go to hospital? Road accident as pedestrian / road accident as driver or passenger / accident at work / accident at home / sports accident / another kind of accident / a violent assault or mugging / rape"

1. Means tested benefits at 23 were supplementary benefit, unemployment and supplementary benefit combined in one payment, sickness benefit, family income supplement, and rent and rates rebates, claimed by cohort member or their partner.
2. Means tested benefits at 33 are supplementary benefit or income support and family credit (Blundell & Walker 2000).
3. Long term unemployment is defined as periods of continuous unemployment lasting for 12 months or more (Begum 2004).
4. For the purposes of calculating Local Housing Allowance, households are assessed as needing a bedroom each for a couple, a person aged 21+, two same sex people aged 10-20, two children both under 10 (Shelter website, downloaded Jan 2018). When the household has insufficient bedrooms according to these guidelines, the variable for overcrowded housing is assigned a positive value. Overcrowding applies during early adulthood and may reflect economic circumstances, but is included because it is associated with family stress. Values of total family and relationship adversity during early adulthood were identical when overcrowded housing was excluded, as every cohort member who reported overcrowding reported additional family or relationship adversities.
5. Child separation takes a negative value if the child is at boarding school.

2.3 Moderating variables

Gender was measured during all sweeps. Respondents reporting different genders over time were assigned a missing value. Internalising childhood temperament is classified also as a confounding variable and atopic history is classified also as a mediating variable, and their measurements are described below.

2.4 Confounding variables

The perinatal survey, conducted soon after the births of cohort members, provided information to measure maternal smoking after the fourth month of pregnancy, bleeding during pregnancy, albuminaria and birthweight below the tenth centile, adjusted for sex and

gestation period. When cohort members were 7, parents were asked whether they had been breastfed for at least one month.

Childhood internalising temperament was indicated using measures of internalising behaviours. These were assessed by parents when cohort members were 7, 11, and 16. Parents were asked about the frequency of behaviours described in the Rutter scale (Rutter et al. 1970). Separate factor analyses were conducted at each age, with rotations allowing factors to correlate. Three factors were identified, reflecting internalising, externalising and hyperactive behaviours, and factor scores were used to measure each type of behaviour. Details are presented in Appendix 3.

Other authors report that the Rutter scale, completed by parents and teachers, identifies three factors, similarly interpreted (Kumpulainen et al. 1999a, McGee et al. 1985, Pereira et al. 2008).

Internalising temperament has not been measured before using maladaption scores, so far as I am aware. Cohort members were classified at each age by comparing their internalising and externalising scores. Based on distributions of each type of behaviour, they were classified as having relatively high internalising behaviours if their internalising score fell into a centile that was at least one decile higher than the centile into which their externalising behaviour fell. The indicator for internalising type took a yes value if the cohort member was classified as having relatively high internalising behaviours at 7, 11, and 16, or in two sweeps if information was missing in one.

2.5 Mediating variables

Data specially provided by the Centre for Longitudinal Studies, which manages the NCDS, were used to create variables indicating residence in an urban industrialised area at age 23, and occupational exposures likely to predict asthma onset. The latter variable was derived by Rebecca Ghosh (Ghosh et al. 2013).

Early respiratory infections were indicated if the cohort member's parent reported that they had had pneumonia by age 7. Household information provided when cohort members were aged 11 indicated the number of children (under 21) who lived in the household and were older than the cohort member. Parental smoking was indicated if at least one parent smoked when the cohort member was 16.

Smoking was measured at ages 16, 23, and 33. At age 16, a value of one was assigned if the cohort member reported currently smoking at least 10 cigarettes a week. At ages 23 and 33, they were assigned a positive value if they reported currently smoking at least one cigarette a day or a history of smoking at least one cigarette a day for a 12 month period since the last sweep.

Obesity was defined as having a body mass index (BMI) of 30 Kg/m^2 or more (Public Health England 2013), measured at ages 23 and 33. Atopic vulnerability was indicated by reported eczema or hay fever by age 33.

Depressive symptoms were measured at ages 23 and 33 using the Malaise Inventory (Rutter et al. 1970). See Appendix 4.

3. Analyses

To increase numbers and reduce bias, missing values were imputed in multiple datasets using as a base the whole sample except for three cohort members with missing data about gender. Details of the process are given in Appendix 5. Analyses were conducted on 20 multiple imputed datasets and the results pooled using the combination rules suggested by Rubin (1987).

Missing values were imputed for each childhood adversity and for indicators of one or more adversity in each domain during transition and early adulthood. After multiple imputation, these measures were used to create additional indices of adversity.

Using the original or observed dataset, summary statistics for each adversity during transition and early adulthood were calculated. In addition, bi-variate correlations were estimated between each childhood adversity, and between adversities in each domain during transition and early adulthood.

Summary statistics were calculated for asthma onsets during childhood, transition, early and mid-adulthood using the whole observed dataset and the twenty imputed datasets, for men and women combined and for men and women separately.

Based on the sample used in the analyses, that is, all cohort members who had not reported asthma symptoms by age 33, descriptive statistics for all other variables were calculated using the observed sample and multiple datasets with imputed values. Comparisons of values of variables in the observed sample and in the imputed datasets provides information about the likely characteristics of cohort members who provided incomplete information.

Using imputed datasets, summary statistics were calculated for men and women separately, and bi-variate logistic regressions were estimated to test gender differences.

In order to address the RQs, logistic regressions were estimated with asthma onset between ages 33 and 42 as the outcome using the imputed datasets and results were pooled. Analyses conditioned on gender because there are known gender differences in asthma onset and exposures to adversity.

RQ1: Do life-course adversities predict asthma onset during mid-adulthood?

RQ1a: Does total life-course adversity predict asthma onset?

Asthma onset during mid-adulthood was regressed onto adversity, conditioning on gender. Separate models were estimated for measures of total adversity during childhood, transition, early adulthood and between birth and the beginning of mid-adulthood.

In order to examine the nature of any correlations between adversity and asthma onset, total levels of adversity were measured using sets of dummies. This uses all available information and makes no assumptions about how increasing levels of exposure are associated with asthma onset. More parsimonious measures of exposure were also used; a continuous measure, and an indicator of exposure to two or more adversities during childhood or in two or more domains thereafter. Fits of models using these measures were compared using F-statistics. The continuous measure assumes a linear relationship between levels of adversity and asthma onset. This assumption was tested by comparing the fits of two models, one using the set of dummies, and the other using a measure of exposure calculated by multiplying the coefficient for one adversity by the number of adversities reported.

RQ1b: Do associations between adversity and adult onset asthma vary by gender, atopic history, or temperament?

Three sets of models were estimated in which asthma onset was regressed onto total adversity during each life stage, conditioning on gender and (1) its interaction with adversity, (2) atopic history and its interaction with adversity, (3) internalising temperament and its interaction with adversity.

RQ1c: Do adversities at any particular life stage matter, and which life stage matters most?

An analogous research question was addressed using a structured modelling approach developed by Mishra and colleagues (2009), which was used in subsequent research (Murray et al. 2011, Robertson et al. 2014). Using this approach, a saturated model was estimated that included as predictors of asthma onset cumulative adversity measured during all three life stages plus all possible interactions between them. Additional specifications that dropped predictors from the saturated model in various combinations were also estimated. Wald tests were used to assess each specification's parsimony and accuracy. The specifications are presented in Table 2.8.

RQ1d: Do social adversities predict asthma onset after adjustment for material and occupation-related adversities?

Asthma onset was regressed onto adversities in each domain, with mutual adjustment. This specification was estimated for men and women together, and for men and women separately, during transition and early adulthood.

RQ2: What confounding and mediating factors explain the association between childhood adversity and adult onset asthma?

For each hypothesised confounding and mediating variable, associations were tested with (1) childhood adversity, and (2) asthma onset during mid-adulthood.

To test for attenuation, models were estimated in which asthma onset was regressed onto childhood adversity conditioning on gender, first without adjustment (the baseline model), and then adjusting for each hypothesised explanatory variable that was associated with both childhood adversity and asthma onset. The baseline (unadjusted) association was compared with adjusted associations.

The Karlson Holm Breen (KHB) method (Karlson et al. 2012, Breen et al. 2013) was used to test for attenuation of the association between childhood adversity and asthma onset. Direct comparisons between nested models are not feasible when the dependent variable is binary because the baseline for each odds ratio (OR) estimated depends upon the other variables in the model. Consequently, changes in ORs when a hypothesised confounder or mediator is added to a model reflect not only attenuation by this variable but also changes resulting from rescaling. The KHB method addresses this complication by decomposing the change in a coefficient across nested logit models into an attenuating component and a rescaling component.

Two factors apart from adversity during subsequent life stages predicted both childhood adversity and asthma onset and attenuated the association between them. KHB tests were performed to examine whether each factor attenuate new baseline associations that included adjustment for adversity and the other factor.

RQ3: What combination of factors best predict asthma onset during mid-adulthood?

Variables that are correlated with asthma onset were identified in analyses conducted to address RQs1 and 2. These were included in a single model with asthma onset as the outcome. Variables were dropped from this model, F-statistics compared, and Wald tests used to identify which variables had coefficients that differed from zero after mutual adjustment.

Sensitivity analyses

Three sets of sensitivity analyses were conducted. The first repeated all the analyses using the observed dataset.

The second used a measure of asthma onset that disregarded history of asthma and wheezy bronchitis reported at age 7. It is not uncommon that individuals report asthmatic symptoms during the first years of life but not thereafter. This is reflected in the NCDS; parents of 1,439 cohort members reported that they had a history of asthma or wheezy bronchitis at age 7, but no history was reported in subsequent sweeps up to and including at age 33. These 1,439 cohort members are excluded from the main analyses but included in the sensitivity analyses.

The third used a measure of childhood adversity that excludes residential mobility. Residential mobility was the most commonly reported adversity during childhood and it is not conventionally included in measures of childhood adversity. I wanted to check whether the results depended upon its inclusion.

4. Results

Summary statistics

Summary statistics for asthma incidences are presented in Table 2.4. Incidence rates are consistently higher in the multiple imputed datasets than in the observed NCDS sample, indicating that at each life stage, cohort members with missing information about asthma onset and other variables of interest were at higher risk of having developed the condition than cohort members who provided complete information.

Table 2.4: Summary statistics for asthma onset

	NCDS sample				Multiple imputed datasets	
Life stage	Missing	Obs	%=yes	No.=yes	%=yes	95% CI
Men and women						
Childhood	6,176	12397	28.6%	3546	33.9%	33.0% - 34.9%
Transition	11,406	7170	5.8%	416	6.5%	5.3% - 7.8%
Early adulthood	11,284	7288	3.3%	241	4.5%	3.5% - 5.4%
Mid-adulthood	11,414	7140	3.7%	264	4.6%	3.6% - 5.6%
Men						
Childhood	3,175	6431	31.7%	2039	37.0%	35.8% - 38.3%
Transition	6,147	3457	4.2%	145	4.9%	3.6% - 6.3%
Early adulthood	6,138	3467	2.5%	87	3.5%	2.4% - 4.5%
Mid-adulthood	6,172	3424	2.6%	90	3.4%	2.2% - 4.6%
Women						
Childhood	3,001	5966	25.2%	1503	30.7%	29.4% - 31.9%
Transition	5,259	3713	7.3%	271	8.3%	7.0% - 9.6%
Early adulthood	5,146	3821	4.2%	160	5.5%	4.4% - 6.7%
Mid-adulthood	5,242	3716	4.7%	174	5.8%	4.7% - 6.8%
Gender difference	p=0.000 for every life stage				P<=0.001 for every life stage	

Onset of asthma is coded for cohort members with no history of asthma at baseline. During childhood and transition, asthma includes wheezy bronchitis. Childhood is 0-16, transition 17-23, early adulthood 24-33, and mid-adulthood 34-42. Multiple imputed datasets have 18,554 observations; 9,596 men, 8,958 women. Obs is the number of respondents for whom the variable has a non-missing value. %=yes and N=yes indicate the percentages and numbers, respectively, of respondents who reported asthma onset.

Percentages of respondents reporting asthma onset vary between life stages partly because they cover different numbers of years. Based on the imputed datasets, mean incidence rates per 1,000 persons per year for asthma are 16.8 (i.e. 286/17) during childhood, 9.7 during

transition, 3.3 during early adulthood, and 4.1 during mid-adulthood. Although incidence rates are not uniform during each life stage, these percentages suggest that incidence rates are greatest during childhood, decline through transition into early adulthood, and begin to rise during mid-adulthood.

Gender differences in asthma onset depend upon life stage. More boys than girls developed asthma during childhood, and thereafter, more women than men developed the condition. In both the observed and multiple datasets with imputed values, these gender differences are statistically significant with very low p-values.

Summary statistics for other variables are presented in Tables 2.5 and 2.6. They are based on cohort members who reported no history of asthma by age 33. The first columns use the observed NCDS sample, and the others use the twenty imputed datasets. Cohort members with missing information were exposed to more adversities during each life stage, with the exceptions of adversities involving child loss and trauma during early adulthood. In addition, higher proportions manifested internalising type behaviours during childhood, had pneumonia by age 7, grew up with older children, lived in urban industrialised areas at age 23, were exposed to toxins or pollutants through their occupations and were obese at age 33. They also smoked and had more depressive symptoms at 23 and 33.

The final column in Tables 2.5 and 2.6 give p-values of gender coefficients estimated from bivariate regressions with each variable included in the analyses. During childhood, there is no evidence of gender differences in exposure to any adversity, except that teachers described more boys than girls as underfed, scruffy or dirty. This could reflect gender bias in teachers' assessments as well as any gender difference in neglect. During both transition and early adulthood, more women reported material adversity and adversities involving

child loss and more men reported occupation-related adversities and trauma. During transition but not early adulthood, women reported more family and relationship adversities than men. More women than men had a history of eczema and/or hay fever by age 33, and they reported more depressive symptoms. Men reported higher levels of occupational exposures, and were more likely to have smoked at ages 23 and 33.

Evidence for associations between adversities is presented in Appendix 6. Those exposed to one childhood adversity were at relatively high risk of being exposed to another. Later in life, those exposed to adversities in one domain were more likely to be exposed to adversity in another. Those exposed to adversities during one life stage were at relatively high risk of being exposed during other life stages.

Table 2.5: Summary statistics for adversities for cohort members without asthma before age 33[1]

	Observed		Multiple datasts with imputed values (n=14,109)[2]						
	Men&women		Men&women		Men (n=7,241)		Women (n=6,868)		Diff.
Adversities	Obs	%	%	95%CI	%=Y	95%CI	%=Y	95%CI	p-val[3]
Childhood adversity (0-16)									
Early parental loss	**7807**	**28.9**	**36.0**	**35.0-37.0**	35.9	34.5-372	36.1	34.4-37.7	0.845
Spent time in care	**10359**	**5.6**	**8.2**	**7.5-8.9**	8.6	7.7-9.4	7.8	6.9-8.6	0.154
Neglect at 7 or 11	**5124**	**8.9**	**12.2**	**11.0-13.4**	**14.6**	**12.9-16.3**	**9.8**	**8.5-11.1**	**0.000**
Parent mentally ill	**8079**	**7.4**	**10.4**	**9.5-11.2**	10.4	9.3-11.5	10.4	9.3-11.4	0.928
High mobility[4]	**7509**	**47.2**	**55.0**	**53.9-56.0**	54.1	52.7-55.5	55.9	54.4-57.4	0.078
Free school meals[5]	**7680**	**22.0**	**30.2**	**28.9-31.4**	30.1	28.3-31.9	30.2	28.8-31.6	0.910
Total adversity[6]									
0	**9281**	**32.5**	**28.2**	**27.2-29.2**	28.2	26.9-29.5	28.1	26.8-29.5	0.916
1	**9281**	**45.6**	**30.8**	**29.7-31.9**	30.4	28.8-32.0	31.2	29.8-32.7	0.420
2	**9281**	**15.1**	**17.0**	**16.1-17.8**	16.9	15.8-18.1	17.0	15.5-18.4	0.953
3	**9281**	**5.1**	**13.7**	**12.8-14.6**	13.4	12.2-14.6	14.0	12.7-15.3	0.540
4	**9281**	**1.5**	**6.6**	**5.9-7.3**	7.0	6.1-7.8	6.2	5.4-7.0	0.135
5-6	**9281**	**0.2**	**3.7**	**3.3-4.2**	4.0	3.4-4.6	3.4	2.8-4.1	0.154
Adversities during transition (17-23)									
Material	**7032**	**18.4**	**24.6**	**23.4-25.8**	**21.7**	**20.3-23.1**	**27.7**	**26.0-29.4**	**0.000**
Occupation-related	**9091**	**20.2**	**24.2**	**23.0-25.4**	**28.2**	**26.5-30.0**	**20.0**	**18.7-21.2**	**0.000**
Family & relationships	**9142**	**12.9**	**16.2**	**15.4-17.1**	**11.7**	**10.7-12.7**	**21.0**	**19.6-22.4**	**0.000**
Child loss	**9124**	**2.2**	**3.5**	**2.9-4.1**	**2.2**	**1.5-2.8**	**4.9**	**3.9-5.9**	**0.000**
Number of domains in which adversities were reported									
0	**7747**	**58.9**	**55.6**	**54.4-56.7**	**56.9**	**55.4-28.5**	**54.1**	**52.5-55.8**	**0.012**
1	**7747**	**29.4**	**26.2**	**25.3-27.2**	26.8	25.4-28.1	25.7	24.4-26.9	0.250
2	**7747**	**9.7**	**13.0**	**12.1-13.8**	12.3	11.2-13.4	13.6	12.6-14.7	0.062
3-4	**7747**	**2.0**	**5.3**	**4.7-5.8**	**4.0**	**3.4-4.7**	**6.5**	**5.6-7.5**	**0.000**
Adversities during early adulthood (24-33)									
Material	**8117**	**10.5**	**14.1**	**12.9-15.3**	**11.7**	**10.3-13.1**	**16.5**	**15.1-18.0**	**0.000**
Occupation-related	**8293**	**23.0**	**26.8**	**25.3-28.4**	**34.3**	**32.2-36.4**	**19.0**	**17.5-20.5**	**0.000**
Family & relationships	**7503**	**24.4**	**30.0**	**28.5-31.5**	30.9	29.0-32.9	29.0	27.3-30.7	0.088
Child loss	8039	20.5	21.4	19.7-23.1	**19.8**	**17.9-21.7**	**23.1**	**21.2-25.0**	**0.001**
Trauma	8243	2.7	3.5	2.7-4.3	**4.8**	**3.7-6.0**	**2.1**	**1.5-2.7**	**0.000**
Number of domains in which adversities were reported									

0	**7692**	**41.8**	**38.6**	**37.4-39.8**	**35.4**	**33.8-37.0**	**42.0**	**40.5-43.5**	**0.000**
1	**7692**	**39.1**	**36.4**	**35.3-37.5**	**37.7**	**36.2-39.2**	**35.0**	**33.6-36.4**	**0.008**
2	**7692**	**14.7**	**17.3**	**16.4-18.2**	**18.8**	**17.5-20.0**	**15.8**	**14.6-16.9**	**0.000**
3-5	**7692**	**4.4**	**7.7**	**6.8-8.6**	8.2	7.0-9.3	7.2	6.3-8.2	0.125
Adversities over the early life-course (0-33)									
0	**4309**	**14.6**	**10.1**	**9.5-10.8**	**9.5**	**8.7-10.3**	**10.8**	**9.9-11.8**	**0.024**
1	**4309**	**28.3**	**19.1**	**18.3-19.9**	18.7	17.5-19.9	19.5	18.5-20.6	0.312
2	**4309**	**22.0**	**18.3**	**17.6-19.1**	18.5	17.3-19.7	18.2	17.0-19.4	0.762
3	4309	16.0	15.6	14.8-16.4	15.9	14.9-17.0	15.2	14.2-16.3	0.333
4	**4309**	**9.7**	**11.8**	**11.1-12.5**	12.1	11.1-13.1	11.5	10.5-12.6	0.441
5	**4309**	**4.9**	**8.6**	**8.0-9.2**	8.9	8.1-9.8	8.2	7.4-9.0	0.219
6	**4309**	**3.0**	**6.0**	**5.5-6.6**	6.1	5.3-6.9	6.0	5.2-6.7	0.784
7-15	**4309**	**1.5**	**10.3**	**9.7-11.0**	10.2	9.4-11.0	10.5	9.5-11.5	0.664

Single adversities in observed dataset	**Transition**		**Early adulthood**	
	Obs	**%=Y**	**Obs**	**%=Y**
Material adversities				
On means-tested benefits[7]	6918	12.4	8116	7.5
Homeless	9087	5.9	8264	3.8
Occupation-related adversities				
Unemployment[8]	10682	6.1	10649	6.7
Redundant/sacked	9066	10.6	8268	17.1
Failed a course[9]	9096	5.4		
Family & relationship adversities				
Broken partnership[10]	9332	9.3	8173	8.0
Lone parenthood	9094	4.0	8174	5.3
Child has chronic illness[11]	8967	1.1		
Separation from child[12]	9095	1.5	7676	6.0
Poor relationship[10]			7833	2.9
Overcrowded home			8292	5.4
Child loss adversities				
Death of child	10234	0.6	7993	1.0
Stillbirth	10299	0.5	8269	0.8
Infertility	9110	1.0	8299	18.6
Trauma				
Assault or rape[13]			8243	2.7

Summary statistics exclude cohort members who reported asthma symptoms by 33. Obs is the number of respondents for whom the variable has a non-missing value. %=Y refers to binary variables and is the percentage of respondents with a yes value for the variable. %=Y if the percentage of men or women with a yes value. Cumulative exposures using the observed sample were coded to maximise variation. Childhood adversities were summed only if information was available for three or more adversities. If information was available for fewer adversities, it was only used if this indicated at least one exposure. Cumulative measures based on incomplete information were not scaled up. Similar approaches were used to code cumulative exposures during the other two life stages. Different distributions of variables in the observed and multiple imputed datasets and between genders are in bold font.

1. No history of asthma or wheezy bronchitis 0-23, no history of asthma 24-33.
2. 20 datasets with missing values imputed. Summary statistics reported for cohort members with no history of asthma/wheezy bronchitis 0-23, asthma 24-33.
3. P-values refer to logit regression analyses of female gender on each variable.
4. Residential mobility is one+ move of home and school during same period 5-16.
5. Any family member on free school meals at ages 11 or 16 or both.
6. Value in imputed datasets is sum of childhood adversities after imputations.
7. On means tested benefits and savings <=£1,000 (transition), not owner occupier (early adulthood).
8. Continuous period of unemployment lasting 12 months +.
9. Full-time accredited courses only.
10. Partnerships defined as romantic relationships including marriage that involved cohabitation for at least six months.
11. Cohort member's biological children living in same household.
12. Only identified if assault or rape led to hospital care.

Table 2.6: Summary statistics for hypothesised modifiers, confounders, and mediators of adversities-adult onset associations.

	Observed sample Men & women		Multiple datasets with imputed values (n=14,109) Men & women		Men (n=7,241)		Women (n=6,868)		Difference
	Obs.	%=Y	%=Y	95%CI	%=Y	95%CI	%=Y	95%CI	p-val[1]
Modifiers[2]									
Female	14109	48.7	48.7	47.9-49.5					
Atopic history[3]	9685	12.8	13.0	12.3-13.7	**9.6**	**8.8-10.5**	**16.5**	**15.4-17.5**	**0.000**
Internalising type[4]	**9812**	**33.8**	**40.9**	**39.8-42.0**	40.2	38.7-41.7	41.6	40.2-43.0	0.139
Confounders									
Bleeding < 28th week[5]	12779	3.4	3.5	3.2-3.8	3.3	2.9-3.7	3.7	3.2-4.2	0.222
Bleeding > 28th week	12779	24.0	24.1	23.4-24.8	24.1	23.0-25.1	24.1	23.1-25.2	0.916
Albuminaria[6]	12512	8.1	8.2	7.7-8.6	8.4	7.8-9.1	7.9	7.2-8.6	0.266
Maternal smoking[7]	12986	32.8	33.0	32.1-33.8	33.0	31.8-34.1	33.0	31.8-34.1	0.998
Low birthweight[8]	11188	9.7	10.1	9.5-10.6	9.9	9.1-10.7	10.3	9.5-11.1	0.525
Breastfed for at least one month	10475	43.7	42.6	41.5-43.6	41.7	40.4-43.0	43.5	42.0-45.0	0.066
Mediators									
Pneumonia by age 7	**10498**	**2.9**	**3.4**	**3.0-3.8**	3.4	2.9-4.0	3.3	2.8-3.8	0.757
Parental smoking[9]	8349	71.3	71.0	69.5-72.5	70.4	68.6-72.1	71.6	69.8-73.4	0.187
Older children[10]	10034	0.952	0.976	0.954-0.998	0.987	0.958-1.017	0.965	0.934-0.996	0.272
Urban residence at 23[11]	**8566**	**20.7**	**23.1**	**22.0-24.1**	22.6	21.1-24.0	23.6	22.0-25.1	0.344
Occupational exposures[12]	8338	1.077	1.105	1.081-1.129	**1.190**	**1.160-1.221**	**1.016**	**0.990-1.041**	**0.000**
Smoker at 23[13]	**9163**	**47.6**	**51.2**	**50.0-52.4**	**53.0**	**51.5-54.5**	**49.2**	**47.7-50.8**	**0.000**
Smoker at 33	**8161**	**43.0**	**45.7**	**44.2-47.1**	**47.5**	**45.7-49.3**	**43.8**	**42.1-45.4**	**0.000**
Obesity at 23[14]	8922	2.5	2.8	2.3-3.3	2.5	2.0-3.0	3.1	2.4-3.8	0.083
Obesity at 33	**8020**	**11.2**	**12.7**	**11.4-14.0**	12.4	10.8-14.1	13.0	11.6-14.3	0.448
Depressive symptoms 23[15]	**9057**	**2.528**	**2.749**	**2.678-2.820**	**2.140**	**2.056-2.224**	**3.391**	**3.293-3.489**	**0.000**
Depressive symptoms 33	**8241**	**2.267**	**2.580**	**2.491-2.670**	**2.234**	**2.130-2.337**	**2.945**	**2.827-3.063**	**0.000**

1. From logits of gender on each variable.
2. Variables may moderate, confound and mediate associations.
3. History of eczema and/or hay fever by age 33.
4. Measurement of internalising type is described in text.
5. Bleeding before and after 28th week of pregnancy.
6. Albuminaria is protein in mother's urine during pregnancy.
7. Maternal smoking after fourth month of pregnancy.
8. Below 10th centile, adjusted for gestation period and sex.9. At least one parent smoked when cohort member 16.
10. No. older children under 21 in same household at 11. Means.
11. Urban industrialized residence at age 23.
12. Likely to increase asthma risk, by 33, range 1-3. Means.
13. Smoking at least 10 per week at 16, and/or smoking one or more cigarette per day 17-33.
14. Obesity defined as BMI of 30 and over.
15. Continuous malaise scores at 23 and 33, ranges 0-16 and 0-21, respectively. Means here but standardised values used in analyses.

Summary statistics for cohort members without asthma by 33. Bold font indicates differences that are statistically significant at p<0.05. Obs is the number of respondents for whom the variable has a value. % refers to binary variables and is the % of respondents with a yes value for the variable. %=Y is the percentage of men or women with a yes value.

RQ1. Do life-course adversities predictor asthma onset during mid-adulthood?

RQ1a: Does total life-course adversity predict asthma onset?

Table 2.7 presents results indicating that risk of asthma onset increases with total adversity from birth to 33, and with levels of adversity during each life stage.

Comparisons of F-statistics for specifications that measure adversity using sets of dummies, binary indicators, and continuous measures indicate that relationships with asthma onset are described most accurately and parsimoniously using continuous measures. Additional tests indicate that relationships with adversity during each life stage are linear.

After conditioning on gender, the odds of asthma onset during mid-adulthood increase with each additional adversity during childhood (OR=1.263, 95% confidence interval 95%CI=1.112-1.434, p=0.001, maximum value of 5 or more), and with exposures in each additional domain during transition (OR=1.559, 95%CI=1.351-1.799, p=0.000, maximum value of 3 or more) and early adulthood (OR=1.430, 95%CI=1.221-1.675, p=0.000, maximum value of 3 or more).

After adjustment for adversity during each life stage, asthma onset during mid-adulthood was more common among women than men.

Table 2.7: Odds ratios for asthma onset between 34 and 42 predicted by life-course adversity, unadjusted, for men and women together.

		Set of dummies			Continuous measure			Indicator of two or more adversities			
		OR	95%CI	p-val	OR	95%CI	p-val	V	OR	95%CI	p-val
Life-course (0-33) adversities											
Female		1.748	1.310-2.333	0.000	1.756	1.318-2,340	0.000		1.752	1.320-2.326	0.000
Adversities	0				1.232	1.140-1.332	0.000	0-1	Reference		
	1	1.062	0.647-1.742	0.813				2+	1.860	1.302-2.659	0.001
	2	1.214	0.699-2.108	0.492							
	3	1.432	0.833-2.460	0.197							
	4	1.513	0.818-2.798	0.192							
	5	2.167	1.204-3.900	0.012							
	6	2.514	1.310-4.822	0.007							
	7-15	4.027	2.089-7.762	0.000							
Wald test		F=8.630,p=0.000									
F-stat. model fit		F=9.362			F=21.967				F=12.880		
Test of linearity					p=0.654						
Childhood adversities (0-16)											
Female		1.761	1.325-2.341	0.000	1.753	1.321-2.326	0.000		1.739	1.307-2.313	0.000
Adversities	0				1.263	1.112-1.434	0.001	0-1	Reference		
	1	1.158	0.796-1.684	0.445				2+	1.723	1.242-2.390	0.003
	2	1.531	1.047-2.238	0.031							
	3	1.555	0.928-2.605	0.102							
	4	2.366	1.333-4.197	0.005							
	5-6	3.770	1.918-7.413	0.001							
Wald test		F=6.017, p=0.000									
F-stat. model fit		F=7.317			F=13.206				F=11.996		
Test of linearity					p=0.561						
Adversities during transition (17-23)											
Female		1.639	1.216-2.210	0.002	1.645	1.222-2.214	0.002		1.662	1.239-2.231	0.002
Adversities	0				1.559	1.351-1.799	0.000	0-1	Reference		
	1	1.432	1.089-1.883	0.012				2+	2.422	1.818-3.225	0.000

	2	2.280	1.659-3.134	0.000							
	3-4	3.943	2.428-6.403	0.000							
Wald test		F=18.676, p=0.000									
F-stat. model fit		F=17.184			F=25.872				F=24.616		
Test of linearity					P=0.718						
Adversities during early adulthood (24-33)											
Female		1.799	1.350-2.397	0.000	1.808	1.359-2.405	0.000		1.784	1.341-2.374	0.000
Adversities	0				1.430	1.221-1.675	0.000	0-1	Reference		
	1	1.287	0.993-1.668	0.058				2+	1.895	1.436-2.501	0.000
	2	1.718	1.247-2.366	0.001							
	3-5	3.156	1.891-5.268	0.000							
Wald test		F=12.132, p=0.000									
F-stat. model fit		F=12.571			F=17.138				F=16.863		
Test of linearity					p=0.279						

Results of 12 models with no other covariates. Within life stage, models were estimated for each measure of adversity using 20 datasets with imputed values, N=14,109 and includes all cohort members with no history of asthma symptoms by 33.

RQ1b: Do associations between adversity and adult onset asthma vary by gender, atopic history or temperament?

There is no evidence that associations between asthma onset and adversity varied by gender, atopic history, or temperament. In models that included interaction terms, after adjusting for gender and adversity during the appropriate life stage, ORs for asthma onset contingent upon the interaction between female gender and adversities during childhood, transition and early adulthood were 1.027 (95%CI=0.889-1.185, p=0.716), 1.046 (95CI%0.856-1.278, p=0.655) and 1.126 (95%CI=0.899-1.412, p=0.293), respectively. After adjustment for gender, atopic history, and adversity during the appropriate life stage, ORs for asthma onset contingent upon interactions between atopic history and adversities were 1.018 (95%CI=0.869-1.192, p=0.823), 1.050 (95%CI=0.862-1.280, p=0.622), and 1.020 (95%CI=0.877-1.187) p=0.795 for the life stages in the same order. Odds ratios for interactions between internalising temperament and adversities during childhood, transition and early adulthood were 0.905 (95%CI=0.622-1.238, p=0.526), 1.112 (95%CI=0.821-1.505, p=0.488), and 0.986 (95%CI=0.748-1.300, p=0.921), respectively.

RQ1c: Do adversities at any particular life stage matter, and if so, which life stage matters most?

Table 2.8 presents information about the accuracy and parsimony of various specifications that constrain the ways in which adversities combine over the life-course to predict asthma onset. F-statistics indicate parsimony and accuracy (how well values predicted by the model match the data given its complexity), and these are highest for the model that includes adversity during transition as a sensitive period and the strict accumulation model. Wald tests report probabilities that coefficients of variables dropped from the saturated model are zero. This indicates that coefficients excluded to create the strict accumulation model did not differ from zero, but that the coefficients excluded to create the model with

transition as a sensitive period did. Therefore, the strict accumulation model was selected. According to this model, each additional adversity during childhood, and adversity in each additional domain during transition and early adulthood is associated with an OR for asthma onset during mid-adulthood of 1.232, 95%CI=1.140-1.332, p=0.000 (Table 2.7). Reporting maximum life-course adversities as opposed to none is associated with increased odds of asthma onset during mid-adulthood by 4.26 (1.23^7).

Table 2.8: Comparison of alternative life-course models of adversities as predictors of adult onset asthma, each adjusted for gender, for men and women together.

Model	Specification	F-stat.	p-val
Saturated	$= \alpha + \beta_1 A_C + \beta_2 A_Y + \beta_3 A_{EA} + \beta_4 A_C A_T + \beta_5 A_Y A_{EA} + \beta_6 A_C A_{EA} + \beta_7 A_C A_Y A_{EA}$	9.22	
Accumulation: strict	$= \alpha + \beta_1 (A_C + A_Y + A_{EA})$	21.97	0.396
relaxed	$= \alpha + \beta_1 A_C + \beta_2 A_Y + \beta_3 A_{EA}$	13.68	0.396
Sensitive periods	$= \alpha + \beta_1 A_C$	13.21	0.000
	$= \alpha + \beta_1 A_Y$	25.87	0.018
Accumulation over sensitive periods	$= \alpha + \beta_1 A_C + \beta_2 A_Y$	16.23	0.147
Chain of risk	$= \alpha + \beta_1 A_{EA}$	17.14	0.000
Accumulation within chains of risk	$= \alpha + \beta_1 A_Y + \beta_2 A_{EA}$	18.93	0.072
Sensitive period with chain of risk	$= \alpha + \beta_1 A_C + \beta_2 A_{EA}$	13.29	0.001

A_C, A_Y, A_{EA} represent total adversity during childhood, transition, and early adulthood, respectively.
All models are estimated for 14,109 respondents and are conditioned on gender.
High values of the F-statistic indicate models' parsimony and accuracy.
p-values are from Wald tests and indicate probabilities that coefficients of parameters dropped from the saturated model equal zero.

RQ1d: Do social adversities predict asthma onset after adjustment for material and occupation-related adversities?

Table 2.9 indicates that after adjustment for material and occupation-related adversities, adversities associated with child loss during transition and adversities associated with family and relationships and trauma during early adulthood each predict asthma onset during mid-adulthood. Evidence for these associations appears to be stronger among women than men.

After adjustment for adversities in other domains, material adversities during transition and early adulthood each predict asthma onset. Associations with occupation-related adversities

are only statistically significant for men during transition, but trends are consistently positive.

Overall, evidence of associations is slightly stronger for women than men. This is expected, as a higher proportion of women than men reported asthma onset during mid-adulthood.

Table 2.9: Odds ratios for asthma onset contingent u*p*on adversity in various domains, with mutual adjustment and adjustment for gender, for men and women together and separately

	Models					
	Men & women (n=14,109)		Men (n=7,241)		Women (n=6,868)	
Variable	Transition	Early adulthood	Transition	Early adulthood	Transition	Early adulthood
Female	**1.610** **1.174-2.208** **0.004**	**1.818** **1.351-2.447** **0.000**				
Material	**1.791** **1.274-2.517** **0.002**	**1.531** **1.058-2.216** **0.029**	**1.708** **1.019-2.856** **0.048**	**1.739** **1.017-2.974** **0.048**	**1.816** **1.249-2.642** **0.003**	1.398 0.905-2.160 0.138
Occupation-related	1.368 0.987-1.896 0.067	1.201 0.862-1.675 0.286	**1.552** **1.029-2.341** **0.039**	1.342 0.866-2.079 0.194	1.252 0.842-1.860 0.272	1.087 0.720-1.641 0.695
Family and relationships	1.202 0.880-1.642 0.252	**1.492** **1.104-2.015** **0.012**	1.095 0.589-2.034 0.776	1.368 0.885-2.114 0.164	1.247 0.871-1.785 0.232	**1.565** **1.109-2.208** **0.013**
Child loss	**2.420** **1.276-4.588** **0.011**	1.101 0.782-1.550 0.583	2.540 1.006-6.416 0.054	0.807 0.475-1.370 0.430	**2.374** **1.183-4.767** **0.021**	1.283 0.898-1.833 0.176
Trauma		**2.333** **1.390-3.916** **0.002**		1.981 0.976-4.018 0.064		**2.792** **1.463-5.328** **0.003**

These are results from six models with asthma onset as the outcome, predicted by adversity in each domain with mutual adjustment and gender, as appropriate. Binary variables are used to indicate exposure to one or more adversity in each domain. ORs of asthma onset are presented, with 95% confidence intervals below, and p-values below these. Results in bold font are statistically significant with p-values<0.05.

RQ2: What confounding and mediating factors explain the association between childhood adversity and adult onset asthma?

Results of bi-variate analyses presented in Table 2.10 found that both childhood adversity and asthma onset were associated with internalising temperament, occupational exposures up to age 33, smoking at 23 and 33, depressive symptoms at 23 and 33 and with adversity during transition and early adulthood. Maternal bleeding after 28 weeks of pregnancy, maternal smoking during pregnancy, low birthweight and not having been breastfed each predicted childhood adversity but not asthma onset. Childhood adversity was associated with early respiratory infections, parental smoking, more older children in the household during childhood and urban industrialised residence at age 33, but these factors did not predict asthma onset.

Of the variables associated with both childhood adversity and asthma onset, there was evidence from KHB tests of attenuation of the association between childhood adversity and asthma onset by adversities and depressive symptoms during transition and early adulthood.

KHB tests report changes in ORs for asthma onset contingent on childhood adversity attributable to dropping variables. After adjustment for gender, subsequent adversity and depressive symptoms during the other life stage, KHB tests find that changes in ORs of asthma onset contingent on childhood adversity attributable to dropping depressive symptoms at ages 23 and 33 are 1.002 (95%CI=-0.994-1.012) p=0.534, 1.012 (95%CI=-1.004–1.021) p=0.004, respectively. This indicates that depressive symptoms at age 33 as opposed to age 23 are the more salient mediator of associations between childhood adversity and asthma onset, after adjustment for adversity after childhood.

Table 2.10: Attenuation of association between childhood adversity and asthma onset during mid-adulthood for men and women together

	Estimated associations between each hypothesised attenuator and:						Estimated associations between childhood adversity and asthma onset					
	Asthma onset			Childhood adversity			As each variable added			Change in OR due to attenuation		
Hypothesised attenuators	OR	95% ci	p-val	OR	95% ci	p-val	OR	95% ci	p-val	OR	95% ci	p-val
None (baseline)							1.263	1.112-1.434	0.001			
Hypothesised confounders												
Internalising temperament	**1.506**	**1.050-2.160**	**0.031**	**0.880**	**0.808-0.959**	**0.004**	1.269	1.117-1.443	0.001	0.997	0.994-1.001	0.109
Bleeding < 28 weeks	0.860	0.394-1.880	0.708	0.946	0.811-1.102	0.477						
Bleeding > 28 weeks	1.108	0.821-1.496	0.504	**1.144**	**1.072-1.221**	**0.000**						
Albuminaria	1.212	0.806-1.822	0.359	1.107	0.991-1.237	0.075						
Maternal smoking pregnancy	1.298	0.991-1.702	0.064	**1.406**	**1.325-1.491**	**0.000**						
Low birthweight	1.427	0.853-2.387	0.185	**1.475**	**1.307-1.665**	**0.000**						
Breastfed	0.895	0.703-1.141	0.374	**0.770**	**0.716-0.829**	**0.000**						
Hypothesised mediators												
Atopic history	**1.875**	**1.438-2.445**	**0.000**	1.053	0.984-1.127	0.141						
Pneumonia by age 7	1.533	0.772-3.044	0.229	**1.475**	**1.249-1.742**	**0.000**						
Parental smoking	1.298	0.991-1.702	0.064	**1.406**	**1.325-1.491**	**0.000**						
Older children in household	0.948	0.836-1.075	0.410	**1.200**	**1.163-1.238**	**0.000**						
Urban residence at 23	1.300	0.911-1.855	0.158	**1.398**	**1.257-1.554**	**0.000**						
Occupational exposures	**1.217**	**1.010-1.465**	**0.045**	**1.279**	**1.232-1.329**	**0.000**	1.246	1.097-1.416	0.002	1.013	1.000-1.027	0.065
Smoking at 23	**1.263**	**1.010-1.580**	**0.044**	**1.625**	**1.502-1.758**	**0.000**	1.252	1.098-1.428	0.002	1.008	0.993-1.024	0.287
Smoking at 33	**1.300**	**1.031-1.638**	**0.030**	**1.658**	**1.554-1.768**	**0.000**	1.250	1.092-1.430	0.003	1.010	0.993-1.028	0.242
Obesity at 23	1.251	0.574-2.726	0.576	**1.360**	**1.050-1.761**	**0.025**						
Obesity at 33	1.193	0.808-1.761	0.380	1.067	0.962-1.184	0.223						
Depressive symptoms at 23	**1.134**	**1.093-1.177**	**0.000**	**1.106**	**1.094-1.118**	**0.000**	**1.190**	**1.037-1.366**	**0.020**	**1.047**	**1.024-1.070**	**0.000**
Depressive symptoms at 33	**1.156**	**1.119-1.195**	**0.000**	**1.094**	**1.081-1.108**	**0.000**	**1.168**	**1.026-1.331**	**0.026**	**1.059**	**1.041-1.077**	**0.000**
Adversities during transition	**1.583**	**1.373-1.826**	**0.000**	**1.620**	**1.560-1.681**	**0.000**	**1.158**	**1.014-1.323**	**0.039**	**1.076**	**1.045-1.107**	**0.000**
Adversities early adulthood	**1.405**	**1.199-1.647**	**0.000**	**1.439**	**1.383-1.498**	**0.000**	**1.200**	**1.057-1.362**	**0.009**	**1.047**	**1.020-1.075**	**0.001**

These are results from 51 models, estimated for 14,109 respondents; 21 estimating bi-variate associations between each hypothesised attenuator and asthma onset (ORs refer asthma onset contingent upon each hypothesized attenuator); 21 more with childhood adversity (ORs refer to childhood adversity contingent upon each hypothesized attenuator). Nine models estimated associations between childhood adversity and asthma onset adjusted for gender (ORs of asthma onset contingent upon childhood adversity), the first as a baseline model, with eight additional models each including one hypothesised attenuating variable. Changes in ORs as hypothesised attenuators are added are estimated using the KHB method, described in the text. Evidence statistically significant at 95% level is in bold font.

RQ3: What combination of factors best predict asthma onset during mid-adulthood?

The first set of columns in Table 2.10 indicate that asthma onset is predicted by internalising temperament during childhood, atopic history, urban industrialised residence, occupational exposures, and depressive symptoms at 23 and 33. Table 2.7 indicates that gender and adversity over the life-course and during each life stage predict asthma onset. Adversities over the life-course are used as a single predictor of subsequent asthma onset because results relating to RQ1c indicate that this measure is a parsimonious and accurate predictor of asthma onset.

Table 2.11 presents results when these variables are included in a single model as predictors of asthma onset. After mutual adjustment, asthma onset during mid-adulthood is predicted by female gender, life-course adversity, atopic history, internalising temperament and depressive symptoms at age 33.

Table 2.11: ORs for asthma onset contingent upon predictors in a single model with mutual adjustment using the whole sample

Variables	OR	95% ci		p-value
Female	1.519	1.146	2.014	0.005
Life-course adversity (0-33)	1.139	1.043	1.244	0.007
Urban industrialised residence at 23	1.181	0.814	1.713	0.386
Occupational exposures	1.115	0.931	1.334	0.243
Atopic history	1.709	1.300	2.248	0.000
Internalising type	1.513	1.035	2.213	0.038
Depressive symptoms at 23	1.020	0.970	1.072	0.448
Depressive symptoms at 33	1.105	1.063	1.149	0.000
F-statistic	13.381			

The model was estimated using 20 datasets with imputed values and 14,109 observations.

Table 2.12 presents F-statistics and the results of Wald tests as variables were dropped from this model. The first model in the table, the full model, is the same as the model presented in Table 2.11. Subsequent models (specifications 1-8 in the top row of Table 2.12) drop one variable at a time. The model selected as the most accurate and parsimonious on the basis of high F-statistic and high p-value from the Wald test drops urban industrialised residence at age 23. This specification is the new 'full' model from which additional variables are dropped. The following 'full' model excludes depressive symptoms at age 23, and the third excludes occupational exposures. All remaining variables independently predicted asthma onset and were retained in the final model. This specification includes female gender, life-course adversity, atopic history, internalising temperament during childhood and depressive symptoms at age 33 as predictors of asthma onset during mid-adulthood. These are the variables that predict asthma onset in the original model presented in Table 2.11.

9.1.2 Sensitivity analyses

Sensitivity analyses produced similar results. Details are presented in Appendices 7-9.

Table 2.12: Comparison of different models estimated to predict asthma onset during mid-adulthood, estimated for men and women together

		Eight models with one variable dropped							
Specifications	Full	1	2	3	4	5	6	7	8
Female	+	-	+	+	+	+	+	+	+
Life-course adversity (0-33)	+	+	-	+	+	+	+	+	+
Urban industrialised at 23	+	+	+	-	+	+	+	+	+
Occupational exposures	+	+	+	+	-	+	+	+	+
Atopic history	+	+	+	+	+	-	+	+	+
Internalising type	+	+	+	+	+	+	-	+	+
Depressive symptoms at 23	+	+	+	+	+	+	+	-	+
Depressive symptoms at 33	+	+	+	+	+	+	+	+	-
F-statistic	13.38	14.17	14.83	15.66	14.72	13.40	14.58	15.17	11.97
Wald test p-value		0.005	0.007	0.386	0.243	0.000	0.038	0.448	0.000

	Seven models with two variables dropped							Six models with three variables dropped					
Specifications	1	2	3	4	5	6	7	1	2	3	4	5	6
Female	-	+	+	+	+	+	+	-	+	+	+	+	+
Life-course adversity (0-33)	+	-	+	+	+	+	+	+	-	+	+	+	+
Urban industrialised at 23	-	-	-	-	-	-	-	-	-	-	-	-	-
Occupational exposures	+	+	-	+	+	+	+	+	+	-	+	+	+
Atopic history	+	+	+	-	+	+	+	+	+	+	-	+	+
Internalising type	+	+	+	+	-	+	+	+	+	+	+	-	+
Depressive symptoms at 23	+	+	+	+	+	-	+	-	-	-	-	-	-
Depressive symptoms at 33	+	+	+	+	+	+	-	+	+	+	+	+	-
F-statistic	16.93	17.87	17.66	16.05	17.45	18.24	14.25	20.23	20.83	21.03	19.16	20.86	14.62
Wald test p-value	0.005	0.005	0.269	0.000	0.039	0.448	0.000	0.005	0.002	0.264	0.000	0.039	0.000

	Five models with four variables dropped				
Specifications	1	2	5	6	8
Female	-	+	+	+	+
Life-course adversity (0-33)	+	-	+	+	+
Urban industrialised at 23	-	-	-	-	-
Occupational exposures	-	-	-	-	-
Atopic history	+	+	-	+	+
Internalising type	+	+	+	-	+
Depressive symptoms at 23	-	-	-	-	-
Depressive symptoms at 33	+	+	+	+	-
F-statistic	24.41	24.84	22.75	24.81	17.20
Wald test p-value	0.008	0.001	0.000	0.047	0.000

+ indicates that the variable is included in each model and – indicates that the variable is dropped from the model. High F-statistics indicate accuracy of fit between the data and the specification given the number of parameters, and p-values from Wald tests indicate the probability that asthma onset is predicted equally well by the reduced model compared against the full model that includes all variables. All models are estimated using 20 imputed datasets with 14,109 respondents.

5. Discussion

As set out in the introduction, this chapter provides evidence about the psychosocial pathways through which asthma develops during mid-adulthood within the context of the model set out in Figure 2.1. It uses large-scale prospective life-course data that include a broad range of adversities and contextualising factors as well as substantial numbers reporting asthma onset. The evidence provided is comprehensive and detailed and many findings are new.

5.1 Discussion of findings

Main findings

For respondents with no history of asthma by age 33, adversities during childhood, transition and early adulthood are associated with substantial increases in the risk of developing asthma during mid-adulthood, that is, between ages 33 and 42. These associations do not differ by gender, atopic history, or internalising temperament. Adversities over the life-course combine cumulatively with an OR of 1.232, 95%CI=1.140-1.332, p=0.000 for each additional adversity during childhood and adversity within each domain during transition and early adulthood. The maximum value of seven or more is associated with a very substantial increase in the risk of asthma onset during mid-adulthood; the OR of asthma onset contingent upon maximum exposure as opposed to none is 4.26.

New evidence is provided through comparison of the importance for asthma onset of different types of adversity. After mutual adjustment for material, occupation-related, relationship-related and child loss adversities, adversities that predict asthma onset during transition are material adversities and adversities associated with child loss. After mutual

adjustment, adversities that predict asthma onset during early adulthood are those associated with material pathways, relationship difficulties and trauma. The importance of non-material adversities as predictors of asthma onset after mutual adjustment indicates the relevance of psychosocial pathways in the development of asthma. They appear to be more salient predictors of asthma for women than for men.

Mediation of associations between childhood adversity and adult onset asthma has not, to my knowledge, been examined before. The findings suggest that the association between childhood adversity and asthma onset decades later is mediated by adversities after childhood and depressive symptoms. Mediation by depressive symptoms suggests a psychosocial pathway, most simply explained by adversity leading to the development of depressive symptoms, which in turn increase risk of asthma onset.

When all predictors of asthma onset are included in a single model, the salient predictors of asthma onset are female gender, internalising temperament during childhood, life-course adversity, history of eczema or hay fever, and depressive symptoms shortly before asthma onset.

RQ1: Do life-course adversities predict onset of asthma during mid-adulthood?

Findings that adversity during each life stage predicts asthma onset during mid-adulthood are consistent with existing evidence, and the magnitudes of associations are comparable. Lietzen et al. (2011) reported roughly doubled odds for asthma onset during adulthood contingent upon high as opposed to low levels of adversity during the previous five years, which is consistent with my findings that exposures in each additional domain (up to five) during early adulthood were associated with increased odds by 43%. Scott et al. (2008) reported that exposure to two as opposed to no childhood adversities was associated with

an OR for asthma onset of 1.49, which is consistent with my finding that each additional childhood adversity is associated with an OR for asthma onset of 1.21, or 1.42 for two adversities. My results add to the small evidence base that exposures to life-course adversities are associated with substantial increases in the risk of developing asthma during adulthood, and suggest that the association is graded as opposed to a threshold effect.

The very substantial association between total life-course adversity and asthma onset during mid-adulthood is an indication of the importance of environmental factors in the development of asthma during adulthood. The magnitude of the association is greater than magnitudes reported in previous studies, presumably because in this study, measures of adversity are comprehensive and encompass the whole life-course.

This chapter provides no evidence that associations between adversity and asthma onset are modified by gender, history of other atopic conditions or internalising temperament during childhood. Other studies report no evidence of gender differences in associations between adversity and asthma onset (Lietzen et al. 2011, Rod et al. 2012), and no evidence of differences by history of hay fever (Lietzen et al. 2011). No studies that I am aware of have examined the importance of internalising temperament as a moderator of the association between adversity and asthma onset.

I am not aware of studies that have examined the relative contributions to adult onset asthma of adversity during different life stages. The approach taken in this chapter was to compare how well different life-course models described the data, assuming that adversities were equivalent during each life stage. This assumption is questionable because the comprehensiveness of adversities differed between life stages as trauma was measured during early adulthood but not during transition. In addition, the same adversity may have

different meanings depending upon the life stage when it is experienced. For example, partnership breakdown may be experienced differently during transition and early adulthood. These differences complicate interpretation of results. In illustration, the strict accumulation model was selected in the chapter. If adversities were measured more comprehensively during early adulthood than during transition, then a different model might better describe how adversities that are truly equivalent to one another combine over the life-course to predict asthma onset. This could be the relaxed accumulation with a higher coefficient for adversities during transition than for adversities during early adulthood.

Findings that adversity during each life stage independently contributes to asthma onset during mid-adulthood may be less affected by differences between life stages in the meanings and measurement of adversities than if a different life-course specification had been selected. For example, interpretation would have been more problematic if the results had indicated that adversities during one life stages mattered more than others.

The life-course model selected suggests that adversities during each life stage contribute to the risk of adult onset asthma and that this risk is cumulative. The finding resonates with evidence that adversities and low socio-economic position (SEP) combine over the life-course in a cumulative way to predict dysregulation across multiple physiological systems, including the immune system (Singer & Ryff 1999, Hale 2004, Gustafsson et al. 2011, Gruenewald et al. 2012).

As with comparisons between adversities during different life stages, comparisons between domains of adversity are complicated because measures differ in terms of comprehensiveness and the severity of adversities included. For example, during transition

there are only two measures of material adversity but four measures of adversities associated with relationships and family.

Not forgetting this caveat, there is evidence that after adjustment for material and occupation-related adversities, social adversities (family and relationship-related, child loss-related and traumatic) predict asthma onset during mid-adulthood. This is consistent with the argument that intense and/or chronic psychological stress has physiological correlates that increase the risk of immune dysregulation resulting in biological hypersensitivity to environmental stimuli and the development of asthma (Wright et al. 2005).

Material adversities during both transition and early adulthood were also salient predictors of adult onset asthma. This is consistent with evidence that asthma onset and prevalence during adulthood are inversely correlated with SEP (Basagna et al. 2004, Simpson & Sheikh 2010).

During early adulthood, adversities associated with family and relationships and traumatic events predicted asthma onset. In contrast, it is during transition that child loss is salient for asthma onset during mid-adulthood. The greater importance of child loss during transition than during early adulthood may reflect differences in the prevalence of child loss during each life stage, and the availability of resources to cope effectively. Based on multiple datasets with imputed values, 3% (494) respondents during transition reported child loss compared to 21% during early adulthood.

Although gender did not moderate associations between total adversity and asthma onset, there is an indication of gender differences in the types of adversities that are most salient. After mutual adjustment, material adversities predicted asthma onset for both men and

women, but occupational adversities appeared more salient for men. In contrast, family and relationship-related adversities during early adulthood predicted asthma onset among women but not men. The importance of family and relationship-related adversity for women is consistent with evidence that breaking a life partnership during the previous eight years predicted asthma onset for women but not men (Loerboks et al. 2009). It is also consistent with evidence that women suffer more psychological distress than men following multiple partnership transitions (Willits et al. 2004).

RQ2: What confounding and mediating factors explain the association between childhood adversity and adult onset asthma?

In order to identify the factors that confounded or mediated the association between childhood adversity and adult onset asthma, bi-variate associations were estimated between hypothesised variables and both childhood adversity and adult onset asthma. Nineteen variables were considered and 38 associations tested. Given that the level of statistical significance was <0.05, two of the associations would be statistically significant by chance. The use of KHB tests of attenuation for the seven variables that were correlated with childhood adversity and asthma onset adds credibility to the findings.

The association between childhood adversity and asthma onset during mid-adulthood was explained by subsequent adversity and depressive symptoms. These are new findings, consistent with evidence that depressive symptoms predict adult onset asthma (Chida et al. 2008, Loerbroks et al. 2010, Scott et al. 2008).

Evidence that depressive symptoms mediated associations between childhood adversity and asthma onset decades later indicates the importance of psychosocial pathways in the development of asthma during adulthood. It suggests that depressive symptoms are a

marker of processes that contribute to the development of asthma during youth and adulthood. Authors suggest that depression affects inflammation via pathways similar to those involved in the stress response, involving the hypothalamic-pituitary-adrenal axis and the autonomic nervous system (Martinac et al. 2014, Penninx et al. 2013). This could result in hypersensitivity to environmental stimuli and the development of asthma (Wright et al. 2005).

I found no evidence that associations between childhood adversity and asthma onset were attenuated by many hypothesised variables, and those that mediated the association only did so partially. Other studies similarly report that associations between adversity and adult onset asthma are not fully explained by similar variables (Lietzen et al. 2011, Loerbroks et al. 2009). Lack of attenuation may reflect measurement error in the hypothesised attenuating variables tested. For example, lifetime exposure to environmental pollution was measured imprecisely by residence in an urban industrialised area at one point in cohort members' lives. Moreover, many factors that plausibly explain the association were not included, for example, parental history of asthma.

RQ3: What combination of factors best predict asthma onset during mid-adulthood?

After mutual adjustment for a wide range of factors, salient predictors of adult onset asthma were female gender, atopic history, internalising temperament, life-course adversity, and depressive symptoms shortly before onset. This highlights the importance of social and psychological factors in the development of asthma during adulthood.

Other evidence suggests that exposures to adversity (Lietzen et al. 2011, Loerbroks et al. 2009, Loerbroks et al. 2010, Scott et al. 2008), and depressive symptoms (Chida et al. 2008, Loerbroks et al. 2010, Scott et al. 2008) predict adult onset asthma. These results add to this

evidence. Further, they indicate that adversity over the life-course and depressive symptoms shortly before asthma onset are particularly salient predictors, even after mutual adjustment, and adjustment for a comprehensive range of co-variates.

Depressive symptoms at age 33 were also the most salient mediator of the association between childhood adversity and asthma onset shortly afterwards. The findings are new and very intriguing. They may reflect associations between depressive symptoms and inflammation that precedes asthma diagnosis. This is consistent with the inflammatory theory of depression (Smith 1991, Miller & Raison 2016) and with epidemiological evidence of small associations between depressive symptoms and chronic low-grade inflammation (Howren et al. 2009).

Another new and intriguing finding is that internalising temperament during childhood predicts asthma onset during adulthood, after adjustment for a range of other factors including atopic history and depressive symptoms. Possible explanations for the association are (1) that internalising temperament reflects atopic vulnerability, and (2) that internalising temperament predicts depressive symptoms, which increase risk of asthma onset. However, the association is robust to adjustment for both atopic history and life-course depressive symptoms. A third explanation is that internalising temperament predicts anxiety (Dingle et al. 2011, Gander & Buchheim 2013) and anxiety is associated with asthma onset (Scott et al. 2008 report trends that were not statistically significant). It may be that internalising temperament is a more accurate predictor than depressive symptoms of the types of anxiety that contribute to asthma onset during adulthood.

Regardless of the explanations, this finding is not backed up by other studies (since they do not exist) and could be specific to this dataset. Existing evidence uses measures of

internalising behaviours, which combine internalising type response with level of mal-adaption. Studies report cross-sectional correlations between internalising behaviours and childhood asthma (Annesi-Maesano et al. 2013), but no evidence that internalising behaviours predict subsequent asthma onset (Alati et al. 2005).

Female gender and atopic history predicted asthma onset. This was expected as there is consistent evidence that adult onset asthma is more common among women than men (Simpson & Shiekh 2010) and among adults who have a history of other atopic conditions (Han et al. 2017, Dharmage et al. 2014, Zheng et al. 2011).

Assessing the relative salience of variables as predictors of asthma onset using a single model with mutual adjustment, such as the model presented in Table 2.11 is complicated by differences between variables in the accuracy and comprehensiveness of their measurement, and by correlations between predictors. For example, neither urban industrialised residence nor occupational exposures predicted asthma onset after mutual adjustment, and this probably reflects correlations between these two factors and life-course adversity. This difficulty is partly addressed by the analyses presented in Table 2.12, in which variables are dropped one at a time from the full model. The results using this method were the same. Given evidence that exposure to air pollutants contributes to the development of asthma (Schmitz et al. 2012, Lillienberg et al. 2013, Ghosh et al. 2013), my interpretation of the final model is that life-course adversities proxy for these exposures as well as measuring other factors such as stress-inducing adversities that are important predictors of adult onset asthma.

5.2 Strengths and limitations

Strengths of this study are that it uses prospective life-course data, and consequently provides evidence relevant to causality. The sample is large, and multiple imputation increases its power and reduces bias. Rates of asthma incidence (4.3 per 1,000 per year) are equivalent to those reported in a study using a large sample of English medical records (Simpson & Sheikh 2010). Simpson & Sheikh (2010) reported incidence rates of 5.3 per 1,000 per year, which is slightly higher, but reflects a younger age range (15-44 as opposed to 33-42) as incidence rates of asthma are higher during transition. A comprehensive range of adversities and other predictors are included. The results are robust to sensitivity analyses that use alternative measures of asthma onset and childhood adversity, and the observed dataset.

The study is also subject to limitations. Firstly, findings relate to individuals born in mainland Britain in 1958, and I cannot be sure to what extent they apply to other populations. Second, long gaps between data collection mean that much information depends upon recall, which could be biased by factors relating to asthma onset, such as emotional and physical wellbeing. Third, comprehensive information was not available for many measures. In particular, I was unable to measure parenting quality, which is critical for assessment of the impacts of childhood adversities (Shonkoff et al. 2012). Neither was information available about several variables thought to predict asthma onset; family history of atopic conditions (Viegi et al. 2003, National health Service 2014), maternal stress during pregnancy (De Marco et al. 2012, Khashan et al. 2012), and living in damp housing (Schmitz et al. 2012). Fourth, the measures of cumulative exposure to adversity assume that each adversity, or adversities in each domain, has equal importance. This is unlikely to be true, although reviews of evidence about the value of combining life events using differential weightings suggest that these do not add to their accuracy in predicting outcomes

(Zimmerman 1983, Turner & Wheaton 1995). Fifth, comparisons are made between adversities by life stage and type, and results may be affected by differences in the comprehensiveness, precision and accuracy of measures.

A final caveat is that many correlations were tested using the conventional but arbitrary cut point for statistical significance of 0.05%. If no correlations existed, the results of one in twenty tests would, on average, attain this level of statistical significance. This should be borne in mind when interpreting findings as some of the correlations, especially those not backed up by other evidence, may reflect patterns specific to the sample used. I have more confidence in findings that are consistent with existing evidence.

5.3 Conclusions and implications

This chapter provides evidence that suggests the importance of psychosocial pathways for asthma onset during mid-adulthood. It is a very comprehensive study and includes good measures of asthma onset, a wide range of adversities and a well-validated measure of depressive symptoms, with measures on multiple occasions throughout the life-course. Evidence about the importance for adult onset asthma of adversities is very limited and this chapter makes an important contribution. It adds new evidence about how adversities during different life stages combine to predict asthma onset, about the relative importance for adult onset asthma of different types of adversity, and about the factors that mediate the association between childhood adversity and asthma onset decades later. Evidence that depressive symptoms predict adult onset asthma is not new, but the chapter adds new evidence about when in the life-course depressive symptoms are most salient for asthma onset.

Adversities combine cumulatively over the life-course to predict risk of asthma onset during mid-adulthood. The magnitude of the association is substantial; maximum as opposed to no adversity is associated with a more than four-fold increase in the odds of asthma onset. This indicates the importance of environmental factors in the development of asthma during adulthood.

Psychosocial pathways involve psychological responses to social exposures. The importance for adult onset asthma of social adversities is indicated by new evidence that associations between asthma onset and social adversities relating to relationship difficulties, child loss and trauma are robust to adjustment for material and occupation-related adversities. Moreover, the correlation between childhood adversity and asthma onset decades later is partially mediated by depressive symptoms, suggesting a psychosocial pathway. Finally, after adjustment for a wide range of carefully chosen factors, life-course adversity (which includes social exposures) and depressive symptoms (psychological response) each predict asthma onset.

Whilst previous studies have found that depressive symptoms predict asthma onset, evidence presented here indicates for the first time that it is shortly before onset that depressive symptoms are salient. This small but consistent association may reflect changes in immunological activity that precede asthma diagnosis and have implications for affective states. In addition, and consistent with evidence that depressive symptoms mediate associations between exposures to childhood adversity and asthma onset, depressive symptoms may reflect psychological experiences of stress (in response to social adversities) that influence immunological function in ways that contribute to asthma risk. The association between depressive symptoms and asthma onset shortly afterwards, if replicated, could be used to facilitate early diagnosis and treatment of asthma.

These findings beg questions about how social conditions and affective states are involved in the development of asthma, and whether there may be a role for psychological as well as pharmacological interventions in its prevention and treatment. They highlight the importance of psychosocial pathways in the development of asthma during adulthood, and the need for more research in this area.

Chapter 3: Does adversity predict onset of rheumatoid arthritis? Do psychosocial pathways play a role?

1. Introduction

This chapter examines relationships between adversities during childhood, transition to adulthood and adulthood and subsequent onset of rheumatoid arthritis (RA).

In this context, I provide new evidence about whether psychosocial mechanisms contribute to the development of RA. As mentioned before, psychosocial mechanisms involve psychological responses to social exposures. I hypothesise that three interlinked pathways contribute over the life-course to the development of rheumatoid arthritis; material, behavioural and psychosocial. The importance for RA onset of social adversities is tested with adjustment for adversities such as financial hardship that are likely to be associated with material pathways. If correlations exist after further adjustment for smoking, this is consistent with the hypothesis that psychological factors mediate associations between social adversities and asthma onset, reflecting a psychosocial pathway. Additional analyses examine whether some types of social adversity are more salient for RA onset than others; family-related adversities and traumas, and chronic and acute adversities.

The introduction describes RA and its importance for public health, and summarises what is known about its epidemiology, with a focus on psychosocial factors. A model is presented that describes how adversities over the life-course might contribute to RA onset. The research questions are set out at the end of the introduction.

1.1 Rheumatoid arthritis

1.1.1 Why is it important to understand the causes of rheumatoid arthritis?

RA is a relatively common chronic inflammatory disease that is classified as autoimmune (Aletaha et al. 2010). Like most diseases of this type, its causes are not understood. Its impacts include the direct costs of health care and associated services (Maravic 2010), indirect costs to the economy including lost productivity (Filipovic et al. 2011), early mortality (John 2012), and the impacts of RA and its complications on people with the condition and their families. RA has been described as one of the diseases associated with poorest quality of life (Furneri et al. 2012). NICE (2009) states that in the UK approximately one third of people with RA stop work within two years of its onset. They add that the total annual cost of RA in the UK, including indirect costs, is estimated to lie between £3.80 and £4.75 billion. This chapter provides evidence that contributes to understanding about why RA develops. The findings indicate whether further research about the social and psychological determinants of RA onset – and possibly onsets of other immune-mediated conditions – will be fruitful. Robust and detailed evidence can be used to inform public health policies aimed at prevention of RA and to facilitate its early diagnosis. This is important because early and effective treatment affects the subsequent course of the disease (Aletaha et al. 2010, Niu & Chen 2014).

1.1.2 Description of rheumatoid arthritis

RA is a disease that is driven primarily by dysregulation of the immune system. This dysregulation leads to chronic inflammation and damage of connective tissues in the joints. RA is chronic and relapsing, that is, it is a condition that people do not recover from but one that is characterised by periods of remission. Damage to the joints caused by RA activity is irreversible and progressive. The most common symptom of RA is pain and stiffness in

affected joints, often in the hands and feet. Other symptoms include inflammation around the tendons, muscle pain, anaemia, fatigue, poor sleep, fever, malaise, weight loss and the development of small, painless, harmless nodules on the skin. The disease is systemic; it can affect any part of the body, including internal organs and tissues such as the lungs, heart, blood vessels and eyes. RA may develop very fast and so, as mentioned above, early diagnosis coupled with effective treatment is important for prognosis in terms of quality of life, joint damage, disability, and systemic complications. However, there is no definitive test for RA and it is difficult to diagnose in its early stages.

Most people with RA have a protein in their blood called rheumatoid factor. Individuals with serum rheumatoid factor are referred to as seropositive, and those without it are referred to as seronegative. Between 50 and 70% people with RA are seropositive, whilst among healthy individuals, 2-10% are seropositive (Del Puente et al. 1988, Aletaha et al. 2010). Whilst rheumatoid factor is not specific enough to be particularly useful for diagnosis of RA, its presence or absence may indicate two types of RA (Sverdrup et al. 2005).

1.2 Epidemiology of rheumatoid arthritis

1.2.1 Prevalence and incidence rates of rheumatoid arthritis

Reviews suggest that prevalence and incidence rates differ markedly between populations, with prevalence rates ranging from 0.2-0.3% in Japan and China to 6.8% among the Chippewa Indians, native to the US (Silman & Pearson 2002, Tobon et al. 2010). In 2009 in the UK, NICE (2009) reported that about 400,000 people have RA, with 12,000 developing it each year. The National Rheumatoid Arthritis Society (Panayi 2014) report a higher number of people with RA; 580,000 in England alone. These numbers are in line with estimated prevalence rates in the US, Canada and Western Europe of around 1% (Tidy 2015, Widdifield

et al. 2014, Tobon et al. 2010, AbdelNasser et al. 1997, Silman & Pearson 2002). Incidence rates in the US and Western Europe are estimated to lie between 0.25 and 0.60 per 1,000 per year (Widdifield et al. 2014, Tobon et al. 2010, Aho et al. 1998, AbdelNasser et al. 1997). Tidy (2015) reports incidence rates in the UK of 0.15 per 1,000 annually for men and 0.36 per 1,000 annually for women.

There is mixed evidence concerning changes over time in prevalence and incidence rates of RA. Some studies and reviews suggest that in the US and Western Europe, incidence rates rose until the 1970s but fell subsequently, possibly due to increasing use of oral contraception and post-menopausal hormone therapies, which are thought to confer protection against progression and possibly onset (Linos et al. 1980, Hochberg & Spector 1990). There is little evidence of changes in incidence rates since the 1990s in Western Europe or the US. For example, a recent large scale study using Canadian medical records reports that incidence rates hardly changed between 1996 (0.62 per 1,000 annually) and 2010 (0.54 per 1,000 annually, Widdifield et al. 2014).

1.2.2 Co-morbidity of rheumatoid arthritis with other health conditions

Progression of RA is associated with increased susceptibility to a range of other serious conditions. These include artherosclerosis and cardiovascular disease (Ross 1999, Solomon et al. 2003), Felty's Syndrome (Panayi 2013), lymphomas and lung cancer (John 2012), interstitial lung disease and pneumonia (Kelly 2011), osteoporosis (Litwic & Dennison 2011), vasculitis (Scott 2008), Sjogren's Syndrome (or dry eyes) and other inflammatory eye disorders (Madgula & Jones 2010). Increased susceptibility to these conditions may reflect both shared disease processes and side effects of the drugs used to treat RA. Co-morbidities

with RA of several of these conditions, in particular cardiovascular diseases and cancers are associated with reduced life expectancy.

Prevalence rates of additional conditions are associated with RA prevalence but not its progression, so it is less clear to what extent they are consequences or predictors of RA, or whether they share common vulnerabilites[1]. For example, type 1 diabetes and Hashimoto's thyroiditis, which are autoimmune diseases (Somers et al. 2006), anxiety and depression (Covic et al. 2012), and periodontal disease (Smolik et al. 2009) are associated with increased rates of RA, whilst negative associations have been reported between RA and multiple sclerosis (Somers et al. 2006) and schizophrenia (Hochberg & Spector 1990).

1.2.3 Demographic distribution of rheumatoid arthritis

RA is more common among women than men. In the UK, the estimated ratio is between two and four to one (Tidy 2015). The gender difference may not be the same in all populations. For example, a recent study reports a four to one ratio of women to men with RA in Pakistan (Alam et al. 2011).

Mean age of RA onset probably differs between populations, genders, and over time. However, onset appears to be most common among all populations during mid or late adulthood. The National Rheumatoid Arthritis Society reports that in the UK, RA onset is most common between 40 and 60 (Panayi 2014), although NICE (2009) report that peak incidence in the UK is during one's 70s. A large study of white Caucasian women in the US estimated mean age of RA onset to be 55.2 years (Karlson et al. 2010), whilst in Pakistan,

[1] Co-morbidity of RA with other conditions may reflect common predictors, as well as RA being a cause or consequence of other conditions. It is likely that most co-morbidities reflect all three mechanisms. However, greater relative importance of RA as a cause of another condition is implied if the second condition is associated with RA progression.

mean age of onset was younger and differed by gender (38.5 for women, 44.8 for men, Alam et al. 2011). Finnish administrative data indicate that mean age of RA onset increased by 7.6 years from 50.2 years to 57.8 years between 1975 and 1990 (Aho et al. 1998).

Evidence suggests that those who are socio-economically disadvantaged are at increased risk of developing RA. Large scale studies using Swedish administrative data report that adults with manual occupations, and adults with qualifications below degree level were at relatively high risks of developing RA (Bergstrom et al. 2011, Bergstrom et al. 2013, respectively). An earlier large population based case-control study of women in the US similarly found that those without a college education were more likely than those with one to develop RA (Voigt et al. 1994).

1.2.4 Biological factors that predict onset of rheumatoid arthritis

Epidemiological evidence suggests that there is a strong genetic component to RA onset. An early review of twin studies reported RA concordance levels between monozygous twins of 12.3% in Finland and 11.1% in England, and concluded that while genetic factors predict RA onset, environmental factors are also of great importance (Hochberg & Spector 1990). Recent reviews estimate that genetic factors explain up to 60% of the risk of RA onset and identify specific genes that are associated with the condition (Oliver et al. 2006, Tobon et al. 2010, Malysheva et al. 2010, Suzuki & Yamamoto 2015).

There is some evidence that the gender bias in RA reflects (in part, at least) the involvement of sex hormones in the development and progression of RA. A systematic review concludes that sex hormones are associated with both progression and onset of RA (Malysheva et al. 2010). For example, studies have found RA onset to be positively associated with early age

of menarche (before 13, Avila et al. 1990), late menarche (Deighton et al. 1993), and early menopause (by age 45, Pikwer et al. 2012). Reviews report that the risk of developing RA is reduced during pregnancy and increases immediately after giving birth, when levels of female sex hormones are changing rapidly (Lahiri et al. 2012, Silman & Pearson 2002). Associations with breastfeeding appear complex (Hoovestol & Mikuls 2011). Despite earlier suggestions that use of oral contraceptives and post-menopausal hormone replacement therapy reduce the risk of RA onset (Silman & Pearson 2002, D'Elia et al. 2003), more recent evidence suggests that use of oral contraceptives confers protection only against progression of the disease (Chen et al. 2014), and that use of post-menopausal hormone replacement therapy confers no protection at all (Lahiri et al. 2012).

Reviews suggest that infections with particular viruses (Epstein-Barr virus and parovirus) and bacteria (proteus and mycoplasma) are associated with the development of RA (Malysheva et al. 2010, Silman & Pearson 2002). More recent studies provide additional evidence consistent with the involvement of bacterial infections in RA onset; in relation to proteus (Ebringer & Rashid 2014), which typically causes urinary tract infections and infections of wounds, mycoplasma (Ataee et al. 2015, Golmohammadi et al. 2014), which are a group of bacteria sometimes associated with pneumonia and sexually transmitted diseases, and porphymonas gingivalis, which is associated with periodontal disease (Smolik et al. 2009). However, a recent systematic review and meta-analysis found no evidence of an association between a history of infections with the Epstein-Barr virus and RA (Ball et al. 2015).

1.2.5 Behavioural, material and psychosocial factors that predict RA onset

Building on a conceptual framework used to explain socio-economic inequalities in health (Benzeval et al. 2014), I classify environmental factors that might contribute to the

development of RA as behavioural, material and psychosocial. While the importance of each group of factors for RA onset is examined, the focus of this chapter – and section – is on psychosocial factors.

Behavioural factors include smoking, drinking patterns, diet, and exercise. Evidence that smoking predicts RA onset seems consistent (Tobon et al. 2010, Lahiri et al. 2012). Systematic reviews also conclude that risk of RA onset is positively associated with obesity and high levels of coffee consumption, whilst moderate levels of alcohol consumption and a diet with plenty of antioxidants, fruit, vegetables and oily fish may be protective (Lahiri et al. 2012, Hoovestol & Mikuls 2011, Tobon et al. 2010).

Material factors that predict health outcomes have been classified as household factors, including housing quality and amenities, occupational factors, including unemployment and exposures to toxins at work, and neighbourhood factors, including exposure to air pollution and poor access to recreational areas (Benzeval et al. 2014). Few studies have examined the material factors that contribute to RA onset, although some studies report that risk of RA onset is higher among individuals living close to traffic, even after adjusting for economic deprivation (Hart et al. 2009, De Roos et al. 2014). These findings suggest that exposure to airborne traffic-related pollutants contributes to the development of RA, but there is no clear evidence about which pollutants are involved (Gan et al. 2013, Hart et al. 2013). There is also evidence that exposure to mineral oils, which are used in the motor industry and in manufacturing, predicts RA (Sverdrup et al. 2005).

Psychosocial factors involve psychological responses to social exposures. Social exposures are circumstances and events that occur in the social world. These, in the context of the

psychosocial pathways that contribute to the development of RA onset, are the focus of this chapter.

Psychological responses to social exposures may contribute to the development of RA through experiences of psychological stress, which is associated with physiological changes that could influence the onset and progression of RA (Huyser & Parker 1998, Li et al. 2005, Affleck et al. 1997, Zautra et al. 1997). As explained in Chapter 1, psychological feelings of stress are believed to evoke and reflect a set of common physiological responses (Selye 1956). Chronic, repeated, and intense experiences of stress can result in lasting changes in the regulation and activity of multiple systems (McEwen & Seeman 1999) including uncontrolled inflammatory behaviours that contribute to the development of RA.

Testing the importance of stress for poor health generally and RA in particular is less straight forward than testing the importance of material and behavioural factors. Material factors such as exposure to silica and behavioural factors such as smoking may not be easy to measure, but they are at least simple to conceptualise. In contrast, stress is a construct and it has been measured in various ways; using cortisol as a physiological marker of stress, perceived stress as an indicator of psychological stress, and life events and stressors as exposures likely to be experienced as stressful.

I refer to life events and stressors as adversities, and use them to indicate stress. Adversities provide a measure of stress that has limited accuracy because stress arises not from adverse exposure alone but from the exposure in combination with the coping response to it. On the other hand, understanding relationships between adverse exposures and RA onset may be useful for policy makers and practitioners who are interested in preventing RA, especially if they can modify risk of exposure to adversity.

Early reviews of stress and RA reported that while some studies found evidence of associations between stressful exposures such as life events and RA onset, others did not (Koehler 1985, Huyser & Parker 1998). Subsequent studies using life events provide inconclusive evidence, and a recent study states that evidence about psychosocial factors as predictors of RA onset is both sparse and inconclusive (Wesley et al. 2014).

A large Swedish population-based study (Wesley et al. 2014) included 2,774 adults with newly diagnosed RA, matched on sex, age, and area of residence with 3,911 controls. It found that slightly more adults with RA than controls (ORs 1.1-1.2) reported at least one life event during the previous five years. The association was statistically significant for men and women together and for women, but not for men. Life events that were particularly salient for RA onset were conflict at work, increased responsibility at work, change of work place, change of residence, and (during the three to five years before RA diagnosis) death of a child or spouse. Divorce, marriage, conflict with spouse, conflict with relative, disease or accident of a close relative or friend, death of a relative or friend, decreased responsibility at work, unemployment and impaired finances were not salient predictors of RA onset.

Bengtsson and colleagues (2009) examined whether psychological stress at work is associated with increased risk of developing RA. They used data from a population-based case-control study of individuals aged 18-65 living in Sweden, with 1,221 incident cases of rheumatologist-diagnosed RA, and 1,454 controls, matched for age, sex, and area of residence. Job stress, defined as high demands combined with low decision latitude, was not associated with onset of RA. However, low decision latitude was positively associated with RA incidence, and there was some evidence that high levels of psychological work demands were associated with lower risk of RA onset.

An earlier, very large Danish study of 21,062 parents whose child had died before the age of 18 between 1980 and 1996, matched on family structure with almost 300,000 controls found no difference in RA risk between bereaved and non-bereaved parents (Li et al. 2005). In the light of the evidence reported by Wesley and colleagues, this finding is rather surprising. It is possible that physiological responses to extremely traumatic adversities differ from responses to other types of adversity.

A much smaller case-control study using retrospective data found no evidence that adverse exposures over the life-course predicted RA onset, although trends were in the expected direction (Carette & Surtees 2000). It included 55 adults with RA who were participants in a larger community-based study in the UK. Each was matched by age and gender with three controls. A wide range of adversities throughout the life-course were measured using retrospective data. The authors suggest that their results "hinted at possible relationships that for the most part fell short of statistical significance" (p.2128).

In line with the earlier reviews (Koehler 1985, Huyser & Parker 1998), these studies provide evidence that RA onset is predicted by some but not all types of adversity. Huyser & Parker (1998) suggest that associations with adversities may depend on the chronicity and intensity of exposures, as well as perceived control over and affective responses to them.

While this suggestion is both interesting and plausible, little evidence exists to test it. There is virtually no evidence about the relative importance for RA onset of chronic as opposed to acute adversities, social or material adversities or adversities experienced in different domains. Neither is there evidence about the relative importance for RA onset of adversities during different life stages. One aim of this chapter is to provide evidence to fill these gaps.

1.3 Model of how adversity may contribute to the onset of RA

Figure 3.1 presents a model illustrating how exposures to adversities over the life-course might contribute to the development of RA. It is similar to that set out in Chapter 1.

Adversities are classified as material and social. Material adversities include financial hardship and unemployment, and affect health through pathways involving material factors. For example, financial hardship may be associated with living in an area or working in an occupation that involves exposure to airborne pollutants, and these exposures may contribute to biological changes that increase risk of RA onset. Social adversities include relationship-related adversities, such as partnership breakdown or long-term caring for a relative, and traumatic adversities, such as being a victim of sexual assault or witnessing a death. These adversities affect health through psychological pathways involving stress. They may also affect self-efficacy, which is associated with the adoption of health-related behaviours and lifestyles (Ogden 2012).

Social adversities may have material consequences, for example, relationship breakdown is associated with loss of income, especially among women (Jarvis & Jenkins 1997, Fisher & Low 2012). Conversely, material adversity is stressful and may contribute to RA onset for this reason.

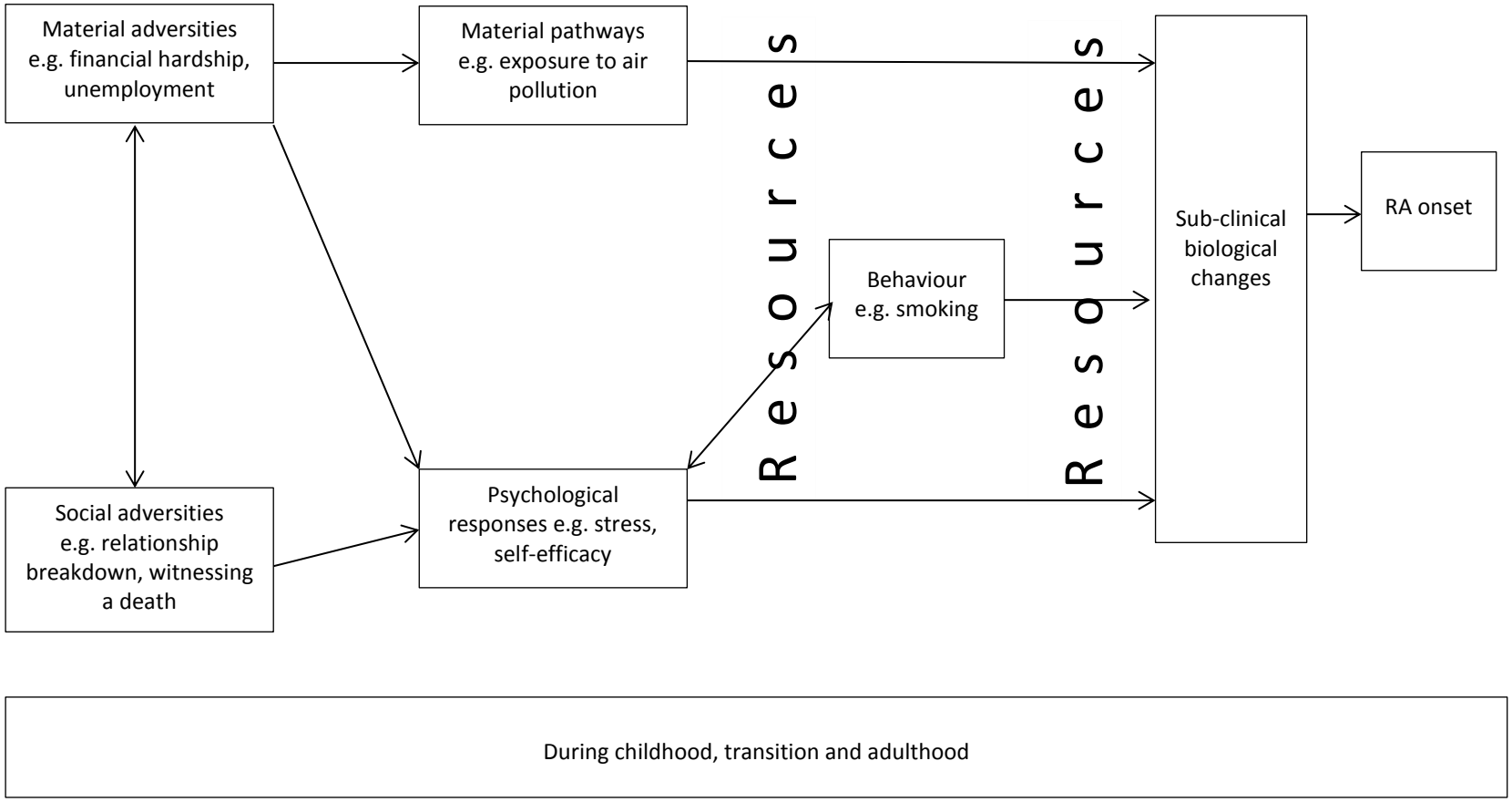
The combination of psychological stress, material factors and health-related behaviours contribute to sub-clinical biological changes that increase the risk of RA onset.

As explained in Chapter 1, exposures to adversity occur during all life stages. People are exposed to different types and levels of adversity during each life stage, and the meanings and consequences of the same exposure may differ depending upon the life stage during

which it is experienced. Adversities earlier in the life-course predict subsequent adversity (Sampson & Laub 1997, Pearlin et al. 1997).

Kuh et al. (2003) propose three life-course models that describe how exposures at different life stages combine to influence subsequent outcomes. The model of sensitive or critical periods applies when adversity during earlier life stages is particularly pertinent for RA with onset not immediately afterwards. For example, childhood adversity may have salience for the development of RA later in life because the immune system develops quickly during early life and so may be at its most sensitive to environmental exposures. If exposures to adversity during childhood have lasting impacts on the immune system, these could increase vulnerability to immune-mediated conditions such as RA, which might not develop until much later in the life-course. The chains of risk model describes outcomes that are predicted by exposures shortly before the outcome occurs. According to this model, RA with onset during mid-adulthood would be predicted by adversities experienced during early adulthood, but earlier exposures would not be directly (or independently) predictive. The third life-course model is the cumulative model, in which exposures during every life stage have an independent and cumulative impact on the outcome. This model would apply to RA onset if adversities experienced during childhood, youth, and early adulthood independently and cumulatively contributed to the dysregulations that ultimately result in RA onset during mid- and late adulthood. The models are not mutually exclusive and may apply in any combination.

Figure 3.1: Model of how adversity may contribute to onset of RA



Personal, social and economic resources buffer the negative impacts of adversity. Personal resources include self-efficacy (Rutter 1987), optimism (Hobfoll, Semmer et al. 2005), problem solving skills (Rutter 1987, Semmer et al. 2005), and a trusting attitude (Semmer et al. 2005). Social and economic resources include social support (Pearlin 1999), social integration (Myers et al. 1975), education, income and assets, housing, and occupational status. In relation to childhood adversities, Shonkoff et al. (2012) argue that having available a supportive adult renders potentially toxic adversities tolerable. The role of resources as buffers of the negative impacts of adversity is central to theories of resilience (Rutter 1987, Schoon & Bynner 2003, Bartley 2006), coping (Lazarus 1966), and the stress process (Pearlin 1999).

The relationships described above may differ between men and women. Further, although not included in the model, factors such as gender, cohort of birth, viral exposures and female sex hormones may confound associations between adversity and RA onset.

This research does not test every part of the model illustrated in Figure 3.1. It focuses on relationships between adversity and RA onset.

1.4 Research questions

Evidence about the importance of adversities for RA onset is sparse and inconclusive (Wesley 2014), and there is no evidence about how adversities combine over the life-course to predict RA onset. While it is likely that relationships between adversities and RA onset differ depending upon characteristics of the adversity (Huyser & Parker 1998), few studies have examined this hypothesis. Furthermore, very little evidence is available about how relationships between adversities and RA onset differ by gender.

Evidence about associations between RA onset and social adversities after adjustment for material adversities is relevant to whether psychosocial pathways contribute to RA onset. Additional adjustment for behavioural factors as mediators of these associations provides further evidence relevant to psychosocial pathways because if associations are fully mediated by behavioural factors, it is less likely that psychological factors play a mediating role. However, no studies that I am aware of have examined the factors that mediate associations between adversity and RA onset.

As evidence in these areas would inform understanding about the importance of psychosocial pathways in the development of RA, the following RQs are addressed:

1. Do adversities predict RA onset?
    a. Does the answer to this question vary by gender?
2. How do adversities combine over the life-course to predict RA onset?
    a. Does the length of exposure matter? For example, does adversity that continues from childhood, through youth, early and mid-adulthood predict RA onset more strongly than the same adversity experienced during just one life stage?
    b. Does the life stage during which one is exposed matter? More specifically, what is the relative importance for RA onset of adversities during childhood, transition to adulthood, early and mid-adulthood?
    c. How do the answers to these questions vary by gender?
3. Do material, psychosocial and behavioural factors independently predict RA onset?
    a. Do material and social adversities independently predict RA onset?
    b. Are any associations found explained by health behaviours?
    c. How do the answers to these questions vary by gender?

4. Are some types of social adversity more salient predictors of RA onset than others?
    a. Comparison of adversities in different life domains: relationship-related and traumatic adversities.
    b. Comparison of chronic and acute adversities.
    c. How do these comparisons differ between men and women?

2. Data and measures

2.1 The dataset

Data from the English Longitudinal Survey of Ageing (ELSA) are used. This study is designed to represent people aged 50 and over living in private households in England. The sample was originally constructed from people aged 50 and over in March 2002, who had participated in one of three cross sectional waves of the Health Survey for England (HSE) conducted in 1998, 1999 and 2001. This sample is referred to as wave 0 and contains common variables from the three HSE studies. Members of wave 0 have been interviewed seven times subsequently, with responses from between just over 9,000 and 12,000 participants (see Table 3.1). They exit from the sample when they die or move away from mainland Britain. See Appendix 10 for more details.

Table 3.1: Waves of data collection in ELSA

Wave	Years	Number of observations
0	1998, 1999, 2001	19,834 with common variables
1	2002-2003	12,099
2	2004-2005	9,432
3	2006-2007	9,711
3 Life history	2006-2007	7,833
4	2008-2009	11,050
5	2010-2011	10,274
6	2012-2013	10,601
7	2014-2015	9,666

Waves 1 to 7 contain comprehensive social, psychological, health and financial data. Wave 3 included a separate interview in which retrospective life history data were collected. This interview is referred to as LIFE, and participants were those who had taken part in the wave 3 main interview and consented to provide information about their lives so far in an additional interview. The exception is that participants who did not provide a wave 3 interview were invited to participate in LIFE if their cohabiting partner had agreed to provide life history data. Those whose wave 3 main interview was conducted late (after April 19th, 2007) were excluded.

A temporal referencing system or life-grid approach was used to collect the information, as this is thought to help full and accurate recall (Berney & Blane 1997; Means et al. 1991). Biases due to sample selection, incomplete reporting, and measurement error are likely to differ systematically between the retrospective and contemporaneous data. For example, cognitive function (more specifically, scores on tests of delayed recall) appears to be associated with accuracy of recall (Brown 2013), but it may not be associated with the reporting of contemporaneous information.

2.2 Onset of RA

Wave 0 does not identify individuals with RA. In wave 1, respondents were asked whether a doctor had ever told them that they had or had ever had arthritis. If they answered yes, they were asked to identify which type or types of arthritis they had; rheumatoid arthritis, osteoarthritis, or some other kind of arthritis. They were also asked their age when they were first told by a doctor that they had arthritis. In subsequent waves, those who had reported arthritis were asked to confirm that they had or had had the condition. In waves 2 to 7, all respondents were also asked questions about new diagnoses of arthritis and RA.

RA onset is identified if it was reported in any wave. Missing values are assigned to respondents who report RA and subsequently report having another type of arthritis but not RA, or who report RA and subsequently report that the condition was never diagnosed. Some respondents who initially report RA, subsequently dispute that they ever had RA, and after this report having RA. For these respondents, it is assumed that they do have RA and age of onset is assigned using the age given when RA was first reported.

For all respondents, age of onset is identified using information provided the first time that RA was reported. Age of onset is coded as missing if multiple types of arthritis were reported when RA was first reported.

Appendix 10 provides details about measurements of RA onset and other variables included in the analyses.

2.3 Adversities

Adversities are measured using retrospective information that in most instances includes the years when circumstances changed or events occurred. This contrasts with the information used in Chapter 2, in which prospective information was collected when cohort members were particular ages. These ages determined the age ranges for life stages in Chapter 2. In contrast, in this chapter age ranges are chosen and include four life stages that each encompass 15 years. Childhood is birth to 15, transition to adulthood, referred to as transition, is 16-29, early adulthood is 30-44 and mid-adulthood is 45-59.

Information about adversity was collected in three ways. First, during the face-to-face life history interview, respondents provided fertility, partnership, housing, employment and

health histories. This information is used to code adversities relating to family and partnerships and periods of unemployment, and the variables are referred to as histories. Second, respondents were asked in self-completion questionnaires whether they had been exposed to a series of adversities during childhood. These variables are referred to as childhood adversities. Third, in the self-completion questionnaire, respondents provided information about life events. If they reported a life event, they were then asked when they first experienced it. These variables are referred to as events.

The adverse exposures measured are listed in Table A3.2.

Adversities were summed to create indices of total adversity during childhood, transition, early and mid-adulthood, and of different types of adversity; material, social, family-related, traumatic, chronic, and acute.

Exposures to adversity were also summed over life stages to create indices of total life-course and cumulative life-course adversity. Indices of total life-course adversity were created by summing total levels of exposure at each life stage. Indices of cumulative exposure measure the number of life stages during which at least one adversity was reported.

Table 3.2: Exposures to adversity and indices of exposure

Adversity	Question type	Index			
Adversities experienced during childhood					
Poor housing amenities and/or crowding at 10*	History	Total	Material	Material	
Severe financial hardship	Event	Total	Material	Material	
Parental unemployment 6m+	Childhood adversity	Total	Material	Material	
Early parental loss	Childhood adversity	Total	Social	Family	
Separation from mother for 6m+	Childhood adversity	Total	Social	Family	
Parents argue often	Childhood adversity	Total	Social	Family	
Parent drank, took drugs, mental health problems	Childhood adversity	Total	Social	Family	
Parent physically abused respondent	Childhood adversity	Total	Social	Family	
Sexual assault	Event	Total	Social	Trauma	
Major natural disaster	Event	Total	Social	Trauma	
Had life threatening illness or injury	Event	Total	Social	Trauma	
Severe physical attack	Event	Total	Social	Trauma	
Witness death or serious injury	Event	Total	Social	Trauma	
Lost close relative or friend	Event	Total	Social	Trauma	
Adversities experienced during adulthood					
Severe financial hardship	Event	Total	Material	Material	
Unemployed and searching for work	History	Total	Material	Material	
Involuntary job loss	History	Total			
Main occupation carer	History	Total	Social	Family	Chronic
Provided long-term care for relative or friend	Event				
Partner or child addicted to a substance	Event	Total	Social	Family	Chronic
Breakdown of cohabiting partnership	History	Total	Social	Family	Chronic
House moves	History	Total	Social	Family	
Death of cohabiting partner	History	Total	Social	Family	
Death of child	History	Total	Social	Family	
Stillbirth, miscarriage or abortion	History	Total	Social	Family	
Death of close friend/relative	Event				
Victim of sexual assault	Event	Total	Social	Trauma	Acute
Victim of serious physical attack	Event	Total	Social	Trauma	Acute
Life threatening illness or accident	Event	Total	Social	Trauma	
Active combat	Event	Total	Social	Trauma	
Witnessed serious injury or death	Event	Total	Social	Trauma	Acute
Natural disaster	Event	Total	Social	Trauma	Acute

*And living in the UK. For indices of total, family and chronic adversity, caring is identified if the respondent reports that their main occupation was a carer or if they report providing long-term care for a relative or friend.

2.4 Resources

A range of factors were considered as resources, relating to parenting, cultural capital during childhood and education at the time of LIFE. In analyses described in Appendix 10,

there was no evidence that any of the variables tested buffered impacts of adversity on RA onset and so they are not included as resources in the analyses.

2.5 Factors to condition upon

All models condition on cohort of birth because it is likely that patterns of RA and its diagnosis differ between cohorts. In addition, levels of adversity and the meanings attributed to them may vary between cohorts.

Models condition on gender for similar reasons. Risk of RA onset differs by gender, as do exposures to adversities and the meanings attributed to them.

As RA prevalence rates vary between ethnic groups, I considered conditioning upon whether the respondent described themselves as white. However, only seven non-white respondents who participated in LIFE reported having RA with onset after age 16.

As explained in the introduction, there are socio-economic inequalities in RA prevalence and onset. Various measures of socio-economic class are available in the dataset. Education was used because occupational class is conceptually closer to material adversity and is probably more highly correlated with it. Education at the time of the LIFE interview was associated with both RA onset and exposure to adversity. Education is not classified as a resource because whilst higher levels of qualification are associated with a lower risk of RA onset, they are associated with a higher risk of total adversity during transition and early adulthood. Models therefore condition on education level at the time of the LIFE interview. A binary indicator of qualifications at Level 2 or above is used.

LIFE includes comprehensive fertility histories and information about use of hormonal contraceptives, ages of menarche and menopause, and removal of ovaries and hysterectomies. As mentioned in the introduction, female sex hormones appear to be involved in the development of RA, and so they were considered as conditioning factors. However, analyses described in Appendix 10 found no evidence that any of them predict RA onset in this sample, and so they are not included in the models.

2.6 Health behaviours

Smoking is the only health behaviour measured in LIFE. Smoking is measured using continuous measures of the numbers of years smoked during early and late adulthood.

2.7 Variables used in sensitivity analyses

Sensitivity analyses were conducted that excluded respondents with low scores on a memory recall test at the time of LIFE, as Brown (2013) reports that poor recall scores in the NCDS were associated with inaccurate retrospective accounts of childhood circumstances. Respondents reporting pain and depressive symptoms at the time of LIFE were also excluded because these are symptoms of RA that could bias recall of childhood adversities (Raphael et al. 2001, Widom & Morris 1997).

Memory function, depressive symptoms, and pain were measured during the main wave 3 interview, shortly before the LIFE interviews took place.

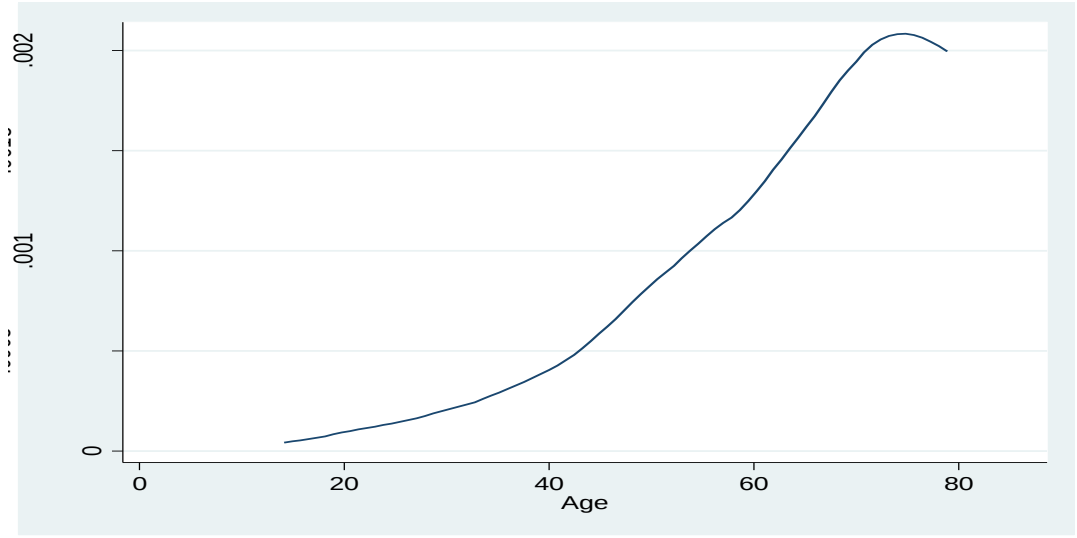
Memory function was measured using a delayed word recall test. Depressive symptoms were measured using the 8 item Centre for Epidemiology depression scale (CESD). Pain was measured using answers to simple questions about perceived pain.

3. Analyses

I use survival analysis to estimate associations between adversity and RA onset. Survival analysis is a set of methods that are used when the outcome variable is the time until the occurrence of an event (Despa 2015), which in this chapter is RA onset. Time to the event is referred to as survival time. The issue that complicates the modelling of survival time is that some people provide incomplete information about it. For example, some ELSA respondents did not report RA onset by the last wave of data collection, and we do not know whether they subsequently developed RA. This type of missing data is referred to as right censoring. In survival analysis, the dependent variable is composed of two parts; time to the event (RA onset) or to right censoring, and whether the event occurred or not.

Figure 3.2 illustrates the outcome function that was modelled using survival analysis techniques. It represents the changing risk of developing RA with age, or the number of respondents who developed RA at each age divided by the number of respondents who had not yet developed it when they were one year younger. It is unadjusted and referred to as the baseline hazard function.

Figure 3.2: Baseline hazard function for RA onset



Note: The figure uses data from 6,626 respondents who participated in the LIFE interview and provided information about RA onset. Of these, 261 respondents reported RA onset.

Hazard functions are usually plotted against time. I use age because conceptually, age is more relevant to the lives of respondents and to the research questions. However, because evidence exists (albeit inconsistent) that the outcome variable (the changing risk of RA onset with age) differs between birth cohorts, all models used in the analyses adjust for birth cohort. If RA onset were plotted against time, it would be adjusted for age. Once these adjustments are made, the results of analyses depend little upon whether the hazard function is plotted against age or time (Pencina et al. 2007).

Most survival analysis techniques assume that time of right censoring is unrelated to the outcome of interest, after conditioning on covariates. In this study, time is measured using age, and many respondents are right censored because they left the sample in 2014, when the last wave of data collection occurred. Their age in 2014 is directly related to their birth cohort, which, as mentioned above, may be associated with the outcome of interest. This is another reason why I condition on cohort of birth.

Various survival analysis models are available, and the choice of which to use is determined by how accurately each can be manipulated to describe the outcome function. The outcome function for this set of analyses is illustrated in Figure 3.2, and the technique of Cox's Proportional Hazards regression was selected to model it, as this specification makes no assumptions about the form of the hazard function.

Cox regression assumes that time to the event (RA onset) is continuous, and that each event occurs at a unique point in time. The measure of time used is age in years, which is discrete, and for many ages, two or more respondents report RA onset. These are referred to as ties. In the sample of respondents who participated in LIFE and provided information about RA onset, 261 reported RA onset between six and 87, with a maximum of 13 respondents reporting RA onset at any one age. The Breslow method is used to handle ties, by assuming (almost always incorrectly) that when each tied observation was taken from the pool of respondents without RA and who have not dropped out of the sample, none of the observations that were tied had yet been extracted. This matters little because even for the age with maximum ties, the proportion reporting RA onset hardly varies between the first and last respondent drawn from the pool. Thirteen respondents reported RA onset at age 60, when 5,820 respondents were in the pool. So, the proportions reporting RA onset at this age varied between 1/5820 (0.0001718) – before any respondents had been drawn – and 1/5808 (0.0001722) – after twelve had been drawn.

While Cox regression makes no assumptions about the form of the baseline hazard function, it does assume that associations between the outcome function and each predictor variable are the same regardless of when RA onset occurs. For example, if a period of unemployment during one's twenties is associated with risk of RA onset, then the assumption is that the magnitude and consistency of this association is the same regardless of whether RA onset

occurs during one's thirties or one's eighties. The assumption is referred to as the proportional hazards (PH) assumption.

The PH assumption was tested for the main predictor variables used in the analyses using the observed dataset with complete cases and RA with onsets from ages 16, 45, and 60. The results, which are presented in Table A11.1 in Appendix 11, provide no evidence that the PH assumption is violated by any of these variables.

To increase numbers and reduce bias, missing values were imputed in multiple datasets based on the sample that participated in at least one sweep of ELSA. Missing values were imputed for all variables used in the analyses except for RA status and age of onset. RA onset was not imputed because the software used (Stata 14, StataCorp. 2015) does not support survival analysis using outcome variables for which missing values have been imputed using multiple imputation. However, variables indicating RA status and age of onset or censoring were used to impute missing values for the other variables of interest. Missing values were imputed for indices of adversity as opposed to single adversities, since indices are used in most of the analyses. Further details about the multiple imputation methods are presented in Appendix 12.

Analyses were conducted in 20 imputed datasets and results pooled using the combination rules suggested by Rubin (1987). The sample used in the analyses excluded sample members who did not participate in LIFE or had missing values for RA onset, gender or date of birth.

Incidence and prevalence rates for RA were estimated for respondents who participated in LIFE and for the whole ELSA sample. In order to illustrate the changing risk of RA onset with

age, the hazard functions of RA onset were estimated with adjustment for birth cohort for the sample who participated in LIFE, and for the whole ELSA sample.

For respondents who participated in LIFE, who are included in the rest of the analyses, hazard functions were plotted separately for five birth cohorts, for men and women separately, and for those who did and did not have fathers with manual or routine occupations when respondents were aged 14. Cox regression models were conducted to estimate the statistical significance of differences in RA onset between cohorts, men and women and between groups with different socio-economic backgrounds.

Because of biases in the observed sample and attrition, the samples used in ELSA and LIFE are not representative of adults aged 50 and over living in the community in England. NatCen used information from earlier ELSA sweeps to compare the characteristics of ELSA participants who did and did not complete the LIFE interview. Based on this information, they constructed weights designed to compensate for biases resulting from attrition and improve the representativeness of the sample. In order to provide indications of the distribution of RA onset that are more representative of older adults living in private households in England, additional hazard functions for RA onset were estimated using the weighted LIFE data.

Descriptive statistics for other variables used in the analyses were calculated without weights for respondents who participated in the LIFE interview and provided information about RA onset, gender, and date of birth, using the observed and multiple imputed datasets. Using the multiple imputed datasets, summary statistics were calculated for men and women separately. The statistical significance of gender differences was indicated by

lack of overlap between confidence intervals for mean values estimated for men and women.

Analyses were conducted to address each research question. Unless stated otherwise, these use the unweighted imputed datasets.

RQ1. Do adversities predict RA onset?

Details of models used to address RQ1 are summarised in Table 3.3, at the end of this section.

Three sets of Cox regression analyses were estimated of risk of RA onset on level of adversity. For RA onset from age 16, associations were estimated with total level of adversity up to age 15. For RA with onset from age 45, associations were estimated with total level of adversity up to age 44. For RA with onset from age 60, associations were estimated with total level of adversity up to age 59.

Each set of regressions was initially conducted using measures of adversity in terciles. Wald tests were used to test whether including these measures of adversity improved the fit of models of RA onset risk. Based on the results of analyses using these measures, summary measures of exposure were created to reflect the nature of any likely associations with RA onset, as either graded or threshold effects. For childhood adversity, a binary indicator of exposure to one or more adversities was created. For the longer periods between birth and ages 44 and 59, continuous measures were created. These summary measures of life-course adversity were used to test associations with RA onset.

All models were adjusted for birth cohort and level of education at the time of LIFE. Models estimated using the whole sample were also adjusted for gender.

To examine whether associations between adversity during each life stage and RA onset were driven by specific adversities, associations were estimated between RA onset and single adversities during each life stage with mutual adjustment. As missing values are not imputed for single adversities, the observed dataset was used. Separate models were estimated for single adversities at each life stage, with mutual adjustment and adjustment for total levels of adversity during other life stages, gender, birth cohort and qualifications.

RQ1a: How does the answer to this question vary by gender?

The analyses were conducted for men and women separately. Interaction terms of gender with total levels of adversity up to ages 15, 44, and 59 were included in models to test whether gender differences in the associations between adversity and RA onset were statistically significant.

Table 3.3: Details of models used to address RQ1

Outcome	Exposures	Controls	Interaction	Sample	Imputed?	N	Method
RQ1: Results in Table 3.9							
RA onset from 16	Adversities 0-15: terciles	Birth cohort, education, gender	No	In LIFE	Yes	6,623	Cox PH, Wald test
		Birth cohort, education		Men in LIFE		2,997	
		Birth cohort, education		Women in LIFE		3,626	
	Adversities 0-15: binary	Birth cohort, education, gender		In LIFE		6,623	Cox PH
		Birth cohort, education		Men in LIFE		2,997	
		Birth cohort, education		Women in LIFE		3,626	
RA onset from 45	Adversities 0-44: terciles	Birth cohort, education, gender	No	In LIFE	Yes	6,560	Cox PH, Wald test
		Birth cohort, education		Men in LIFE		2,975	

		Birth cohort, education		Women in LIFE		3,585	
	Adversities 0-44: continuous	Birth cohort, education, gender		In LIFE		6,560	Cox PH
		Birth cohort, education		Men in LIFE		2,975	
		Birth cohort, education		Women in LIFE		3,585	
RA onset from 60	Adversities 0-59: terciles	Birth cohort, education, gender	No	In LIFE	Yes	5,525	Cox PH, Wald test
		Birth cohort, education		Men in LIFE		2,593	
		Birth cohort, education		Women in LIFE		2,932	
	Adversities 0-59: continuous	Birth cohort, education, gender		In LIFE		5,525	Cox PH
		Birth cohort, education		Men in LIFE		2,593	
		Birth cohort, education		Women in LIFE		2,932	
RQ1. Results in Table A14.1 in Appendix 14.							
RA onset from 45	14 childhood adversities	Indices of adversity during other life stages, birth cohort, gender, L2+ qualifications	No	In LIFE with complete information about gender and birth	No	3,256	Cox PH
	16 transition adversities					3,239	
	16 early adulthood adversities					3,319	
RA onset from 60	14 childhood adversities	Indices of adversity during other life stages, birth cohort, gender, L2+ qualifications	No	In LIFE with complete information about gender and birth	No	2,586	Cox PH
	16 transition adversities					2,570	
	16 early adulthood adversities					3,319	
	16 mid-adulthood adversities					2,743	
RQ1a: Results in text							
Outcome	Exposures	Controls	Interaction	Sample	Imputed?	N	Method
RA onset from 16	Adversities 0-15: binary	Birth cohort, education, gender	Adv 0-15 *gender	In LIFE	Yes	6,623	Cox PH
RA onset from 45	Adversities 0-44: binary	Birth cohort, education, gender	Adv 0-44 *gender	In LIFE		6560	
RA onset from 60	Adversities 0-59: binary	Birth cohort, education, gender	Adv 0-59 *gender	In LIFE		6560	

RQ2: How do adversities combine over the life-course to predict RA onset?

Various specifications were used to address RQs 2a, 2b and 2c. They each include adjustment for birth cohort, education level in 2006 and, if not stratified by gender, gender. Details are summarised in Table 3.4, which is presented at the end of the section.

RQ2a: Does the length of exposure matter?

Cox regression analyses were conducted to estimate associations between the risk of RA onset from age 45 and cumulative adversity during childhood, transition and early adulthood using an indicator of the number of life stages during which at least one adversity was reported. Associations were also estimated between risk of RA onset from age 60 and cumulative adversity during childhood, transition, early and mid-adulthood.

RQ2b: Does the life stage during which one is exposed matter?

Cox regression analyses were used to estimate associations between adversities during each life stage with mutual adjustment for RA with onsets from 45 and 60. While RQ1 was addressed using a binary indicator of childhood adversity and continuous measures of adversity during subsequent life stages, I thought that it would be a fairer comparison to use the same type of measure of adversity in all life stages when comparing their salience for RA onset. Binary indicators of one or more adversity were used.

Sensitivity analyses were conducted using indices of adversity that excluded life events, as information was available only about the first time that the respondent experienced the event and this could affect the results.

RQ2c: How do the answers to these questions vary by gender?

The analyses were conducted for men and women separately and tests conducted with the whole sample using models that included interaction terms between adversity and gender.

Table 3.4: Details of models used to address RQ2

Outcome	Exposures	Controls	Interaction	Sample	N	Method
RQ2a. Results in Table 3.10						
RA onset from 45	No.life stages to 44 when adversity reported: dummies	Birth cohort, gender, education	No	In LIFE	6,560	Cox PH, Wald
	continuous					Cox PH
RA onset from 60	No. life stages to 59 when adversity reported: dummies	Birth cohort, gender, education	No	In LIFE	5,525	Cox PH, Wald
	continuous					Cox PH
RQ2b. Results in Table 3.11						
RA onset from 45	Summary measures of childhood, transition early adulthood adversity	Birth cohort, gender, education	No	In LIFE	6,560	Cox PH
RA onset from 60	Summary measures childhood, transition early and mid-adulthood adversity	Birth cohort, gender, education	No	In LIFE	5,525	
RQ2c. Results in Table A15.2						
RA onset from 45	No. life stages 44 adv. reported: dums	Birth cohort, education	No	Men in LIFE	2,975	Cox PH, Wald test
				Women in LIFE	3,585	
	Continuous			Men in LIFE	2,975	
				Women in LIFE	3,585	
RA onset from 60	No. life stages 59 adv. reported: dums	Birth cohort, education	No	Men in LIFE	2,593	Cox PH
				Women in LIFE	2,932	
	continuous			Men in LIFE	2,593	
				Women in LIFE	2,932	
RQ2c. Results in text						
RA onset 45	No. life stages to 44 adversity reported: continuous	Birth cohort, gender, education	Adv* gender	In LIFE	6,560	Cox PH
RA onset 60	No. life stages to 59 adversity reported: continuous	Birth cohort, gender, education	Adv* gender	In LIFE	5,525	Cox PH
RQ2c. Results in Table A15.3, Appendix 15.						
RA onset 45	Childhood, transition early adulthood adversity	Birth cohort, education	No	Men in LIFE	2,975	Cox PH
				Women in LIFE	3,585	
RA onset 60	Childhood, transition early, mid-adulthood adversity	Birth cohort, education	No	Men in LIFE	2,593	Cox PH
				Women in LIFE	2,932	
RQ2c. Results in text						

RA onset 45	Childhood, transition early adulthood adversity	Birth cohort, gender, education	Adv* gender	In LIFE	6,560	Cox PH
RA onset 60	Childhood, transition early, mid-adulthood adversity	Birth cohort, gender, education	Adv* gender	In LIFE	5,525	Cox PH

All models estimated using twenty imputed datasets. A15.2 and A15.3 refer to tables in Appendix 15.

RQ3: Do material, psychosocial and behavioural factors independently predict RA onset?

Details of models used to address RQ3a and RQ3b are summarised in Table 3.5, presented at the end of the section.

RQ3a: Do material and social adversities independently predict RA onset?

Three sets of Cox regression analyses were conducted of RA with onsets from ages 16, 45 and 60 on material and social adversity, with mutual adjustment for each type of adversity and adjustment for birth cohort, gender and education. Total material and social adversities were measured from birth to ages 15, 44, and 59. Models were estimated using sets of dummies and then, depending upon the pattern of relationship indicated by the results, more parsimonious binary or continuous measures.

RQ3b: Are any associations found explained by smoking behaviour?

Models were estimated of material and social adversities up to age 29 (childhood and transition) as predictors of RA onset from ages 45 and 60, adjusting for the factors in previous models and also for smoking.

RQ3c: How do the answers to these questions vary by gender?

The models estimated to address RQs 3a and 3b were conducted for men and women separately. Tests using interaction terms between gender and each type of adversity were conducted to see whether or not gender differences were statistically significant.

Table 3.5: Details of models used to address RQ3a and b.

Outcome	Exposures	Controls	N
RQ3a. Table A16.1, Appendix 16			
RA from 16	Material adversities 0-16 (dummies)	Social adversities 0-16 (cont.), birth cohort, gender, education	6,623
	Social adversities 0-16 (dummies)	Material adversities 0-16 (cont.), birth cohort, gender, education	
RA from 45	Material adversities 0-16 (dummies)	Social adversities 0-16 (cont.), total adversity 17-29 and 30-44, birth cohort, gender, education	6,560
	Social adversities 0-16 (dummies)	Material adversities 0-16 (cont.), total adversity 17-29 and 30-44, birth cohort, gender, education	
	Material adversities 0-44 (dummies)	Social adversities 0-44 (cont.), birth cohort, gender, education	
	Social adversities 0-44 (dummies)	Material adversities 0-44 (cont.), birth cohort, gender, education	
RA from 60	Material adversities 0-16 (dummies)	Social adversities 0-16 (cont.), total adversity 17-29, 30-44, 45-59, birth cohort, gender, education	5,525
	Social adversities 0-16 (dummies)	Material adversities 0-44 (cont.), total adversity 17-29, 30-44, 45-59, birth cohort, gender, education	
	Material adversities 0-44 (dummies)	Social adversities 0-44 (cont.), total adversity 45-59, birth cohort, gender, education	
	Social adversities 0-44 (dummies)	Material adversities 0-44 (cont.), total adversity 17-29, 30-44, 45-59, birth cohort, gender, education	
	Material adversities 0-59 (dummies)	Social adversities 0-59 (cont.), birth cohort, gender, education	
	Social adversities 0-59 (dummies)	Material adversities 0-59 (cont.), birth cohort, gender, education	
RQ3a.	Table 3.12		
RA onset from 16	Material adversities (binary), social adversities (cont.) 0-16	Birth cohort, gender, education	6,623
RA onset from 45	Material adversities (binary), social adversities (cont.) 0-16	Birth cohort, gender, education, total adversity 17-29, 30-44	6,560
	Material adversities (binary), social adversities (cont.) 0-44	Birth cohort, gender, education	
RA onset from 60	Material adversities (binary), social adversities (cont.) 0-16	Birth cohort, gender, education, total adversity 17-29, 30-44, 45-59	5,525

	Material adversities (binary), social adversities (cont.) 0-44	Birth cohort, gender, education, total adversity 45-59	
	Material adversities (binary), social adversities (cont.) 0-59	Birth cohort, gender, education	
RQ3b. Table A16.2			
RA onset from 45	Material adversities (binary), social adversity (cont.) 0-29	Birth cohort, gender, education	6,560
	Material adversities (binary), social adversity (cont.) 0-29, years smoked 30-44	Birth cohort, gender, education	
RA onset from 60	Material adversities (binary), social adversity (cont.) 0-29	Birth cohort, gender, education	5,525
	Material adversities (binary), social adversity (cont.) 0-29, years smoked 30-44, 45-59	Birth cohort, gender, education	

All models are estimated using Cox PH regressions and twenty datasets with information from LIFE participants with imputed values. All models adjust for birth cohort, gender and education and there are no interaction terms.

RQ4: Are some types of social adversity more salient predictors of RA onset than others?

Models used to address RQ4 are equivalent to those used to address RQ3, but instead of comparisons between material and social adversities, the comparisons are between (1) family/relationship and trauma, and (2) chronic and acute adversities.

Sensitivity analyses

As mentioned above, sensitivity analyses were conducted in relation to RQ2b using alternative indices of adversity that excluded life events. Two additional sets of sensitivity analyses were conducted for all the results, each using different samples. The first sample excluded respondents who in Wave 3 of data collection reported pain or depression or scored poorly on a memory recall test.

Respondents with low recall scores were excluded because a study using data from the NCDS found that recall by 50 year old cohort members of childhood circumstances such as household composition was less accurate among respondents who did not perform well on a memory test of delayed recall (Brown 2014).

Respondents reporting pain and depressive symptoms were excluded because these are symptoms of RA that could bias recall of childhood adversities. If recall was affected by symptoms of RA, the bias could contribute to associations between adversity and RA onset, and one would not know to what extent the relationship was prospective. Chronic pain is a symptom of RA, and studies have found pain in adulthood (at the time of recall) to be associated with retrospective reports of childhood adversity (sexual and physical abuse and neglect) but not with formal documentation of abuse and neglect that was recorded at the time it took place (Raphael et al. 2001). Evidence of a similar type suggests that diagnosed depression is associated with over-reporting of sexual abuse (Widom & Morris 1997), which is relevant to this study because individuals with RA are at elevated risk of having depression (Covic et al. 2012) and sexual abuse is one of the adversities measured in childhood.

The second set of sensitivity analyses uses imputed datasets derived from alternative indices of adversity in the observed data. For the main analyses, indices were created in the observed data for respondents who provided complete information about adversity and values were imputed during multiple imputation for all other respondents. For the sensitivity analyses, indices of adversity were created in the observed dataset that assigned values to indices for respondents who provided partial information about adversities as well as for those who provided complete information.

Details of sensitivity analyses are given in Appendices 18 and 19.

4. Results

Descriptive statistics

Numbers of respondents who participated in LIFE and reported RA at each life stage are presented in Table 3.6.

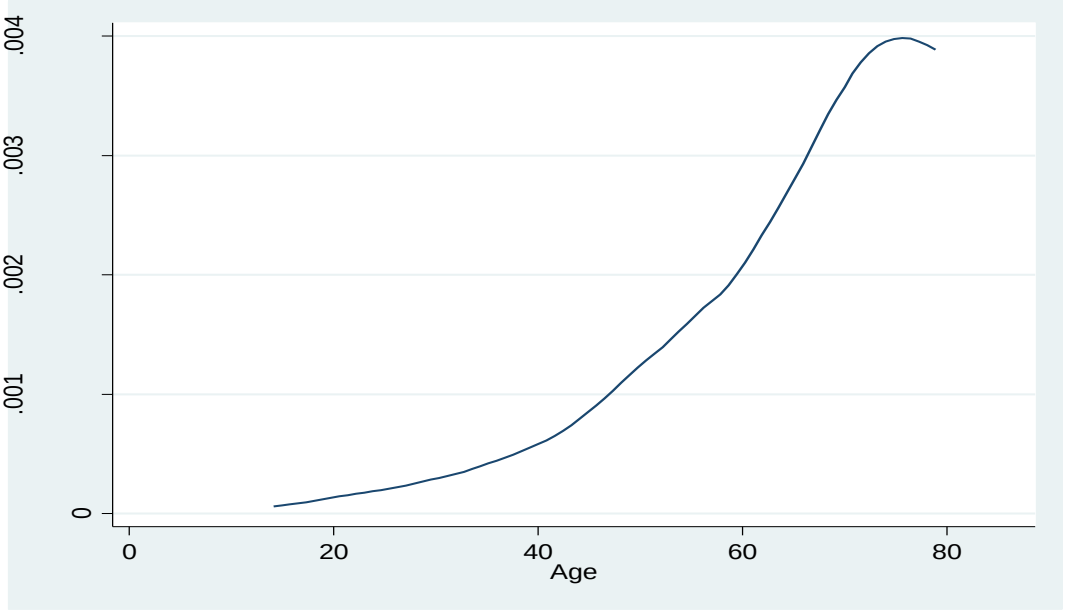
Table 3.6: Numbers of LIFE participants who reported RA onset during each life stage

Life stage	All	Men	Women
Childhood (0-15)	1	1	0
Transition (16-29)	10	2	8
Early adulthood (30-44)	29	12	17
Mid-adulthood (45-59)	84	33	51
Late adulthood (60+)	137	67	70
All stages	261	115	146

Two hundred and sixty of 6,624 (3.94%) LIFE interview participants who provided information about RA onset, gender, and date of birth reported RA with onset after age 16. Gender differences in lifetime prevalence rates among LIFE participants are 1.28:1.00 (women:men). Incidence rates of RA for LIFE participants are 0.57 (95%CI=0.50-0.64) per 1,000 per year.

The baseline hazard function for RA onset is presented in Figure 3.2. Figure 3.3 presents the equivalent hazard function after adjustment for cohort of birth. Relationships between risk of RA onset and age are similar in the two figures, and show that risk of RA onset increases until the late seventies, when risk levels off and may even decline.

Figure 3.3: Hazard function for RA onset, adjusted for birth cohort



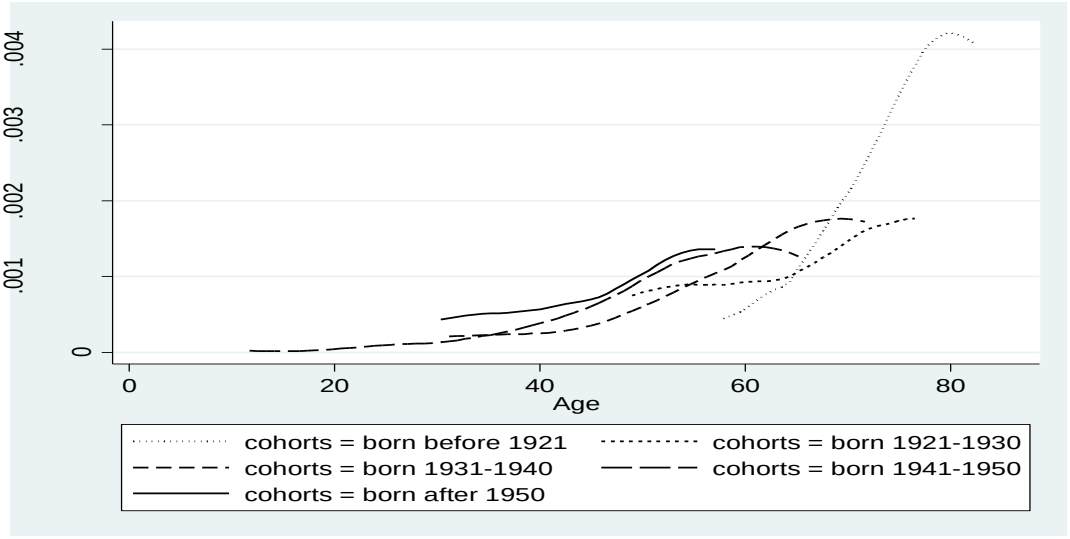
Note: The figure uses data from 6,626 respondents who participated in the LIFE interview and provided information about RA onset and date of birth. 261 respondents reported RA onset.

Hazard functions for RA onset for LIFE respondents born in different decades, of different genders, and with different socio-economic backgrounds are presented in Figures 3.4, 3.5 and 3.6. These illustrate differences in RA onset over the life-course for respondents included in the analysis. Equivalent hazard functions are presented in Appendix 13 that include weights designed to address sample bias so that results are more likely to be representative of adults aged 50 and over living in England. The results using weights are very similar to those presented here.

Figure 3.4 indicates that RA onset has been diagnosed earlier in life for younger cohorts. The mean age of RA onset is 47 for those born after 1950, 54 for those born between 1941 and 1950, 62 for those born between 1931 and 1940, 68 for those born between 1921 and 1930, and 77 for those born before 1921. The proportion of respondents reporting RA onset is higher for the oldest cohort, probably because some of those with other health conditions

have died, or are no longer eligible (if they live in an institution) or able to participate in ELSA surveys.

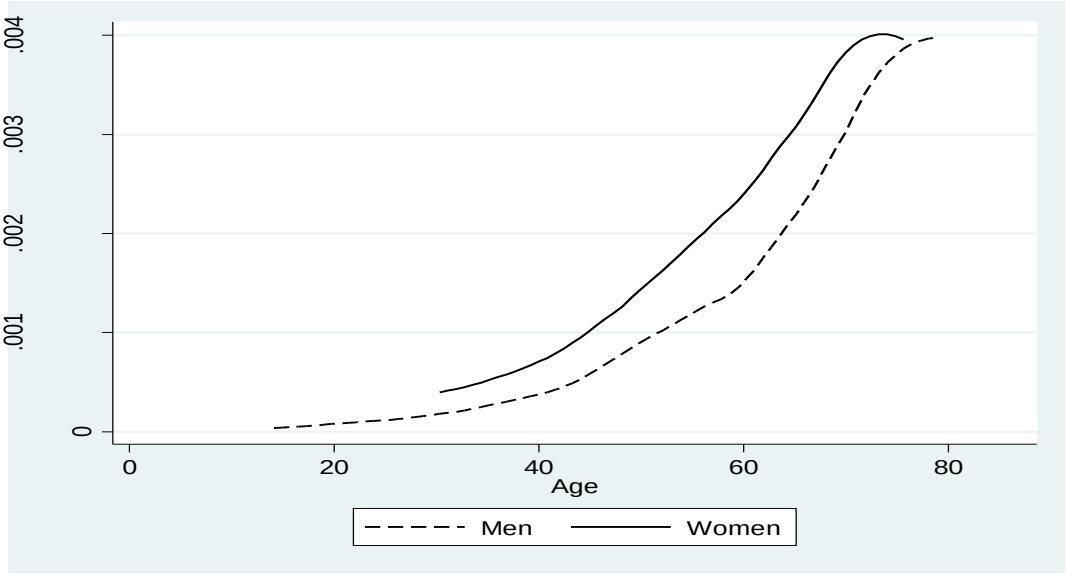
Figure 3.4: Hazard functions for RA onset for different birth cohorts of respondents who participated in LIFE



Note: The figure uses data from 6,626 respondents who participated in the LIFE interview and provided information about RA onset and date of birth. 247 of these were born before 1921, 854 between 1921 and 1930, 1,581 between 1931 and 1940, 2,297 between 1941 and 1950, 1,647 born after 1950. 261 reported RA onset.

Figure 3.5 indicates that more women than men reported RA, and that onset tended to occur earlier in their lives. However, a test conducted using a Cox regression model of RA onset on gender with adjustment for birth cohort finds that the gender difference is not statistically significant; the hazard ratio (HR) for women as opposed to men developing RA is 1.061, (95%CI=0.831-1.356, p=0.634, N=6,624).

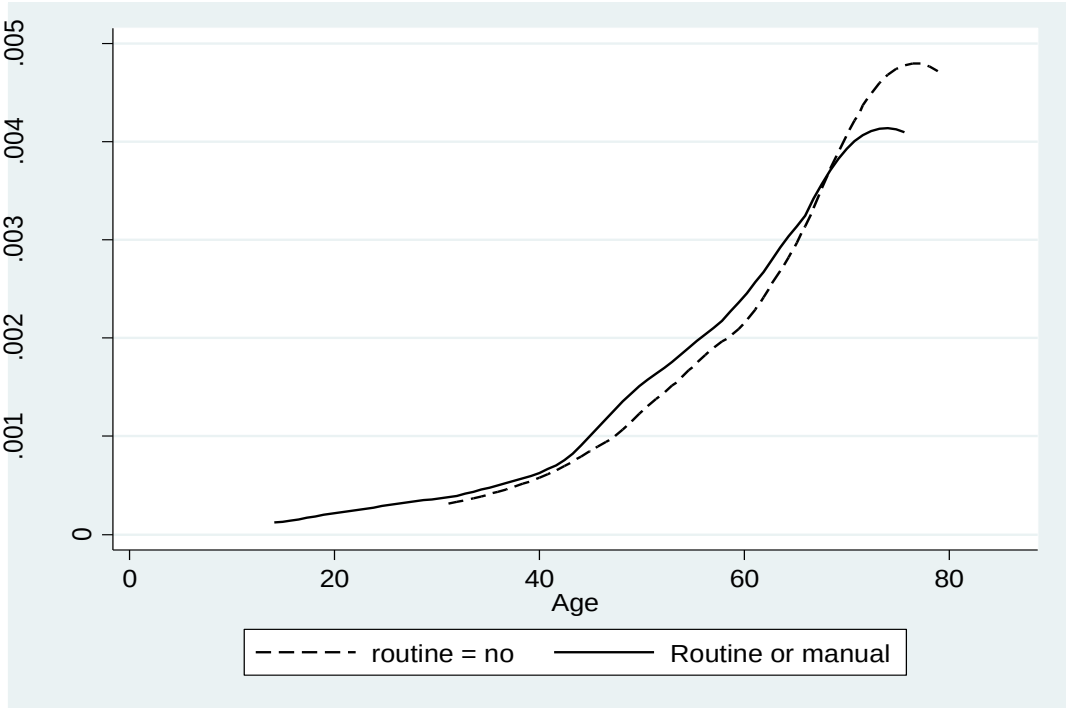
Figure 3.5: Hazard functions for RA onset for men and women who participated in LIFE, adjusted for birth cohort



Note: The figure uses data from 6,624 respondents who participated in the LIFE interview and provided information about RA onset, date of birth and gender. 2,998 of these were men and 3,626 were women. 261 reported RA onset.

Figure 3.6 indicates that respondents who, at age 14, had a main carer who worked in a routine or manual occupation are at increased risk of developing RA, and that they tend to develop it earlier in their lives. After adjusting for birth cohort, the HR is 1.690, (95%CI=1.203-2.227, p=0.000, N=5,386).

Figure 3.6: Hazard functions for RA onset for LIFE respondents with different socio-economic backgrounds, adjusted for birth cohort



Note: Note: The figure uses data from 5,386 respondents who participated in the LIFE interview and provided information about RA onset, date of birth and socio-economic background, measured by whether the respondent reported that their father had a manual or routine occupation when they were 14 years old. 1,726 respondents reported their father's occupation as manual or routine and 3,660 reported other occupation, classified as reflecting a higher occupational status. 261 respondents reported RA onset.

Summary statistics from the 20 imputed datasets for all variables used in the main analyses are presented in Table 3.7.

Table 3.7: Summary statistics

Variable	Measure	Values	Mean/ %	95% ci
Childhood adversity	terciles	0	43.9	41.9-45.9
		1	29.6	27.9-31.4
		2+	26.4	24.9-28.0
	binary	1+	56.1	54.1-58.1
Adversity 0-44	terciles	0-1	36.4	35.0-37.8
		2-3	37.5	36.1-38.9
		4+	26.1	24.8-27.5
	continuous	0-6+	2.4	2.3-2.5
Adversity 0-59	terciles	0-1	27.3	26.0-28.6
		2-3	36.2	34.8-37.5
		4+	36.6	35.2-37.9
	continuous	0-7+	3.0	2.9-3.0
Cumulative adversity 0-44	dummies	0	15.1	14.1-16.1

		1	34.4	33.0-35.9
		2	34.0	32.7-35.3
		3	16.4	15.3-17.6
	continuous	0-3	1.5	1.5-1.5
Cumulative adversity 0-59	dummies	0	9.9	9.1-10.8
		1	26.7	25.5-27.9
		2	33.4	32.1-34.8
		3	22.5	21.3-23.6
		4	7.5	6.6-8.3
	continuous	0-4	1.9	1.9-1.9
Transition adversity	binary	1+	51.0	49.7-52.2
Early adulthood adversity	binary	1+	44.8	43.4-46.1
Mid-adulthood adversity	binary	1+	39.0	37.7-40.4
Material adversity 0-15	binary	1+	16.7	15.6-17.9
Material adversity 0-29	binary	1+	19.5	18.3-20.7
Material adversity 0-44	binary	1+	22.1	20.8-23.3
Material adversity 0-59	binary	1+	25.0	23.7-26.3
Social adversity 0-15	continuous	0-3+	0.7	0.7-0.7
Social adversity 0-29	continuous	0-3+	1.3	1.2-1.3
Social adversity 0-44[1]	continuous	0-6+	1.1	1.1-1.1
Social adversity 0-59[2]	continuous	0-3+	1.2	1.2-1.3
Family adversity 0-15	binary	1+	35.8	34.5-37.1
Family adversity 0-29[2]	continuous	0-3+	0.6	0.6-0.7
Family adversity 0-44[2]	continuous	0-3+	0.8	0.8-0.8
Family adversity 0-59[3]	continuous	0-4+	0.8	0.8-0.8
Traumatic adversity 0-15	continuous	0-2+	0.3	0.3-0.3
Traumatic adversity 0-29	binary	1+	39.6	38.2-41.0
Traumatic adversity 0-44	binary	1+	43.4	42.0-44.8
Traumatic adversity 0-59	binary	1+	48.1	46.6-49.5
Chronic adversity 16-29	binary	1+	13.1	12.2-14.0
Chronic adversity 16-44	binary	1+	28.0	26.8-29.2
Chronic adversity 16-59	binary	1+	39.2	37.9-40.5
Acute adversity 16-29	binary	1+	11.2	10.4-12.1
Acute adversity 16-44	binary	1+	15.1	14.1-16.1
Acute adversity 16-59	binary	1+	18.0	16.9-19.0
Female gender	binary		54.7	53.5-55.9
Level 2+ quals in 2006	binary		67.7	66.5-68.9
Born by 1920	binary		3.7	3.3-4.2
Born 1921-1930	binary		12.9	12.1-13.7
Born 1931-1940	binary		23.8	22.8-24.9
Born 1941-1950	binary		34.7	33.5-35.8
Born 1951 or after	binary		24.9	23.8-25.9
Years smoked 30-44	continuous		5.6	5.4-5.7
Years smoked 45-59	continuous		3.4	3.2-3.5

Notes: The summary statistics are from 20 imputed datasets that include 6,623 respondents who participated in LIFE and provided information about RA onset, gender, and date of birth, excluding one participant, who reported RA with onset before age 16. Childhood is 0-15, transition 15-29, early adulthood 30-44, mid-adulthood 45-59. Mean is for continuous variables. % is for binary variables and indicates the percentage of respondents for whom the variable has a yes value.
1. Social adversity between birth and 44 is a continuous variable with values of zero, one or two, three to five, and six or more adversities.
2. These continuous variables have values of zero, one or two, and three or more.
3. Family adversity from birth to age 59 has values of zero, one to three, and four or more adversities.

Appendix 12 presents comparisons between summary statistics using the observed dataset with complete information and the multiple datasets with imputed values. These comparisons suggest that respondents who provided complete information report slightly fewer adversities than those for whom missing values are imputed.

Appendix 13 presents summary statistics for men and women separately using the multiple datasets with imputed values. Women reported more adversities than men, especially social, family-related and chronic adversities. Men reported more material, traumatic and acute adversities. Men smoked for more years than women and were more likely to have Level 2 or higher qualifications in 2006. Women are over-represented among the cohorts born before 1921 and after 1950 (aged 85+ and below 56 in 2006).

RQ1: Do adversities predict RA onset?

Table 3.8 presents results of Cox regressions of RA onset on adversity over the life-course with adjustment for birth cohort, gender and education level at the time of LIFE. For the whole sample (men and women together), there is evidence that adversity earlier in the life-course predicts RA with onsets from 16, 45, and 60.

For RA onset from age 16, the HRs associated with each tercile of exposure to childhood adversity suggests a threshold effect. Exposure to one or more childhood adversities is associated with a hazard ratio of 1.645 (95%CI=1.165-2.323, p=0.005). For RA onset later in life, HRs associated with each tercile of adversity suggests graded relationships. Using continuous measures of adversity, the HRs for each additional adversity (maximum of 6 or more) from birth to age 44 is 1.152 (95%CI=1.054-1.260, p=0.002), and from birth to age 59 (maximum of 7 or more) is 1.142 (95%=1.042-1.251, p=0.004).

Table 3.8: Adjusted associations between total exposure to adversity and risk of RA onset for men and women together and separately

					RA onset from 16					
Adversity 0-15		Men and women (n=6,623)			Men (n=2,997)			Women (n=3,626)		
Measure	Adv.	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Terciles	0	Reference			Reference			Reference		
	1	**1.603**	**1.133-2.269**	**0.008**	1.436	0.838-2.460	0.188	**1.753**	**1.093-2.812**	**0.020**
	2+	**1.688**	**1.106-2.577**	**0.015**	1.540	0.840-2.824	0.163	**1.811**	**1.049-3.126**	**0.033**
	Wald test									**0.037**
Binary	1+	**1.645**	**1.165-2.323**	**0.005**	1.487	0.902-2.452	0.120	**1.785**	**1.134-2.809**	**0.012**
					RA onset from 45					
Adversity 0-44		Men and women (n=6,560)			Men (n=2,975)			Women (n=3,585)		
Measure	Adv.	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Terciles	0-1	Reference			Reference			Reference		
	2-3	**1.542**	**1.066-2.229**	**0.021**	1.601	0.919-2.788	0.096	1.475	0.876-2.483	0.144
	4-11	**1.939**	**1.264-2.974**	**0.002**	**2.108**	**1.170-3.797**	**0.013**	1.785	0.972-3.279	0.062
	Wald test			**0.006**			**0.048**			0.137
Continuous		**1.152**	**1.054-1.260**	**0.002**	**1.177**	**1.041-1.332**	**0.010**	1.129	0.997-1.279	0.057
					RA onset from 60					
Adversity 0-59		Men and women (n=5,525)			Men (n=2,593)			Women (n=2,932)		
Measure	Adv.	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Terciles	0-1	Reference			Reference			Reference		
	2-3	**1.729**	**1.009-2.962**	**0.046**	2.298	0.956-5.523	0.063	1.407	0.707-2.803	0.331
	4-12	**2.130**	**1.257-3.610**	**0.005**	3.219	1.404-7.384	**0.006**	1.504	0.725-3.120	0.273
	Wald test			**0.023**			**0.002**			0.515
Continuous		**1.142**	**1.042-1.251**	**0.004**	**1.202**	**1.057-1.368**	**0.005**	1.086	0.951-1.240	0.222

HR refers to hazard ratios of RA onset contingent upon adversity. For men and women together, two models are estimated for RA onset from each age. One includes adversity measured in terciles, and the other includes either a binary or continuous measure of adversity. The same applies to the separate samples of men and women. Models are adjusted for birth cohort and Level 2+ qualifications at time of LIFE and gender, as appropriate. Continuous measures have maximum values of 6 for adversities 0-44, of 7 for adversities 0-59.

Additional analyses presented in Appendix 14 suggest that during childhood, poor housing amenities is a particularly important predictor of RA onset. During transition, a high number of house moves is protective against RA onset. Partnership breakdown and a life-threatening illness or injury during transition are particularly important predictors of RA onset from age 60. Otherwise, there is no evidence that associations between RA onset and indices of adversity are driven by specific adversities.

RQ1a: How do the answers to this question vary by gender?

Table 3.8 presents results for men and women separately. HRs for RA onset contingent upon adversity are greater than one for RA onset at all life stages for men and women. However, the magnitude and consistency of associations differ slightly by gender, with stronger associations for women than men between childhood adversity and RA onset from age 16, and stronger associations for men between adversity up to age 59 and subsequent RA onset. Additional analyses using the same models as those presented in the first columns of Table 3.8 but also including interaction terms between adversity and gender provide no evidence of gender differences. HRs for the interactions between female gender and adversity during childhood, 0-44, and 0-59 are 1.552 (95%CI=0.946-2.541) p=0.081 N=6,623, 0.959 (95%CI=0.803-1.146) p=0.644 N=6,560, and 0.948 (95%CI=0.785-1.146) p=0.579 N=5,525, respectively.

Sensitivity analyses described in Appendices 18 and 19 provide similar results.

RQ2: How do adversities combine over the life-course to predict RA onset?

RQ2a: Does the length of exposure matter?

Table 3.9 presents the results of Cox regression analyses of RA onset on the number of life stages in which at least one adversity was reported. Two measures of cumulative adversity are used; a set of dummies and a continuous measure. The latter assumes that any association with RA onset is linear. Results for both measures are consistent with a cumulative model of life-course exposure.

Table 3.9: Adjusted associations between cumulative exposure to adversity and risk of RA onset for men and women together

Number of life stages exposed to adversity		RA onset from age 45 (n=6,560)				RA onset from age 60 (n=5,525)			
	Values	HR	95%CI		p-value	HR	95%CI		p-value
Dummies	0								
	1	1.802	0.909	3.572	0.092	2.237	0.771	6.489	0.138
	2	**2.603**	**1.353**	**5.009**	**0.004**	**3.484**	**1.304**	**9.305**	**0.013**
	3	**2.611**	**1.282**	**5.315**	**0.008**	**3.849**	**1.429**	**10.370**	**0.008**
	4					**3.688**	**1.070**	**12.712**	**0.039**
	Wald test				**0.010**				0.067
Continuous measure		**1.339**	**1.134**	**1.582**	**0.001**	**1.310**	**1.107**	**1.551**	**0.002**

Notes: Models are adjusted for birth cohort, gender, and education level at the time of LIFE. HR is hazard ratio, 95% ci is 95% confidence interval.

The magnitudes of HRs for the sets of dummies suggest graded relationships with RA onset from ages 45 and 60, except for the final life stage added. This suggests that the impact (for RA onset) of adversity accumulates over the life-course during most (but not all) life stages. Using the continuous measure, the mean HR for each additional life stage during which adversity is reported is 1.339 (95%CI=1.134-1.582, p=0.001) for RA with onset from 45, and 1.310 (95%CI=1.107-1.551, p=0.002) for RA with onset from 60.

Sensitivity analyses described in Appendices 15, 18 and 19 provide very similar results.

RQ2b: Does the life stage at which one is exposed matter?

RQ1 was addressed using a binary indicator of childhood adversity and continuous measures of adversity during subsequent life stages. In order to compare the salience of adversities during different life stages, the binary measure was used to measure adversity during each life stage.

Table 3.10 presents the results of Cox regression analyses of RA onset on adversity during each life stage with mutual adjustment. The results suggest that adversity during childhood and transition is particularly salient for RA onset from ages 45 and 60. After adjustment for adversity during childhood and transition, adversity during early and mid-adulthood does not increase the risk of RA onset. After mutual adjustment for exposures at each life stage, birth cohort, gender and education at the time of LIFE, HRs for exposure to at least one childhood adversity are 1.579 (95%CI=1.095-2.277) p=0.015 for RA with onset from 45, and 1.685 (95%CI=1.116-2.544) p=0.013 for RA with onset from 60. The equivalent HRs for at least one adversity during transition are 1.574 (95%CI=1.164-2.130) p=0.003 for RA with onset from 45, and 1.890 (95%CI=1.278-2.796) p=0.001 for RA with onset from 60.

Table 3.10: Associations between RA onset and adversity during each life stage, with mutual adjustment and adjustment for demographic variables, for men and women together

Adversity during each life stage	RA onset from age 45 (n=6,560)				RA onset from age 60 (n=5,525)			
	HR	95%CI		p-value	HR	95%CI		p-value
Childhood	**1.579**	**1.095**	**2.277**	**0.015**	**1.685**	**1.116**	**2.544**	**0.013**
Transition	**1.574**	**1.164**	**2.130**	**0.003**	**1.890**	**1.278**	**2.796**	**0.001**
Early adulthood	0.985	0.721	1.346	0.926	0.834	0.550	1.263	0.391
Mid-adulthood					1.163	0.795	1.702	0.436

These are results from two models, each adjusted for birth cohort, gender, and Level 2+ qualifications at the time of LIFE. HR is of RA onset contingent upon adversity, and 95%CI is 95% confidence interval. Childhood is ages 0-15, transition 16-29, early adulthood 30-44, mid-adulthood 45-59. Measures of adversity at each life stage are binary indicators of exposure to one or more adversities.

Sensitivity analyses were conducted using indices of adversity that exclude life events, which were measured using questions about first time of exposure. Associations between RA onset and adversity during childhood and transition have slightly reduced magnitude and consistency, especially for childhood adversity. There is no longer evidence that childhood adversity predicts RA onset from age 60 (HR=1.326, 95%CI=0.914-1.922, p=0.137). See Appendix 15, Table A15.1. Very similar results to those reported in Table 3.10 are reported in Table A19.4 Appendix 19, which uses datasets imputed from indices of adversity created in the observed data that include partial information.

In contrast, the sensitivity analyses, described in Appendix 18, provide inconsistent evidence. These sensitivity analyses use a smaller sample that excludes respondents who, in wave 3, reported depression, pain or who performed poorly on a memory recall test. Using this sample, although all HRs are greater than one, there is evidence only that childhood adversity predicts RA onset; the association with transition adversity is no longer statistically significant. Still using this sample, when indices of adversity are used that exclude life events, HRs for adversity during each life stage are all greater than one (except for mid-adulthood), but it is adversity during early adulthood that appears particularly salient.

RQ2c: How do the answers to these questions vary by gender?

Results of analyses conducted separately for men and women are presented in Appendix 15. There is no evidence for gender differences in associations between cumulative adversity over the life-course.

RQ3: Do material, psychosocial and behavioural factors independently predict RA onset?

RQ3a: Do material and social adversities independently predict RA onset?

In order to examine whether any relationships between material and social adversities and RA onset are graded or reflect threshold effects, associations were tested using sets of dummies for each level of exposure. The results, which are presented in Appendix 16, suggest that relationships between RA onset and material adversities are likely to be threshold effects of one or more material adversities, and that relationships with social adversities are likely to be graded. Consequently, binary indicators of material adversity and continuous measures of social adversity were used in the models.

Six Cox regression models were estimated of material and social adversity during different life stages on RA with onsets from ages 16, 45 and 60. The results are presented in Table 3.11.

All HRs for RA onset contingent upon material and social adversities are greater than one. Evidence that material adversities predict RA onset from ages 16 and 45 is not statistically significant. However, respondents who reported at least one material adversity between birth and age 59 had a hazard of RA onset from age 60 that was 1.491 (95%CI=1.025-2.168, p=0.037) times greater than that for respondents reporting no material adversities, after adjustment for birth cohort, gender, qualifications and social adversities.

Table 3.11: HRs for RA onset contingent upon material and social adversities, adjusted for demographics, for men and women together

	RA onset from age 16 (n=6,623)			RA onset from age 45 (n=6,560)			RA onset from age 60 (n=5,525)		
Life stage and type	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Childhood									
Material (0,1+)	1.324	0.920-1.905	0.131	1.288	0.877-1.891	0.197	1.488	0.937-2.361	0.092
Social (0,1,2,3+)	**1.183**	**1.003-1.394**	**0.046**	**1.206**	**1.010-1.440**	**0.038**	1.104	0.881-1.385	0.390
Birth to age 44									
Material (0,1+)				1.243	0.902-1.713	0.184	1.455	0.973-2.176	0.068
Social(0,1-2,3-5,6+)				**1.374**	**1.144-1.651**	**0.001**	**1.302**	**1.019-1.662**	**0.035**
Birth to age 59									
Material (0,1+)							**1.491**	**1.025-2.168**	**0.037**
Social (0,1-2,3+)							**1.359**	**1.029-1.795**	**0.031**

These are results of six models with mutual adjustment for material and social adversities and total adversity during other life stages, birth cohort, gender and Level 2+ qualifications at time of LIFE. HR is for RA onset contingent upon each type of adversity. Material adversity is measured using an indicator of one or more adversity. Social adversities are measured using continuous variables with values indicated in the table.

After adjustment for the same controls and for material adversity, social adversity predicted RA with onsets from ages 16, 45 and 60. For example, each additional social adversity during childhood is associated with a HR for RA onset from age 16 of 1.183 (95%CI=1.003-1.394) p=0.046, and a HR for maximum social adversity as opposed to none of 1.656 (1.183^3). Each additional social adversity between birth and age 44 is associated with a HR for RA onset from age 45 of 1.374 (95%CI=1.144-1.651) p=0.001, and the HR for maximum social adversity as opposed to none is 2.594. Each additional social adversity up to age 59 is associated with a HR for RA onset from age 60 of 1.359 (95%CI=1.029-1.795) p=0.031, and the HR for maximum social adversities is 2.510.

These results are robust to sensitivity analyses presented in Appendices 18 and 19.

RQ3b: Are any associations found explained by smoking behaviour?

Smoking behaviours during early and mid-adulthood (as appropriate) were included in models of RA onset on total levels of material and social adversity up to the end of transition. The results, which are presented in Appendix 16 , provide little evidence that smoking mediates effects of adversity on RA onset. HRs for adversities are reduced, but minimally. After adjustment for birth cohort, gender, education and adversity, there is no evidence that smoking during early adulthood predicts RA onset from age 45 or 60, and the associations between smoking during mid-adulthood and RA onset from age 60 is not quite statistically significant. However, adjusting only for gender, smoking does predict RA onset.

RQ3c: How do the answers to these questions vary by gender?

Results for men and women separately are presented in Appendix 16. They suggest that for RA onset from 45, material adversities matter more for men than women and that social adversities matter for both men and women. For RA onset from 60, material and social adversities matter for men but not for women. When interaction terms were included in the analyses, there was no evidence of gender differences.

There is no evidence that associations between RA onset and adversities were mediated by smoking among men or women.

RQ4: Are some types of social adversity more salient predictors of RA onset than others?

RQ4a: Comparison of adversities in different life domains: relationship-related and traumatic adversities.

In order to examine whether associations between relationship-related and traumatic adversities and RA onset are likely to reflect threshold or graded effects, associations were estimated using sets of dummies. The results, which are presented in Table A17.1 Appendix 17, suggest that relationships between RA onset and relationship-related adversities between birth and ages 44 and 59 are likely to be graded. However, during the relatively short period of childhood, the relationship reflects a threshold effect of one or more relationship-related adversity. Relationships between RA onset and traumatic adversity appear to reflect threshold effects of one or more trauma, except for during childhood, when the relationship appears graded.

Six Cox regression models were estimated of family-related and traumatic adversity during different life stages on RA with onsets from ages 16, 45, and 60. The results are presented in Table 3.12.

All hazard ratios for RA onset contingent upon relationship-related and traumatic adversities are greater than one.

Table 3.12: HRs for RA onset contingent upon relationship-related and traumatic adversities after mutual adjustment and adjustment for demographic variables, for men and women together

Life stages and type	RA onset from 16 (n=6,623) HR	95%CI	p-val	RA onset from 45 (n=6,560) HR	95%CI	p-val	RA onset from 60 (n=5,525) HR	95%CI	p-val
Childhood									
Relationship	1.106	0.835-1.465	0.481	1.185	0.874-1.606	0.275	1.053	0.711-1.560	0.795
Trauma	**1.288**	**1.026-1.618**	**0.029**	1.252	0.983-1.595	0.068	1.184	0.848-1.653	0.323
Birth to age 44									
Relationship				**1.302**	**1.055-1.607**	**0.014**	1.252	0.946-1.657	0.116
Trauma				1.298	0.955-1.764	0.095	1.164	0.771-1.757	0.469
Birth to age 59									
Relationship							1.327	0.968-1.818	0.079
Trauma							1.179	0.784-1.773	0.429

These are results from six models. HRs are for RA onset, contingent upon each type of adversity. Models are adjusted for birth cohort, gender, and Level 2+ qualifications at time of LIFE with mutual adjustment for relationship-related and traumatic adversities, material adversity during the life stage in which relationship-related and traumatic adversities are included, and total adversity during other life stages. Childhood relationship-related adversity is measured using an indicator of 1+ adversities. Family adversity during other periods is measured using continuous variables with values for 0-29 of 0, 1-2, 3+ adversities, for 0-44 of 0, 1-2, 3+ adversities, and for 0-59 of 0, 1-3, 4 adversities. Traumatic adversities are measured using indicators of 1+ during all periods except childhood, when the variable takes values of 0, 1, 2+.

During childhood, traumatic adversities appear more salient for RA onset, especially with onset from age 16. After adjustment for other types of childhood adversity (i.e. family-related and material adversity), each additional traumatic adversity (maximum value is two or more) is associated with a HR for RA onset from age 16 of 1.288 (95%CI=1.026-1.618) p=0.029. For RA onsets from ages 45 and 60, relationship-related adversity during the life stages after childhood appears more important. For example, after adjustment for other types of adversity during transition and total adversity during other life stages, each traumatic adversity between birth and age 44 is associated with a HR for RA onset from age 45 of 1.302 (95%CI=1.055-1.607) p=0.014.

Sensitivity analyses described in Appendices 18 and 19 provide similar results.

RQ4b: Comparison of chronic and acute adversities.

Results of analyses of RA onset on sets of dummies representing levels of exposure to chronic and acute adversities, reported in Appendix 17 Table A17.2, indicate that it is most likely that any relationships found reflect threshold effects of one or more adversity. Consequently, measures for chronic and acute adversities indicate exposure to one or more adversity. Binary indicators of one or more adversity are also used to measure adversities not classified as either chronic or acute. Numbers of respondents reporting each type of adversity and RA are small, and vary between 72 (those reporting at least one chronic adversity between 16 and 44 and RA with onset from age 45) and 19 (those reporting at least one acute adversity between 16 and 59 and RA with onset from age 60). See Appendix 17, Table A17.3.

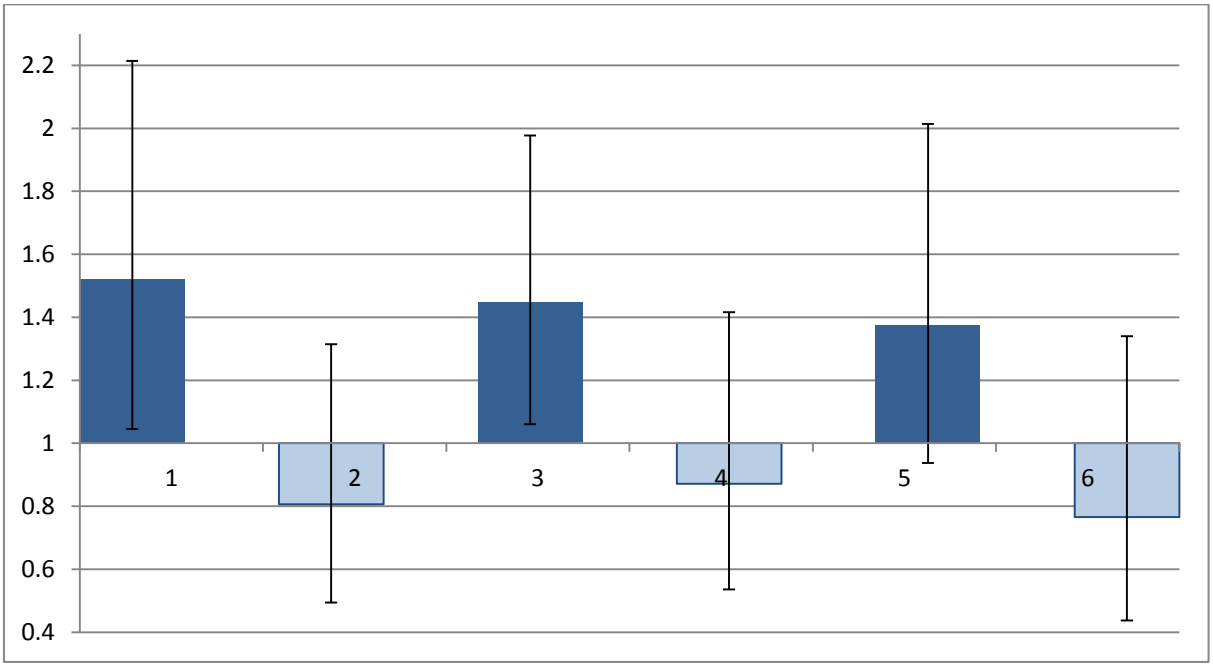
Table 3.13 presents results of six models of RA onset on chronic and acute adversities from age 16. Figure 3.7 presents a selection of these results in graphical form. It appears that chronic but not acute adversities predict RA onset.

Table 3.13: HRs for RA onset contingent upon chronic and acute adversities, with mutual adjustment and adjustment for demographics, for men and women together.

Life stage	RA onset from 30 (n=6,613)			RA onset from 45 (n=6,560)			RA onset from 60 (n=5,525)		
and type	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
16-29									
Chronic	**1.521**	**1.045-2.214**	**0.029**	**1.685**	**1.119-2.537**	**0.013**	**2.429**	**1.470-4.014**	**0.001**
Acute	0.806	0.494-1.315	0.388	0.821	0.485-1.391	0.463	0.876	0.457-1.678	0.690
16-44									
Chronic				**1.448**	**1.060-1.977**	**0.020**	**1.653**	**1.105-2.472**	**0.014**
Acute				0.871	0.536-1.416	0.578	0.781	0.415-1.468	0.443
16-59									
Chronic							1.374	0.938-2.014	0.103
Acute							0.766	0.438-1.340	0.351

These are results from six models. HRs are for RA onset contingent upon each type of adversity. Models are adjusted for chronic and acute adversities, and adjustment for adversities not classified as chronic or acute, childhood adversity measured using an indicator of one or more adversities, birth cohort, gender and Level 2 qualifications or above at the time of LIFE. Chronic adversities are main occupation as carer and/or reporting being a carer, having a partner or child who is addicted to alcohol or drugs and breaking up with a cohabiting partner. Acute adversities are being a victim of sexual assault, being a victim of a serious physical attack, witnessing a death or serious injury, or a major natural disaster. Measures of chronic and acute adversity and of adversities not classified as chronic or acute are indicators of one or more adversity.

Figure 3.7: HRs for RA onset contingent upon chronic and acute adversities with full adjustment for men and women together



Darker bars represent HRs contingent upon one or more chronic adversity. Lighter bars represent hazard ratios contingent upon one or more acute adversity. Bars 1 and 2 refer to adversity between ages 16 and 29 and RA onset from age 30. Bars 3 and 4 refer to adversity between ages 16 and 44 and RA onset from age 45. Bars 5 and 6 refer to adversity between ages 16 and 59 and RA onset from age 60. Chronic adversities are caring for a relative or friend, partnership breakdown and having a child or partner who abuses alcohol or drugs. Acute adversities are witnessing a death or serious injury, and being a victim of a major natural disaster, sexual assault, or serious physical attack. Results are from three models, each with mutual adjustment for chronic and acute adversities, other adversities, total childhood adversity, birth cohort, gender, and qualifications at Level 2 or above at the time of LIFE. Black lines represent 95% confidence intervals.

Appendix 18 reports results of sensitivity analyses that exclude respondents who, in wave 3, reported pain, depression or who scored poorly in a memory test. The pattern of results is similar, although reduced sample size means that relationships with chronic adversities do not reach statistical significance. Sensitivity analyses using alternative multiple imputed datasets, reported in Appendix 19, also provide similar results.

RQ4c: How do the answers to these questions vary by gender?

Results of analyses conducted for men and women separately are presented in Appendix 17 Tables A17.4 and A17.5. The results suggest that, especially for RA onset from age 45, traumatic adversities are more important for men and relationship-related adversities are more important for women. While there is no evidence that acute adversities predict RA onset for either gender, in relation to women, there is an indication that if numbers were greater, acute adversities would be negatively associated with RA onset.

Sensitivity analyses

Sensitivity analyses were conducted excluding respondents who reported in the wave concurrent with LIFE pain or depression, or whose level of cognitive functioning was low. Whilst there is a loss of power due to the reduced sample size, the pattern of results is generally similar. However, there were a few differences, which are noted above. The most important difference is that conclusions drawn about life stages when adversity is particularly salient for RA onset are unreliable. See Appendix 18.

Sensitivity analyses using indices of adversity that included respondents who provided partial information about adversity before imputing missing values produced very similar results to those presented here. Results of this set of sensitivity analyses are reported in Appendix 19.

5. Discussion

5.1 Discussion of findings

This chapter provides new evidence relevant to the psychosocial pathways that contribute to RA onset. It does so by estimating the contribution of social adversities to RA onset after adjustment for material adversities and behavioural factors. Further, it examines the relative importance of different types of social adversities; relationship-related and traumatic social adversities, and chronic and acute social adversities. This evidence is contextualised by evidence about how adversities (material and social adversities together) combine over the life-course to predict RA onset.

The evidence is based on information from 6,624 respondents, of whom 261 reported RA onset. Retrospective life-course information is used to model the importance for RA onset of a wide range of adversities at different life stages. The findings provide an important contribution to a rather sparse evidence base concerning the social determinants of RA. Main conclusions are presented in Table 3.14.

Research Question 1: Does adversity predict RA onset?

This study finds stronger evidence for associations between adversity and RA onset than do previous studies. This is probably because it is a large study that includes measures of a wide range of adversities over the life-course. In relation to numbers, Carette and Surtees (2000) found trends between adversity and RA onset but included just 55 respondents with RA onset, whereas this study includes 260[2]. In relation to the wide range of adversities measured from birth through the life-course, this study contrasts with Wesley's, which

[2] Two hundred and sixty respondents reported RA onset after age 16, and one reported onset before age 16.

included many more respondents with RA (2,774) but examined adversities reported during the previous five years (Wesley et al. 2014). The difference between the results reported here and those reported by Wesley and colleagues suggest that adversity earlier in the life-course is important for RA onset.

There is no evidence of gender differences in associations between life-course adversity and RA onset. However, the findings suggest that small differences may exist that would be statistically significant in a larger sample. The association between childhood adversity and RA onset from age 16 is statistically significant for women but not men, whereas associations between life-course adversity and RA with onsets from ages 45 and 60 are statistically significant for men but not women. No explanation comes to mind for the first difference. However, a possible explanation for the second is that part of the variation in RA onset during adulthood is explained by female sex hormones (Malysheva et al. 2010), which would reduce the relative importance of social and material exposures for women but not men.

The indication of a gender difference (it is not statistically significant) reported here contrasts with evidence from the larger study (Wesley et al. 2014), which found an association between RA onset and life events during the previous five years among women but not men. The difference may reflect differences between the adversities measured in Wesleys's study and this one. As mentioned above, I included a wide range of adversities from birth, while Wesley's study included fewer life events and only during the five years before diagnosis of RA. As RA onset is often insidious, the association reported by Wesley and colleagues may relate to progression as well as onset of the disease.

Table 3.14: Summary of conclusions

1.	Total levels of life-course adversity predict RA onset.	Exposure to at least one adversity during childhood is associated with increased risk of RA onset from age 16 (HR=1.65, 95%CI=1.17-2.32, p=0.005). The HR for each additional adversity between birth and age 44 (maximum value is 6 or more) is 1.15, 95%CI=1.05-1.26, p=0.002.The HR for maximum adversity as opposed to none is 2.34. The HR for each additional adversity between birth and age 59 (maximum value is 7 or more) is 1.14, 95%CI=1.04-1.25, p=0.004. The HR for maximum adversity is 2.53.
2a.	Adversities during different life stages combine cumulatively to predict increased risk of RA onset.	Each additional life stage in which at least one adversity is experienced is associated with a HR of 1.34 (95%CI=1.13-1.58, p=0.001) for RA onset from age 45, and of 1.31 (95%CI=1.11-1.55, p=0.002) for RA with onset from age 60.
2b.	Using these data, it is not possible to draw conclusions about the relative salience for RA onset of adversity during particular life stages.	
3a.	Material and social adversities independently predict RA onset.	After adjustment for material adversity, associations between RA onset and social adversities are statistically significant. For example, each additional social adversity during childhood (maximum value of 3 or more) is associated increased hazard of RA onset from age 16 by 1.18 (95% CI=1.00-1.39) p=0.046. The HR associated with maximum social adversity during childhood as opposed to none is 1.66. For RA with onsets from 45 and 60, the HRs associated with maximum life-course social adversity as opposed to none are 3.56 and 2.51, respectively. Associations with material adversity after adjustment for social adversities are positive but most are not statistically significant. However, exposure to one or more adversities between birth and age 59 is associated with increased risk of RA onset from age 60; HR=1.49, 95%CI=1.03-2.17, p=0.037.
3b.	Associations between RA onset and material and social adversities are not mediated by smoking. This is a new finding.	
4a.	Both relationship-related and traumatic adversities appear to contribute to RA onset.	Exposure to one or more traumatic adversity during childhood is associated with RA onset from age 16 (HR=1.29, 1.03-1.62, p=0.029). Exposure to each additional group of relationship-related adversities between birth and age 44 (maximum of three) is associated with an increased hazard of RA onset from age 45 by 1.30 (95%ci 1.06-1.61, p=0.014). The HR for maximum as opposed to no relationship-related adversity is 2.20.
4b.	Chronic adversities predict RA onset. Acute adversities do not.	Exposure to one or more chronic adversities between ages 16 and 44 is associated with an increased risk of RA onset from age 45; HR=1.45, 95%CI=1.06-1.98, p=0.020. Exposure to one or more chronic adversities between ages 16 and 44 is associated with an increased hazard of RA onset from age 60 by 1.65, 95%CI=1.11-2.47, p=0.014.
	There is no evidence of gender differences for any of the results	
	These findings are robust to sensitivity analyses that exclude respondents whose recall may have been inaccurate or biased by symptoms of RA, and also to sensitivity analyses that used multiple imputation based on indices of adversity in the observed datasets that are created for all respondents who provided information about most adversities, rather than only for those who provided complete information.	

Research Question 2: How do adversities combine over the life-course to predict RA onset?

This is the first study that I am aware of which tests how exposures during different life stages combine to predict RA onset. The evidence presented here is consistent with a cumulative life-course model; the more life stages during which one is exposed to adversity, the greater the risk of developing RA later in life. This finding is robust to a range of sensitivity analyses.

The finding resonates with theories about allostatic load, which is conceptualised as a marker of physiological wear and tear resulting from stress that accumulates over the life-course (McEwen & Stellar 1993). Gustafsson and colleagues describe the development of physiological disadvantage across multiple inter-related systems as, "an 'historical index' of physiological toll" (2012,p.118). Several studies provide evidence consistent with the accumulation of physiological disadvantage over the life-course (Gustafsson et al. 2012, Singer & Ryff 1999, Robertson et al. 2014). The evidence provided here is consistent, but applies to a specific form of physiological disadvantage, associated with immune function.

More detailed tests of how adversities combine over the life-course to predict RA onset provided results that were not robust to sensitivity analyses. RA onset was regressed on adversity during all life stages with mutual adjustment but sensitivity analyses indicate that results depended upon the sample used and the questions used to measure adversities and their timings.

I therefore conclude that retrospective information about timings of adversity is not very accurate. This casts doubts on the validity of the evidence used to test the cumulative life-

course model, and means that no conclusions could be drawn about whether adversity during any particular life stage is salient for RA onset.

Nevertheless, these results indicate that the timing of adversity may be important for RA onset. Ideally, prospective data should be used to examine life-course patterns of adversity as predictors of RA onset.

Research Question 3: Do material, psychosocial and behavioural factors independently predict onset of rheumatoid arthritis?

Material and social adversities independently predicted RA onset. These associations were not explained by smoking. This is consistent with existing theory that socio-economic inequalities in health develop over the life-course through interlinked material and psychosocial pathways (Benzeval et al. 2014). Psychosocial pathways are the focus of this thesis and additional findings relating to social adversities are discussed below in relation to Research Question 4.

Adversities hypothesised to affect health through material pathways are poor household amenities during childhood and self-reported severe financial hardship and unemployment. Evans & Kantrowitz (2002) summarise evidence showing that those living on lower incomes are more likely to reside in neighbourhoods with higher levels of factory emissions and other ambient air pollutants, and Finkelstien et al. (2003) similarly report that in Ontario, mean levels of pollutants tended to be higher in lower income neighbourhoods. Thus, it seems plausible that respondents who reported material hardship tended to spend periods living in areas with relatively high levels of air pollution. As explained in the introduction, studies provide evidence consistent with the hypothesis that air pollution leads to RA onset

(Hart et al. 2009, De Roos et al. 2014). In addition, respondents reporting severe financial hardship and periods of unemployment are more likely than those who did not to have worked in occupations associated with exposures to silica (e.g. mining, stone working, masonry, glass and ceramics manufacturing, stone drilling, rock crushing), and mineral oils (e.g. the motor industry), which have been found to predict onset of RA (Sverdrup et al. 2005).

Of course, material hardship has social and psychological consequences. Some of these are adjusted for as social adversities were included in the models. As explained in the introduction, psychosocial pathways leading to the development of RA are likely to involve psychological and physiological stress responses, as discussed in relation to Research Question 4 below.

Adjustment for smoking did not attenuate associations between material or social adversities and RA onset. Interestingly, Bergstrom, who found that adults with manual occupations were at relatively high risk of developing RA, similarly reports that smoking did not mediate the association (Bergstrom et al. 2011). Other behaviours and their consequences thought to predict RA, such as diet, BMI, and (low) alcohol consumption (Lahiri et al. 2012, Hoovestol & Mikuls 2011, Tobon et al. 2010) were not included in these analyses because relevant information was not collected in LIFE. These behaviours may mediate associations between adversity and RA onset.

After adjustment for material and social adversities, birth cohort, education and gender, there was no strong evidence of an association between smoking and RA onset. Adjusting only for gender, there is stronger evidence that smoking predicts RA onset. This is consistent with existing evidence that smoking predicts RA onset (Tobon et al. 2010, Lahiri et al. 2012).

Research Question 4: Are some types of social adversity more salient predictors of RA onset than others?

The inclusion of a wide range of social adversities made it possible to compare the importance for RA onset of different types of social adversity. The finding that family-related and traumatic adversities independently predict RA onset has important policy implications as it is an added incentive for policy makers to target interventions that minimise exposure to these types of adversity and support those who are nevertheless exposed to them.

New evidence that chronic but not acute adversities predict RA onset is strong. Even though numbers are small, associations with chronic adversities are statistically significant. The results are robust to sensitivity analyses.

The evidence is consistent with theories of allostatic load (McEwen & Seeman 1999), and of the impacts of stress on the immune system (Miller et al. 2014, Cohen et al. 2012). As explained in the introduction, whilst acute experiences of stress elicit physiological responses that are unlikely to have long term harmful effects, chronic stress can result in lasting damage and dysregulation of multiple inter-related physiological systems. More specifically, continued exposure to cortisol, one of the hormones released during the stress response, can result in a type of dysregulation of immune function called glucocorticoid resistance, resulting in uncontrolled inflammation. Glucocorticoid resistance is associated with RA and other immune-mediated conditions such as asthma and ulcerative colitis (Pace et al. 2007, Pariante & Miller 2001). Evidence that exposure to chronic social stressors predicts subsequent RA onset suggests a chain of causal relationships in which exposure to certain stressors results in chronic experiences of stress, that lead to in the development of glucocorticoid resistance, which in turn contributes to the development of RA.

As I was unable to measure chronic stress directly, I used as a proxy measure exposure to adversities that one would expect to be associated with chronic stress. Adversities that one would expect to have acute impacts were similarly used as a proxy for acute stress. Using these proxy measures, I found evidence that is consistent with theory. Therefore, the findings are of importance, not only substantively, but also because they indicate that exposure to particular types of adversity may be useful measures of chronic and acute stress. Information about adversities over the life-course is available in longitudinal and cohort studies, and is particularly useful for examining impacts of stress over long periods of time. Hair cortisol, which is a relatively new and precise measure of stress cannot yet be used to examine long term impacts of stress.

The chronic adversities used were partnership breakdown, living with a partner or child who abused drugs or alcohol, and caring for a friend or relative. The acute adversities were witnessing a death or serious injury, a major natural disaster, being a victim of a sexual assault, and being a victim of a serious physical attack. Other adversities could be added to each list.

The results reported above are robust to sensitivity analyses that create indices of adversity in different ways, and that exclude information given by participants whose recall may have been inaccurate or biased by symptoms of RA.

5.2. Limitations

1. Accuracy of RA measurement

Three point nine four per cent of the sample used for the analyses (who participated in LIFE and provided information about RA onset, date of birth and gender) reported a history of

RA. Whilst it is impossible to assess with any certainty the accuracy with which these prevalence rates reflect prevalence rates in the English population, they are much higher than estimates of around 1% reported in other studies of Western countries.

Abdel-Nasser and colleagues (1997) discuss the difficulties associated with comparing prevalence rates of RA. The severity of RA symptoms fluctuate, and it is more likely to be reported when symptoms are severe, which results in under-reporting of the condition. This type of under-reporting may apply less to participants in the ELSA study, as they have been asked whether they have a history of RA on 7 occasions over 13 years. For example, Widdifield et al. 2014 found an increase in prevalence rates in Ontario, Canada between 1996 (0.49%) and 2010 (0.90%), which they partly attribute to more time in the survey and consequently more opportunities to report the existing condition.

Abdel-Nasser and colleagues also suggest that comparison of prevalence rates is complicated by differences in the denominator population. In ELSA, the population is an ageing one; prevalence rates of RA are higher among older age groups, and there are high rates of attrition due to mortality. Incidence rates, measured in person years from birth, side-steps this issue to some degree. Incidence rates among LIFE participants (0.57 per 1,000 per year) are fairly close to those reported in Ontario by Widdefield et al. (2014) (0.54 per 1,000 per year).

However, the gender difference in RA prevalence, whilst in the expected direction, is much smaller than the gender difference reported elsewhere. This suggests that women with RA are under-represented in this sample. It is possible that among women with RA, those who participated differ from those who did not. For example, those with more severe symptoms

of RA maybe less likely to participate in the HSE surveys from which the ELSA samples were drawn. It is impossible to know how the exclusion of these women affects the results.

The finding that older birth cohorts tend to report RA onset at older ages than younger birth cohorts is consistent with evidence that RA became a more common diagnosis in the UK up to the late 1960s (Abdel-Nasser 1997). Similarly, the socio-economic patterning of RA in these data is consistent with evidence from other studies, described in the introduction (Bergstrom et al. 2011, Bergstrom et al. 2013, Voigt et al. 1994).

2. Accuracy of retrospective information

Another limitation is the accuracy with which adversities and health behaviours were recalled. In relation to life events, Gorman (1993) reviewed studies that compare retrospective accounts of life events using checklists, similar to those used in ELSA, and in-depth interviews. He concludes that checklists do not distinguish the intensity of events and compared against in-depth interviews, over-report life events. In relation to childhood adversity, Susser & Widom (2012) summarise evidence that individuals who experienced sexual and physical abuse during childhood tend to under-report it as adults. These types of measurement error would tend to reduce the consistency and magnitudes of associations with RA, lending confidence to any associations found.

Recall may also be less accurate among respondents with poor recall (Brown 2013). In addition, symptoms of RA may bias reporting of childhood adversities (Raphael et al. 2001, Widom & Morris 1997). To address this possibility, sensitivity analyses were conducted that excluded 3,173 cohort members who scored poorly on a memory recall test or reported pain or depression. The general pattern of results was much the same. However, evidence

about the relative importance for RA onset of adversity experienced during different life stages was unreliable. I conclude that retrospective information about the timings of events and circumstances is not sufficiently accurate to make this sort of comparison.

Consequently, evidence about how adversity during each life stage combines to affect risk of RA onset may not be robust. Conclusions about the cumulative impact of adversities experienced during different life stages are based on this evidence, and should be tested using other datasets.

3. Representativeness of the sample

An additional limitation is that we cannot be sure to what extent associations reported here reflect patterns common to other populations. Firstly, the sample is drawn from adults living in England and the results may not apply to adults living elsewhere. Second, the sample used is a sub-sample (those who participated in LIFE and provided information about RA onset, gender and date of birth) of a sample (ELSA wave 3 participants) of a sample (drawn from HSE). It is therefore unlikely to be representative of people aged 50 and over living in private households in England.

Multiple imputation addresses part of these sample biases because it uses information from all waves of ELSA to impute missing values. Thus, one would expect the distribution of variables among LIFE participants in multiple imputed datasets to be similar to those who participated in any wave of ELSA.

ELSA documentation (Ward et al. 2009) lists the characteristics of individuals who participated in at least one wave of ELSA but did not participate in LIFE. Non-participants are more likely than LIFE participants to live in an area of multiple deprivation, have low levels

of qualifications and be renting or paying a mortgage as opposed to owning their home outright. These characteristics suggest that compared to LIFE participants, non-participants are likely to have been exposed to more adversities during their lives. Thus, the additional bias in the LIFE sample (over and above the sample bias in ELSA) would tend to reduce mean levels of adversity. This is addressed by multiple imputation, as evidenced by mean levels of adversity being consistently higher in the imputed datasets than in the observed sample. This lends confidence to the validity of the datasets with imputed values.

To the extent that sampling bias remains after multiple imputation, it probably serves to reduce the variation in adversity because those exposed to high levels of adversity were less likely to participate. This would result in under-estimations of associations between adversity and other variables, including RA onset, which means that we can be more confident about the associations found.

On the other hand, because this is an ageing sample it is subject to survival bias. Lifetime prevalence rates are highest for the cohort born before 1921, which probably reflects survival bias as respondents with other health conditions die or fail to participate. To the extent that non-participation occurs not due to mortality but for age -related reasons, RA rates among older ELSA respondents will be higher than they are in the population. This would lend power to the analyses but would mean that associations found in the sample might not be found in a more representative sample of the population.

4. Low numbers reported RA, multiple testing and new findings

A further limitation is that numbers reporting RA are not high. RA is not common and so numbers are likely to be low in most population surveys, which is probably partly why so

little evidence exists about its social determinants. By using a large study of ageing adults combined with multiple imputation, it has been possible to provide relatively robust evidence. Findings that are statistically significant despite a lack of power indicate strong associations, but some trends are not statistically significant. Furthermore, numerous associations were tested and some may be statistically significant by chance, and many findings were new and so were unsupported by similar findings from other studies. While the originality of the evidence is a strength, findings should now be tested using other datasets.

5. Sub-types of RA not examined

As mentioned in the introduction, about 70% of people diagnosed with RA are seropositive. Various authors suggest that the factors that predict seropositive RA and seronegative RA differ (Huyser & Parker 1998). It has not been possible to investigate this possibility, as no information was available in the ELSA dataset about the presence or otherwise of serum rheumatoid factor.

5.3 Main conclusions and their implications

This chapter provides new evidence consistent with the importance of psychosocial pathways in the development of RA. After adjustment for a wide range of material adversities, social adversities predicted RA onset and this association was not mediated by smoking. Additional analyses indicate that family-related and traumatic social adversities predicted RA onset after mutual adjustment and adjustment for material adversities. Further, chronic as opposed to acute social adversities predicted RA onset, which is consistent with physiological evidence about the effects of stress on immune dysregulation.

In addition, new evidence suggests that adversities (material and social) combine cumulatively over the life-course to predict RA onset. Evidence that adversities predict RA onset is stronger than in previous studies, probably reflecting the scope of the data and measures used.

These findings have implications for policy makers, clinicians, and researchers.

Policy makers should focus on limiting exposure to social adversities likely to cause chronic and/or intense stress, especially relating to relationships and trauma, during all life stages and on providing support to those individuals who are nevertheless exposed. For example, additional support could be extended towards individuals who care for older relatives, and the parents and partners of those who are addicted to alcohol or drugs. In relation to material pathways, the evidence presented here highlights findings from other studies that exposure to airborne pollutants contribute to RA onset. Policy makers should seek ways to reduce such exposures.

The findings have clinical relevance because better understanding of environmental factors that predict RA onset will help doctors to diagnose and treat the condition sooner. This is important because progression of RA causes irreversible damage, which can be prevented by therapeutic interventions.

The findings provide insights for future research into the social epidemiology of RA and of other systemic immune-mediated conditions. In particular, it may be fruitful to examine the relative importance of chronic and acute stress, which has been measured here using different types of adversity. Further research is needed not only to test the reliability of findings presented here, but also to examine in more detail the aspects of adversities (e.g.

chronicity and timing) that are associated with the dysregulations of immune function found in RA and other immune-mediated conditions.

Chapter 4: Prospective associations between low-grade inflammation and depressive symptoms, and the factors that moderate and mediate them

1. Introduction

Scientific interest in relationships between immune activity and psychological symptoms has developed recently and is reflected in the emergence of a discipline called psychoneuroimmunology (Ader 2000). Physiological evidence indicates links between immune function and psychological symptoms, which can inform studies in social epidemiology. This area of social epidemiology is relatively new and under-researched, partly because the physiological evidence is relatively new and partly because immune function is difficult to measure without the use of biomarkers, and these have only been introduced in surveys in the last few years. This chapter provides prospective epidemiological evidence about relationships between chronic low-grade inflammation and depressive symptoms.

This section introduces the rationale for this chapter, describes inflammation and summarises evidence about relationships between inflammation and depressive symptoms. It discusses pathways that might explain the association, and whether these vary by gender, age category and health status. Health status includes specific health conditions; rheumatoid arthritis (RA) and asthma, as these conditions are driven by immune dysregulation and were the subjects of earlier chapters. Research questions are presented at the end of the section.

1.1 Rationale

There is a growing literature about the biological pathways that link inflammation with depressive symptoms. Epidemiological evidence indicates that inflammation is associated with depressive symptoms, but large-scale prospective evidence is limited and results are not entirely consistent.

Evidence about prospective relationships between inflammation and depressive symptoms and the factors that mediate them is important because it may inform earlier diagnosis and treatment of both depression and disorders involving high levels of inflammation.

This information can be used to inform the design and targeting of interventions that protect individuals from developing depressive symptoms as a consequence of inflammation, and inflammation as a consequence of depressive symptoms. A meta-analysis of evidence concerning prospective associations between inflammation and depression concludes that it is,

> "imperative that prospective studies of both community-based and clinical samples be undertaken to test the directionality of the relationship between depression and inflammation and to further elucidate mediating and confounding factors. Such knowledge will help inform interventions to increase the quality of life in patients with pathological inflammatory conditions […] and to decrease the risk of such diseases in individuals who are otherwise healthy but suffer from depression" (Howren et al. 2009:182).

1.2 Inflammation

Injury and infections provoke an acute inflammatory response, in which levels of inflammation increase enormously and then return to baseline levels once the trigger is controlled or eliminated. Immune-mediated diseases such as RA and asthma develop when acute inflammation does not resolve and chronic high-grade inflammation develops (Calder et al. 2013). However, in individuals free of these diseases, full resolution occurs and inflammation levels return to baseline.

Baseline levels of inflammation vary between individuals and under different conditions. For example, an elevated baseline level of inflammation, referred to as chronic low-grade inflammation, can develop in obesity and with age (Calder et al. 2013). It predicts cardiovascular disease, type II diabetes and mortality (Maes et al. 2011, Liu et al. 2016, Padayachee et al. 2009, Zhang 2011).

Symptoms of acute inflammation include redness, swelling, heat and pain (Calder et al. 2013). Acute inflammation is also accompanied by sickness behaviours, such as fatigue, social withdrawal, negative mood, loss of appetite and sleep disturbance, as well as increased arousal and anxiety (Miller & Raison 2016, Dantzer & Kelly 2007).

CRP is routinely used in clinical settings to measure inflammation. In healthy individuals, the median plasma concentration is 0.8mg/litre, but levels rise by up to 1,000-fold in response to injury or infection (Slaats et al. 2016, Kushner 1982). It has the practical advantages of a long half-life, meaning that it is relatively stable in blood samples (Pearson et al. 2003), little diurnal variation (Dominguez-Rodriguez et al. 2009), and insensitivity to factors that affect plasma levels of many other biomarkers of inflammation, such as feeding state, physical

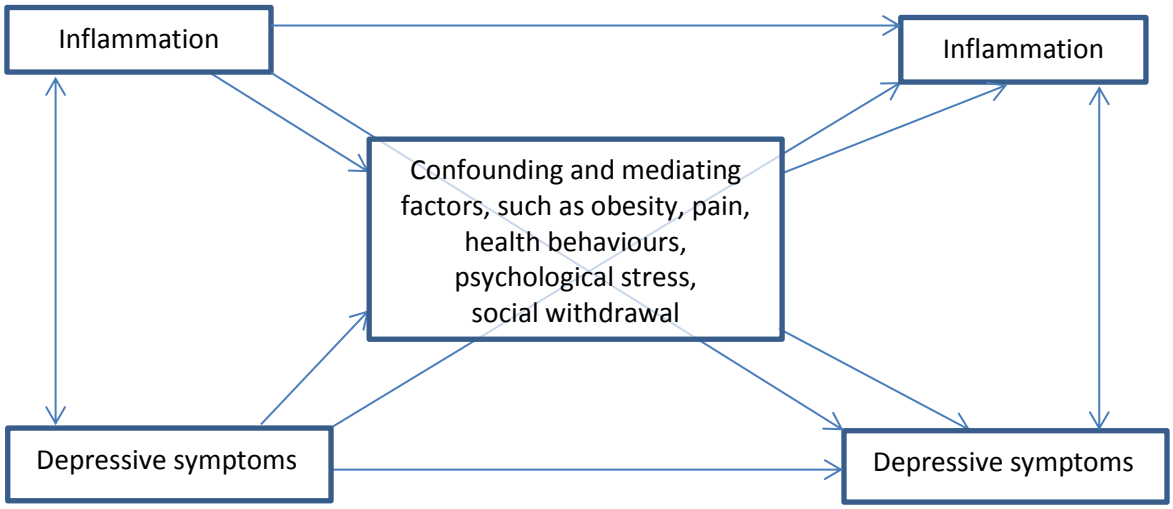
activity and acute psychological stress. Consequently, CRP is a highly sensitive and accurate marker of inflammation.

1.3 Relationships between inflammation and depressive symptoms

Associations between inflammation and depression were first reported in small-scale clinical studies (Maes et al. 1993a, Maes et al. 1993b). Subsequent large-scale studies and meta-analyses provide convincing evidence of small associations between many inflammatory markers and both clinical depression (Jiang et al. 2014, Hiles et al. 2012, Dowlati et al. 2010) and symptoms of depression (Howren et al. 2009). Relationships with depressive symptoms appear to be dose-dependent (Howren et al. 2009). However, the evidence is not entirely consistent; for example, a recent large-scale study in Brazil found no evidence of a cross-sectional association between clinical depression and chronic low-grade inflammation after adjustment for lifestyle and co-morbidities, as well as medication use and socio-demographic variables (de Menezes et al. 2017).

Cross-sectional associations between inflammation and depressive symptoms could reflect various underlying pathways, which are set out in Figure 4.1. This illustrates auto-correlations over time for both inflammation and depressive symptoms, cross-sectional and prospective correlations between inflammation and depressive symptoms, and prospective associations that are mediated and/or confounded by additional factors. These relationships may differ by moderating factors such as gender, age, SEP and health status.

Figure 4.1: Model of relationships between depressive symptoms and inflammation



All relationships may differ by moderating factors, such as gender, age, SEP and health status

1.4 Direct effects of inflammation on depression: The inflammatory theory of depression

The inflammatory theory of depression (Smith 1991, Miller & Raison 2016) is described in Chapter 1. In brief, the theory proposes that sickness behaviours associated with inflammation – fatigue, social withdrawal, negative mood, loss of appetite and sleep disturbance, increased arousal and anxiety – correspond with, and also contribute to the development of, various psychiatric disorders, including schizophrenia, anxiety and depression.

As mentioned in Chapter 1, understanding is developing about the physiological mechanisms that link inflammatory processes with psychological changes that characterise sickness behaviours (Byrne et al. 2016, Miller & Raison 2016). It is likely that psychological stress interacts with these mechanisms as activation of the HPA axis, which is central to the physiological stress response, is one of the mechanisms involved (Jiang et al. 2014, Makhija & Karunakaran 2013, Capuron & Miller 2011). Further, clinical and animal studies report evidence consistent with the theory. These studies involve administration of pro-

inflammatory cytokines, which have been found to induce depressive symptoms in humans and depressive-like behaviours in animals (Byrne et al. 2016, Dantzer & Kelly 2007).

In addition, some studies report that anti-inflammatory drugs reduce depressive symptoms (Kohler et al. 2014, Kohler et al. 2016). These findings have received particular attention because they raise questions about whether anti-inflammatories could be used to treat some forms of depression (Miller & Raison 2016), especially those that are resistant to conventional anti-depressants (Strawbridge et al. 2015, Hughes & Kumari 2017). However, the evidence is not consistent, probably reflecting small effect sizes if they exist and differences in methodologies and sample characteristics (Eyre et al. 2015).

As mentioned above, most epidemiological studies using cross-sectional data report that inflammatory biomarkers are raised among individuals with depression and depressive symptoms. Fewer epidemiological studies use longitudinal data and so conclusions about prospective associations between inflammation and subsequent depression or depressive symptoms remain tentative.

Various issues may contribute to differences in findings between epidemiological and clinical or animal studies. One issue, discussed by Dantzer et al. (2011) is that depression is defined and diagnosed by symptoms and probably encompasses a range of disorders with multiple causes. They refer to “inflammation-associated depression” as one type of depression that is characterised by elevated plasma levels of pro-inflammatory cytokines, and which may be more responsive to anti-inflammatories. This type of depression may be identified in clinical and laboratory studies, but in drug tests and epidemiological studies, it is not distinguished from other forms of depression that are not affected by inflammation.

In addition, laboratory and clinical studies involve the acute inflammatory response, while drug treatments are given to patients who mostly have lower levels of inflammation, and epidemiological studies measure chronic low-grade inflammation. In illustration, epidemiological studies using CRP levels to indicate chronic inflammation often exclude measures over 10mg/litre and use a cut-point indicating chronic inflammation of 3mg/litre. In contrast, during acute inflammation, CRP levels can reach 800mg/litre (Slaats et al. 2016). It is in relation to low-grade inflammation that the evidence is less consistent. Magnitudes of associations between chronic low-grade inflammation and depressive symptoms may be very small, if they exist at all, and consequently difficult to identify.

More fundamentally, it is not necessarily the case that chronic low-grade inflammation has the same psychological correlates (albeit scaled-down) as an acute inflammatory response.

Further, the timing of any relationship with depressive symptoms may differ depending upon whether an acute inflammatory response or chronic low-grade inflammation is measured. As explained in chapter 1, Dantzer et al. (2011) suggest that whilst sickness behaviours occur at the same time as the acute inflammatory response, depressive symptoms develop over time in response to the sickness behaviours. Little is known about the relative timings of any relationships between chronic low-grade inflammation, sickness behaviours, and the development of depressive symptoms, and so it is unclear what follow-up times are appropriate for testing any prospective association. Follow-up times vary widely between epidemiological studies, but tend to be measured in years.

1.5 Direct effects of depressive symptoms on inflammation

Depression may affect inflammation via pathways similar to those associated with the stress response, involving HPA axis hyperactivity, glucocorticoid resistance and dysfunction of the

autonomic nervous system (Martinac et al. 2014, Penninx et al. 2013, Kop & Gottdiener 2005).

It is more difficult to test direct effects of depressive symptoms on inflammation than vice versa because whilst inflammation can be induced artificially, depressive symptoms cannot. However, two studies found that people with more depressive symptoms had greater and more prolonged inflammatory responses to influenza vaccinations than people with fewer depressive symptoms (Glaser et al. 2003, Christian et al. 2010). Also, inflammation following birth appears to be greater among mothers with a history of major depression (Maes et al. 2001).

In contrast, evidence about the efficacy of anti-depressants on inflammation is inconsistent (Alexopoulos & Morimoto 2011, Hamer et al. 2011), and so is evidence from epidemiological studies using longitudinal data.

1.6 Epidemiological evidence about prospective associations between inflammation and depressive symptoms

1.6.1 Evidence of prospective associations

A systematic review and meta-analyses of evidence about associations between inflammatory biomarkers and subsequent depressive symptoms concluded that there is a small but statistically significant association, which is robust to adjustment for a wide range of factors, although evidence of publication bias cast doubt on this conclusion (Valkanova et al. 2013). Three subsequent large-scale studies similarly report prospective associations that are robust to age, gender, and other sociodemographic variables (Das 2016, Au et al. 2015, Chocano-Bedoya et al. 2014). Das and Au report prospective associations with depressive symptoms that were robust to inclusion of additional covariates; health-related behaviours,

metabolic factors, health conditions and medication use. The third study (Chocano-Bedoya) finds no evidence of an association when additional factors were included, possibly because the number of covariates included was higher than in the other studies, the sample consisted of women only, and the outcome was incident depression as opposed to depressive symptoms. A fourth study (Baune et al. 2012) reports no evidence of a prospective association between CRP and depressive symptoms two years later. This may reflect lack of power, as the sample is relatively small (about 700), and results are only presented for models that adjust for all covariates.

Evidence about the prospective association between depressive symptoms and subsequent inflammation is less consistent. Several epidemiological studies report no evidence that depressive symptoms predict CRP (Das 2016, Au et al. 2015, Gimeno et al. 2009). In contrast, Stewart et al. (2009) found a prospective association with a biomarker of inflammation called IL-6, and Matthews et al. (2010) report an association with CRP that was marginally non-significant after adjustment for covariates (baseline CRP, race, education, medication use, and health behaviours, p=0.10). It appears that cumulative episodes of depression predict subsequent CRP (Copeland et al. 2012, Duivis et al. 2011, Hamer et al. 2009, Deverts et al. 2010), whilst acute fluctuations in depressive symptoms predict IL-6 (Rohleder & Miller 2008).

The lack of strong epidemiological evidence about prospective associations in both directions probably reflects associations of very small magnitude if they exist at all. Furthermore, levels of inflammation and depressive symptoms change together over time and unless they are measured on multiple occasions, it is problematic to draw firm conclusions about whether inflammation precedes depressive symptoms or vice versa. Because biomarkers of inflammation have only recently been included in large-scale

longitudinal surveys, most epidemiological evidence relies on data about inflammation measured on just two occasions.

Inconsistent epidemiological evidence may result from differences between studies in biomarkers used to measure inflammation, and in measures of depressive symptoms. Various instruments are used to measure depressive symptoms and to identify incident depression, including instruments such as the GHQ, which is designed to measure wellbeing, not depressive symptoms. Studies also vary in terms of sample size, sample characteristics, time to follow-up, and which covariates are included (Das 2016, Engler et al. 2016).

The research presented here provides valuable epidemiological evidence about prospective associations between inflammation and depressive symptoms, especially because it uses large-scale data in which inflammation is measured on three occasions. It also provides new evidence about the factors that might confound or mediate these associations.

1.6.2 Evidence of confounders and mediators

Confounders and mediators predict both inflammation and depressive symptoms. Confounders occur earlier in causal pathways than either inflammation or depressive symptoms, and mediators occur after either inflammation or depressive symptoms but earlier than the predicted outcome. If a variable confounds or mediates an association between inflammation and depression, then adjustment for this variable will change (usually reduce) the magnitude and consistency of the association.

It is likely that factors mediate associations between inflammation and depressive symptoms found in prospective epidemiological studies because follow-up times are

typically measured in years. During these periods, respondents are exposed to circumstances and events and engage in activities that could affect predicted outcomes.

Confounders, mediators and moderators (discussed in 1.6.3) are conceptually distinct but some factors occupy more than one role. For example, obesity is classified here as a possible mediator, but it could also be classified as a confounder. SEP is classified as a possible confounder, but could also be a moderator.

Little evidence exists about the factors that confound, mediate and moderate prospective associations between inflammation and depressive symptoms, although studies include similar co-variates. The factors I consider as possible confounders, mediators and moderators draw on these studies. I also include factors that are linked to sickness behaviours as these may mediate associations between inflammation and subsequent depressive symptoms, and health behaviours as these may mediate associations between depressive symptoms and subsequent inflammation.

I classify SEP, personality traits, childhood adversity, functional limitations and medications as possible confounders. Factors classified as possible mediators include psychological stress and social withdrawal (because each is likely to be associated with sickness behaviours), health behaviours, pain, obesity and other metabolic biomarkers. Psychological stress is classified as both a confounder and a mediator.

SEP is likely to confound the association between inflammation and depressive symptoms because it predicts not only inflammation and depressive symptoms, but also the factors that may confound or mediate the association.

Friedman (2008) suggests that personality could be associated with a range of health outcomes, including depressive symptoms and inflammation. He describes two mechanisms through which personality could affect health. One is that personality affects responses to stressful exposures, and the other is that genetic factors and very early experiences shape personality and affect health outcomes in ways that are systematically related.

There is some evidence that baseline levels of CRP are associated with personality traits, for example, high harm avoidance and low self-directedness predict high levels of CRP (Henningsson et al. 2008). Conscientiousness (one of the Big Five) predicts positive health behaviours (Bogg & Roberts 2004), low risk of chronic illness (Goodwin & Friedman 2006), and longevity (Friedman 2008), and it is possible that it predicts low inflammation also. In addition, certain aspects of personality predict depressive symptoms. Internalising behaviours during childhood predict depressive symptoms (Toumbourou et al. 2011, Dingle et al. 2011), and neurotic personality trait, another of the Big Five, is thought to involve depression (Friedman 2008).

Childhood adversity predicts a wide range of negative outcomes (Felitti et al. 1998) that include in adulthood both depressive symptoms (Nelson et al. 2017, Li et al. 2016) and chronic inflammation (Berk et al. 2013, Fagundes et al. 2013, Hansal et al. 2010, Taylor et al. 2006). A small-scale study of cancer patients reports a prospective association between CRP and depressive symptoms 6 and 12 weeks later that is no longer statistically significant after adjustment for childhood trauma (Archer et al. 2012).

Functional limitations are associated with both higher levels of inflammation (Brinkley et al. 2009) and depressive symptoms (Redmond & Barrett 2015). Van den Biggelaar et al. (2007) report a prospective association between baseline CRP levels and depressive symptoms over

5 years that was robust to adjustment for numerous covariates, including functional limitations.

As mentioned above, there is some evidence that anti-inflammatory medications reduce depressive symptoms and that anti-depressants reduce inflammation, although reviews and meta-analyses conclude that the evidence is inconsistent (Eyre et al. 2015, Alexopoulos & Morimoto 2011). Most prospective studies adjust for medication use if information is available, but just one study examines attenuation by medication alone. Gimeno et al. (2009) compared associations between CRP and depressive symptoms almost 12 years later adjusting for age, gender, and ethnicity, and for these covariates plus medication use, and the magnitude and consistency of the association barely changed.

Stress may lead to chronic inflammation through the development of glucocorticoid resistance. In line with this hypothesis, reviews of studies examining work, unemployment, caregiving, interpersonal stress and loneliness conclude that chronic psychological stress predicts CRP levels (Johnson et al. 2013, Hansel et al. 2010). In relation to acute stress, a review and meta-analysis of 30 studies found that acute stress was followed by increased levels of inflammation measured using plasma cytokines (IL-1 and IL-6), although the evidence was marginal in relation to CRP (Steptoe et al. 2007). Berk et al. (2013) examined the causes of chronic inflammation, and identified psychosocial stress, which involves psychological responses to social exposures, as a robust predictor.

Psychological stress may also mediate associations between inflammation and depressive symptoms. Gutman and Nemeroff (2011) state that “no experienced practitioner would doubt the fact that stress and depression are inexorably linked” (p.345). Studies report that depression and depressive symptoms are predicted by stressful life events (Hammen 2005,

Leggett et al. 2016) and that bi-directional relationships exist between depressive symptoms and relationship stress (Whisman & Ubelacker 2009). Depressive symptoms may affect exposure to stressors, their appraisal, coping responses and inflammatory responses. Kiecolt-Glaser et al. (2015) draw on a range of studies to argue that people with a history of depression report a relatively high number of stressors but have fewer resources to cope effectively with them because they have fewer close family relationships.

Sickness behaviours associated with inflammation include increased arousal, anxiety and negative mood, which are likely to affect appraisals of adversities such that they are perceived as more stressful. Consistent with this argument, Das (2016) reports that low-grade inflammation measured using CRP predicted perceived stress five years later, although the association was only statistically significant among women.

Social withdrawal is a sickness behaviour associated with inflammation. It is a feature of both inflammation and depressive symptoms (Dantzer et al. 2008). It also relates to stress as social withdrawal leads to isolation and this contributes to psychological stress (Cruces et al. 2014).

Pain is associated with both inflammation and depressive symptoms (Kiecolt-Glaser et al. 2015). Pain and depressive symptoms are highly correlated and relationships between them appear to be bi-directional (Zis et al. 2017). Recent evidence and reviews suggest that pain and depression share numerous neurobiological mechanisms, including neuro-inflammation (Sheng et al. 2017, Zis et al. 2017). The increased arousal associated with the inflammatory response could heighten sensitivity to pain. Pain also appears to provoke an inflammatory response (Griffis et al. 2013). I am not aware that any epidemiological studies of associations between inflammation and depressive symptoms include pain as a covariate.

Zis et al. (2017) classify sub-types of pain due to seven causes among elderly people. One sub-type is chronic primary pain syndrome, which has no known cause and is typically experienced as lower back pain. It is possible that relationships between depressive symptoms, inflammation and pain differ between this type of pain and other sub-types. Zis et al. (2017) report that evidence about chronic pain subtypes and co-morbid depression is lacking.

Health behaviours that may confound or mediate associations between inflammation and depressive symptoms include smoking, drinking patterns and physical inactivity. Most studies of the association between inflammation and depressive symptoms adjust for health behaviours, but few estimate how much they attenuate the association. Gimeno et al. (2009) report negligible attenuation of the prospective association between CRP and depressive symptoms (already adjusted for age, gender, and ethnicity) by diet, exercise, smoking and alcohol consumption, combined.

Reviews report associations between smoking and depression, probably reflecting effects of depression on smoking behaviours (Mathew et al. 2017), and strong evidence that current and past smoking are associated with low-grade chronic inflammation (Berk et al. 2013, Calder et al. 2013, O'Connor et al. 2009). More specifically, smoking has been reported to attenuate associations between cumulative depressive episodes and recurrent depressive symptoms and subsequent elevations in CRP (Copeland et al. 2012, Hamer et al. 2009).

The link between alcoholism and depression is well established (Boden & Fergusson 2011), and inflammatory markers are raised among heavy drinkers and abstainers compared against moderate drinkers (O'Connor et al. 2009). Hamer et al. (2009) report that alcohol use mediated an association between recurrent depressive symptoms and CRP.

Relationships between physical inactivity and depressive symptoms appear to be bi-directional (Mammen & Faulkner 2013, Pereira et al. 2014). Studies suggest that exercise has anti-inflammatory effects (Gleeson et al. 2011) and sedentary behaviour predicts inflammation (Berk et al. 2013). This may be because people who are physically inactive are more likely to be obese, and obesity is the salient predictor of inflammation. Mixed evidence about the positive impacts on chronic inflammation of exercise programmes is consistent with this explanation (Calder et al. 2013). However, a large-scale study using ELSA data that included both physical inactivity and obesity found that the prospective association between recurrent depressive symptoms and elevated CRP (the outcome) was mediated independently by each factor (Hamer et al. 2009).

Obesity is associated with both depression (Daly 2013, Capuron et al. 2017, de Wit et al. 2010, Luppino et al. 2010) and inflammation (Daly 2013, Castanon et al. 2014, Calder et al. 2013). Some studies report that the inflammation-depression association is attenuated by body mass index (Howren et al. 2009, Copeland et al. 2012) and weight gain (Hamer et al. 2009).

Metabolic dysregulation appears to be associated with both inflammation (Yudkin et al. 2000, Brunner et al. 2002, Tamakoshi et al. 2003, Au & Schmitz 2013) and depressive symptoms (Penninx et al. 2013). Tully et al. (2013) found that metabolic markers and obesity each moderated associations between CRP and depressive symptoms; associations were statistically significant only among those not overweight and without metabolic symptoms. However, Gimeno et al. (2009) do not report attenuation of the CRP-depressive symptoms association by metabolic biomarkers.

1.6.3 Evidence about Moderators

A factor moderates an association if the association differs depending on the value of the moderator. For example, if the association between inflammation and subsequent depressive symptoms is stronger for men than women, then gender moderates the association. Gender, age and chronic illness are classified as potential moderators, although they may also confound associations between inflammation and depressive symptoms.

In their review, Howren and colleagues (2009) report that there is little evidence about gender differences in associations between inflammation and depressive symptoms. However, associations appear stronger among men than women and associations between inflammation and depression is stronger among samples with a higher proportion of men. Evidence published after Howren's review found prospective associations between CRP and depression (incident and depressive symptoms) among men but not women (Luukinen 2010, Vetter et al. 2013, Das et al. 2016). Gimeno et al. (2009) found prospective associations between CRP and depressive symptoms that were of greater magnitude among men than women.

In contrast, Derry et al. (2015) argue that women have greater inflammatory responses than men to childhood adversity, interpersonal difficulties, obesity and physical inactivity. They further argue that among women, inflammation more strongly predicts perceived loneliness, which contributes to onset of depression. These arguments suggest that stronger associations between inflammation and depressive symptoms exist among women than men.

It is likely that relationships between inflammation and depressive symptoms differ between elderly and younger populations. Alexopoulos & Morimoto (2011) review evidence

about inflammation and depressive symptoms among older adults and suggest that some of the biological processes involved apply to older but not younger populations.

One of the differences between older and younger populations is the prevalence of chronic illness. Stewart et al. (2009) suggest that samples of healthy respondents manifest little variation in inflammation or depressive symptoms, and that effects may be more easily identified among samples with relatively poor health. Their own empirical study of 263 respondents with mean age of 61 found no evidence of a prospective association between inflammation and subsequent depressive symptoms. The authors cite a study using a sample size similar to theirs (267) but of adults aged 85-90, most of whom had chronic health conditions, which reports evidence of prospective associations (Van den Biggelaar 2007).

More specifically, relationships between inflammation and depressive symptoms may be different in populations with immune-mediated diseases, that is, diseases characterised by chronic high-grade inflammation resulting from poor resolution of the acute inflammatory response (Calder et al. 2013). These are distinct from diseases that are characterised by low-grade inflammation, which may be a consequence rather than a cause of the disease. Two relatively common immune-mediated diseases are asthma and rheumatoid arthritis (RA).

Both inflammation and depressive symptoms are relatively high in populations with asthma and RA. Asthma is characterised by high levels of inflammation (Arif et al. 2007) and depressive symptoms (Frieri et al. 2015, Jiang et al. 2014). RA is similarly characterised by high levels of inflammation (Pincus & Tuulikki 2009, Dessein et al. 2004) and depressive symptoms (Odegard et al. 2007).

Few epidemiological studies have examined associations between inflammation and depressive symptoms in populations with immune-mediated conditions. However, biological evidence suggest that comorbidity of depression and asthma may result directly from immune dysregulation; IL-4 is raised in depression and may contribute to allergic responses, such as those that characterise asthma (Jiang et al. 2014). RA is characterised by elevated levels of pro-inflammatory cytokines IL-1, IL-6, TNF-α, and IFN-Ɣ, which in turn are linked to the development of major depressive disorder (Malemud & Miller, 2008). Studies have found that among populations with RA, there is an association between IL-6 and depression (Zautra et al., 2004), and between CRP (levels are regulated by the cytokines mentioned above) and depressive symptoms (Dessein et al. 2004, Odegard et al. 2007, Low et al. 2009, Kojima et al. 2009). The last two studies (Low, Kojima) report attenuation of the CRP-depressive symptoms association by pain and functional limitations among populations with RA.

Asthma and RA are also associated with some of the mediators and confounders listed above. For example, both conditions are exacerbated by stress (RA: de Brouwer et al. 2010, asthma: Chida et al. 2008). RA is painful (Watkins & Maier 2000, Odegard et al. 2007), and among adults with RA, depression predicts pain and functional limitations (Katz & Yelin 1993). In the reverse direction, among adults with RA, functional limitations predict depressive symptoms (Odegard et al. 2007).

1.7 Research Questions

More epidemiological evidence is needed to address the research topic addressed in this chapter. Physiological investigations and clinical and animal studies provide fairly consistent evidence about links between inflammation and depressive symptoms. Epidemiological evidence is needed to understand these links in real-life social and economic contexts. The

RQs ask about prospective relationships between inflammation and depressive symptoms because existing evidence is sparce and not all results are consistent. In addition, new RQs are asked about factors that mediate, confound and moderate associations found. These RQs are open and exploratory, although the ways in which they are addressed and interpretations of findings are informed by existing evidence and theory.

1. What are the prospective relationships between inflammation and depressive symptoms?
    a. Does inflammation at time t-1 predict depressive symptoms at time t?
    b. Do depressive symptoms at time t-1 predict inflammation at time t?
2. Which factors confound and mediate prospective associations between inflammation and depressive symptoms?
3. How do the answers to the first two RQs differ:
    a. By gender?
    b. By age group?
    c. For populations with a longstanding illness?
    d. For populations with asthma, and RA?

2. Methods

2.1 Data

Information about the sample is taken from the ELSA user guide waves 1-6, and the ELSA nurse user guide waves 2, 4 and 6, which were downloaded from the UK Data Service website in 2017.

The sample consists of core members and their cohabiting partners. Original core members participated in the Health Survey for England (HSE) in 1998, 1999, or 2001 (ELSA wave 0) and in ELSA wave 1, which took place between 2002 and 2003. They were all aged 50 or over at the time of wave 1 data collection. Refreshment samples of new core members were

added in waves 3, 4, and 6 to maintain numbers and the age distribution as the original core members aged. Core members exit from ELSA when they die, move away from mainland Britain, or do not participate for any other reason. Core members who move into institutions are still eligible for interviews.

During alternate waves of data collection, nurse interviews were conducted with core sample members who had had an interview in person (i.e. not by proxy) during the same wave. In addition, partners of core members participating in nurse interviews were given a nurse interview if they requested one.

Nurse interviews took place in respondents' homes and comprised a face-to-face computer-assisted interview and the collection of biological measurements and samples. With respondents' consent, if any results were outside the healthy range, letters were sent to respondents and their GPs. All nurse interview participants were eligible to have a blood sample taken, except for those with bleeding or clotting disorders, taking anti-coagulant medications and with a history of convulsions. Blood samples were analysed in external laboratories.

Wave 3 included an additional interview in which retrospective life history data were collected using a temporal referencing system or life-grid approach to help full and accurate recall (Berney & Blane 1997; Means et al. 1991).

Dates of data collection and numbers participating are presented in Table 4.1. Nurse interviews were conducted about one month after main interviews. Additional information about the dataset is provided in Appendix 20.

Information from all waves was used to code variables.

Table 4.1: Waves of data collection in ELSA

Wave	Years	Number of observations
0	1998, 1999, 2001	19,834 with common variables
1	2002-2003	12,099
2	2004-2005	9,432
2 nurse	2004-2005	7,666
3	2006-2007	9,771
3 LIFE	2006-2007	7,833
4	2008-2009	11,050
4 nurse	2008-2009	8,643
5	2010-2011	10,274
6	2012-2013	10,601
6 nurse	2012-2013	8,054

Wave 0 numbers obtained from UK Data Archive (2017) ELSA User Guide for Wave 0

2.2 Measures

Time differences in months between the main and nurse interviews in waves 2, 4 and 6 were calculated.

2.2.1 Inflammation and depressive symptoms

Inflammation was measured using CRP obtained from blood samples taken during the nurse interviews. All blood samples were sent for analysis to the Royal Victoria Infirmary in Newcastle-upon-Tyne. CRP was analysed using the Behring Nephelometer during waves 2 and 4, and the Roche Modular system during wave 6. As in other studies (Copeland et al. 2012), observations with values of CRP over 10mg/litre were excluded, as high levels of CRP indicate an acute inflammatory response. Because the distribution of CRP values is skewed, values were logged.

Depressive symptoms were measured during the main interviews using the 8 item CESD. The items are set out in Appendix 20 Table A20.1. This version of the CESD is shorter than the original, its internal consistency and factor structure are similar to those of earlier versions and it predicts clinical outcomes (Turvey et al. 1999). It is used in the Health

Retirement Survey (Steffick 2000). Depressive symptoms were measured rather than incident depression because the association between CRP and depressive symptoms appears to be dose-dependent (Howren et al. 2009). A second measure was constructed for use in sensitivity analyses that had three values; no, one and two or more depressive symptoms.

2.2.2 Hypothesised confounders

Hypothesised confounders are SEP, personality traits, childhood adversity, functional limitations and medication use. To facilitate comparisons, these measures and measures of hypothesised mediators were scaled to have values between zero and one.

2.2.2.1 Hypothesised confounder: SEP

SEP was measured using three variables; childhood SEP, education and accumulated wealth. Childhood SEP was measured by the occupational status of the respondent's main carer at age 14; professional or managerial, skilled, semi-skilled, routine or manual, and casual or unemployed. Respondents living with an un-partnered mother at age 14 were particularly likely to report their main carer's occupation as casual or unemployed. In other studies, measures of childhood SEP are supplemented by maternal education, but this information is not available in ELSA.

Education was measured by an indicator of whether the respondent had qualifications at Level 2 or above; Level 2 indicates one GCE 'O' level pass or NVQ2. Accumulated wealth was assumed to summarise lifetime SEP, and was measured by total assets reported. Values were divided into terciles, and reverse coded to give a value of low wealth. All available information was used to create variables for education and low wealth, using information as

close as possible to 2004 (wave 2), as explained in Appendix 1. All three SEP variables are time-invariant.

2.2.2.2 Hypothesised confounder: Stable psychological factors

Stable psychological factors are five dimensions of personality, referred to as the Big Five, measured in wave 5. A version of the Midlife Development Inventory was used, in which respondents were asked to rate how well each of 26 adjectives described them. The same instrument was used in the US Health and Retirement Survey (HRS) in 2006 and 2008. Scores were assigned to each dimension of personality based on unpublished guidelines written when the instrument was developed, which are set out on the HRS website (Lachman & Weaver 1997). They have been followed in studies that include measurement of personality using ELSA data (Gale et al. 2015, Gale et al. 2017). The items used and how they were combined are presented in Appendix 1.

2.2.2.3 Hypothesised confounder: Childhood adversity

Childhood adversities were poor housing amenities at age ten and up to age 15, severe financial hardship, parental unemployment for at least six months, early parental loss through divorce, separation, or death, separation from mother for at least six months, frequent parental arguments, parental substance abuse or mental health problems, physical abuse from a parent, sexual abuse or assault, major natural disaster, life threatening illness or injury, severe physical attack, witnessing a death or serious injury and loss of a close relative or friend. Information about these adversities was provided in the life history interview conducted in wave 3 and the questions asked are presented in Appendix 1. A variable was constructed to indicate exposure to zero, one, two, or three or more adversities. This was assigned a value if information was provided about at least 10 of the 14 adversities, and the value was scaled up if information about some items was missing.

2.2.2.4 Hypothesised confounder: Functional limitations

Functional limitations are measured by combining two sets of questions used to ascertain whether respondents need help with activities of daily living or ADLs (dressing, walking across a room, bathing, eating, getting in and out of bed and using the toilet), and with independent activities of daily living or IADLs (using a map, preparing a hot meal, shopping for groceries, making a phone call, taking medications, doing housework and managing money).

2.2.2.5 Hypothesised confounder: Medication use

A time-invariant variable was constructed to indicate between waves 0 and 6 use of medications likely to affect inflammation and/or depressive symptoms. Medications included were those used to treat conditions of the Central Nervous System, coronary heart disease and diabetes, pain killers, non-steroidal anti-inflammatory drugs, corticosteroids, hormone replacement therapy and oral contraceptives, as these are the medications that have been included in similar studies (Gimeno et al. 2009, Matthews et al. 2010). Detailed information collected in wave 0 and the wave 6 nurse interview was combined with less detailed information collected during main interviews in waves 2 to 6. Further details are given in Appendix 20.

2.2.3 Hypothesised mediators

Hypothesised mediators are psychological stress, social withdrawal, pain, health behaviours, obesity and other metabolic biomarkers.

2.2.3.1 Hypothesised mediators: Psychosocial factors that contribute to psychological stress

Because it appears that chronic as opposed to acute psychological stress is an important predictor of negative health outcomes (Cohen et al. 2012, Miller et al. 2014), each indicator

of stress was measured using mean measures over two consecutive waves, if this information was available.

Psychological stress involves psychological responses to exposures that are likely to be stressful. Measures were constructed that captured both perceived psychological stress and exposures that are likely to be stressful.

Measures that primarily capture psychological experiences are financial strain, subjective social status, perceived low control and high demands at home and/or at work, effort:reward imbalance at work, perceived job insecurity, distressing relationships, community stress, loneliness and perceived strain. Measures that mainly encompass stressful exposures are financial limitations, being financially worse off than one's neighbours and friends, getting a partner since the previous wave, losing a partner since the previous wave, and caring for a partner, parent or parent-in-law.

The distinction between measures that capture mainly stressful exposures and psychological stress experiences is illustrated by measures of financial limitations and strain. Financial strain is based on a rating of how well the respondent felt that they were getting along financially, with responses ranging from "managing very well" to "severe financial difficulties". Financial limitations are based on whether the respondent reported that having too little money had prevented them from doing any of a list of specific activities, such as having family and friends round for a drink or meal, and replacing or repairing broken electrical goods. This is closer to an objective measure of financial limitations that respondents were exposed to than the more subjective measure of perceived financial strain. Information about the questions used to elicit information and how items were combined is included in Appendix 20.

Subjective social status, “an individual’s perception of his or her position within the social hierarchy” (Haught et al. 2015:357), was included because it has implications for health (Sapolsky 1982, Singh-Manoux et al. 2003) and has been found to predict health outcomes after adjustment for objective social status (Bradshaw et al. 2017, Han 2014). Two types of measure were used, the first being slightly more subjective than the second. The more subjective rating was based on respondents’ assessments of where they should be positioned on a ladder that represents where people stand in society, with “those who have the most money, most education and best jobs” at the top and the “worst off” at the bottom. The other type used respondents’ ratings of how well off financially they were compared against their friends and neighbours.

Respondents were also asked about levels of control and demands at home. Mean values were calculated to measure self-efficacy and demands.

Work stress was estimated using two measures; effort reward imbalance, and low control at work. Effort reward imbalance is a measure derived from a model of psychosocial conditions at work and occupational stress (Siegrist et al. 2004). Low control is a measure of occupational stress derived from an alternative model that combines low control, high demands and low social support (Karasek & Theorell 1990). These two measures have been used to measure work stress in ELSA (Dragano et al. 2011, Lunau et al. 2013).

Job insecurity was indicated by responses to the item, “My job security is poor”.

Relationship distress was measured using items adapted from an instrument developed to measure marital satisfaction (Schuster et al. 1990). It consists of three items that measure positive interactions, and three that measure negative interactions. Positive and negative

interactions are sometimes measured separately, but here they are combined because all six items have been found to load onto one factor (Whisman & Ubelacker 2009). As other authors have done using this measure in ELSA, negative items were reverse scored and then all items summed to give a single value (Whisman & Ubelacker 2009, Whisman et al. 2010).

The measure of community stress was developed using cognitive piloting techniques, and its validity was tested in a larger study (Stafford et al. 2003). Bell et al. (2014) used the same measure in ELSA, referring to it as a measure of subjective neighbourhood disorder. It consists of nine pairs of opposing statements, and respondents are asked to rate how closely they agree with each. For example, "Most people in this area can be trusted", and, "Most people in this area can't be trusted". Following the process used by Bell and colleagues (2014), negative items were reverse coded, values summed and scores grouped into quintiles.

Loneliness was measured using a three-item version of the Revised UCLA (University of California, Los Angeles) loneliness scale (Hughes et al. 2004), used previously to measure loneliness in ELSA (Shankar et al. 2011).

Perceived strain was measured using one question from the 12 item General Health Questionnaire. Although the item is not designed to be used independently, it asks directly about perceived chronic strain. The wording is:

> "We should like to know how your health has been in general over the past few weeks. Have you recently…
> … felt constantly under strain?
> "Not at all, No more than usual, Rather more than usual, Much more than usual"

Respondents were asked in every wave whether they lived with a partner, and this information was used to identify respondents whose partnership status had changed since the previous wave.

A caring role was indicated if respondents reported caring for their spouse, parent or parent-in-law during the previous week, regardless of whether they lived in the same household.

The measure for social withdrawal combined information provided about social engagement (reading the paper, using the internet or a mobile, hobbies, holidays and day trips), memberships of organisations, and activities such as going to the cinema or theatre and eating out.

Because of results presented below, an index of psychological stress and social withdrawal was constructed that summed perceived financial strain, low subjective social status, low control in general and social withdrawal. Social withdrawal was included in the index as a behavioural correlate of psychological stress, although an additional index was created that excluded it for sensitivity analyses. For both indices, each variable was weighted equally and summed. To maximise the number of participants included in the analyses, this index was assigned a value when information was available for any of the component variables, using mean values in place of the missing values.

2.2.3.2 Hypothesised mediator: Pain

Level of pain was measured using information from two questions. The first asked, “Are you often troubled by pain?” The second, which was only addressed to those reporting pain, asked whether most of the time the pain was mild, moderate, or severe. Two additional

measures of pain indicated whether the respondent reported pain in their back or elsewhere, that is, in their hips, knees, feet or mouth.

2.2.3.3 Hypothesised mediators: Health behaviours

Health behaviours are physical activity, current smoking status and drinking alcohol. Physical activity was measured using questions in which respondents rated how frequently they engaged in activities that involve vigorous, moderate and mild levels of activity. From this information, respondents' activity levels were classified as high, moderate, low and sedentary. Appendix 20 provides more details.

2.2.3.4 Hypothesised mediator: Obesity and metabolic biomarkers

Height, weight, and waist circumference were measured during nurse interviews. Mean values of BMI and waist circumference in waves 2 and 4 were used to create estimates for wave 3, and data from waves 4 and 6 were used to create estimates for wave 5. Obesity is indicated by BMI of 30 or above (NHS 2017). A substantial increase in risk of metabolic complications by waist circumference of 88cms or more for women and 102cms or more for men (WHO 2000, Davillas & Benzeval 2016).

Waist circumference and BMI are highly correlated and so one measure was used in the main analyses. The measure chosen was waist circumference because this measure appears to be more sensitive to socio-economic inequalities (Davillas & Benzeval 2016, Chen & Tunstall-Pedoe 2005) and is a more direct measure of abdominal adiposity, which is associated with inflammation (Castanon et al. 2014). However, BMI is more often used in relation to inflammation and depressive symptoms (Penninx et al. 2013, Chocano-Bedoya et al. 2014, Copland et al. 2012) and was used in sensitivity analyses.

Metabolic biomarkers were HDL cholesterol, triglycerides and glycosylated haemoglobin, each measured from the blood samples, blood pressure and obesity. As mentioned above, the blood samples were analysed at the Royal Victoria Infirmary in Newcastle-upon-Tyne. Cholesterol, HDL, and triglycerides were analysed using the Olympus AU during waves 2 and 4, and the Roche Modular system during wave 6. Glycosylated haemoglobin was analysed using the TOSOH G7 during waves 2 and 4, and the GOSOH G8 during wave 6. Values of glycosylated haemoglobin are provided as percentages in waves 2 and 4, and as concentrations in wave 6. Values in the earlier waves were converted to concentrations using a "master equation" provided by the National Glycohemoglobin Standardization Program NGSP (2017):

> Concentration (mmol/mol) = (Percentage * 2.152) / 0.09148

Nurses measured systolic and diastolic blood pressures three times using an automated machine, and mean values were calculated. Appendix 20 describes the procedure.

2.2.4 Moderators

Gender was measured with a binary variable indicating male or female. Age was measured at each wave and a variable created to indicate respondents aged 70 and over.

Respondents with longstanding illnesses and limiting longstanding illnesses were identified from answers to two questions:

> "Do you have any long-standing illness, disability or infirmity? By long-standing I mean anything that has troubled you over a period of time, or that is likely to affect you over a period of time"

"Does this/do these illness/es or diability/ies limit your acitivities in any way?"

Histories of asthma and RA were reported in each wave of data collection, and all available information was used. Current asthma was also measured, as asthma can have long periods of remission. This was indicated if respondents reported attacks of wheezing or whistling in the previous 12 months, and that their breathing was normal between attacks. This information was only available in waves 1 to 5. The items used are presented in Appendix 20.

3. Analyses

Summary statistics were calculated for variables in each wave and using data pooled across waves. Using the pooled data, summary statistics were calculated for the whole sample and for 4 sub-samples; (1) the sub-sample used to address RQ1, (2) respondents excluded from the sub-sample used to address RQ1, (3) respondents included in random effects (RE) models used to address RQ2, and (4) respondents excluded from RE models used to address RQ2. Logistic regression analyses with REs were used to estimate differences between distributions of variables in sub-samples (1) and (2), and (3) and (4).

Summary statistics were also calculated for the number of months between main and nurse interviews in waves 2, 4, and 6.

RQ1. What are the prospective relationships between inflammation and depressive symptoms?

a. Does inflammation at time t-1 predict depressive symptoms at time t?

b. Do depressive symptoms at time t-1 predict inflammation at time t?

Associations between standardised measures of depressive symptoms and logged CRP were estimated using three waves of data (2, 4 and 6) and RE models.

To address RQ1a, depressive symptoms at time t was regressed onto Ln(CRP) at time t-1 (two waves earlier), with adjustment for depressive symptoms at time t-1 (model 1). To address RQ1b, Ln(CRP) at time t was regressed onto depressive symptoms at time t-1 with adjustment for Ln(CRP) at time t-1 (model 2).

$$Model\ 1:\ D_{it} = \alpha + \beta_1 I_{it-1} + \beta_2 D_{it-1} + \beta_3 G_i + \beta_4 A_{it} + \beta_5 A^2{}_{it} + \beta_6 Q_i + \beta_7 W_i + \beta_8 M_i + \beta_9 LI_{it-1} + U_i + \varepsilon_{it}$$

$$Model\ 2:\ I_{it} = \alpha + \beta_1 D_{it-1} + \beta_2 I_{it-1} + \beta_3 G_i + \beta_4 A_{it} + \beta_5 A^2{}_{it} + \beta_6 Q_i + \beta_7 W_i + \beta_8 M_i + \beta_9 LI_{it-1} + U_i + \varepsilon_{it}$$

I=Ln(CRP), D=depressive symptoms, G=gender, A=age, Q=Level 2 qualifications in wave 2, W=total wealth in wave 2, M=use of medications that could affect depressive symptoms and inflammation between waves 0 and 6, LI=longstanding illness.

The outcome at the previous time-point (lag dependent variable) was included because (1) earlier measures of depressive symptoms and CRP predict later measures of depressive symptoms and CRP, respectively, referred to as auto-correlations, and (2) if depressive symptoms and CRP were correlated previously, then earlier CRP is likely to predict subsequent depressive symptoms simply because of its correlation with depressive symptoms earlier. Including in the model the lag dependent variable means that we can interpret any prospective associations as net of cross-sectional associations at the earlier time-point.

All models were adjusted for gender, age and age squared at time t, use of medications that affect inflammation and/or depressive symptoms at time t, longstanding illness at time t-1, qualifications below Level 2 in 2004, and low accumulated wealth in 2004.

These controls were included because they have been used in previous studies. Childhood SEP was not included because it is highly correlated with the other SEP variables and has more missing values (Table 4.6). Age squared has not been included in previous studies, but was used here because age combined with age squared predicts log(CRP) and depressive symptoms more accurately than age alone. See Appendix 21.

In order to examine moderation by gender, age group and health status (RQ3), the same models were estimated for respondents of each gender, age group and health status. In addition, models estimated using the whole sample and including interaction terms with each moderator; models 3-8. In models that examine moderation by RA or asthma, longstanding illness was replaced by a variable indicating longstanding illness excluding the specific condition, which took a no value if the specific condition was reported.

Moderation by gender

$$Model\ 3:\ D_{it} = \alpha + \beta_1 I_{it-1} + \beta_2 D_{it-1} + \beta_3 G_i + \beta_4 I_{it-1} * G_i + \beta_5 A_{it} + \beta_6 A^2{}_{it} + \beta_7 Q_i + \beta_8 W_i + \beta_9 M_i + \beta_{10} LI_{it-1} + U_i + \varepsilon_{it}$$

$$Model\ 4:\ I_{it} = \alpha + \beta_1 D_{it-1} + \beta_2 I_{it-1} + \beta_3 G_i + \beta_4 D_{it-1} * G_i + \beta_5 A_{it} + \beta_6 A^2{}_{it} + \beta_7 Q_i + \beta_8 W_i + \beta_9 M_i + \beta_{10} LI_{it-1} + U_i + \varepsilon_{it}$$

Moderation by age

$$Model\ 5:\ D_{it} = \alpha + \beta_1 I_{it-1} + \beta_2 D_{it-1} + \beta_3 A70_i + \beta_4 I_{it-1} * A70_i + \beta_5 G_i + \beta_6 A_i + \beta_7 Q_i + \beta_8 W_i + \beta_9 M_i + \beta_{10} LI_{it-1} + U_i + \varepsilon_{it}$$

$$Model\ 6:\ I_{it} = \alpha + \beta_1 D_{it-1} + \beta_2 D_{it-1} + \beta_3 A70_i + \beta_4 D_{it-1} * A70_i + \beta_5 G_i + \beta_6 A_i + \beta_7 Q_i + \beta_8 W_i + \beta_9 M_i + \beta_{10} LI_{it-1} + U_i + \varepsilon_{it}$$

Moderation by health status

$$Model\ 7:\ D_{it} = \alpha + \beta_1 I_{it-1} + \beta_2 D_{it-1} + \beta_3 H_i + \beta_4 I_{it-1} * H_i + \beta_5 G_i + \beta_6 A_i + \beta_7 A^2{}_i + \beta_8 Q_i + \beta_9 W_i + \beta_{10} M_{it-1} + U_i + \varepsilon_{it}$$

$$Model\ 8:\ I_{it} = \alpha + \beta_1 D_{it-1} + \beta_2 I_{it-1} + \beta_3 H_i + \beta_4 D_{it-1} * H_i + \beta_5 G_i + \beta_6 A_i + \beta_7 A^2{}_i + \beta_8 Q_i + \beta_9 W_i + \beta_{10} M_{it-1} + U_i + \varepsilon_{it}$$

I=Ln(CRP), D=depressive symptoms, G=gender, A=age, A70=age 70 or over, Q=Level 2 qualifications in wave 2, W=total wealth in wave 2, M=use of medications that could affect depressive symptoms and inflammation, LI=longstanding illness, H=health status (longstanding illness, asthma, RA).

Sensitivity analyses

Linear regression models assume that the outcome is distributed normally. However, the distribution of depressive symptoms is not normal, with the highest frequency of respondents reporting no depressive symptoms. Other studies have used raw scores of the CESD measure in ELSA for analyses that assume normality (Daly 2013, Hamer et al. 2009, Rafnsson et al. 2017) and I do the same. However, sensitivity analyses were conducted using a measure of depressive symptoms in three categories with ordered probit models.

RQ2. Are prospective associations between inflammation and depressive symptoms confounded or mediated by other factors?

Salient confounders and mediators, referred to as explanatory variables, were selected in two stages. In the first stage, associations were estimated between each explanatory variable and (1) depressive symptoms and (2) Ln(CRP) (models 9 and 10). The second stage was used for all variable found to be associated with both depressive symptoms and Ln(CRP). This compared the extent of attenuation (or magnification) by each variable by examining differences in the inflammation-depressive symptoms association when it is estimated using a baseline model (model 11) and in models that include each explanatory variable in turn (model 12).

RE models were used, and every model was adjusted for gender, age, and age squared. Gender was treated as time-invariant, and age and age squared as time varying. Measures of Ln(CRP) and depressive symptoms were standardised.

Associations between hypothesised explanatory variables and the two outcomes

$$Model\ 9:\ D_{it} = \alpha + \beta_1 V_{it} + \beta_2 G_i + \beta_3 A_{it} + \beta_4 A^2{}_{it} + U_i + \varepsilon_{it}$$

$$Model\ 10:\ I_{it} = \alpha + \beta_1 V_{it} + \beta_2 G_i + \beta_3 A_{it} + \beta_4 A^2{}_{it} + U_i + \varepsilon_{it}$$

Attenuation of the inflammation-depressive symptoms association

$$Model\ 11:\ I_{it} = \alpha + \beta_1 D_{it} + \beta_2 G_i + \beta_3 A_{it} + \beta_4 A^2{}_{it} + U_i + \varepsilon_{it}$$

$$Model\ 12:\ I_{it} = \alpha + \beta_1 D_{it} + \beta_2 V_{it} + \beta_3 G_i + \beta_4 A_{it} + \beta_5 A^2{}_{it} + U_i + \varepsilon_{it}$$

V=hypothesised explanatory variable, I=Ln(CRP), D=depressive symptoms, A=age, G=gender.

Variables were selected as salient confounders or mediators if they predicted both Ln(CRP) and depressive symptoms, and attenuated the baseline association between Ln(CRP) and depressive symptoms so that it changed the magnitude of the association by more than 15%.

To simplify the structural equation model (SEM) described below, the same tests were used to select a single measure of SEP. In addition, an index of psychological stress and social withdrawal was constructed that summed salient psychosocial factors hypothesised to be associated with sickness behaviours.

Pairwise correlations were estimated between all variables included in the SEM to check whether any variables were highly correlated.

SEMs were estimated to examine temporal relationships between inflammation, depressive symptoms, and the most salient confounders and mediators. The specification is set out in

Figure 4.2. It represents a simplified version of reality, due to limitations in the measures available, the number of observations and processing power. This is why more hypothesised confounders and mediators are not included, and why auto-correlations in inflammation and depressive symptoms are not estimated between waves 2 and 6.

The final SEM was built in stages so that changes in relationships could be observed as additional factors were included.

Multiple likelihood with missing values (MLMV) was the estimation method used. It assumes joint normality of all variables in the model, and so age squared was not included. The assumption is violated, and this affects the accuracy of results. However, MLMV has the advantage that it uses all available information, whilst other estimation methods include only respondents for whom complete information is available. In illustration, if a respondent has complete information for all variables except for CRP in wave 2, other methods will drop them altogether, whereas the MLMV method includes this respondent in estimations of every part of the model that does not include CRP in wave 2.

The specification was fitted using MLMV for the whole sample, men, women, respondents with at least one longstanding illness, RA, and asthma.

Sensitivity analyses

The SEM used in the main analyses was built in stages to test whether associations found in the final model were evident in simpler specifications.

The final specification was estimated for the whole sample using the asymptotic distribution free (ADF) estimation method, as this method makes no assumptions about the distributions of variables.

The SEM model was estimated for the whole sample using MLMV but excluding respondents whose nurse interviews occurred more than two months before or after the main interview. This provides a stronger test for concurrent associations between inflammation and depressive symptoms.

The index of psychological stress and social withdrawal summed low self-efficacy, subjective social status, financial strain and social withdrawal. Sensitivity analyses were conducted using three alternative indices.

Subjective social status is included in the index in the main analyses because it has implications for health (Sapolsky 1982, Singh-Manoux et al. 2003) and has been found to predict health outcomes after adjustment for objective social status (Bradshaw et al. 2017, Han 2014). However, it is not clear exactly what scores on the variable used mean. Assessments of social status have been found to depend upon whether respondents compare themselves against global or local referents (Haught et al. 2015) and we do not know which type of referent respondents used when reporting social status. For this reason, sensitivity analyses used an alternative index that excludes subjective social status.

The measure of psychological stress-and-withdrawal includes financial strain, which is likely to be correlated with SEP. Although the SEMs include SEP, sensitivity analyses were conducted using an alternative index that excludes financial strain.

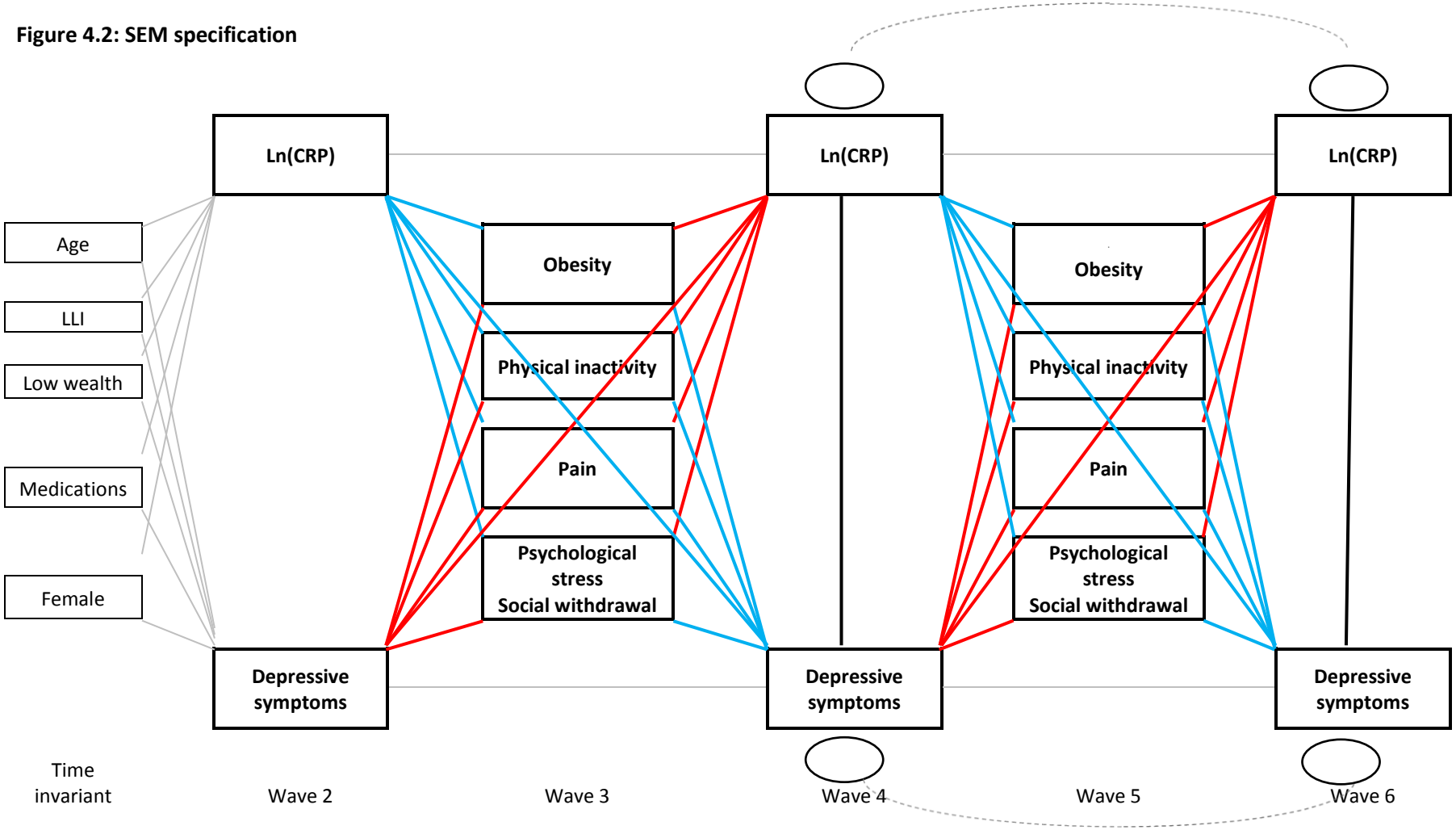
The index includes social withdrawal and measures of psychological stress. Additional sensitivity analyses excluded social withdrawal from this index to better test the importance of psychological stress as a mediator.

Alternative measures of pain were also used in sensitivity analyses used to select mediators for the SEM, and in the SEM specification. It is possible that relationships between pain and both inflammation and depressive symptoms differ depending upon the site of the pain. For example, Zis et al. (2017) identify primary pain syndrome. This is typically experienced as lower back pain and has no known cause, and it is possible that it is more closely associated with depressive symptoms than pain in other parts of the body.

SEMs were also estimated using alternative measures of obesity as obesity can be measured using waist circumference and BMI, and because relationships between weight and inflammation could be continuous rather than threshold effects of obesity.

Using sub-samples of respondents with a history of asthma and with current asthma, alternative SEM specifications that excluded pain were estimated. This is because pain is not a common symptom of asthma.

Figure 4.2: SEM specification



Notes: The model also includes correlations between error terms for the hypothesised explanatory factors in wave 3, and autocorrelations between each measure in waves 3 and 5. Oval shapes represent error terms for Ln(CRP) and depressive symptoms.

4. Results

RQ1. What are the prospective relationships between inflammation and depressive symptoms?

a. Does inflammation at time t-1 predict depressive symptoms at time t?

b. Do depressive symptoms at time t-1 predict inflammation at time t?

Summary statistics for the variables used to address RQ1 are presented in Tables 4.2 and 4.3.

Table 4.2 presents summary statistics for variables in each wave, and shows that for most variables, values are comparable across waves.

Table 4.2: Summary statistics for variables in each wave

	Wave 2 or time-invariant					Wave 4					Wave 6				
Variables used to address all RQs	M/%	SD/ N	Min	Max	N	M/%	SD/ N	Min	Max	N	M/%	SD/ N	Min	Max	N
Depressive symptoms	1.578	1.961	0	8	9215	1.431	1.944	0	8	10518	1.362	1.914	0	8	9905
CRP	2.497	2.139	0.2	9.9	5434	2.418	2.131	0.2	9.9	5990	2.123	1.923	0.1	9.8	5781
Ln(CRP)	0.532	0.930	-1.609	2.293	5434	0.479	0.956	-1.61	2.29	5990	0.363	0.919	-2.30	2.28	5781
Standardised DS	0.000	1.000	-0.804	3.275	9215	0.000	1.000	-0.74	3.38	10518	0.000	1.000	-0.71	3.47	9905
Standardised Ln(CRP)	0.000	1.000	-2.302	1.893	5434	0.000	1.000	-2.18	1.90	5990	0.000	1.000	-2.90	2.09	5781
Depressive symptoms change w2-w4	-0.107	1.891	-8	8	6402										
Depressive symptoms change w4-w6	-0.010	1.828	-7	8	8166										
Depressive symptoms changew2-w6	-0.106	1.974	-8	8	5386										
CRP change w2-w4	0.067	1.932	-9.2	9.3	3044										
CRP change w4-w6	-0.303	1.876	-8.9	9.3	3746										
CRP change w2-w6	-0.243	2.014	-9.5	9.4	2566										
Female	55.4%	15891	0	1	28688										
Age	65.7	10.5	17	90	9432	65.1	10.2	24	90	11050	66.5	10.2	28	90	10601
Age in 2004	63.5	12.7	17	96	26356										
Low wealth in 2004	2.037	0.824	1	3	17845										
Variables used to address RQ1															
Below L2 qualification in 2004	42.7%	6933	0	1	16245										
Medication use	86.4%	7001	0	1	8105	86.8%	8012	0	1	9228	81.7%	7312	0	1	10597
Longstanding illness	56.5%	5323	0	1	9426	54.2%	5984	0	1	11041	54.6%	5780	0	1	10594
Aged 70 and over	35.3%	9988	0	1	28296	23.8%	7890	0	1	33150	36.0%	11456	0	1	31822
Ever had RA	3.8%	323	0	1	8532	4.1%	411	0	1	10054	6.8%	666	0	1	9732
Ever had asthma	15.4%	1445	0	1	9385	15.7%	1720	0	1	10986	13.8%	1458	0	1	10541
Active asthma	6.7%	628	0	1	9418	6.1%	673	0	1	11034					0
Variables used to address RQ2															
Limiting longstanding illness by w2	0.835	0.896	0	2	15942	0.732	0.869	0	2	10266	0.630	0.837	0	2	9739
RA by wave 6	12.4%	1289	0	1	10355										
Asthma by wave 6	29.1%	3483	0	1	11984										
Active asthma by wave 6	20.8%	2234	0	1	10735										

	Wave 3					Wave 5				
	Mean	SD	Min	Max	N	Mean	SD	Min	Max	N
High risk waist circumference	0.533	0.480	0	1	10918	0.541	0.474	0	1	10136
Physical inactivity	1.008	0.906	0	3	9766	1.034	0.925	0	3	10264

Pain	0.718	1.023	0	3	9527	0.755	1.032	0	3	9722
Functional limitations	0.833	1.982	0	13	9767	0.842	2.011	0	13	10266
Psychological stress index	0.513	0.097	0.216	0.921	8204	0.504	0.098	0.216	0.972	8980
Low control	3.074	0.849	1	6	8170	2.992	0.866	1	6	8915
Low subjective social status	40.76	16.75	0	95	7919	40.85	16.79	0	95	8645
Financial strain	1.997	0.893	1	4	9084	1.968	0.895	1	4	9538
Work stress	0.352	0.509	0	4	7880	0.299	0.488	0	4	8606
Relationship distress extended family	0.437	0.199	0	1	8012	0.449	0.196	0	1	8795
Relationship distress friends	0.397	0.147	0	1	8081	0.397	0.152	0	1	8845
Social withdrawal	2.242	0.612	1	3	8124	2.139	0.595	1	3	8897

Age, below Level 2 qualifications and low wealth, each in 2004, were coded using all available information, so timing is not exact; where information is unavailable in wave 2 (2004), information is used from wave 1, then from waves 3,4,5 and 6, in that order. Limiting longstanding illness takes zero for no longstanding illness, one for longstanding illness that is not limiting, and two for limiting longstanding illness. Loneliness, low control, low subjective social status, financial strain and social withdrawal were weighted equally and summed for the psychological stress index. M is mean and applies to continuous variables. % applies to binary variables and is th % of respondents for whom the variable has a yes value. N is the number of respondents with a non-missing value for the variable.

Table 4.3: Summary statistics of variables pooled across waves for the whole sample and for the sub-sample used to address RQ1

	(1) Whole sample					(2) Excluded from RQ1			(3) Included in RQ1			Differences (2)vs(3)	
	Mean	SD				Mean	SD		Mean	SD			
Variable	%=y	N=y	Min	Max	N	%=y	N=y	N	%=y	N=y	N	OR	p-value
CRP 2,4,6	2.344	2.072	0.1	9.9	17205	2.178	1.984	3335	2.383	2.091	13870	6.415	0.000
Ln(CRP) 2,4,6	0.457	0.938	-2.303	2.293	17205	0.374	0.942	3335	0.476	0.936	13870	3.129	0.000
Depressive symptoms 2,4,6	1.453	1.941	0	8	29638	1.557	2.017	15768	1.335	1.845	13870	0.915	0.000
Female (time invariant)	55.4%	47679	0	1	86064	55.6%	40140	72194	54.3%	7531	13870	0.899	0.037
Age 2,4,6	65.8	10.3	17	90	31083	65.2	11.2	17213	66.4	9.1	13870	1.017	0.000
Below L2 quals 2004 (time invariant)	42.7%	20810	0	1	48735	45.3%	15794	34865	36.1%	5007	13870	0.512	0.000
Low wealth in 2004 (time invariant)	0.679	0.275	0.333	1	53535	0.696	0.274	39665	0.630	0.269	13870	0.210	0.000
Age 70 or above 2,4,6	34.6%	10755	0	1	31083	34.5%	5938	17213	34.9%	4841	13870	0.998	0.975
Longstanding illness 12,34,56	55.1%	20373	0	1	36974	55.6%	12846	23104	54.3%	7531	13870	0.927	0.102
Medication use (time invariant)	90.3%	45984	0	1	50904	93.1%	34479	37034	82.8%	11484	13870	0.151	0.000

Summary statistics for each variable refer to measures pooled over three occasions, indicated by wave numbers to the right of the variable description. Measures are based on information provided in the wave when inflammation and depressive symptoms are measured (waves 2, 4 and 6), and if available, information provided in the previous wave (1, 3 and 5). When information is available in both waves, the mean value is used. ORs are odds ratios that respondents are included in analyses for RQ1 if they have high values for the variable. Bold font indicates variables with distributions that differ between the two sub-samples. %=Yand N=y apply to binary variables and are the percentages and numbers, respectively, of observations for which the variable takes a yes value. N is the number of observations for which the variable has a non-missing value.

For both CRP and depressive symptoms, the between and within individual variation is of a similar magnitude. For example, variation in depressive symptoms between individuals in wave 2 is 3.846, as this is the square of the standard deviation (1.961^2). This is of a similar magnitude to the variation in depressive symptoms within individuals between waves 2 and 4; 3.576 (1.891^2). Similarly, the variation in CRP between individuals is 4.575 (2.139^2), which is of a similar magnitude to the average difference in CRP within individuals between waves 2 and 4, of 3.733 (1.932^2). This means that associations should be identifiable (that is, identified if they exist) equally easily within individuals over time and between individuals regardless of time.

Average numbers of depressive symptoms, CRP levels, and proportions with at least one longstanding illness reduce slightly between waves 2 and 6, possibly because healthier respondents are less likely to drop out of the study (Bridges et al. 2015). However, lifetime prevalence of RA increases over time, as respondents are given more opportunities to report it.

Table 4.3 provides summary statistics for variables used to address RQ1, pooled across waves. In the sample used to address RQ1, mean levels of CRP were 2.4mg/l, and the mean number of depressive symptoms was 1.3 out of 8. Just over half (54%) were women, the mean age was 66, and about one third (35%) did not have Level 2 qualifications in 2004. A high proportion (83%) reported using medications that could affect inflammation and/or depressive symptoms, and just over half (51%) had at least one chronic illness.

Compared against those who did not provide complete information and were therefore excluded from the analyses used to address RQ1, the sample used had slightly lower levels of depressive symptoms, and medication use. They were better educated, wealthier, and slightly older. Men were over-represented. CRP levels were slightly higher.

After adjustment for gender, age, age squared, education, wealth, medication use and longstanding illness, each SD increase in Ln(CRP) predicted a 0.030SD increase in depressive symptoms four years later (95% confidence interval 95%ci=0.010-0.050, p=0.004, n=7,829). That is, each 0.919mg/L CRP was associated with an increase of 0.05 depressive symptoms, or each mg/L increase in CRP predicted 0.06 depressive symptoms. The association between depressive symptoms and Ln(CRP) four years later was not statistically significant (β=0.004, 95%ci=-0.019-0.028, p=0.708, n=5,869).

Tables 4.4 and 4.5 present results by gender, age group and health status. They provide no evidence that prospective associations differ by any of these factors. After adjustment for medications, education, wealth, and if applicable, age, age squared, gender and longstanding illness, CRP predicts depressive symptoms four years later among all groups, although associations do not reach statistical significance among men and those with no longstanding illness.

There is no evidence that depressive symptoms predict CRP four years later among any sub-sample and no evidence of interaction effects.

Table 4.4 shows that after adjustment for the lagged dependent variables, inflammation, SEP, age, medication use and longstanding illness, women have higher levels of depressive symptoms than men, but Table 4.5 provides no evidence that after equivalent adjustments, there are gender differences in relation to Ln(CRP). After the same adjustments, older age category, longstanding illness, RA, and asthma are each associated with depressive symptoms, and longstanding illness and asthma are each associated with Ln(CRP).

Sensitivity analyses

When depressive symptoms were measured in three categories and ordered probit models, the results were almost identical. See Appendix 22.

Table 4.4: Adjusted associations between inflammation and depressive symptoms four years later for whole sample and by gender, age category and health status.

	Whole sample				Men				Women			
Outcome is depressive symptoms at t	beta	95% CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	0.026	-0.003-0.056	0.081	7829	0.026	-0.001-0.052	0.055	3596	**0.032**	**0.003-0.062**	**0.033**	**4233**
Gender	**0.141**	**0.099-0.183**	**0.000**									
Gender*Ln(CRP)(t-1)	0.006	-0.033-0.046	0.763									

	Whole sample				Aged under 70				Aged 70 plus			
	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	**0.029**	**0.005-0.052**	**0.016**	7830	**0.030**	**0.007-0.053**	**0.012**	**5485**	**0.051**	**0.012-0.089**	**0.011**	**2345**
70 plus(t-1)	**0.081**	**0.036-0.125**	**0.000**									
70 plus(t-1)*Ln(CRP)(t-1)	0.022	-0.021-0.066	0.318									

	Whole sample				No longstanding illness				With longstanding illness			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	0.015	-0.013-0.043	0.306	7829	0.021	-0.004-0.046	0.103	3685	**0.033**	**0.004-0.063**	**0.028**	**4144**
Longstanding illness(t-1)	**0.178**	**0.138-0.217**	**0.000**									
Longstanding illness(t-1)*Ln(CRP)(t-1)	0.028	-0.009-0.066	0.139									

	Whole sample				With RA			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	**0.030**	**0.008-0.051**	**0.006**	6962	-0.013	-0.149-0.124	0.857	165
RA(t-1)	**0.194**	**0.054-0.333**	**0.006**					
RA(t-1)*Ln(CRP)(t-1)	-0.031	-0.161-0.099	0.639					

	Whole sample				With history of asthma			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	0.020	-0.002-0.042	0.069	7788	0.046	-0.013-0.104	0.125	1200
Asthma(t-1)	**0.221**	**0.159-0.283**	**0.000**					
Asthma(t-1)*Ln(CRP)(t-1)	0.038	-0.016-0.092	0.168					

	Whole sample				With active asthma			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	**0.030**	**0.009-0.051**	**0.005**	7825	0.021	-0.074-0.116	0.664	472
Active asthma(t-1)	**0.277**	**0.194-0.360**	**0.000**					
Active asthma(t-1)*Ln(CRP)(t-1)	0.006	-0.075-0.087	0.889					

15 random effects models using linear regressions and depressive symptoms as a continuous variable. Betas refer to increases in depressive symptoms associated with each unit increase in Ln(CRP) and other variables in the model. Models adjusted for depressive symptoms at time t-1, age, age squared at time t, gender, medication at time t, qualifications below Level 2 in 2004, wealth in 2004. First two sets of models are also adjusted for longstanding illness at time t-1. Model with age 70+ does not include additional adjustment for age, and the specifications for sub-samples aged below 70 and 70+ adjust for age but not age-squared. Ln(CRP) and depressive symptoms are standardized. Bold font indicates p-values below 0.05.

Table 4.5: Adjusted associations between depressive symptoms and Ln(CRP) four years later for the whole sample and by gender, age category and health status.

	Whole sample				Men				Women			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.001	-0.038-0.040	0.956	5869	0.003	-0.038-0.044	0.876	2659	0.005	-0.023-0.033	0.719	3210
Gender	0.046	0.000-0.093	0.050									
Gender*Depr(t-1)	0.005	-0.043-0.053	0.835									

	Whole sample				Aged below 70				Aged 70+				
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	Ci1	Ci2	p_val	N
Depr(t-1)	0.005	-0.021-0.032	0.686		0.004	-0.023-0.031	0.776	4265	0.023	-0.022	0.067	0.320	1605
70+(t-1)	0.029	-0.020-0.078	0.245										
70+(t-1)*Depr(t-1)	0.014	-0.034-0.063	0.565										

	Whole sample				No longstanding illness				With longstanding illness			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.022	-0.016-0.060	0.255	5870	0.023	-0.015-0.060	0.238	2828	-0.008	-0.037-0.022	0.605	3041
Longstanding illness(t-1)	**0.045**	**0.001-0.088**	**0.043**									
Longstanding illness(t-1)*Depr(t-1)	-0.027	-0.073-0.019	0.251									

	Whole sample				With RA			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.006	-0.019-0.032	0.632	5240	-0.062	-0.218-0.093	0.432	114
RA(t-1)	0.076	-0.079-0.231	0.339					
RA(t-1)*Depr(t-1)	-0.054	-0.200-0.092	0.467					

	Whole sample				With history of asthma			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.001	-0.025-0.027	0.961	5837	0.003	-0.050-0.056	0.908	870
Asthma(t-1)	**0.103**	**0.037-0.169**	**0.002**					
Asthma(t-1)Depr(t-1)	0.016	-0.039-0.070	0.572					

	Whole sample				With active asthma			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	-0.002	-0.026-0.022	0.847	5866	0.063	-0.017-0.143	0.121	346
Active asthma(t-1)	**0.111**	**0.022-0.200**	**0.014**					
Active asthma(t-1)*Depr(t-1)	0.073	-0.001-0.147	0.053					

15 random effects models, with Ln(CRP) at time t as the outcome. Beta values refer to the increases in Ln(CRP) associated with each unit increase in depressive symptoms and the other variables specified. All models are adjusted for Ln(CRP) at time t-1, age and age squared at time t, gender, medication for inflammation or depression at time t, qualifications below Level 2 in 2004, and wealth in 2004. The first two sets of models are also adjusted for longstanding illness at time t-1. The model that includes the indicator of age 70+ does not include additional adjustment for age, and the specifications for sub-samples above and below 70 adjust for age but not age squared. Measures of Ln(CRP) and depressive symptoms are standardised.

Bold font indicates associations with p-values below 0.05.

RQ2. Are prospective associations between inflammation and depressive symptoms confounded or mediated by other factors?

Table 4.6 presents summary statistics for variables used to address RQ2, pooled across waves. In the sample used in the analyses (3), mean plasma CRP was 2.3mg/l, and the mean number of depressive symptoms was 1.1 out of 8. 55% were women, the mean age was 65, and almost one third had no GCSE equivalents in 2004.

Just over half had a longstanding illness, a quarter had a limiting longstanding illness and over three-quarters were using medications that could affect depressive symptoms or inflammation, or both. Mean waist circumference was 95cms, which indicates risk of metabolic complications for white Europeans, as cutpoints are 94cms for men and 80cms for women (Albert et al. 2006. Mean blood pressure was 133/75, which is slightly higher than the clinically healthy range (Blood Pressure Association 2017). Mean plasma level of glycosylated haemoglobin is 39mmol/mol , which is below the reference range (48-59mmol/mol, GP Notebook 2017a), probably because respondents fasted before the blood samples were taken. Mean plasma triglycerides were 1.6mmol/l and high density lipid (HDL) cholesterol was 1.6mmol/L, which are within clinical ranges (GP Notebook 2017b, 2017c). Low levels of pain and functional limitations were reported. Almost one in 10 smoked, and almost one fifth drank frequently.

Most respondents had children, other family and friends, and about three-quarters lived with partners. Very low proportions (less than 2%) had lost or acquired a partner between waves. On average, relationships with other family and friends were more stressful than relationships with partners or children. Just under one third were in paid work, and 2.3% reported job insecurity. About one fifth reported feeling worse off than their neighbours and a similar proportion reported feeling worse off than their friends. Mean subjective

social status was over 50 out of 100, at 61. Almost a quarter of the sample reported financial limitations and just under one tenth cared for a partner or parent.

The sub-sample used to address RQ2 is likely to be less representative of adults aged 50 and over living in England than the sample of ELSA respondents from which it is drawn. The sub-sample consists of respondents who provided complete information about depressive symptoms, CRP and hypothesised confounders and mediators.

Compared against respondents who were excluded from the analyses conducted to address RQ2, the sample used had fewer depressive symptoms, reported more advantaged backgrounds, were better qualified and had more wealth. They were also healthier. Fewer reported longstanding illness, limiting longstanding illness and medication use and fewer had high waist circumference. Plasma levels of glycosylated haemoglobin and triglycerides were lower, HDL cholesterol levels were higher and their blood pressures were higher. They reported less pain and fewer functional limitations. A lower proportion smoked and they were more physically active.

The sample used reported lower levels of loneliness, social withdrawal, community stress, work stress, perceived financial strain and financial strain and higher levels of self-efficacy and subjective social status. Those in paid employment are under-represented and higher proportions had a partner, child, and friends. Those used in the analyses reported slightly higher levels of distress in their relationships with partners, possibly because a higher proportion had lived with partners. They reported fewer childhood adversities and were more conscientious and extravert and less neurotic.

Table 4.6: Summary statistics of variables pooled across waves for the whole sample and for the sub-sample used to address RQ2

	(1) Whole sample					(2) Excluded from RQ2			(3) Included in RQ2			Diff. (2)vs.(3)	
	M/%	SD/ N	Min	Max	N	M/%	SD/ N	N	M/ %	SD/ N	N	OR	p-val
CRP	2.344	2.072	0.100	9.900	17205	2.382	2.083	10437	2.285	2.054	6768	0.976	0.187
Ln(CRP)	**0.457**	**0.938**	**-2.303**	**2.293**	**17205**	0.478	0.933	10437	0.424	0.944	6768	0.924	0.061
Depressive symptoms	**1.453**	**1.941**	**0**	**8**	**29638**	**1.547**	**1.999**	**22870**	**1.136**	**1.692**	**6768**	**0.859**	**0.000**
Hypothesised moderators													
Female	55.4%	47673	0	1	86064	55.5%	43970	79296	0.547	3703	6768	0.934	0.271
Age	65.8	10.3	17	90	31083	65.7	10.8	24315	66.0	8.472	6768	1.002	0.384
Longstanding illness 12,34,56	**55.1%**	**20387**	**0**	**1**	**36974**	**56.2%**	**16977**	**30206**	**50.4%**	**3409**	**6768**	**0.705**	**0.000**
Limiting longstanding illness 12,34,56	**35.2%**	**13008**	**0**	**1**	**36974**	**37.1%**	**11194**	**30206**	**26.8%**	**1813**	**6768**	**0.445**	**0.000**
Hypothesised confounders													
Main carer's occupation at age 14	**2.087**	**1.111**	**1**	**5**	**39960**	**2.099**	**1.119**	**34789**	**2.002**	**1.049**	**5171**	**0.852**	**0.000**
Below L2 qualifications in 2004	**42.7%**	**0.495**	**0**	**1**	**48735**	**44.5%**	**0.497**	**41967**	**0.315**	**0.464**	**6768**	**0.338**	**0.000**
Low accumulated wealth in 2004	**0.679**	**0.275**	**0.333**	**1.000**	**53535**	**0.691**	**0.275**	**46767**	**0.597**	**0.261**	**6768**	**0.091**	**0.000**
Agreeable	0.878	0.120	0.25	1.00	26601	0.878	0.121	19833	0.877	0.116	6768	0.861	0.595
Conscientious	**0.822**	**0.125**	**0.25**	**1.00**	**26529**	**0.821**	**0.127**	**19761**	**0.828**	**0.117**	**6768**	**2.109**	**0.006**
Neurotic	**0.526**	**0.149**	**0.25**	**1.00**	**26547**	**0.531**	**0.151**	**19779**	**0.513**	**0.144**	**6768**	**0.257**	**0.000**
Open	0.719	0.140	0.25	1.00	26472	0.719	0.142	19704	0.720	0.134	6768	1.120	0.639
Extravert	**0.787**	**0.140**	**0.25**	**1.00**	**26565**	**0.785**	**0.142**	**19797**	**0.792**	**0.136**	**6768**	**1.753**	**0.020**
Childhood adversity	**0.995**	**1.048**	**0**	**3**	**19566**	**1.008**	**1.051**	**13914**	**0.964**	**1.041**	**5652**	**0.931**	**0.047**
No. physical limitations 12,34,56	**0.222**	**0.360**	**0**	**1**	**36867**	**0.241**	**0.373**	**30099**	**0.136**	**0.276**	**6768**	**0.254**	**0.000**
Medication use 2,4,6	**90.3%**	**45984**	**0**	**1**	**50904**	**92.2%**	**40686**	**44136**	**78.3%**	**5298**	**6768**	**0.085**	**0.000**
Hypothesised mediators													
Perceived strain 1,3,3	0.477	0.183	0.25	1.00	27090	0.479	0.185	20322	0.472	0.178	6768	0.898	0.470
Perceived loneliness 2,34,56	**0.280**	**0.100**	**0.2**	**0.6**	**29998**	**0.284**	**0.103**	**23230**	**0.267**	**0.090**	**6768**	**0.098**	**0.000**
Social withdrawal	**2.201**	**0.578**	**1**	**3**	**33786**	**2.242**	**0.579**	**27018**	**2.034**	**0.544**	**6768**	**0.393**	**0.000**
Lives with partner 2,4,6	**73.6%**	**19359**	**0**	**1**	**26290**	**72.9%**	**14229**	**19522**	**75.8%**	**5130**	**6768**	**1.250**	**0.001**
Acquired partner since last wave	0.6%	135	0	1	21170	0.7%	94	14402	0.6%	41	6768	0.849	0.571
Lost partner since last wave	2.1%	450	0	1	21170	2.2%	323	14402	1.9%	127	6768	0.828	0.234
Has children 2,4,6	**86.5%**	**22795**	**0**	**1**	**26346**	**85.9%**	**16824**	**19583**	**88.3%**	**5971**	**6763**	**1.436**	**0.000**
Has other family 2,4,6	92.8%	24521	0	1	26424	92.6%	18236	19690	93.3%	6285	6734	1.135	0.208
Has friends 2,4,6	**94.6%**	**24996**	**0**	**1**	**26418**	**94.2%**	**18533**	**19684**	**96.0%**	**6463**	**6734**	**1.603**	**0.000**
Stressy partner relationship 12,34,56	**0.295**	**0.205**	**0**	**1**	**32893**	**0.293**	**0.209**	**26125**	**0.304**	**0.191**	**6768**	**1.417**	**0.011**
Distressing child relationship 12,34,56	0.360	0.185	0	1	32881	0.359	0.189	26113	0.362	0.170	6768	1.145	0.382
Distressing other family relationship	0.443	0.187	0	1	32621	0.443	0.192	25853	0.444	0.166	6768	1.171	0.255

12,34,56													
Distressing friend relationship 12,34,56	0.400	0.141	0	1	32710	0.400	0.146	25942	0.402	0.121	6768	1.177	0.370
Community stress 1,3,3	**0.383**	**0.144**	**0.143**	**1.000**	**26944**	**0.388**	**0.148**	**20176**	**0.369**	**0.133**	**6768**	**0.350**	**0.000**
Low control generally 12,34,56	**0.498**	**0.135**	**0.167**	**1.000**	**32976**	**0.503**	**0.138**	**26208**	**0.481**	**0.124**	**6768**	**0.215**	**0.000**
High demands generally 12,34,56	**0.520**	**0.156**	**0.167**	**1.000**	**32897**	**0.523**	**0.158**	**26129**	**0.508**	**0.148**	**6768**	**0.424**	**0.000**
In paid employment 2,4,6	**35.1%**	**9173**	**0**	**1**	**26144**	**35.9%**	**6974**	**19433**	**32.8%**	**2199**	**6711**	**0.847**	**0.003**
Effort:reward at work 2,34,56	**0.082**	**0.123**	**0**	**1**	**29345**	**0.084**	**0.125**	**22577**	**0.078**	**0.116**	**6768**	**0.627**	**0.033**
Low control at work 2,34,56	**0.183**	**0.255**	**0**	**1**	**29628**	**0.186**	**0.258**	**22860**	**0.174**	**0.244**	**6768**	**0.807**	**0.040**
Job security 2,34,56	0.025	0.142	0	1	32770	0.025	0.144	26002	0.023	0.133	6768	1.012	0.942
Worse off than neighbours 2,34,56	0.186	5606	0	1	30189	0.187	4387	23421	0.180	1220	6768	0.931	0.284
Worse off than friends 2,34,56	0.213	6481	0	1	30371	0.216	5103	23603	0.203	1377	6768	0.928	0.235
Subjective social status 12,34,56	**0.581**	**0.162**	**0.05**	**1.00**	**32335**	**0.574**	**0.165**	**25567**	**0.605**	**0.148**	**6768**	**5.419**	**0.000**
Can't buy things 2,34,56	**29.3%**	**9589**	**0**	**1**	**32782**	**30.5%**	**7942**	**26014**	**24.3%**	**1647**	**6768**	**0.644**	**0.000**
Perceived financial strain 12,34,56	**0.509**	**0.210**	**0.25**	**1.00**	**35422**	**0.520**	**0.213**	**28654**	**0.463**	**0.190**	**6768**	**0.161**	**0.000**
Carer partner/parent/in-law 12,34,56	7.9%	2931	0	1	36996	7.8%	2360	30228	8.4%	570	6768	1.113	0.284
Pain 12,34,56	**0.252**	**0.318**	**0**	**1**	**35768**	**0.262**	**0.326**	**29000**	**0.212**	**0.278**	**6768**	**0.499**	**0.000**
Pain in back 12,34,56	**19.5%**	**6942**	**0**	**1**	**35595**	**20.1%**	**5791**	**28827**	**17.0%**	**1150**	**6768**	**0.746**	**0.000**
Pain in limbs 12,34,56	**24.6%**	**8852**	**0**	**1**	**35934**	**25.1%**	7330	**29166**	**22.5%**	1522	**6768**	**0.849**	**0.013**
Current smoker 12,34,56	**17.0%**	**5820**	**0**	**1**	**34197**	**18.4%**	**5043**	**27429**	**11.5%**	**777**	**6768**	**0.453**	**0.000**
Drinks daily 12,34,56	18.8%	6314	0	1	33556	18.6%	4993	26788	19.5%	1321	6768	1.118	0.118
Physically inactive 12,34,56	**0.349**	**0.287**	**0**	**1**	**36805**	**0.369**	**0.295**	**30037**	**0.260**	**0.224**	**6768**	**0.132**	**0.000**
High waist circumference 2,4,6	**53.4%**	**12643**	**0**	**1**	**23691**	**54.3%**	**9182**	**16923**	**51.1%**	**3461**	**6768**	**0.837**	**0.002**
Glycosylated haemoglobin 2,4,6	**39.887**	**8.131**	**11.456**	**137**	**18230**	**40.160**	**8.368**	**11462**	**39.425**	**7.692**	**6768**	**0.983**	**0.000**
Triglycerides 2,4,6	**1.686**	**1.050**	**0.30**	**25**	**18468**	**1.711**	**1.095**	**11700**	**1.641**	**0.966**	**6768**	**0.917**	**0.008**
HDL cholesterol 2,4,6	**1.580**	**0.435**	**0.4**	**4.7**	**18456**	**1.570**	**0.436**	**11688**	**1.598**	**0.431**	**6768**	**1.301**	**0.003**
Diastolic blood pressure 2,4,6	**74.272**	**10.983**	**34**	**128**	**22108**	**74.128**	**11.168**	**15340**	**74.599**	**10.546**	**6768**	**1.007**	**0.008**
Systolic blood pressure 2,4,6	133.2	18.1	74	259	22108	133.3	18.4	15340	133.1	17.3	6768	1.000	0.853

Summary statistics for each variable refer to its measurement on three occasions. Waves in which each variable was measured are indicated to the right of the variable name. Measures are based on information provided in the wave when inflammation and depressive symptoms are measured (waves 2, 4 and 6), and if available, information provided in the previous wave (1, 3 and 5). When information is available in both waves, the mean value is used. When information is available in just one wave, information from this wave is used. ORs are odds ratios that respondents are included in analyses for RQ2 if they have high values for the variable. Bold font indicates variables with distributions that differ between the two sub-samples. M indicates mean and applies to continuous variables. % applies to binary variables and is the percentage of observations with a yes value for the variable. N is the number of observations for which the variable has a non-missing value.

Table 4.7 presents evidence used to identify the most salient confounders or mediators of the association between CRP and depressive symptoms. The first two sets of columns give statistics for estimated associations between each hypothesised confounder/mediator and depressive symptoms, and Ln(CRP). The final set of columns present results of comparisons between baseline associations of Ln(CRP) and depressive symptoms and attenuated associations, as each hypothesised confounder or mediator is added to the model. All models are adjusted for gender, age and age squared.

Variables that confound or mediate the association between Ln(CRP) and depressive symptoms, i.e. that predict both outcomes, are longstanding illness, limiting longstanding illness, main carer's occupation at age 14, below Level 2 qualifications in 2004, accumulated wealth in 2004, agreeableness, conscientiousness, childhood adversity, functional limitations, medication use, community stress, self-efficacy, subjective social status, financial limitations, social withdrawal, pain, smoking, frequency of drinking, physical inactivity, obesity, glycosylated haemoglobin, triglycerides and HDL cholesterol.

Variables selected as particularly salient reduced the magnitude of the unadjusted association between Ln(CRP) and depressive symptoms by at least 15%; longstanding illness, limiting longstanding illness, childhood SES, qualifications, low accumulated wealth, functional limitations, medication use, community stress, low control or self-efficacy, subjective social status and perceived financial strain, social withdrawal, pain, physical inactivity, obesity, triglycerides and HDL cholesterol.

Table 4.7: Associations between each hypothesised explanatory variable and (1) Ln(CRP), (2) depressive symptoms, and estimated associations between Ln(CRP) and depressive symptoms as each hypothesised explanatory variable is added to the baseline model. All models are adjusted for gender and age and estimated for the whole sample

	Estimated associations between each hypothesised explanatory variable and:								Ln(CRP)-depressive symptoms associations as each variable added to the baseline model				
	Depressive symptoms				Ln(CRP)								
Hypothesised explanatory variable	β	95%CI	p-val	N	β	95%CI	p-val	N	% base	β	95%CI	p-val	N
None = baseline model									100.0	0.084	0.039-0.130	0.000	6768
Hypothesised confounders													
Longstanding illness 12,34,56	0.639	0.543-0.734	0.000	6768	0.134	0.084-0.184	0.000	6768	72.2	0.061	0.016-0.106	0.008	6768
Limiting longstanding illness 12,34,56	1.053	0.948-1.158	0.000	6768	0.191	0.135-0.248	0.000	6768	50.7	0.043	-0.001-0.087	0.058	6768
Main carer's occupation at age 14	0.096	0.044-0.148	0.000	5171	0.058	0.027-0.089	0.000	5171	79.8	0.067	0.017-0.118	0.009	5171
Below L2 qualifications in 2004	0.372	0.264-0.480	0.000	6768	0.275	0.214-0.337	0.000	6768	80.4	0.068	0.022-0.114	0.004	6768
Low accumulated wealth in 2004	0.997	0.812-1.182	0.000	6768	0.572	0.465-0.678	0.000	6768	62.0	0.052	0.007-0.098	0.024	6768
Agreeable	-0.577	-1.009- -0.145	0.009	6768	0.545	0.297-0.794	0.000	6768	104.7	0.088	0.043-0.134	0.000	6768
Conscientious	-2.005	-2.423- -1.588	0.000	6768	-0.459	-0.701- -0.216	0.000	6768	89.0	0.075	0.030-0.120	0.001	6768
Neurotic	3.533	3.210-3.856	0.000	6768	-0.106	-0.303-0.092	0.295	6768					
Open	-1.671	-2.035- -1.307	0.000	6768	-0.124	-0.336-0.087	0.250	6768					
Extravert	-2.601	-2.955- -2.247	0.000	6768	-0.114	-0.324-0.095	0.285	6768					
Childhood adversity	0.189	0.138-0.240	0.000	5652	0.068	0.037-0.098	0.000	5652	97.8	0.083	0.034-0.131	0.001	5652
No. functional limitations 12,34,56	1.823	1.673-1.972	0.000	6768	0.317	0.235-0.399	0.000	6768	36.1	0.030	-0.013-0.074	0.172	6768
Medication use waves 0-6	0.543	0.422-0.664	0.000	6768	0.310	0.239-0.380	0.000	6768	74.2	0.063	0.017-0.108	0.007	6768
Hypothesised mediators													
Perceived strain 1,3,3	2.222	1.990-2.454	0.000	6768	0.068	-0.055-0.191	0.281	6768					
Loneliness 2,34,56	8.265	7.836-8.694	0.000	6768	0.234	-0.019-0.487	0.070	6768					
Acquired partner since last wave	-0.715	-0.826--0.603	0.000	6768	-0.034	-0.096-0.027	0.278	6768					
Lost partner since last wave	-0.457	-0.919-0.005	0.053	6768	-0.054	-0.278-0.170	0.637	6768					
Distressing partner relationship 12,34,56	3.311	2.892-3.730	0.000	6768	0.180	-0.048-0.408	0.122	6768					
Distressing child relationship 12,34,56	2.859	2.462-3.256	0.000	6763	0.078	-0.137-0.293	0.475	6763					
Distressing other family rel. 12,34,56	1.399	1.106-1.691	0.000	6734	0.028	-0.124-0.180	0.721	6734					
Distressing friend relationship 12,34,56	1.693	1.289-2.096	0.000	6734	0.087	-0.123-0.296	0.418	6734					
Community stress 1,3,3	2.287	1.963-2.612	0.000	6768	0.371	0.196-0.547	0.000	6768	80.6	0.068	0.023-0.113	0.003	6768
Low control generally 12,34,56	3.132	2.803-3.462	0.000	6768	0.240	0.066-0.414	0.007	6768	82.2	0.069	0.025-0.113	0.002	6768

High demands generally 12,34,56	1.729	1.440-2.019	0.000	6768	0.040	-0.112-0.193	0.605	6768						
Work effort:reward imbalance 2,34,56	1.910	1.215-2.606	0.000	6711	0.053	-0.301-0.407	0.771	6711						
Low work control 2,34,56	0.351	-0.026-0.727	0.068	6711	-0.065	-0.253-0.123	0.497	6711						
Job insecurity 2,34,56	0.273	-0.018-0.564	0.066	6711	-0.049	-0.194-0.096	0.506	6711						
Worse off than people nearby 2,34,56	0.498	0.387-0.609	0.000	6768	0.054	-0.003-0.111	0.062	6768						
Worse off than friends 2,34,56	0.536	0.432-0.641	0.000	6768	0.018	-0.036-0.071	0.520	6768						
Subjective social status 12,34,56	-2.516	-2.806--2.226	0.000	6768	-0.478	-0.636--0.320	0.000	6768	60.9	0.051	0.007-0.096	0.024	6768	
Can't buy things 2,34,56	0.744	0.640-0.849	0.000	6768	0.063	0.009-0.118	0.023	6768	85.9	0.072	0.028-0.117	0.001	6768	
Perceived financial strain 12,34,56	1.657	1.438-1.877	0.000	6768	0.362	0.245-0.479	0.000	6768	65.9	0.056	0.011-0.100	0.015	6768	
Cares for partner or parent	0.272	0.099-0.444	0.002	6768	-0.048	-0.134-0.039	0.279	6768						
Social withdrawal	0.553	0.471-0.635	0.000	6768	0.170	0.125-0.214	0.000	6768	64.1	0.054	0.009-0.099	0.019	6768	
Pain 12,34,56	1.582	1.433-1.730	0.000	6768	0.329	0.248-0.409	0.000	6768	38.3	0.032	-0.012-0.076	0.151	6768	
Back pain 12,34,56	0.878	0.753-1.003	0.000	6768	0.169	0.104-0.234	0.000	6768	74.3	0.063	0.018-0.108	0.006	6768	
Pain hips, knees, feet or mouth 12,34,56	0.816	0.701-0.931	0.000	6768	0.256	0.196-0.316	0.000	6768	58.7	0.050	0.005-0.095	0.031	6768	
Currently smokes 12,34,56	0.490	0.343-0.636	0.000	6768	0.247	0.164-0.330	0.000	6768	86.2	0.073	0.027-0.118	0.002	6768	
Drinks at least daily 12,34,56	-0.170	-0.292- -0.048	0.006	6768	-0.072	-0.137--0.008	0.028	6768	97.6	0.082	0.037-0.128	0.000	6768	
Physical inactivity 12,34,56	1.401	1.215- -1.587	0.000	6768	0.493	0.396-0.590	0.000	6768	46.0	0.039	-0.006-0.084	0.092	6768	
High waist circumference 2,4,6	0.152	0.065-0.239	0.001	6768	0.483	0.439-0.527	0.000	6768	80.1	0.068	0.020-0.115	0.005	6768	
Glycosylated hb (mmol/mol) 2,4,6	0.010	0.004-0.015	0.001	6768	0.010	0.007-0.013	0.000	6768	92.7	0.078	0.033-0.124	0.001	6768	
Triglycerides (mmol/l) 2,4,6	0.089	0.046-0.132	0.000	6768	0.149	0.127-0.171	0.000	6768	83.2	0.070	0.024-0.116	0.003	6768	
HDL cholestrol 2,4,6	-0.315	-0.426- -0.205	0.000	6768	-0.486	-0.544- -0.427	0.000	6768	71.3	0.060	0.014-0.107	0.011	6768	
Diastolic blood pressure (mmHg) 2,4,6	0.001	-0.003-0.005	0.737	6768	0.008	0.006-0.010	0.000	6768						
Systolic blood pressure (mmHg) 2,4,6	0.002	-0.001-0.004	0.153	6768	0.005	0.003-0.006	0.000	6768						

Each row presents results from three RE models, each using three waves of data and adjusted for age, age squared and gender. Models are estimated for the sample of respondents with complete information for all variables in the table, with the exception of childhood SES and childhood adversity, as numbers reporting these variables are lower than for the other variables. Models for stressful relationships with partner, children, other family members and friends adjust for having a partner, children, other family and friends, respectively. Models for effort:reward imbalance, control at work and job insecurity adjust for being in paid work during the previous month. The first set of columns present estimated associations of each hypothesised explanatory variable with depressive symptoms, and the second set with Ln(CRP). Beta values in these columns refer to increases in depressive symptoms and Ln(CRP), respectively, associated with unit increases in each hypothesized explanatory variable. The third set presents estimated associations between Ln(CRP) and depressive symptoms for a baseline model (top row), adjusted only for gender, age, and age squared, and models in which one explanatory variable is added. All models are estimated using the same sample with complete information for all variables, except for childhood SES and childhood adversity. Beta values represent increases in depressive symptoms for each unit increase in Ln(CRP). Measures use information from two consecutive waves, if available, as indicated by wave numbers to the right of each variable description. High waist circumference is over 88 cms for women and over 102 cms for men. Bold font indicates variables that attenuate the unadjusted association by at least 15%.

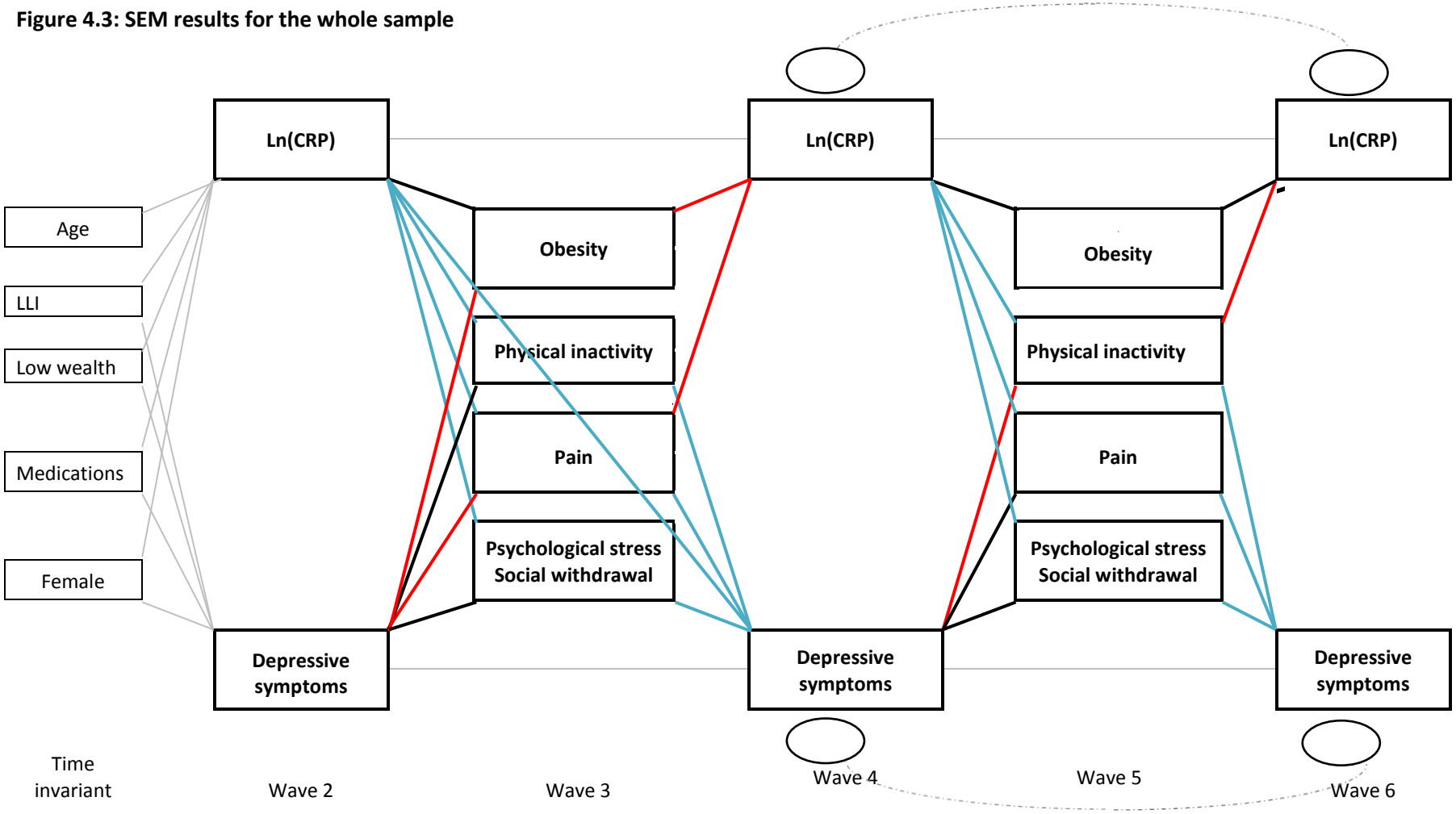
In order to simplify SEM models, some variables were excluded because they overlapped conceptually or were highly correlated. Longstanding illness and functional limitations were excluded because they overlap with limiting longstanding illness. HDL cholesterol and triglycerides were excluded because these, like waist circumference, are biomarkers of metabolic dysregulation (Lacey et al. 2016, McMunn et al. 2016) and it was simpler to use just one marker. Waist circumference was selected over HDL cholesterol and triglycerides because it of more direct interest to policy makers in public health.

Community stress was excluded because it was only measured in waves 1 and 3. An index of psychological stress-and-withdrawal was created that combined low control or self-efficacy, subjective social status, perceived financial strain and social withdrawal. The index represented the psychosocial manifestations of sickness behaviours.

Results presented in Appendix 22 Table A22.3 indicate that selected variables have pairwise correlation coefficients below 0.4 with the exception of age and limiting longstanding illness (r=0.42) and stress in waves 3 and 5 and limiting longstanding illness (r=0.46, r=0.44, respectively).

Selected variables were included in an SEM model using the MLMV estimation method. Results are presented in Figure 4.3 and Table 4.8.

Figure 4.3: SEM results for the whole sample



The SEM model uses MVML method of estimation, with 11,986 observations. All lines indicate associations with p-values <0.05. Unbroken lines indicate positive associations and dashed lines indicate negative associations. All measures in waves 3 and 5 are auto-correlated. Error terms for all mediators at wave 3 are positively correlated except for psychological stress and obesity, which are not correlated.

Table 4.8: Magnitudes of prospective associations between Ln(CRP) and depressive symptoms for the whole sample

	Associations between baseline Ln(CRP) and depressive symptoms four years later					
	Waves 2,3,4			Waves 4,5,6		
Mediator	Ln(CRP)-Med	Med-DS	Pathway	Ln(CRP)-Med	Med-DS	Pathway
None			**0.041**			**NS**
Stress&withdrawal	0.024	0.937	**0.022**	0.004	0.571	**0.002**
Obesity	0.157	NS	**---**	0.020	NS	**---**
Physical inactivity	0.072	0.190	**0.014**	0.035	0.214	**0.007**
Pain	0.056	0.389	**0.022**	0.034	0.168	**0.006**
	Associations between depressive symptoms and Ln(CRP) four years later					
	Waves 2,3,4			Waves 4,5,6		
Mediator	Ln(CRP)-Med	Med-DS	Pathway	Ln(CRP)-Med	Med-DS	Pathway
None			**NS**			**NS**
Stress&withdrawal	0.039	NS	**---**	0.015	NS	**---**
Obesity	0.020	0.214	**0.004**	NS	0.069	**---**
Physical inactivity	0.069	NS	**---**	0.043	0.094	**0.004**
Pain	0.097	0.088		0.052	NS	**---**

These are results of SEM models using the MLMV method with 11,986 observations. NS is not statistically significant. Prospective associations between Ln(CRP) and depressive symptoms were measured on two occasions. On the first occasion, Ln(CRP) was measured in wave 2 (2004), mediators in wave 3 (2006), and depressive symptoms in wave 4 (2008). On the second occasion, Ln(CRP) was measured in wave 4 (2008), mediators in wave 5 (2010), and depressive symptoms in wave 6 (2012). There is adjustment for gender, age, accumulated wealth, limiting longstanding illness and medication use. Pathway magnitudes are calculated by multiplying the two associations with the mediator. Because each mediator has values between zero and one and the other variables are standardised, sizes are comparable. High waist measure indicates >=88cms for women and >=102cms for men.

Mean delays between measurements of depressive symptoms (in the main interviews) and CRP (in nurse interviews) are set out in Table 4.9. During the same wave, measures of depressive symptoms were mostly made one to two months before measures of CRP. SEM results provide no evidence of direct effects of Ln(CRP) on depressive symptoms during the same wave. Neither is there evidence of this in sensitivity analyses that include only respondents whose nurse and main interviews were one month or less apart (Appendix 22).

Table 4.9: Delays between main and nurse interviews

	Number of months between main and nurse interview						
	Mean	S.D.	Min	Max	Mode	Median	Inter-quartile range
Wave 2	1.25	1.23	-3	11	1	0-1	>0-<2
Wave 4	1.83	1.89	0	13	1	0-1	>0-<2
Wave 6	1.01	0.87	-6	7	1	0-1	>0-<1

Most nurse interviews took place after main interviews. Information is only available about year and month of interviews, to protect the anonymity of respondents.

There are autocorrelations between waves 3 and 5 for each hypothesised mediator, and their error terms in wave 3 are all positively correlated.

Ln(CRP) in wave 2 has a direct effect on depressive symptoms in wave 4, but this is not repeated between waves 4 and 6, after fuller adjustment for history of CRP and the hypothesised mediators.

Associations between Ln(CRP) and depressive symptoms four years later are mediated by physical inactivity, pain and stress-and-withdrawal. Magnitudes of associations are small. For example, after adjustment for gender, age, wealth, limiting longstanding illness, medication use and earlier measures of CRP, depressive symptoms and all hypothesised mediators, physical inactivity in wave 5 mediates an association in which each SD increase in Ln(CRP) in wave 4 is associated with an increase in depressive symptoms in wave 6 (4 years

later) by 0.7%SD. This is equivalent to an association between 1mg/L CRP in wave 4 and an increase in depressive symptoms in wave 6 of 0.06. Prospective associations mediated by pain and stress-and-withdrawal are even smaller; 0.6% and 0.2%, respectively. Mediated associations between Ln(CRP) in wave 2 and depressive symptoms in wave 4 are of much greater magnitudes, but do not include adjustment for earlier levels of each mediator.

There is no evidence of direct effects of depressive symptoms on CRP four years later and very weak evidence of a small association mediated by physical inactivity, in which each SD increase in depressive symptoms is associated with an increase in Ln(CRP) by 0.4%SD.

Obesity predicts and is predicted by inflammation. One SD increase in Ln(CRP) in wave 4 is associated with a 2.4% increase in risk of very high waist circumference two years later. Having a very high waist circumference in wave 5 is associated with an increase in Ln(CRP) two years later by 6.9%SD, which is equivalent to 1.14mg/L. These associations are net of all confounding variables and earlier measures of CRP, depressive symptoms, waist circumference, physical inactivity, pain and stress.

As expected, there is evidence of autocorrelations between time-points for depressive symptoms and Ln(CRP). Co-variances of error terms in waves 4 and 6 are negative.

Age predicted Ln(CRP) and was negatively associated with depressive symptoms. Female gender, low wealth, limiting longstanding illness and medication use are each positively associated with both outcomes.

Results of sensitivity analyses are consistent with these results. See Appendix 22 Figures A22.1 and A22.2.

Building the final SEM from simpler specifications indicates that most associations and mediated associations are found regardless of the complexity of the specification.

The ADF estimation method was used with a much smaller sample; 1,762 as opposed to 11,986 using MLMV estimation. This method makes no assumptions about the distributions of variables, but only includes respondents who provided complete information. The ADF method produced some negative correlations, probably due to difficulties fitting the specification to the data with small numbers, but otherwise the results are remarkably consistent with those produced when the MOMV method is used.

Excluding respondents whose main and nurse interviews were more than two months apart made no difference to the results.

SEM models that used alternative measures of psychological stress that excluded, one at a time, social withdrawal, subjective social status and financial strain, and that used an alternative measure of pain that excludes back pain produced identical results.

When BMI of 30 of above was used to measure obesity instead of high waist circumference, results were similar. However, relationships between depressive symptoms and subsequent continuous measures of both waist circumference and BMI were negative and statistically significant.

RQ3. Moderation by gender, age and health status

Results presented in Figure 4.4 and Table 4.10 suggest that these results do not differ substantially by gender or between those with and without at least one longstanding illness.

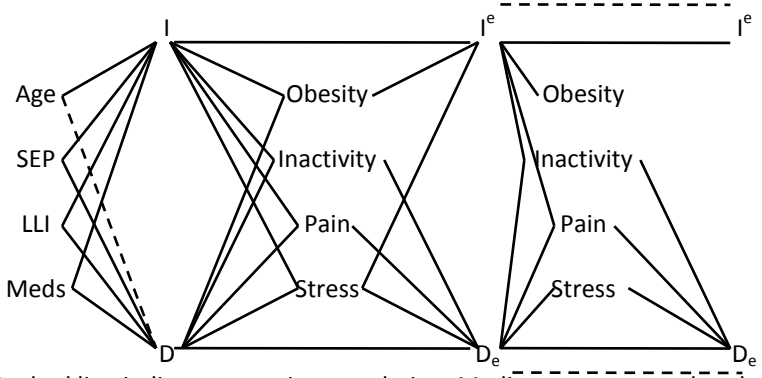
However, effect sizes are slightly larger for women than men, and among respondents with at least one longstanding illness compared with the whole sample.

For the sub-sample of respondents with RA, none of the prospective associations between inflammation and depressive symptoms, direct or mediated, are statistically significant. This is probably because few respondents reported RA (N=1,058) and the model is complex. Although numbers are also small for those with a history of asthma (n=2,935), prospective associations between inflammation and depressive symptoms are mediated by stress-and-withdrawal and inactivity.

Results of analyses using the sub-samples with asthma history and current asthma that exclude pain as a hypothesised mediator are similar. See Appendix 22.

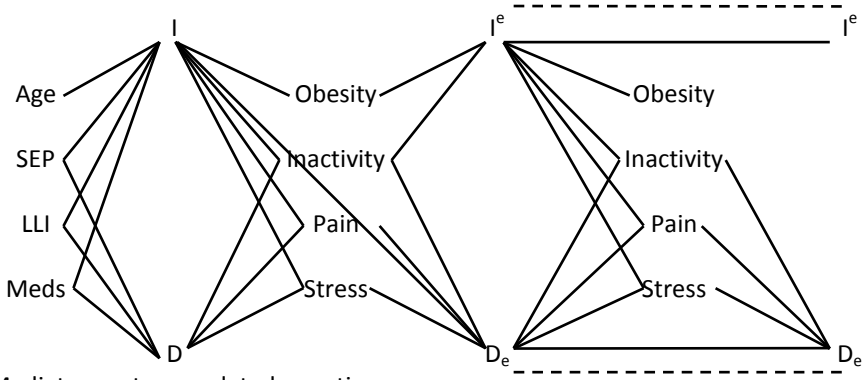
Figure 4.4: SEM results for sub-samples

Men (n=5,325)



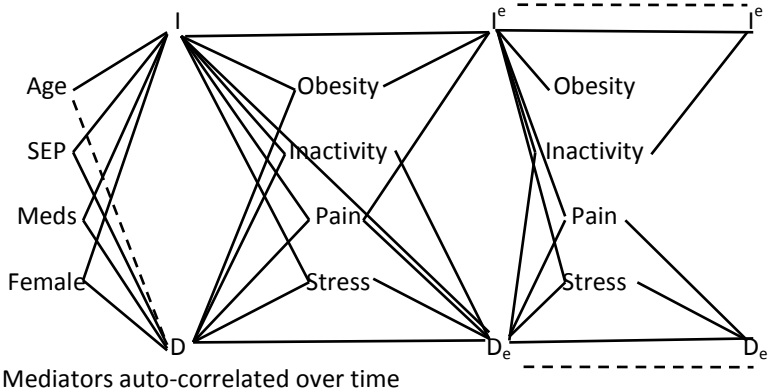
Dashed line indicates negative correlation. Mediators auto-correlated over time. Wave 3 mediators inter-correlated, except stress & obesity

Women (n=6,661)



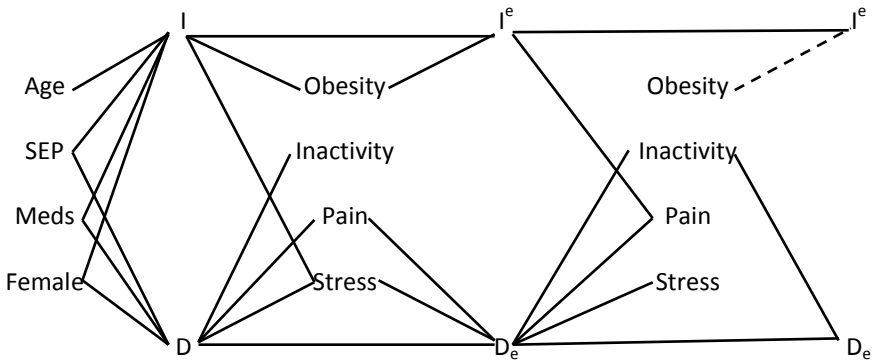
Mediators auto-correlated over time
Wave 3 mediators inter-correlated, except stress and obesity

Respondents with longstanding illness (n=10,625)



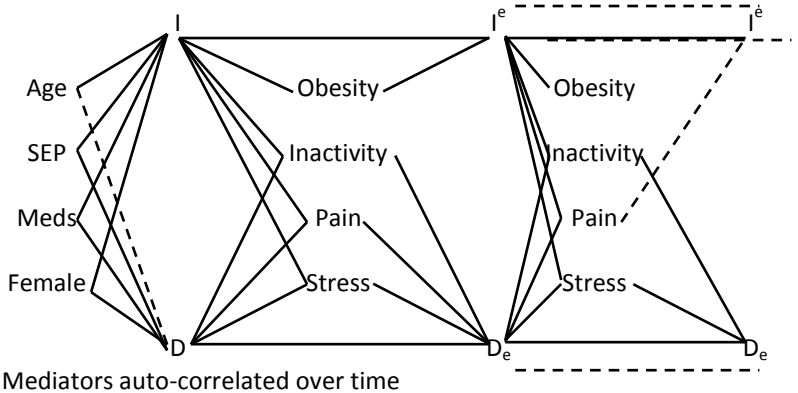
Mediators auto-correlated over time
Wave 3 mediators inter-correlated, except stress and obesity

Respondents with RA (n=1,058)

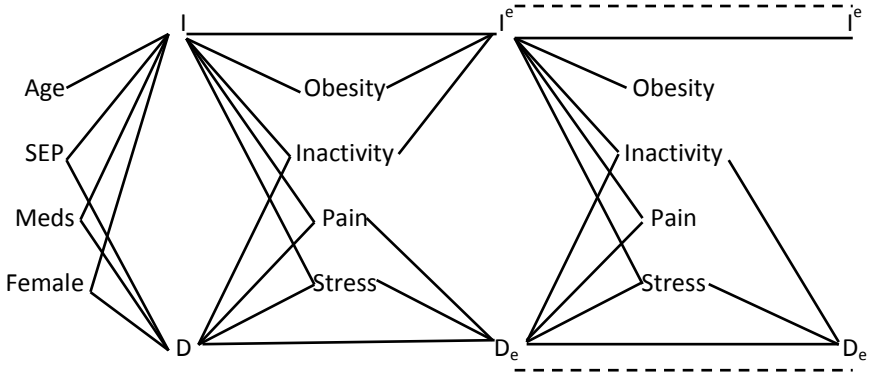


Mediators auto-correlated over time
Wave 3 mediators inter-correlated, except obesity and (1) stress (2) pain

Respondents with a history of asthma (n=2,935)



Respondents with currently active asthma (n=1,949)



Mediators auto-correlated over time
Wave 3 mediators inter-correlated, except obesity and (1) stress (2) pain (3) inacitivity

Table 4.10: Direct and mediated prospective associations between Ln(CRP) and depressive symptoms for each sub-sample

	Associations between baseline Ln(CRP) and depressive symptoms four years later													
	Whole sample		Men		Women		Chronic illness		RA		History of asthma		Current asthma	
Mediators	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6
None	0.054	---	---	---	0.061	---	0.067	---	---	---	0.090	---	0.105	---
Stress	0.104	0.002	0.006	---	0.016	0.003	0.012	0.003	---	---	0.015	0.006	0.043	---
Obesity	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Inactivity	0.016	0.008	0.020	0.005	0.013	0.010	0.016	0.010	---	---	0.017	0.003	---	0.004
Pain	0.022	0.006	0.009	0.004	0.032	0.005	0.021	0.005	---	---	0.040	---	0.042	---
	Waves:		**Associations between baseline depressive symptoms and Ln(CRP) four years later**											
Mediators	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6	2,3,4	4,5,6
None	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Stress	---	---	0.020	---	---	---	---	---	---	---	---	---	---	---
Obesity	0.004	---	0.004	---	---	---	0.009	---	---	---	---	---	---	---
Inactivity	---	0.004	---	---	---	---	---	0.004	---	---	---	---	0.006	---
Pain	0.008	---	---	---	---	---	0.010	---	---	---	---	*-0.007*	---	---
Observations	11,986		5,325		6,661		10,625		1,058		2,935		1,949	

Pathways are calculated by multiplying estimated associations between each mediator and (1) depressive symptoms, (2) Ln(CRP). If both associations are statistically significant ($p<0.05$), a value is given. Otherwise, the cell is filled with a blank. Measures of depressive symptoms and Ln(CRP) are standardised. One negative correlation is italicised.

5. Discussion

This section discusses finding, strengths and weaknesses, summarises conclusions and presents ideas about policy implications and directions for future research.

5.1 Discussion of findings

5.1.1 Relationship between inflammation and depressive symptoms four years later

This study adds confidence to a small body of epidemiological evidence that chronic low-grade inflammation predicts depressive symptoms. It provides an important contribution because depressive symptoms and inflammation were measured on three occasions and RE models were used so that prospective associations were estimated net of pre-existing levels.

Inflammation predicted depressive symptoms four years later, after adjustment for gender, age, education, wealth, longstanding illness and medication use. The magnitude of the association is small; each SD increase in baseline Ln(CRP) predicted an increase in depressive symptoms by 3.3%SD (95%ci=1.4%-5.2%, p=0.001, n=8,549). This is consistent with epidemiological evidence of prospective associations of small magnitudes between CRP and depressive symptoms after adjustment for similar covariates (Valkanova et al. 2013, Au et al. 2015, Das 2016).

The chapter provides new evidence about factors that mediate associations between inflammation and depressive symptoms. Using an exploratory approach, a wide range of factors were considered as mediators and those that were found to attenuate associations between inflammation and depressive symptoms were selected. SEMs with three measures of CRP and depressive symptoms at four year intervals included as hypothesised mediators

obesity, physical inactivity, pain and psychological stress-and-withdrawal. Physical inactivity, pain and an index of psychological stress-and-withdrawal mediated associations between inflammation and depressive symptoms four years later. The associations were robust to adjustment for hypothesised confounders (gender, age, SEP, limiting longstanding illness and medication use) and to a range of sensitivity analyses.

There were no direct effects of CRP on depressive symptoms, either concurrently or over four years. Obesity did not mediate associations between inflammation and depressive symptoms.

These are new findings and should be tested in other datasets.

This study did not set out to test the inflammatory theory of depression. To do so would require information about chronic inflammation and subsequent measures of depressive symptoms repeated at short intervals. Nevertheless, the evidence is relevant. At first sight, the results are inconsistent with the theory because there is no evidence of direct effects of CRP on depressive symptoms, either after four years, or during the same wave. But this may reflect the times between measurements of CRP and depressive symptoms. As mentioned in the introduction, laboratory evidence uses measures of inflammation and depressive symptoms a few minutes or hours later (Smith 1991, Miller et al. 2009), which is obviously very different from measuring depressive symptoms after a gap of four years. Although the SEM also estimated associations between CRP and depressive symptoms during the same wave of data collection, depressive symptoms were measured in the main interviews, and blood samples from which CRP was assayed were taken during the nurse interviews, most of which took place about a month after the main interview. Therefore, while the lack of

evidence for direct associations between CRP and depressive symptoms does not support the inflammatory theory of depression, neither does it indicate that the theory is incorrect.

However, the results, (which I emphasise are new and need to be tested in other datasets), are consistent with the hypothesis that chronic low-grade inflammation is associated with sickness behaviours that over time contribute to the development of depressive symptoms (Dantzer & O'Connor 2008, Miller & Raison 2016, Dantzer & Kelly 2007). CRP predicts psychological stress-and-withdrawal two years later. Social withdrawal is a sickness behaviour, which is associated with isolation and depression (Dantzer et al. 2008).

Social withdrawal and other sickness behaviours (increased arousal and anxiety and negative mood) probably affect how individuals respond to events and circumstances such that they are appraised as stressful. This explanation is consistent with evidence that cytokines affect the regulation of the HPA axis (Makhija & Karunkaran 2013, Capuron & Miller 2011), affecting physiological and psychological responses to stressors. Jiang et al. (2104) describe three biological mechanisms through which they suggest inflammation leads to depressive symptoms, and one of these involves activation of the HPA axis.

The importance of psychological stress as a mediator is indicated by findings that the psychosocial measures that most effectively attenuated the inflammation-depressive symptoms association are measures of perceived psychological stress as opposed to potentially stressful events and circumstances. Perceived stress reflects both stressful exposures and their psychological appraisal. Variables that most effectively attenuated the CRP-depressive symptoms association were subjective social status, self-efficacy and financial strain. In contrast, the role of caring, which is an exposure that is likely to be

stressful and which has been described as a stressor (Miller et al. 2014, Pearlin et al. 1997) did not attenuate the association.

More specifically, a single item rating of perceived financial strain attenuated the CRP-depressive symptoms association more effectively than a relatively objective measure of financial limitations based on the number of activities that respondents reported being unable to participate in because of financial limitations. Similarly, subjective social status, measured using a rating ladder, attenuated the association more effectively than more objective measures of status based on assessments of whether respondents were better off than specific groups; friends, neighbours and work colleagues.

Thus, although no evidence is provided that inflammation has immediate and direct effects on depressive symptoms, sickness behaviours associated with inflammation may contribute to social withdrawal and also to the appraisal of circumstances and events as stressful. Over time, both of these outcomes are likely to contribute to the development of depressive symptoms. It is also possible that sickness behaviours associated with chronic inflammation also affect perceptions of pain and motivation to participate in physical activities.

The finding that pain mediates associations between CRP and depressive symptoms is new but not unexpected. It is consistent with evidence of associations between pain and both inflammation and depressive symptoms, as set out by Kiecolt-Glaser and colleagues (2015). It is possible that perceptions of pain are increased by heightened arousal that is associated with inflammation. Pain is unpleasant and disabling, and if chronic it could contribute to the development of depressive symptoms.

Physical inactivity also mediated the association between CRP and depressive symptoms, independent of obesity. This is consistent with evidence of correlations between physical inactivity and inflammation (Gleeson et al. 2011), and with the hypothesis that fatigue induced by inflammation reduces motivation to engage in physical activity. Other studies report that physical inactivity is associated with depressive symptoms (Mammen & Faulkner 2013, Pereira et al. 2014). In addition, a study using ELSA waves 1 and 2 reports prospective associations between recurrent depressive symptoms and elevated CRP that was mediated by physical inactivity and obesity, after mutual adjustment Hamer et al. (2009).

9.1.2.1 5.1.2 Relationship between depressive symptoms and inflammation four years later

After adjusting for gender, age, education, wealth, longstanding illness and medication use, this study found is no evidence that depressive symptoms predicted CRP either concurrently or four years later. This is consistent with evidence from some large-scale epidemiological studies (Das 2016, Au et al. 2015, Gimeno et al. 2009). Other studies report prospective associations, but it appears that it is cumulative episodes of depression as opposed to single measures of depressive symptoms that predict inflammation (Copeland et al. 2012, Duivis et al. 2011, Hamer et al. 2009).

More detailed evidence from the SEM suggests that a small association is mediated by low physical activity. This finding should be tested in other datasets, possibly including cumulative episodes of depression.

In the context of the other variables included in the SEMs, there was little evidence that psychological stress-and-withdrawal predicted inflammation. Sensitivity analyses that excluded social withdrawal found no evidence that psychological stress predicted

inflammation either. This was not expected, as other studies provide evidence that chronic psychological stress predicts CRP levels (Johnson et al. 2013, Hansel et al. 2013, Berk et al. 2013). However, the relationships between psychological stress and inflammation are complex, since psychological stress has been found to predict both suppression of immune function (Chida & Mao 2009, Kiecolt-Glaser et al. 1995) and uncontrolled pro-inflammatory behaviours (Miller et al. 2002, Chrousos et al. 1996).

9.1.2.2 5.1.3 Variables that attenuated the CRP-depressive symptoms association: Consistency with existing evidence

After adjustment for gender and age, each of the following variables attenuated the cross-sectional association between CRP and depressive symptoms, rendering it non-significant; accumulated wealth, limiting longstanding illness, obesity, pain, physical inactivity, functional limitations, loneliness, self-efficacy, subjective social status, financial strain and social withdrawal.

Valkanova's critical review and meta-analysis of prospective associations between inflammation and subsequent depressive symptoms report associations of small magnitude that are robust to adjustment for a wide range of factors (Valkanova et al. 2013). On the face of it, this is inconsistent with our findings that the same prospective association is fully attenuated by individual variables. However, samples and analysis models differ between studies and this could explain apparent inconsistencies.

For example, Gimeno et al. (2009) tested attenuation of the prospective association between CRP and depressive symptoms and report no attenuation by SEP, health-related behaviours, biological factors, health conditions or medication use. Our study finds no or marginal evidence of full attenuation by metabolic factors, longstanding illness or

medication use. SEP was measured differently in this study; Gimeno and colleagues used occupational position, and this study uses accumulated wealth. In addition, this study does not measure health behaviours together, but rather physical inactivity. Gimeno's measure included physical inactivity combined with smoking and heavy drinking, which together attenuated to a very small degree the prospective association between CRP and depressive symptoms.

Another example is a study by Matthews et al. (2010), who report associations between CRP and depressive symptoms that are robust to adjustment for ethnicity, education, hormone therapy and menopausal status, smoking, health conditions, anti-depressant use, physical activity, BMI and waist circumference. The set of covariates differs from those included in my models, and so does the sample, as Matthews used a sample of Caucasian and African-American women with mean age of 42. Further, their study had more power because although the sample size was smaller (3,302 women), data were used from 7 sweeps of data collection.

The most comparable study to this one uses two waves of ELSA to examine prospective associations between CRP and depressive symptoms (Au et al. 2015). In line with the findings presented here, they report prospective associations between CRP and subsequent depression that are robust to adjustment for gender, age, education, marital status, employment status and smoking, but not to metabolic factors that included BMI. Unlike the results presented here, Au and colleagues do not find that physical inactivity fully attenuates the CRP-depressive symptoms association. However, their measure is not the same as mine and is combined with smoking.

In addition to the factors that fully attenuated the association, others partly attenuated it. These included low qualifications, which, as expected, were associated with higher levels of depressive symptoms and inflammation. Plasma levels of triglycerides and total:HDL cholesterol also predicted both outcomes, which is consistent with existing evidence (Tamakoshi et al. 2003, Au et al. 2013, Penninx et al. 2013). Medication use predicted depressive symptoms and CRP, and partially attenuated the association between them, in line with findings reported by Gimeno et al. (2009).

Consistent with existing evidence, smoking was associated with both depressive symptoms and CRP, and attenuated the association between them (Mathew et al. 2017, Berk et al. 2013, Calder et al. 2013, O'Connor et al. 2009, Copeland et al. 2012, Hamer et al. 2009).

Frequent alcohol consumption was associated with fewer depressive symptoms and lower CRP, and slightly attenuated the CRP-depressive symptoms association. This is consistent with findings from another study using ELSA data (Hamer et al. 2009). The measure used by this study and Hamer's is a binary indicator of daily or almost daily alcohol consumption. Studies using more detailed measures of alcohol consumption report that abstinence and heavy drinking predict higher, not lower, levels of depression and inflammation (O'Connor et al. 2009).

Several of the stress measures partly attenuated the association between CRP and depressive symptoms; namely, perceived strain, stressful relationships with partner, children, and friends, high perceived demands, feeling worse off than one's friends, and financial limitations. Measures of stress that did not attenuate the association were caring role and getting or losing a partner, which are exposures rather than experiences of stress. Community stress and work stress did not attenuate the association either, but numbers

were limited for these variables as community stress was measured in waves 1 and 3 only, and a minority of respondents were in paid work.

As expected, childhood adversity predicted both outcomes and partly attenuated the association. Other studies provide evidence that childhood adversity predicts depressive symptoms (Nelson et al. 2017, Li et al. 2016) and chronic low-grade inflammation (Fagundes et al. 2013, Hansel et al. 2010 , Taylor et al. 2006). A small-scale study of adult cancer patients reports that childhood adversity explained a prospective association between CRP and depressive symptoms (Archer et al. 2012).

A conscientious personality predicted lower levels of depressive symptoms and inflammation, partly attenuating the association between them. This is consistent with other evidence that conscientiousness is associated with positive health behaviours (Bogg & Roberts 2004) and positive health (Goodwin & Friedman 2006, Friedman 2008). The other dimensions of personality did not attenuate the association, although they were all associated with depressive symptoms.

9.1.2.3 5.1.4 Moderation by gender, age category and health status

I find no evidence of moderation by gender. The magnitude of associations between CRP and depressive symptoms four years later was slightly greater among women than men, but the difference was far from being statistically significant. This lends little support to the hypothesis that the association is stronger among women (Derry et al. 2015). But neither does it support the hypothesis that associations are stronger among men, suggested by some pre-existing evidence (Howren et al. 2009, Gimeno et al. 2009, Das 2016, Luukinen 2010, Vetter et al. 2013), although none of these studies formally tested for gender

differences. It is possible that no gender difference was apparent in this study because most of the women included were post-menopausal.

There was also no evidence that associations between inflammation and depressive symptoms differed between respondents aged 70 and over and those under 70. Inflammation predicted depressive symptoms for both age groups, and depressive symptoms predicted inflammation for neither. Stewart et al. (2009) found no evidence of a prospective association between inflammation and depressive symptoms in a relatively small sample with mean age of 61, and note that the association was reported using a sample of similar size but with respondents who were substantially older and reported poor health (Van den Biggelaar et al. 2007). The analyses presented here adjust for health status and medications, which probably differ between age categories. Nevertheless, the similarity of findings between the two age categories does not support the suggestion that biological processes differ among older populations (Alexopoulos & Morimoto 2011).

Although the difference was not quite statistically significant, associations between Ln(CRP) and subsequent depressive symptoms were greater for those with at least one longstanding illness. This is consistent with the argument presented in the introduction by Stewart et al. (2009) that among healthy populations, there is insufficient variation in inflammation and depressive symptoms to detect an association unless large samples are used. In our sample, the variances of depressive symptoms and CRP among those without a limiting longstanding illness were 2.1 and 3.5, respectively, compared against the higher values of 4.7 and 4.8 among those with at least one limiting longstanding illness. This would make it easier to detect existing associations.

The same factors mediated prospective associations between CRP and depressive symptoms for those with longstanding illness and the whole sample.

I thought that associations between CRP and depressive symptoms might be relatively strong among respondents with RA and asthma. However, there is no evidence of differences for respondents with histories of each condition. For respondents with RA, there was no evidence of mediated or direct associations between CRP and depressive symptoms, possibly because the sample size was small. However, among those with asthma, physical inactivity and stress-and-withdrawal each mediated the association between inflammation and depressive symptoms. Pain did not. This is not surprising, as pain is not a symptom of asthma. In fact, the results were unchanged when pain was excluded from the specification.

Additional findings about obesity, inflammation and depressive symptoms are discussed in Appendix 23.

5.2 Strengths and limitations

The evidence presented here draws on a very rich large-scale longitudinal dataset. ELSA includes comprehensive information encompassing biological, psychosocial and socio-economic factors, collected from adults aged 50 and over, who have been tracked since 2000. This chapter uses information collected during six waves, including biomarkers of inflammation collected on three occasions. Large sample sizes, measures on multiple occasions and the use of sophisticated statistical techniques means that analyses have been conducted using over 7,500 observations. Consequently, it has been possible to model several hypotheses simultaneously that explain prospective associations between depressive symptoms and inflammation. This provides new evidence about prospective associations between CRP and depressive symptoms and the factors that mediate them.

Furthermore, it has been possible to examine how these prospective associations differ by gender, age and health status.

Values in the dataset indicate its representativeness and validity. For example, in the sample, mean CRP is 2.3mg/L. Guidelines produced by the World Health Organisation suggest that baseline CRP over 3mg/l indicates increased vulnerability to a range of health conditions (Whicher 1998). Consequently, the mean level in the sample is quite high, probably reflecting its age, and the high proportion (55%) with longstanding illness. Other studies using samples of a similar age find similar levels of CRP (Stewart et al. 2009, Das 2016, Pasco et al. 2010, Baune et al. 2012).

Similarly, levels of depressive symptoms reported here are consistent with those reported in other studies that use the same measure in ELSA (Hamer et al. 2009, Daly 2013). About one in fourteen respondents reported active asthma, which is equivalent to rates reported among adults by Asthma UK (2013). In wave 2, 3.8% reported a history of RA, which is higher than national estimates (Widdifield et al. 2014), but very similar to the rate reported in a sample of adults of this age living in the US (Stewart et al. 2009).

The study also has limitations, one of which is that it is based on a sample of adults aged 50 and over living in England who are almost entirely white, and the results may not apply to other populations. Another limitation is selection into and attrition from the ELSA samples, which reduces sample size and can introduce bias. Reduced sample size decreases power, reducing the chances of detecting associations that exist in the population. Bias affects the accuracy of results in ways that are less predictable, and so is of more concern for the interpretation of findings.

Tables 4.3 and 4.6 present distributions of variables in the whole and analysis samples. These indicate that compared against the whole sample, respondents included in the analyses were better off economically, had higher qualifications, and better health, and reported healthier lifestyles, more social support, and lower levels of childhood adversity and adult psychosocial challenges.

Additional information about sample biases resulting from attrition is available from ELSA documentation (Scholes et al. 2008, Scholes et al. 2009, Cheshire et al. 2012, Bridges et al. 2015). This indicates that respondents who provided usable blood samples tended to live outside London and the North West of England, to be white, aged below 75, have qualifications at Level 2 or above, have higher status occupations, own their home, live alone or in households of at least four people, be divorced, widowed, or separated, retired, with no limiting longstanding illness, in good self-rated health, with vision and hearing, to be non-smokers and take regular exercise.

The biases in the samples used are likely to result in under rather than over estimations of associations between inflammation and depressive symptoms. Thus, the results presented here are conservative, and we can have all the more confidence in them.

This is for several reasons. First, those who live their lives in socio-economically advantaged positions tend to have better health. Therefore, sample bias excludes those who are disadvantaged and who have poor health outcomes, which serves to reduce the variation in inflammation and depressive symptoms. This makes it more difficult to identify existing associations between inflammation and depressive symptoms than it would be using a more representative sample. Further, results reported in this chapter indicate that accumulated wealth, level of qualifications, having at least one limiting longstanding illness, self-rated

health, physical activity, and smoking status each partially explain the magnitude and consistency of associations between inflammation and depressive symptoms. Reducing the variation in each of these variables due to sampling bias may make it more difficult to identify raw associations between inflammation and depressive symptoms that exist in the wider population. It will also make it more difficult to identify that each of these variables explains associations between CRP and depressive symptoms.

CRP was used to measure inflammation, but many other biomarkers could be used, possibly generating different results. Baune et al. (2012) examined associations between baseline levels of a variety of biomarkers of inflammation and subsequent depressive outcomes, and found relatively weak evidence of associations for CRP. In their review, Valkanova et al. (2103) suggest alternative biomarkers to CRP that may be more relevant to pathways linking inflammation to subsequent depressive symptoms. Ideally, a combination of biomarkers should be used to measure inflammation (Calder et al. 2013, Zhou et al. 2010).

Childhood adversity was measured using retrospective information, and biases due to sample selection, incomplete reporting, and measurement error are likely to differ between the retrospective and contemporaneous data. For example, cognitive function (more specifically, delayed recall) appears to be associated with accuracy of recall (Brown 2013), but it may not be associated with the reporting of contemporaneous information. In addition, this measure was available for relatively few respondents.

Numerous associations were tested and some may be statistically significant by chance. Evidence about factors that confound, mediate and moderate associations between inflammation and depressive symptoms is new, and while this is a strength of the study, the findings should be tested using other datasets

Low numbers meant that only a selection of hypothesised explanatory variables was included.

The selection of variables as salient attenuators of the association between inflammation and depressive symptoms depends on the accuracy and comprehensiveness with which they are measured. Other measures in different datasets might find evidence for a different group of mediators.

The SEMs were complex, and some negative auto-correlations within depressive symptoms and inflammation were almost certainly artefacts resulting from difficulties in fitting the data to the specifications. The research questions asked and the complex SEMs used to address them are new. Results are tentative. Nevertheless, a strength of this study is that the scope of the dataset made it possible to estimate even simplified SEMs. The findings should be tested in other datasets, but indicate that further research is needed about factors that mediate associations between chronic inflammation and depressive symptoms.

5.3 Conclusions, policy implications, and future research

This study provides an important contribution to a growing body of evidence indicating that chronic low-grade inflammation predicts depressive symptoms. It is particularly valuable because inflammation and depressive symptoms were measured on three occasions, which is one occasion more than in most studies to date. This is important because depressive symptoms and inflammation change over time together, and adjustment for earlier history lends more confidence to findings about the direction of prospective associations.

Prospective associations of very small magnitude were found between CRP and depressive symptoms four years later, after adjustment for gender, age, education, wealth, chronic

illness and medication use. Although effect sizes are small, they apply to a large population of community-dwelling adults aged 50 and over in England.

There is no evidence that depressive symptoms predict subsequent inflammation. It is possible that repeated episodes of depression predict inflammation but this hypothesis was not tested.

Prospective associations did not differ by gender, age group or health status. Gender differences have been indicated in previous studies and lack of such an indication in this study may reflect the predominance of women who were post-menopausal. Evidence about differences by age and health status is new. There is an indication that associations are stronger for those aged 70 and over and for those reporting at least one longstanding illness.

New evidence is provided about the factors that mediate prospective associations between chronic inflammation and depressive symptoms. Few studies, if any, provide such comprehensive evidence about mediated effects and further research using other datasets is needed to explore the roles of other potential mediators and to test the reliability of these findings.

In particular, the evidence presented here indicates that it will be fruitful to examine the how sickness behaviours affect outcomes that over prolonged periods may lead to further difficulties, such as the development of depressive symptoms. These outcomes include social participation and withdrawal, appraisal of potentially stressful exposures, engagement in physical activities and experiences of pain.

If replicated, the findings provide useful and specific information for policy makers and practitioners in public health who wish to address the negative consequences of chronic inflammation. As there is no evidence that inflammation directly affects depressive symptoms, antidepressant medication is not indicated in the first instance. Instead, for those at risk of chronic inflammation, interventions should focus on addressing pain, promoting physical activity and social participation, and helping individuals to cope more effectively with stressful events and circumstances. Doctors typically identify chronic inflammation and pain and prescribe appropriate pharmaceuticals. Policies should be developed that encourage doctors also to emphasise to patients with chronic inflammation the importance of physical activity, social participation and to explore whether they feel stressed. They should be encouraged to make referrals for support in relation to physical activity, social participation and experiences of stress.

Many additional questions remain that have not been addressed here. For example, to what extent do these results apply to ethnic groups that are not white Caucasian? What would the results be if other biomarkers of inflammation were used? Does the duration of inflammation matter for the subsequent development of depressive symptoms? If persistent depressive symptoms predict inflammation, is this association mediated by health behaviours? What are the relationships between inflammation and depressive symptoms among those with medically unexplained symptoms?

Chapter 5: Discussion

The thesis provides new evidence that illustrates the importance of relationships between psychological factors and immune dysregulation in a life-course context. Chapters 2 and 3 provide comprehensive evidence, much of it new, about social adversities that predict onsets of asthma and RA during adulthood, suggesting the importance of psychosocial pathways in the development of these immune-mediated conditions. The role of psychosocial pathways is exemplified by a new finding that depressive symptoms partially mediated associations between childhood adversity and the development of asthma decades later. Evidence of a small but consistent positive association between depressive symptoms and asthma onset shortly afterwards is new and intriguing, and partly motivated the choice of RQs addressed in Chapter 4. This chapter provides valuable evidence that among white adults in mid and late life, chronic inflammation predicts depressive symptoms four years later, and new evidence suggests that the association is mediated by psychological and behavioural factors associated with sickness behaviours.

This chapter discusses the strengths and limitations of the research and then summarises the main conclusions. Each conclusion is discussed in the context of existing evidence together with its implications for policy makers, practitioners and researchers.

1. Strengths and limitations

A strength of the thesis is that it draws on theory and evidence from multiple disciplines; Sociology, Psychology and Psychoneuroimmunology, the last being a hybrid of Neurology, Endocrinology and Immunology (Ader 2000). Biological evidence informed the choice of research questions and interpretations of findings.

The research questions addressed involve relationships between multiple factors over the life-course, and the research was only possible because of the availability of high quality datasets, excellent software and a wide range of simple and sophisticated statistical techniques. The NCDS and ELSA each contain comprehensive information collected using well validated instruments, and track large samples with repeated waves of data collection over many years. Large sample sizes and the use of multiple imputation meant that it was possible to examine rare outcomes; adult onset asthma and RA.

ELSA includes nurse interviews, and biomarkers of inflammation have been collected on three occasions. Combined with the extensive economic, social, psychological and behavioural information available, this meant that it was possible to examine prospective relationships between chronic inflammation and symptoms of depression and provide evidence about the socio-economic, behavioural and biological factors that confound and mediate the associations found.

The NCDS has some advantages over ELSA. It tracks the sample from birth, and so provides life-course data collected contemporaneously, although there is still some recall because sweeps of data collection are up to 10 years apart. ELSA collects data every two years, but most respondents joined the sample when they were aged 50 or over. Information about their lives before participation in the study was collected but it is retrospective and this limits its scope and quality. For example, psychological factors and health behaviours other than smoking are not measured, and sensitivity analyses reported in Chapter 3 indicated that recall of the ages when adversities were experienced was inaccurate.

Both the NCDS and ELSA are based on samples of predominantly white individuals. Findings could be different for other ethnic groups. In addition, the studies are subject to sample bias

because individuals who participate differ from those who do not. Sample bias may be amplified in ELSA, as core participants of ELSA are drawn from waves of HSE, which uses a sample designed to be representative of adults in England. Based on the ELSA sample, chapter 3 uses the sub-sample of respondents who participated in LIFE, and chapter 4 uses the sub-samples of respondents who participated in the nurse interviews, both drawn from the ELSA sample, which is itself a sample of the HSE.

Attrition bias develops over time, as participants with certain characteristics are more likely to drop out of the sample than others. Attrition rates are lower in the NCDS than in ELSA; 61.5% of the observed NCDS sample participated at age 42, and 49.8% of ELSA wave 1 respondents participated in wave 6. However, ELSA included refreshment samples in waves 3, 4 and 6, which addresses attrition bias.

Multiple imputation, which is used in chapters 2 and 3, addresses biases resulting from missing values and attrition but it does not address sample bias.

Incidence rates of asthma in chapter 2 and of RA in chapter 3 are very close to those reported in other studies (Simpson & Shiekh 2012, Widdefield et al. 2014). This lends confidence to the generalisability of findings. Further, most findings are about relationships between variables, which may not be much affected by sample and attrition biases. In fact, biases may serve to reduce evidence of relationships between adversity and poor health, in which case the evidence would err on the side of conservatism. This is because individuals who participate in surveys and follow-up surveys tend to be more socio-economically advantaged and healthier than non-participants (Ward et al. 2009, Atherton et al. 2007).

Another limitation of the evidence is that multiple relationships are tested and the conventional level of probability of 5% is used as a shorthand indicator of statistical significance. On average, 5% of the correlations estimated would be statistically significant if there were no relationships in the population from which the sample was drawn. Most of the relationships were tested because there were theoretical grounds for expecting them to exist, and many have been tested in other datasets. Nevertheless, some reported findings are new and could be specific to the dataset used. It is therefore necessary to test their reliability and validity using other datasets.

2. Main conclusions and implications for policy, practice and research

Five headline new findings, six research recommendations and three policy recommendations are summarised in Box 1.

2.1 Psychosocial factors predict onsets of asthma and RA

The thesis provides new evidence about the psychosocial factors that contribute to onsets of asthma and RA.

The importance of psychosocial factors was tested using a conceptual framework that classifies the pathways that lead to health inequalities as material, psychosocial (involving psychological responses to social exposures) and behavioural (Benzeval et al. 2014). Findings that social adversities (family and relationship-related adversities and traumatic events) predict onsets of asthma and RA after adjustment for material and occupation-related adversities is consistent with the involvement of psychosocial pathways, and adjustment for behavioural factors further isolates pathways involving psychological factors.

Box 1: Headline findings and recommendations for research and policy

Headline new findings

1. After adjustment for material adversities and behavioural factors, social adversities (relationship-related and traumatic) predict onsets of asthma during mid-adulthood and RA. This is consistent with the hypothesis that psychosocial pathways contribute to the development of these immune-mediated conditions.
2. Chronic but not acute adversities predict RA onset. This is consistent with biological evidence about the effects of psychological stress on the immune system.
3. Depressive symptoms mediate associations between childhood adversity and onset of asthma decades later, indicating that psychosocial pathways are involved in the development of asthma during adulthood.
4. Depressive symptoms shortly before mid-adulthood are a salient predictor of asthma onset soon afterwards.
5. Prospective associations between low-grade chronic inflammation and depressive symptoms years later are mediated by behavioural and psychological factors associated with sickness behaviours.

Research recommendations

1. Additional evidence is needed about how psychological stress contributes to immune dysregulation and other health outcomes. While relevant information has been collected in earlier sweeps of longitudinal surveys, it would be useful to devise and include in future surveys additional measures of stress, such as hair cortisol as a marker of physiological stress and measures of global and chronic psychological stress.
2. It may be fruitful to examine the different health impacts of chronic and acute adversities.
3. Further evidence is needed to test whether depressive symptoms or other psychological factors mediate associations between childhood adversities and health outcomes such as asthma onset.
4. The association between depressive symptoms and asthma onset soon afterwards is an intriguing finding and should be tested in other datasets. Depressive symptoms and other psychological factors may be proximal predictors of the onsets of asthma and of other immune-mediated conditions also.
5. More evidence is needed about the factors that mediate prospective associations between chronic inflammation and depressive symptoms using measures on multiple occasions. Likely mediators include sickness behaviours and the psychological, behavioural and biological outcomes associated with them.
6. Prospective associations may depend upon the chronicity of baseline inflammation or depressive symptoms. More evidence is needed to test this hypothesis.

Policy recommendations

1. Include in the training of practitioners in health and social care information about the importance of helping people to cope effectively with both traumatic events and ongoing situations that are likely to be stressful. These might include caring for a sick relative, living with a family member who is addicted to alcohol or other drugs, or relationship difficulties.
2. Provide training to health practitioners about the social and psychological predictors and consequences of immune-mediated diseases such as asthma and RA. This may facilitate early diagnosis and treatment, and inform management of these conditions.
3. Include inflammatory theories of depression in the training of health professionals.

After adjustment for material and occupation-related adversities, social adversities predicted onsets of both asthma and RA. Associations with RA onset were not mediated by smoking behaviour. The approach used to provide evidence about psychosocial pathways that lead to onsets of these conditions is new and so is the evidence. It is consistent with the hypothesis that psychological and physiological stress responses contribute to the development of asthma and RA.

New evidence was provided about the relative importance of chronic and acute social adversities for RA onset; chronic but not acute adversities predicted onset. The findings is consistent with theories of allostatic load (McEwen & Seeman 1999) and biological evidence and theory about impacts of stress on the immune system (Miller et al. 2014, Cohen et al. 2012).

Information about the types of adversity that predict onsets of asthma and RA is relevant for policy makers because it indicates the need to develop interventions that minimise the risk of exposure to these adversities and mitigate their impacts. For example, chronic family adversities predicted onsets of both asthma and RA after adjustment for material adversities and traumatic events. Family adversities included caring for a parent, partner or sick child, partnership breakdown and living with a partner or child addicted to a substance. The findings add weight to other arguments that carers should be offered practical support including opportunities for respite care. Interventions should be funded that help couples in difficulty and substance users who live with family members. Further, this evidence indicates that practitioners who work to support vulnerable individuals living in families communicate well not only with the individual, but also with every member of the family so that they all feel supported. Other evidence indicates that circumstances and events are perceived as more stressful if they feel out of one's control (Fairbank & Hough 1979, Averill

1973, Fusilier & Ganster 1989, Glass & Singer 1972), are unpredictable (Glass & Singer 1972) and not normative (Pearlin 2010). Practitioners have experience, knowledge and skills that mean that they do not feel that the situation is out of their control, unpredictable or not normative. If they communicate well with the families of their clients, they may be able to help them to deal more positively with these situations. This type of communication and support may be useful also for individuals who have faced traumatic events.

Evidence that depressive symptoms partly mediate associations between childhood adversity and asthma onset is a direct indication of the importance of psychosocial pathways in the development of asthma. However, it is not necessarily the case that depressive symptoms are the most salient psychological mediator of the association; they are the variable that was measured in the study and they may be associated with more salient mediators, such as psychological stress. Chronic psychological stress appears to predict both depressive symptoms (Kiecolt-Glaser et al. 2015) and asthma onset (Wright et al. 2005).

If psychological symptoms affect immune function, this begs questions about whether psychological interventions could be used to prevent or treat asthma, and about whether this might apply to other immune-mediated conditions. It also highlights the importance of developing policies that (1) minimise exposures to adversities that are likely to be stressful and distressing and (2) help people to cope effectively with them so that experiences of psychological stress and distress are minimised.

Chapters 2 and 3 provide evidence about additional factors that predict onsets of asthma and RA after adjustment for life-course adversity. For the first time, so far as I am aware,

contributions of psychological, behavioural and biological factors are assessed net of a comprehensive set of social and material adversities.

One of the factors that predicts asthma onset, after adjustment for life-course adversity and other carefully chosen factors, is depressive symptoms shortly before onset. The association is small in magnitude but consistent. Few studies have examined prospective associations between depression and asthma onset, although those that do report evidence of them (Jonas et al. 1999, Loerbroks et al. 2010, Scott et al. 2008). Chapter 2 adds to these findings by providing new evidence that depressive symptoms are particularly salient shortly before asthma onset.

An explanation is that diagnosed asthma is preceded by chronic low-grade inflammation, which leads to the development of both depressive symptoms (Smith 1991, Miller & Raison 2016, Hughes & Kumari 2017) and asthma. It raises questions about how inflammation leads to the development of depressive symptoms in the context of asthma onset and more generally, which are addressed in Chapter 4.

2.2 Additional evidence about adversities as predictors of asthma and RA onsets during adulthood

Life-course adversities summarise the environmental exposures that might contribute to negative health outcomes and, specifically, to onsets of asthma and RA. The adversities measured are neither exhaustive nor perfectly measured and consequently under-estimate total adversity. Whilst it is widely accepted that asthma and RA develop through interactions between genetic and environmental factors, the evidence presented in chapters 2 and 3 nevertheless illustrates the very substantial contribution made by environmental exposures to the development of each condition. These findings are

consistent with evidence provided by a handful of studies that examine the importance of adversities as predictors of asthma and RA, although the evidence presented here provides an important contribution because it includes a more comprehensive range of adversities measured over the life-course.

Findings that life-course adversities contribute substantially to the development of asthma and RA suggest that adversities may play an important role in the development of other immune-mediated conditions. They also indicate that prevalence rates of asthma and RA (and possibly other immune-mediated conditions) might be reduced by policy interventions as well as by prescription of pharmaceutical medicines. Understanding the environmental contributions to these conditions should therefore be a priority for public health.

Few studies provide evidence about gender differences in relationships between adversity and onsets of asthma and RA, and so the evidence provided in Chapters 2 and 3 constitutes an important contribution. Two large-scale studies report no evidence of gender differences in relationships between adversity and adult onset asthma (Lietzen et al. 2011, Rod et al. 2012) and chapter 2 similarly finds no gender differences. In relation to RA onset, existing evidence is even more sparse; just one study finds no statistically significant differences by gender (Wesley et al. 2014). Results presented in chapter 3 are not statistically significant either but suggest that risk of RA onset from mid-adulthood onwards is predicted more strongly by childhood adversity for women than men, and by adversity during adulthood for men than women. This implies that any gender differences are likely to be complex but not great in magnitude, and suggests that public health should be concerned with these relationships for men and women.

Only one study provides evidence about whether associations between life-course adversity and risk of adult onset asthma differ by atopic history (Lietzen et al. 2011). Chapter 2 reports findings consistent with Lietzen's that these associations are the same regardless of whether respondents report a history of hay fever or eczema. This evidence is relevant to understanding about why hay fever predicts asthma onset. There are numerous asthma phenotypes (Halder et al. 2008) and it is possible that hay fever predicts asthma onset because it reflects a biological vulnerability to atopic conditions that is a feature of some but not all asthma phenotypes. Development of asthma phenotypes not predicted by hay fever might therefore be more sensitive to environmental factors, measured by adversity. However, results presented in chapter 2 do not support this hypothesis but rather suggest that life-course adversities are equally important for asthma onset regardless of previous atopic history.

Differences in relationships between adversity and asthma onset by childhood temperament have not been investigated before and the evidence presented here is new. The hypothesis was that internalising temperament affects psychological and behavioural responses to adversities in ways that lead to asthma onset. If the hypothesis were true, if would imply that adversities predict asthma onset more among those with an internalising temperament during childhood. However, no evidence of differences was found between those with and without an internalising temperament and so the evidence did not support this hypothesis.

The ways in which adversities combine over the life-course to predict onsets of asthma and RA have not previously been examined. The thesis compares life-course models and concludes that adversities experienced during different life stages combine cumulatively to predict asthma onset. There is an indication that this cumulative model applies also to RA

onset, but the quality of the retrospective data used means that no conclusions can be drawn. The cumulative model is consistent with theories of allostatic load, which is conceptualised as a marker of physiological wear and tear that accumulates over the life-course (McEwen & Stellar 1993). It indicates that policies designed to minimise the risk of adverse exposures and mitigate their impacts should be developed for populations during all life stages.

After adjustment for social adversities, material adversities also predicted onsets of both asthma and RA. No other studies have examined the contributions of material adversities to onsets of asthma and RA during adulthood. However, financial hardship is an approximate marker of SEP, and a handful of studies have examined relationships between these diseases and SEP (Verstappen 2017, Basagna et al. 2004, Simpson & Sheikh 2010). Differences between studies in terms of samples, measures and methods used complicate comparisons. Nevertheless, the associations presented in the thesis between material adversities and disease onsets, after adjustment for social adversities and gender, are equivalent to or slightly smaller than positive associations with low SES reported in other studies (Simpson & Shiekh 2010, Ekerljung et al. 2010, Bergstrom et al. 2011, Bergstrom et al. 2013).

2.3 Additional evidence about behavioural and biological predictors of asthma and RA onsets during adulthood

Factors that predicted onset of asthma during mid-adulthood after adjustment for life-course adversity were depressive symptoms (as mentioned above), female gender, history of eczema and/or hay fever and internalising temperament during childhood. RA onset is predicted by life-course adversity, female gender, low educational qualifications and number of years smoking. This evidence is important because better understanding about

the predictors of each disease could facilitate their early diagnosis and treatment, which is associated with better prognoses. In particular, progression of RA can cause irreversible damage, which may be prevented if it is diagnosed and treated quickly.

Findings that asthma onset during adulthood is predicted by female gender and a history or other atopic conditions are consistent with evidence from numerous studies. However, evidence that adult onset asthma is predicted by depressive symptoms shortly before onset is new.

Evidence about the predictors of RA is consistent with existing evidence but is nevertheless valuable because it contributes to confidence in its reliability and validity. The gender difference in RA is well established (patient.co.uk 2016). Fewer studies report that RA onset is more common among individuals with lower levels of education (Bergstrom et al. 2013, Voigt et al. 1994) and those with a history of smoking (Tobon et al. 2010, Lahiri et al. 2012).

2.4 Prospective associations between chronic inflammation and depressive symptoms

Chapter 4 provides an important contribution to epidemiological evidence about prospective relationships between chronic low-grade inflammation and depressive symptoms. It finds no evidence that depressive symptoms predict chronic low-grade inflammation four years later, which is consistent with existing evidence (Copeland et al. 2012, Duivis et al. 2011, Hamer et al. 2009, Das 2016, Au et al. 2015, Gimeno et al. 2009).

However, there is evidence of a small prospective relationship between chronic inflammation and depressive symptoms four years later. This finding is consistent with most other studies (Valkanova et al. 2013) and with the inflammatory theory of depression (Smith

1991, Miller & Raison 2016, Hughes & Kumari 2017). While the magnitude of the association is small, it affects large numbers. It may be fruitful to investigate the nature of this relationship further, for example by examining whether prolonged inflammation matters more than shorter periods for depressive symptoms.

New evidence is provided relating to differences in these prospective associations by gender, age category and health status. No differences are statistically significant. In relation to prospective associations between chronic inflammation and depressive symptoms subsequently, effect sizes are slightly greater among those aged 70 and over and among those with at least one longstanding illness. There is no indication that these prospective associations differ by gender of between groups with and without asthma and RA.

It would be interesting to examine these relationships differ between people with and without heart disease and ME/CFS. Heart disease is characterised by both inflammation and depressive symptoms. Symptoms of ME/CFS resemble severe forms of the sickness behaviours (fatigue, malaise, and lack of motivation) that are typical of both chronic inflammation and depression, so there is high co-morbidity between ME/CFS and depression, and the condition is exacerbated by stress (Wessely et al. 1998).

2.5 Prospective associations between chronic inflammation and depressive symptoms are mediated by social withdrawal, psychological stress, pain and physical inactivity

A new finding is that the association between chronic low-grade inflammation and depressive symptoms four years later is fully explained by psychological stress and social withdrawal, physical inactivity and pain. The association was not mediated by obesity and findings relating to obesity are discussed in Appendix 23.

Few studies have tested mediation, possibly because inflammation, depressive symptoms and hypothesised mediators are auto-correlated over time and so it is difficult to assess the directionality of associations without multiple measures. Fortunately, repeated measures at three different time points made this possible.

As explained in Chapter 4, mediation by these factors is consistent with existing evidence of associations between physical activity, pain, psychological stress and social withdrawal and (1) chronic inflammation and (2) depressive symptoms.

A plausible explanation for the results is that sickness behaviours contribute to each factor. Social withdrawal has been described as a sickness behaviour (Miller & Raison 2016, Dantzer & Kelly 2007) and this, combined with fatigue (another sickness behaviour) could reduce motivation to engage in physical activity. Heightened arousal may increase sensitivity to pain. Heightened arousal and anxiety, negative mood and social withdrawal, which are sickness behaviours associated with inflammation, may affect how adversities are appraised, increasing the likelihood that they are perceived (and reported) as stressful. Consistent with this explanation is physiological evidence that indicates the involvement of pro-inflammatory cytokines in behaviours of the hypothalamic pituitary adrenal (HPA) axis, which is central to the stress response (Makhija & Karunkaram 2013, Capuron & Miller 2011, Jiang et al. 2014).

Physical inactivity, pain, social withdrawal and psychological stress could contribute over time to the development of depressive symptoms.

An important caveat is that the factors identified as particularly salient mediators may not be salient in other datasets, as salience depends upon the accuracy and comprehensiveness

of measurement, as well as sample characteristics. However, they suggest that behavioural and psychological factors associated with sickness behaviours mediate prospective associations between chronic inflammation and depressive symptoms. This hypothesis should be tested in other datasets. If the findings presented here are replicated, they have important implications.

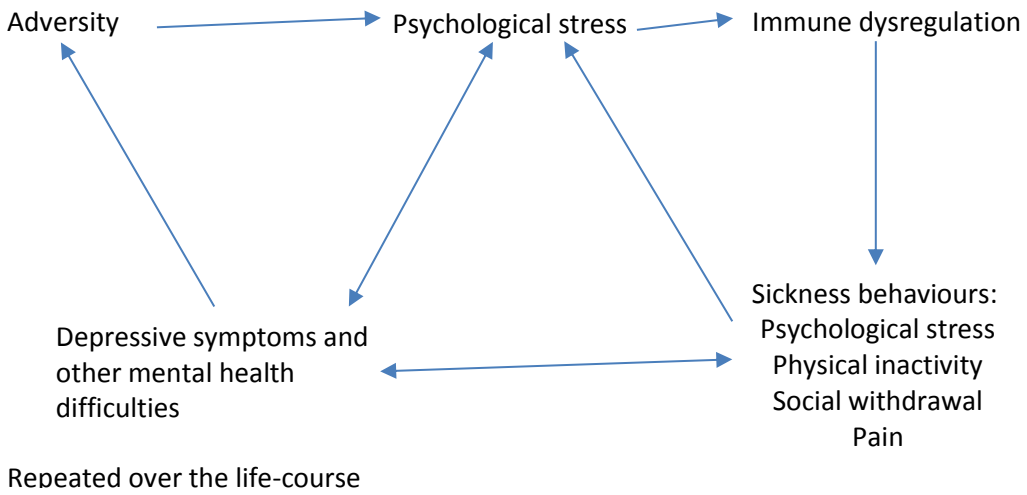
Health practitioners working with people likely to have chronic inflammation, for example people with immune-mediated diseases or heart disease, should be aware (and probably are already) that these people are likely to feel down and have increased depressive symptoms. This is not a necessary consequence of inflammation and so anti-depressants should not be used in the first instance. Rather, practitioners should treat consider treating inflammation and its causes, pain if patients are experiencing it, encourage social participation and physical activity unless this is contra-indicated by their condition, and do what they can to help patients cope with psychological stress. Simply knowing that feeling stressed can be a biological consequence of inflammation may help patients as it provides understanding that could contribute to feeling more in control. Policy makers could promote training about the inflammatory theory of depression, and also the more immediate outcomes of chronic inflammation. These findings suggest the importance of funding existing interventions that promote social participation and physical activity and provide support for those likely to feel stressed, as it appears that social withdrawal, physical inactivity and experiences of chronic stress may contribute to the development of depressive symptoms.

2.6 Psychological factors and immune dysregulation in a life-course context

The thesis includes three empirical projects that examine relationships between psychological factors and immune dysregulation. Immune dysregulation is measured using

an allergic disease (asthma), and autoimmune disease (RA) and chronic low-grade inflammation. These measures represent various types of immune dysregulation. Taken together, the results are consistent with a model illustrated in Figure 5.1.

Figure 5.1: Model representing hypothesised relationships between psychological factors and immune dysregulation within a life-course context



In the model, adversities lead to an increased risk of psychological stress, which impacts on immune function and increases the risk of immune dysregulation. Acute and chronic inflammatory responses, which are forms of immune dysregulation, are associated with sickness behaviours, and these contribute to psychological stress. Sickness behaviours also contribute to a heightened sensitivity to pain, physical inactivity and social withdrawal, and these, together with psychological stress contribute to the development of depressive symptoms and other mental health difficulties. These psychiatric symptoms may lead to additional adversities and to their negative appraisals. They may also affect motivation to participate in social and physical activities.

The model illustrates numerous vicious cycles in which immune dysregulation and negative outcomes reinforce one another. The evidence presented in the thesis is consistent with the model, but more evidence is needed to test it. If further research indicates that this model is a valid representation, policy makers must consider ways of breaking these vicious cycles.

Epidemiological evidence about psychological stress as a predictor of immune dysregulation is scarce, and research about the psychological correlates of chronic inflammation has mostly focussed on depressive symptoms and depression. This focus is probably because depression is recognised by clinicians as a medically important health outcome and well validated instruments exist to measure it based on depressive symptoms. These instruments focus on psychological symptoms, although depression and depressive symptoms unequivocally have a biological basis. Stress similarly has both biological and psychological manifestations and causes. Like depression, stress is a construct, but it does not have anything like the same clinical importance as depression, and its measurement is less developed.

Biological stress is measured by concentrations of cortisol excreted in saliva, urine and hair, but methods of measurement and their interpretations are still developing (Miller et al. 2016, Abell et al. 2016). Perceived psychological stress is measured in various contexts; relationship stress (Locke-Wallace 1959, Schuster et al. 1990), work stress (Siegrist 1996, Karasek et al. 1998), loneliness (Hughes et al. 2004) and community stress (Stafford et al. 2003). However, these experiences have cumulative effects and it would be useful to develop ways of combining existing measures to create indices of overall or global perceived psychological stress that are used across studies.

Findings presented in chapters 2 and 3 indicate that when other measures of psychological stress are unavailable, social adversities may provide useful proxy measures. Social adversities can affect health through material, behavioural and psychological pathways, but availability of large datasets with comprehensive information means that it is possible to adjust for factors that could affect health through pathways not involving stress. Evidence about relationships between adversities and health outcomes has the unrelated advantage of direct policy relevance.

It would also be valuable to continue developing well-validated measures of psychological and biological stress that are included in surveys. These measures can be used to investigate relationships between adversities, psychological stress, biological stress and immune dysregulation and other health outcomes.

Evidence about these relationships will contribute to understanding how the social becomes biological (Blane et al. 2013). The immune system developed early in the evolution of vertebrates and is closely integrated with all other physiological systems (Deng et al. 2013). Evidence exists about the physiological mechanisms through which psychological stress affects immune function (Wright 2005) and there is growing evidence about the physiological mechanisms that link chronic inflammation with psychological outcomes that are likely to affect appraisals of exposures as stressful (Byrne et al. 2016, Miller & Raison 2016). Evidence from the Social Sciences and Social Epidemiology is relatively sparse but, including the evidence from this PhD, it further highlights the importance of psychological stress for immune dysregulation. The development of high quality measures for both biological and psychological manifestations of stress that are included in surveys would provide the opportunity to investigate relationships likely to be central to understanding

about the psychosocial pathways through which socio-economic factors get under the skin (Bartley 2012) and inequalities in health develop over the life-course.

Oral presentations at peer reviewed conferences

March 2018 (London) 60 years of our lives: A scientific conference celebrating the National Child Development Study at 60, “Psychosocial predictors of asthma onset during mid-adulthood: Evidence from the NCDS”.

September 2016 (York) Annual Scientific Meeting of the Society for Social Medicine, “How do adversities predict onset of rheumatoid arthritis? Evidence from the English Longitudinal Study of Ageing”.

September 2016 (Winchester) Annual conference of the British Society of Population Studies, “The importance of material hardship and psychosocial factors for onset of rheumatoid arthritis”.

October 2015 (Dublin) Conference of the Society of Life Course and Longitudinal Studies, “Does adversity predict onset of rheumatoid arthritis? Evidence from the English Longitudinal Study of Ageing”.

September 2014 (Oxford) Annual Scientific Meeting of the Society for Social Medicine, “Does exposure to stressors predict onset of asthma during mid-adulthood? Evidence from the British 1958 birth cohort”.

October 2014 (Lausanne) Conference of the Society of Life Course and Longitudinal Studies, “Do internalising type behaviours during childhood predict onset of asthma during mid-adulthood? Evidence from the British 1958 birth cohort”.

July 2014 (Oxford) Conference of the National Centre for research methods. Poster. “Stress, temperament, and onset of asthma in adulthood.”

Published conference abstracts

Hammond, C. (2016) 'How do adversities predict onset of rheumatoid arthritis? Evidence from the English Longitudinal Study of Ageing', Journal of Epidemiology and Community Health, 70: Supplement:A21.

Hammond, C. (2014) 'Does exposure to stressors predict onset of asthma during mid-adulthood? Evidence from the British 1958 birth cohort', Journal of Epidemiology and Community Health, 68, Supplement:A29.

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Appendix 1: Evidence of associations between adversities and negative health outcomes.

Table A1.1: Evidence that adversities used in Chapter 2 predict negative health outcomes

Adversity	Health outcome	Reference	Brief description
During childhood			
Cumulative adversity	Disrupted development of the brain, nervous, and immune systems; alcoholism; depression; eating disorders; heart disease; cancer	Middlebrooks & Audage 2008	Summary of evidence, published by the Centers for Disease Control and Prevention (CDC).
	Development during childhood and adult functioning of nervous, endocrine, and immune systems; in adulthood type 2 diabetes and cardiovascular disease.	Danese & McEwen 2012	Review.
	Ischaemic heart disease, cancer, chronic lung disease, skeletal problems, liver disease, sexually transmitted diseases, depression, suicide attempts, poor self-rated health, obesity, smoking, alcoholism, drug abuse; at least fifty sexual partners, physical inactivity.	Felitti et al. 1998	Following a routine medical examination, adults provided retrospective information about childhood exposures to adversities in the Adverse Child Experiences (ACE) Study, n=9,508.
	Early mortality up to age 50.	Kelly-Irving et al. 2013a	NCDS, n=15,221.
	Cancer by age 50 for women, evidence of a trend for men.	Kelly-Irving et al. 2013b	NCDS, n=6,138.
	Adult onset arthritis	Von Korff et al. 2009	World Mental Health Survey, a cross-sectional study with retrospective information about childhood adversity, n=18,309.
	Hospital admissions for asthma among adults	Wainwright et al. 2007	Longitudinal study of English residents, retrospective data about childhood adversities, n=20,854.
	Lifetime asthma prevalence	Scott et al. 2008	World Mental Health Survey, n=18,303.
Time spent in care	Poor preventive health care whilst in care, in terms of annual health assessments, immunisations, and dental checks.	Department of Health 2001.	Report of national statistics using data from 42,200 children who had been looked after continuously for 1yr+ in 2000
	In adulthood, lower self rated health; depression; smoking; less exercise amongst younger cohort only	Jackson et al. 2002	Longitudinal prospective data from the NCDS and 1970 British Cohort Study. N depends on outcome but 728 and 722 cohort members spent time in care in the NCDS and BCS70, respectively.
	Depression in adulthood	Hobcraft 1998.	NCDS, n=18,558.
Early parental loss	Parental death associated with depression among women,	Maier &	Current health data with retrospective data about

	parental divorce associated with physical health problems among men.	Lachman 2000	early parental loss from adults aged 30-60 in MIDUS, n=2,988.
	Parental death is associated with adult onset asthma.	Scott et al. 2008	World Mental Health Survey, a cross-sectional study with retrospective information about parental death, n=18,303.
Neglect	Dysregulation of the stress response, measured using cortisol, at age 45 among women but not men.	Power et al. 2012	NCDS, n=4,777.
Parental mental illness	Adult onset asthma.	Scott et al. 2008	World Mental Health Survey, n=18,303.
Financial adversity	Low birthweight, death, disability, illness and psychological ill health during infancy and childhood.	Spencer 2008	Summary of evidence.
	Lung function at age 44-46, measured using fev_1.	Bartley et al. 2011	NCDS, n=6,287.
	After adjustment for demographics, no associations with number of serious health conditions, illness symptoms, functional impairment, self-rated health, or depressive symptoms in old age.	Kahn & Pearlin 2006	Retrospective information about financial hardship collected from US residents aged 65+, n=1,167.
Residential mobility	Reduced continuity of health care and emotional and behavioural problems during childhood, early use of illegal drug use, depression during adolescence, teenage pregnancy.	Jelleyman & Spencer 2008	Review.
	Use of illegal drugs at ages 18 and 36; psychological distress, suicidal ideation, and smoking at age 18 but not at 36.	Brown et al. 2012	Longitudinal study in Scotland, n=850.
	Among boys, more behavioural problems and health risk behaviours, measured using smoking, drinking, marijuana use and sexual behaviours.	Duncan 2013	Evaluations of the US Gautreaux program, which moved thousands of families out of socio-economically deprived areas.
During adulthood			
Material			
Income	Graded relationship with mortality risk.	Sorlie et al. 1995	Income data for adults aged 25+ in the US, tracked using national mortality statistics, the Death Indices, n=530,000.
Perceived financial strain	Number of serious conditions; depressive symptoms; poor self-rated health; illness symptoms; poor physical functioning	Kahn & Pearlin 2006	Retrospective information about financial hardship collected from US residents aged 65+, n=1,167.
Homelessness	Poor physical and mental health, drug and alcohol dependency.	Griffiths 2002	Literature review.
Occupation-related			

Unemployment	Mortality. Associations particularly strong among men and for periods of unemployment during early-middle stage of careers	Roelfs et al. 2011	Review and meta-analysis
	Poor psychological health; poor physical health; suicide	Wanberg 2012	Review
Involuntary job loss during mid-life	Depressive symptoms among men but not women	Wahrendorf et al. 2013	Depressive symptoms measured contemporaneously using a longitudinal European survey (SHARE) which includes retrospective employment histories, n=4,822.
Occupational stress	Incident coronary heart disease	Kuper & Marmot 2003	Longitudinal study of civil servants working in London, n=10,308.
	Smoking, alcohol consumption, obesity, physical inactivity	Kouvonen et al. 2006	Cross sectional study of public sector employees in Finland, n=36,127.
Relationship-related			
Divorce and separation	Temporary increase in psychological distress	Booth & Amato 1991	Eight year longitudinal study of married persons living in the US , n=2,033
	Poor mental health measured using GHQ, especially soon after separations	Willitts et al. 2004	The British Household Panel Study (BHPS) aged under 65, n=4,430.
Death of partner	Increased mortality risk especially among men and younger survivors	Stroebe et al. 2007	Review.
Relationship difficulties with partner	Mortality; morbidity; poor self rated health; dysregulation of the cardiovascular, immunological and endocrine systems	Loving & Slatcher 2013	Review.
	High allostatic load	Seeman et al. 2004	Longitudinal study of Taiwanese residents aged 54-90, n=950.
Overcrowded housing	Depression; psychological symptoms; accidental and violent deaths, including suicide	Page 2002	Summary of evidence.
Loss of child			
Death of child	Early mortality, especially among women	Stroebe et al. 2007	Review.

NCDS is National Child Development Study, a prospective study of all babies born March 3-9 1958 in mainland Britain, followed up on multiple occasions.
World Mental Health Survey is a cross sectional study of adults living in countries that include Colombia, Mexico, United States, Belgium, France, Germany, Italy, Netherlands, Spain, Ukraine, Lebanon, Nigeria, Japan, and China.
MIDUS is the Midlife Development in the US Survey, a nationally representative survey of adults living in the US aged 25+ conducted in 1995-1996 and followed up between 2002 and 2006.
SHARE is the Survey of Health and Retirement in Europe, a longitudinal study of adults aged 50+ living in 19 European countries. It includes LIFESHARE, a survey of retrospective information that includes employment histories.
BHPS is the British Household Panel Survey, a stratified general population sample that has been followed up every two years.

Appendix 2: Measurement of quality of relationship with partner

The quality of cohort members' relationships with their current partner was assessed at age 33 using the Locke-Wallace Marital Adjustment Test. Locke & Wallace (1959) report that this test has good reliability and validity. A binary variable was created to indicate relationship quality likely to cause distress using a cut point of 100, which is the score generally used to identify distressed persons (Crane et al. 2000). The items are listed below.

How happy is your relationship, all things considered?
1 (extremely happy) to 7 (extremely unhappy)

Most people have disagreements with their partner. Please show how much you and your partner agree or disagree about the things listed below:

1. Handling family finances
2. How to spend your time
3. Showing affection for each other
4. Liking the same friends
5. Having sex together
6. Behaving generally in the right and decent way towards other people
7. Sharing household tasks
8. Outlook on life
9. Relationships with parents or parents-in-law
10. Deciding if or when to have children
11. How children should be brought up

When disagreements arise between you and your partner how do they usually end?

a) You give in
b) your partner gives in
c) agreement by mutual give and take
d) you both agree to differ
e) varies/depends/don't know

Do you and your partner share any outside interests?

a) Yes, we share all our outside interests
b) Yes, we share some outside interests
c) Yes, we share a few outside interests
d) No, we don't share any outside interests

In leisure time do you usually prefer to be out and about or stay at home?

a) I prefer to be out and about
b) I prefer to stay at home

In leisure time does your partner usually prefer to be out and about or stay at home?

a) My partner prefers to be out and about
b) My partner prefer to stay at home

Do you ever wish you had not married (or lived as a couple)?

a) Yes, frequently
b) Yes, occasionally
c) Only rarely
d) No, never

If you had to live your life over again, which of these do you think you would do?

a) Marry (or live as a couple with) the same person
b) Marry (or life as a couple with) a different person
c) Not marry (or live as a couple) at all
d) Don't know

Do you share your problems with your partner?

a) Yes, I share all of them
b) Yes, I share most of them
c) Yes, I share some of them
d) No, I share none or hardly any of them

Appendix 3: Factor analyses of responses to items of Rutter scale

Factor analyses were conducted using maximum likelihood estimation, and specifying three factors that might be correlated. The factor loadings after rotation are presented in Table A3.1.

Table A3.1: Factor loadings on items of Rutter parent scale

	7			11			16		
Wording of items	Ext	Int	Rst	Ext	Int	Rst	Ext	Int	Rst
Difficulty settling to anything[1]	-0.03	-0.05	0.65	-0.01	-0.04	0.61	0.14	0.01	0.48
Prefers to do things on his/her own[2]	0.08	0.18	-0.03	0.09	0.15	-0.08	-0.02	0.34	-0.02
Is bullied by other children[3]	0.07	0.29	0.09	0.1	0.23	0.1			
Destroys own or others belongings[4]	0.26	-0.11	0.25	0.28	-0.07	0.16	0.42	-0.08	0.08
Is miserable or tearful[5]	0.31	0.28	0.01	0.37	0.23	0.01	0.27	0.39	-0.03
Is squirmy or fidgety[6]	0.07	0.03	0.55	0.03	-0.01	0.61	-0.03	-0.01	0.71
Worries about many things[7]	-0.05	0.73	-0.03	-0.02	0.77	-0.04	-0.06	0.59	0.01
Is irritable, quick to fly off handle	0.5	0.12	0.04	0.56	0.1	0.00	0.50	0.21	0.06
Sucks thumb or finger during day[8]	-0.02	0.06	0.05	0	0.04	0.09	0.05	0.08	0.03
Is upset by new situation[9]	-0.04	0.5	-0.02	-0.04	0.49	0.03	-0.09	0.49	0.01
Has twitches, mannerisms or tics of the face[10]	-0.01	0.1	0.18	-0.01	0.07	0.18	0.04	0.1	0.14
Fights with other children[11]	0.53	-0.16	-0.02	0.51	-0.15	-0.01	0.62	0.03	-0.08
Bites nails[12]	0.04	0.06	0.11	0.05	0.02	0.14	0.07	0.06	0.14
Is disobedient at home[13]	0.63	-0.05	0	0.57	-0.07	0.03	0.06	-0.06	0.06
Often tells lies[14]							0.56	-0.06	0.05
Bullies other children[14]							0.57	-0.04	-0.10
Very restless. Has difficulty staying seated for long[14]							-0.04	-0.01	0.73
Not much liked by other children[14]							0.25	0.13	0.00
Fussy or over-particular[14]							-0.01	0.33	-0.03
Has the study child had attacks of migraine or recurrent sick headaches in the past 12 months?[14]							0	0.2	0.01

1. Wording at 7 and 11: "Has difficulty settling to anything for more than a few moments". Wording at 16: "Cannot settle to anything for more than a few moments"
2. Wording at 7 and 11: "Prefers to do things on his/her own rather than with others. Wording at 16: "Tends to do things on own – rather solitary"
3. Asked at age 7 and 11 only.
4. Wording at 7 and 11: "Destroys own or others belongings (tears or breaks)". Wording at 16: "Often destroys own or other's property"
5. Wording at 16: "Often appears miserable, unhappy, tearful or distressed"
6. Wording at age 16 is, "Squirmy, fidgety child"
7. Wording at 16: "Often worried, worries about many things"
8. Wording at 16: "Frequently sucks thumb or fingers".
9. Wording at 7 and 11: "Is upset by new situations, by things happening for the first time". Wording at 16: "Tends to be fearful or afraid of new things or new situations"
10. Wording at 7 and 11: "Has twitches or mannerisms of the face, eyes or body" Wording at 16: "Has twitches, mannerisms or tics of the face or body"
11. Wording at 16: "Frequently fights or is extremely quarrelsome with other children"
12. Wording at 16: "Frequently bites nails or fingers"
13. Wording at 16: "Is often disobedient"
14. Asked at age 16 only.

Ext=externalising, int=internalising, rst=restlessness.
Factor analyses using maximum likelihood estimation conducted allowing three factors, followed by rotations allowing correlations between factors.

Appendix 4: The Malaise Inventory

Respondents ticked yes or no boxes for each item, as instructed:
"These questions are concerned with how you are feeling generally. Please answer them by ticking either the 'Yes' or 'No' box for each one. It is important that you try to answer ALL the questions."

1. Do you often have back-ache?
2. Do you feel tired most of the time?
3. Do you often feel miserable or depressed?
4. Do you often have bad head-aches?
5. Do you often get worried about things?
6. Do you usually have great difficulty in falling or staying asleep?
7. Do you usually wake unnecessarily early in the morning?
8. Do you wear yourself out worrying about your health?
9. Do you often get into a violent rage?
10. Do people often annoy and irritate you?
11. Have you at times had a twitching of the face, head or shoulders?
12. Do you often suddenly become scared for no good reason?
13. Are you scared to be alone when there are no friends near you?
14. Are you easily upset or irritated?
15. Are you frightened of going out alone or of meeting people?
16. Are you constantly keyed up and jittery?
17. Do you suffer from indigestion?
18. Do you suffer from an upset stomach?
19. Is your appetite poor?
20. Does every little thing get on your nerves and wear you out?
21. Does your heart often race like mad?
22. Do you often have bad pains in your eyes?
23. Are you troubled with rheumatism or fibrosis?
24. Have you ever had a nervous breakdown?

Appendix 5: How multiple imputed datasets were created

Missing values were imputed in 20 datasets using stata version 15. No assumptions were made about patterns of missingness and therefore an imputation strategy was used that is referred to as the chained approach (Van Buuren 2007). The whole sample was used, except for three cohort members with missing values for gender.

Variables for which missing values were imputed were all those used in the analyses, referred to as variables of interest, and auxiliary variables. Criteria used to select auxiliary variables were that they should have few missing values and correlate with both values and missingness of each variable of interest. In order to select auxiliary variables, correlations were estimated between each proposed auxiliary variable and values and missingness for all variables of interest. Scores were devised to summarise the results as follows: evidence of associations with missingness and values for adult onset asthma were scored three, for total adversity at each life stage were scored two, and with other variables of interest were scored one. Results are presented in Table A5.1.

Auxiliary variables chosen were the number of sweeps in which cohort members participated up to age 55; at birth, occupational class of the cohort member's father or grandfather, maternal marital status, maternal age below 22, pain relief, foetal distress; during childhood, levels of maladjustment reported by parents and teachers.

Continuous measures were imputed using predictive mean matching, which does not assume that values of the outcome variable are normally distributed. Values were taken from respondents predicted to have a similar value, and a pool of 10 values was used from which one was sampled (Morris et al. 2014).

Table A5.1: Numbers of observations and evidence of correlations with missingness and values of variable of interest

Proposed auxiliary variable	Score[1]	Obs.	P-values for associations between proposed auxiliary variable and: Asthma onset		Childhood adversity		Transition adversity		Early adulthood adversity		Number of other variables of interest[2] with p-values<0.05 for values and missingness
			Value	Miss	Value	Miss	Value	Miss	Value	Miss	
Number of sweeps cm participated in[3]	**18**	**18557**	**0.727**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**12**
Participated in sweep 1	8	18557	0.268	0.000	0.011	0.000	0.312	0.000	0.000	0.000	4
Participated in sweep 3	5	18557	0.716	0.000	0.000	0.000	0.701	0.000	0.196	0.000	3
White British, Irish, other white	14	14501	0.342	0.000	0.000	0.000	0.015	0.000	0.007	0.000	8
Occupational class father/maternal grandfather	**15**	**17170**	**0.213**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**9**
Mother left school after minimum leaving age	10	17352	0.253	0.000	0.000	0.158	0.000	0.000	0.000	0.011	6
Mother under 18 at birth	6	17400	0.188	0.009	0.000	0.000	0.001	0.017	0.696	0.188	2
Both parents under 18 at birth	0	16729		0.417	0.823	0.699		0.234	0.998	0.805	0
Mother under 20 at birth	14	17400	0.877	0.000	0.000	0.000	0.000	0.000	0.000	0.011	8
Mother under 22 at birth	14	17400	0.396	0.000	0.000	0.000	0.000	0.000	0.000	0.003	8
Mother 40+ at birth	0	17400	0.498	0.477	0.739	0.000	0.274	0.015	0.772	0.854	0
Firstborn	6	14269	0.838	0.140	0.000	0.179	0.000	0.027	0.001	0.219	4
Mother not married at birth	**13**	**17404**	**0.834**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.003**	**0.000**	**7**
Worked >40hrs/wk 32+ wks pregnancy	3	16169	0.129	0.757	0.000	0.200	0.823	0.203	0.320	0.798	3
Any difficulty[4] during pregnancy	11	17405	0.193	0.042	0.043	0.009	0.783	0.411	0.515	0.032	11
Born before 30 weeks	4	15571		0.000	0.586	0.000	0.001	0.000	0.263	0.000	2
Born before 31 weeks	5	15571		0.000	0.799	0.000	0.001	0.000	0.114	0.000	3
Born before 32 weeks	7	15571		0.000	0.568	0.000	0.000	0.000	0.015	0.000	3
Born before 33 weeks	7	15571	0.811	0.000	0.245	0.000	0.000	0.000	0.007	0.000	3
Born before 34 weeks	6	15571	0.623	0.000	0.105	0.000	0.000	0.000	0.106	0.000	4
Born before 35 weeks	6	15571	0.739	0.000	0.005	0.000	0.002	0.000	0.124	0.000	2
Born before 36 weeks	7	15571	0.244	0.000	0.000	0.000	0.000	0.000	0.398	0.000	3
Born before 37 weeks	10	15571	0.973	0.000	0.000	0.000	0.000	0.000	0.027	0.000	4
Pain relief during birth	**16**	**17371**	**0.259**	**0.002**	**0.000**	**0.000**	**0.016**	**0.000**	**0.002**	**0.000**	**10**
Foetal distress during birth	**13**	**17407**	**0.342**	**0.561**	**0.001**	**0.000**	**0.011**	**0.208**	**0.000**	**0.006**	**9**
Any complication during delivery	12	17408	0.842	0.175	0.044	0.000	0.114	0.000	0.005	0.000	8
C-section elective delivery	3	17408	0.516	0.822	0.003	0.000	0.394	0.546	0.154	0.007	1

Number of family difficulties at age 7[5]	19	14210	0.143	0.000	0.000	0.000	0.000	0.000	0.000	0.000	13
One/both parents have chronic physical illness by 16	6	14654	0.092	0.170	0.000	0.000	0.025	0.194	0.000	0.553	4
Shared loo/bathroom/cooking facilities/hot water at 7	16	14550	0.079	0.000	0.000	0.369	0.000	0.000	0.000	0.000	12
>2persons/room[6] at 7	12	13951	0.507	0.000	0.000	0.002	0.000	0.015	0.000	0.000	6
Maternal separation >1 month at 7	14	14226	0.348	0.000	0.000	0.000	0.000	0.000	0.000	0.000	8
Maternal separation >6 months at 7	14	14226	0.096	0.000	0.000	0.000	0.001	0.000	0.000	0.001	8
Maternal separation >1 year at 7	13	14226	0.421	0.000	0.000	0.000	0.003	0.000	0.004	0.001	7
Maternal separation >2 years at 7	12	14226	0.482	0.002	0.000	0.000	0.021	0.001	0.024	0.007	6
Maternal separation >1m between 6-24m	11	13945	0.862	0.000	0.000	0.048	0.042	0.006	0.368	0.026	7
Maternal separation >6m between 6-24m	5	14028	0.289	0.006	0.000	0.004	0.026	0.003	0.217	0.607	1
Maternal separation >1yr between 6-24m	5	14038	0.179	0.061	0.000	0.004	0.004	0.007	0.623	0.263	1
% children in school from manual background at 7	17	10956	0.576	0.000	0.000	0.000	0.000	0.000	0.000	0.000	11
% children in class from manual background at 7	7	7439	0.116	0.028	0.000	0.013	0.000	0.000	0.000	0.463	3
Poor vision, hearing or speech at 7	13	13992	0.035	0.002	0.000	0.219	0.001	0.011	0.030	0.000	10
Limiting longstanding illness at 7	2	14596	0.888	0.000	0.000	0.777	0.299	0.813	0.211	0.055	2
Disabling condition/handicap age 7	3	14551	0.834	0.000	0.000	0.334	0.349	0.366	0.012	0.043	1
Had immunisations by 7	10	14264	0.261	0.000	0.000	0.972	0.000	0.013	0.000	0.023	6
Number common childhood diseases by 7	4	14580	0.554	0.188	0.000	0.705	0.990	0.086	0.903	0.041	4
History of infections[7]	1	14477	0.226	0.000	0.001	0.062	0.817	0.300	0.359	0.178	1
Cognitive ability at age 7	21	14406	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	12
Teacher rates child below average at 7[8]	21	14946	0.043	0.000	0.000	0.000	0.000	0.000	0.000	0.000	12
BMI at age 7	1	13295	0.172	0.008	0.107	0.000	0.512	0.455	0.921	0.161	1
BMI at age 11	4	12498	0.704	0.544	0.000	0.020	0.581	0.854	0.237	0.402	2
BMI at age 16	2	11040	0.561	0.642	0.040	0.275	0.032	0.353	0.155	0.119	2
Smokes at least 10 per week at 16	14	11969	0.571	0.000	0.000	0.000	0.000	0.000	0.000	0.006	8
Smokes at all at age 16	14	11969	0.621	0.000	0.000	0.000	0.000	0.000	0.000	0.006	8
Lifetime prevalence of asthma at 33[9]	15	12667			0.000	0.000	0.000	0.000	0.000	0.000	9
Maladaption score parent Rutter scale at 7	9	13650	0.078	0.000	0.000	0.000	0.000	0.136	0.000	0.013	5
Maladaption score from BSAG[10] at 7	18	14926	0.136	0.000	0.000	0.000	0.000	0.000	0.000	0.000	12
Maladaption score parent Rutter at 11	15	12408	0.005	0.000	0.000	0.000	0.000	0.001	0.000	0.022	6
Maladaption score from BSAG[10] at 11	21	14156	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	12
Maladjustment score parent Rutter at 16	17	10982	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	8
Maladaption score teacher Rutter at 16	20	11610	0.001	0.000	0.000	0.001	0.000	0.000	0.000	0.000	11

Mean maladaption parent Rutter score 7,11,16[10,11]	**16**	**16297**	**0.037**	**0.218**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**10**
Mean maladaption teacher BSAG/Rutter 7,11,16[10,11]	**21**	**16843**	**0.004**	**0.000**	**0.000**	**0.001**	**0.000**	**0.000**	**0.000**	**0.000**	**12**
Parent reports cm sensitive/highly strung at 7	4	14392	0.010	0.000	0.000	0.081	0.704	0.848	0.683	0.023	1
Parent's assessment of child's activity at 7	4	14585	0.640	0.007	0.000	0.000	0.000	0.338	0.000	0.064	2
BSAG[10] unforthcomingness score age 7	7	14928	0.420	0.000	0.000	0.554	0.000	0.000	0.000	0.000	3
BSAG[10] withdrawel score age 7	7	14927	0.622	0.000	0.000	0.257	0.000	0.000	0.000	0.000	3
BSAG[10] depression score age 7	17	14927	0.155	0.000	0.000	0.024	0.000	0.000	0.000	0.000	11
BSAG[10] anxiety score age 7	9	14929	0.967	0.000	0.000	0.035	0.001	0.088	0.049	0.010	5
BSAG[10] hostility twds adults score age 7	17	14927	0.264	0.000	0.000	0.001	0.000	0.000	0.000	0.000	11
BSAG[10] writing off adults and their standards 7	14	14927	0.362	0.000	0.000	0.118	0.000	0.000	0.000	0.000	10
BSAG[10] anxiety for acceptance by children 7	10	14927	0.267	0.000	0.000	0.025	0.000	0.054	0.001	0.000	6
BSAG[10] hostility towards children score age 7	14	14927	0.845	0.000	0.000	0.001	0.000	0.000	0.000	0.000	8
BSAG[10] restlessness score age 7	15	14926	0.189	0.000	0.000	0.001	0.000	0.000	0.000	0.000	9
BSAG[10] unforthcomingness score age 11	12	14156	0.958	0.000	0.000	0.509	0.000	0.002	0.000	0.000	8
BSAG[10] withdrawel score age 11	11	14157	0.020	0.000	0.000	0.130	0.000	0.000	0.000	0.000	4
BSAG[10] depression score age 11	19	14158	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	10
BSAG[10] anxiety score age 11	15	14158	0.275	0.000	0.000	0.042	0.000	0.000	0.000	0.001	9
BSAG[10] hostility twds adults score age 11	21	14158	0.000	0.000	0.000	0.003	0.000	0.000	0.000	0.000	12
BSAG[10] writing off adults and their standards 11	13	14158	0.011	0.000	0.000	0.371	0.000	0.000	0.000	0.000	6
BSAG[10] anxiety for acceptance by children 11	14	14158	0.849	0.000	0.000	0.034	0.000	0.000	0.000	0.000	8
BSAG[10] hostility towards children score age 11	22	14158	0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	13
BSAG[10] restlessness score age 11	15	14158	0.485	0.000	0.000	0.190	0.000	0.000	0.000	0.000	11
Cautious-impulsive score age 16	15	12304	0.051	0.000	0.000	0.003	0.000	0.000	0.000	0.003	9
Moody-even tempered score age 16	16	12355	0.077	0.000	0.000	0.000	0.000	0.000	0.000	0.000	10
Timid-aggressive score age 16	10	12331	0.001	0.009	0.000	0.020	0.000	0.004	0.000	0.087	3
Flexible-rigid score age 16	11	12285	0.081	0.000	0.000	0.691	0.000	0.000	0.000	0.000	7
Sociable-withdrawn score age 16	8	12377	0.081	0.000	0.000	0.585	0.000	0.000	0.000	0.000	4
Lazy-hard working score age 16	18	12352	0.433	0.000	0.000	0.005	0.000	0.000	0.000	0.000	12
Extraversion score age 50	1	8549	0.439	0.002	0.125	0.776	0.492	0.738	0.733	0.388	1
Agreeableness score age 50	3	8524	0.599	0.765	0.168	0.211	0.484	0.300	0.000	0.882	3
Conscientiousness score age 50	4	8415	0.000	0.001	0.001	0.231	0.000	0.663	0.000	0.090	1
Emotional stability score age 50	7	8531	0.000	0.001	0.000	0.069	0.000	0.872	0.000	0.026	2
Intellect score age 50	0	8449	0.866	0.034	0.000	0.504	0.675	0.000	0.000	0.181	0

Variables in bold font are those selected as auxiliary variables.

1. Summary score is calculated by assigning scores for correlations with both missingness and values for asthma onset (scores 3), for total adversity during each life stage (scores 2), all other variables of interest (score 1).
2. Other variables of interest are smoking during pregnancy, low birth weight, breastfeeding, number of older siblings, history of eczema or hay fever up to age 33, pneumonia by age 7, urban industrialised residence at age 23, and at ages 23 and 33 smoking, obesity, and psychological distress (malaise score).
3. If cohort member participated in fewer than three sweeps, they are assigned a value of three.
4. High blood pressure, low haemoglobin, or other difficulty during pregnancy.
5. Reported by health visitor.
6. Excluding bathroom, skullery, and kitchen.
7. Three or more throat/ear infections in last 12m or ever pneumonia/urine infection by 7.
8. Rated below average ability in all areas; oral, awareness, creativity, and numbers.
9. Prevalence of asthma or wheezy bronchitis up to age 23 and onset of asthma between 24 and 33.
10. Bristol Social Adjustment Guide.
11. Scaled up for those with missing values in up to two of the three sweeps.

Appendix 6: Correlations between adversities

Results in Tables A6.1, A6.2 and A6.3 are from separate logistic bi-variate logistic regressions. Results in Table A6.4 are from separate linear regressions.

Table A6.1: ORs for one adversity contingent upon another during childhood

	Parental loss	Time in care	Neglect at 7/11	Parental mental illness	Mobility
Spent time in care	8.47				
Neglect at 7 / 11	2.61	5.69			
Parental mental illness	3.88	5.33	3.67		
Mobility	3.57	3.01	1.46	1.86	
Free school meals	10.58	5.84	5.72	3.66	2.72

All p-values 0.001 or below. Odds ratios are from bi-variate logistic regressions with adversities at the heads of columns as outcomes N=14,109

Table A6.2: ORs for adversity in one domain contingent upon adversity in another during youth

	Material	Occupation-related	Relationship-related
Occupation-related	3.37		
Relationship-related	6.99	1.71	
Child loss	5.97	1.51	4.19

All p-values below 0.001, except for between child loss and occupation-related (p=0.006). Odds ratios are from bi-variate logistic regressions with adversities at the heads of columns as outcomes. N=14,109.

Table A6.3: ORs for adversity in one domain contingent upon adversity in another during early adulthood

	Material	Occupation-related	Relationship-related	Child loss
Occupation-related	1.77			
Relationship-related	3.58	1.48		
Child loss	1.69	0.96	1.27	
Trauma	3.70	1.69	3.31	1.42

All p-values below 0.001, except for between child loss and occupation-related (p=0.525) and between child loss and trauma (p=0.024). Odds ratios are from bi-variate logistic regressions with adversities at the heads of columns as outcome. N=14,109.

Table A6.4: Coefficients for levels of adversity at one life stage contingent upon level of exposure in another

	Youth	Early adulthood
Childhood	0.36	0.27
Youth		0.87

All p-values below 0.001. Coefficients ratios are from bi-variate linear regressions with adversities at the heads of columns as outcomes. N=14,109.

Appendix 7: Analyses using the observed sample.

These analyses used indices of adversity that were constructed for cohort members who provided complete or partial information about adversity. For cohort members who provided partial information, indices of adversity during each life stage were constructed so as to capture as much variation in exposure as possible. In order to do this, I adopted the following principles.

1. Con-current information was used to measure each adversity. Retrospective information was only used when this information was missing.

2. For coding each adversity, a no value was coded only if complete information was available.

3. For coding each adversity, a yes value was coded if this was indicated from the information available, even if this was incomplete.

4. Total childhood adversity was measured for all cohort members with information about three or more of the six adversities. For cohort members with information about one or two childhood adversities, total childhood adversity was measured only if they reported at least one adversity.

5. Total adversity during youth and early adulthood was only coded for cohort members who participated in the relevant sweep, i.e. at ages 23 and 33, respectively. They were assigned values of zero if cohort members provided information in all domains, but were assigned positive values if adversity was reported in at least one domain.

6. Values of total adversity that included missing information were not scaled up. This is a conservative approach because cohort members for whom data are missing tend to be those who are more disadvantaged and so would be more likely to score highly on the measure had fuller information been available for them. Not scaling the variable up for missing values is therefore likely to reduce the variation in adversity, which would make estimates of associations less likely to be statistically significant.

Using the original dataset, most findings are equivalent to those using multiple imputed datasets. The only notable difference is that the life-course model of adversity that is most parsimonious and accurate includes adversities during childhood and transition but not during early adulthood.

Appendix 8: Sensitivity analyses using a measure of asthma onset that disregards symptoms up to age 7

These sensitivity analyses are based on a measure of asthma onset during mid-adulthood (34-42) that includes those who did not report a history of asthma between ages 7 and 33. For 1,452 cohort members, a history of asthma or wheezy bronchitis was reported at age 7 but not subsequently. These cohort members are excluded from the main analyses but included in the sensitivity analyses reported here.

Missing values were imputed in 20 datasets and information from 18,554 participants was used in the sensitivity analyses. Numbers reporting asthma onset during mid-adulthood in the original and multiple imputed datasets are presented in Table A8.1.

Table A8.1: Summary statistics for asthma onset during mid-adulthood, including respondents with asthma symptoms up to age 7

	NCDS sample			Multiply imputed datasets	
	Obs	%=yes	No.=yes	%=yes	95% CI
Men and women	7885	3.9%	308	4.5%	3.2%-5.7%
Men	3809	2.8%	107	3.3%	2.1%-4.6%
Women	4076	4.9%	200	5.7%	4.2%-7.1%
Gender diff.		p=0.000		p=0.000	

18,544 respondents in the multiply imputed datasets.

In the original sample, proportions reporting asthma onset during mid-adulthood ignoring asthma symptoms up to age 7 are slightly higher than in the main analyses (3.9% compared to 3.7% for men and women together), but gender differences are very similar. After multiple imputation, proportions reporting asthma onset are almost identical regardless of whether respondents with asthma symptoms up to age 7 are included. The similarity in rates of asthma onset when respondents are included who reported asthma symptoms before age 7 lends confidence to the validity of imputed values in both these and the main analyses.

3. RQ1. Do life course adversities predict asthma onset during mid-adulthood?

Table A8.2 presents results of logistic regressions of asthma onset during mid-adulthood on life course adversity, including respondents who reported asthma symptoms up to age 7. The results are very similar to those presented in the main text. There are positive graded associations between adversities during each life stage and asthma onset during mid-adulthood but magnitudes of these associations are slightly smaller than those reported in the main text. This suggests that adversities predict asthma onset during mid-adulthood more strongly for respondents who have no history of asthma symptoms compared to respondents who had symptoms of asthma during early life.

There is no evidence that associations differ by gender, atopic history or temperament. These results are the same as those reported in the main text.

Because the results are so similar, no further sensitivity analyses using this measure of asthma onset.

Table A8.2: Odds ratios for asthma onset 34-42 predicted by life course adversity, including respondents with asthma symptoms up to age 7

		Set of dummies			Continuous measure			Indicator of two or more adversities			
		OR	95%CI	p-val	OR	95%CI	p-val		OR	95%CI	p-val
Life course (0-33)											
Female		1.781	1.412-2.246	0.000	1.788	1.419-2.254	0.000		1.784	1.414-2.250	0.000
Adversities	0				1.181	1.103-1.265	0.000	<2	Reference		
	1	1.033	0.664-1.609	0.885				2+	1.607	1.199-2.155	0.002
	2	1.121	0.725-1.733	0.609							
	3	1.328	0.809-2.179	0.265							
	4	1.336	0.813-2.179	0.256							
	5	1.815	1.105-2.980	0.020							
	6	2.051	1.161-3.624	0.016							
	7-15	3.061	1.744-5.372	0.000							
Wald test		F=6.686, p=0.000									
F-statistic		F=8.650			F=22.620				F=15.994		
Test of linearity					P=0.674						
Childhood (0-16)											
Female		1.795	1.429-2.255	0.000	1.787	1.419-2.250	0.000		1.776	1.406-2.243	0.000
Adversities	0				1.209	1.076-1.359	0.003	<2	Reference		
	1	1.092	0.806-1.481	0.571				2+	1.565	1.175-2.084	0.004
	2	1.397	0.982-1.987	0.067							
	3	1.442	0.966-2.153	0.079							
	4	1.986	1.249-3.156	0.005							
	5-6	2.903	1.357-6.214	0.010							
Wald test		F=4.274, p=0.001									
F-statistic		F=6.816			F=13.830				F=14.420		
Test of linearity					P=0.731						
Transition to adulthood (17-23)											
Female		1.694	1.339-2.143	0.000	1.699	1.343-2.149	0.000		1.711	1.354-2.162	0.000
Adveristies	0				1.399	1.231-1.589	0.000	<2	Reference		
	1	1.309	0.996-1.721	0.057				2+	1.946	1.482-2.555	0.000
	2	1.833	1.346-2.494	0.000							
	3-4	2.895	1.864-4.495	0.000							
Wald test		F=11.353, p=0.000									
F-statistic		F=14.267			F=25.284				F=23.119		

Test of linearity					P=0.759					
Early adulthood (24-33)										
Female		1.822	1.448-2.292	0.000	1.831	1.455-2.304	0.000	1.810	1.438-2.277	0.000
Adversities	0				1.352	1.170-1.562	0.000	<2 Reference		
	1	1.240	0.987-1.558	0.065				2+ 1.694	1.246-2.302	0.002
	2	1.521	1.037-2.230	0.037						
	3-4	2.730	1.817-4.101	0.000						
Wald test		F=9.583, p=0.000								
F-statistic		F=12.565			F=18.883			F=15.504		
Test of linearity					P=0.258					

Results of 12 models with no other co-variates. Within life stage, models were estimated for each measure of adversity using 20 datasets with imputed values, N=15,548.

Appendix 9: Sensitivity analyses using an index of childhood adversity that excludes residential moves

In these sensitivity analyses, an index of childhood adversity is used that sums exposures to early parental loss, time in care, neglect, parental mental illness and free school meals. It differs from the measure used in the main analyses because it excludes residential moves. Summary statistics for this measure in the original and multiple imputed datasets are presented in Table A9.1

Table A9.1: Summary statistics for childhood adversity among cohort members without asthma before 33

	Observed sample			Twenty imputed datasets					
	Men & women			Men & women		Men		Women	
Adversity	Obs	Mean/ %=Y	SD /N=Y	Mean /%=Y	95%CI	Mean /%=Y	95%CI	Mean/ %=Y	95%CI
Total	7941	0.555	0.866	0.914	0.888-0.941	0.935	0.900-0.970	0.892	0.859-0.926
0	7941	64.0	5082	49.5	48.2-50.7	48.8	47.2-50.4	50.2	48.5-51.9
1	7941	21.5	1707	21.7	20.7-22.7	21.8	20.5-23.1	21.6	20.0-23.2
2	7941	10.4	826	16.8	15.8-17.7	16.5	15.2-17.8	17.1	15.7-18.5
3-5	7941	4.1	326	12.1	11.2-12.9	12.9	11.9-14.0	11.2	10.1-12.3

The imputed datasets include 14,109 respondents

Compared with the index of childhood adversity that includes residential moves, this index has a lower mean value and a higher proportion of respondents reporting no childhood adversities. This is not surprising as high residential mobility was the most common childhood adversity, reported by almost half (47.2%) of the cohort members. As with the measure that includes high residential mobility, values of the index presented here are higher in the multiple imputed datasets than in the original dataset. This suggests that compared with cohort members who provided complete information, those who did not had experienced relatively high levels of childhood adversity, regardless of whether the index included or excluded high residential mobility. There was no evidence of gender differences in either index of childhood adversity. Although not reported in the table, logit regressions of female gender on childhood adversity provided no evidence of associations; p=0.401 for the original sample, p=0.188 for the multiple imputed samples.

4. RQ1. Do life course adversities predict asthma onset during mid-adulthood?

Table A9.2 presents results of logistic regressions of asthma onset during mid-adulthood on childhood adversity using the index that excludes residential moves. The results are almost identical to those presented in the main text. Because results are so similar, no further sensitivity analyses using this index of childhood adversity were conducted.

Table A9.2: Odds ratios for asthma onset between 34 and 42 predicted by life course adversity, using index of childhood adversity that excludes residential moves

		Set of dummies				Continuous measure				Indicator of two or more adversities				
		OR	95%CI		p-val	OR	95%CI		p-val		OR	95%CI		p-val
Childhood (0-16)														
Female		1.764	1.330	2.340	0.000	1.755	1.324	2.326	0.000		1.743	1.313	2.312	0.000
Adversities	0					1.297	1.106	1.522	0.003	<2				
	1	1.184	0.881	1.593	0.266					2+	1.665	1.168	2.373	0.008
	2	1.324	0.895	1.959	0.167									
	3	2.392	1.497	3.823	0.001									
	4	1.000												
	5-6	1.000												
Wald test		F=7.110, p=0.002												
F-statistic		F=8.759				F=11.547				F=10.348				
Test of linearity						P=0.177								

Results of 12 models with no other covariates. Within life stage, models were estimated for each measure of adversity using 20 datasets with imputed values, N=14,109.

Appendix 10: Additional information about data and measures

5. The dataset

The sample consists of core members and their cohabiting partners. Original core members were interviewed in HSE in 1998, 1999, or 2001 and in ELSA wave 1. They were all aged 50 or over at the time of wave 1 data collection. Refreshment samples of new core members were added in waves 3, 4, 6 and 7 to maintain numbers and the age distribution as the original core members aged. Participants of HSE between 2001 and 2004 who were aged 50-53 at the time of wave 3 data collection were included in wave 3. In wave 4, participants of HSE 2006 who were aged 50-74 at the time of wave 4 data collection were interviewed. In wave 6, the refreshment sample included respondents from HSE 2009-2011 aged 50-55, and in wave 7, it included respondents from HSE 2011 who were aged 50-53. Members of the refreshment samples for waves 6 and 7 are included in imputation models but not in the main analyses, as they did not participate in the life history interview in 2006, referred to as LIFE. Core members exit from ELSA when they die, move away from mainland Britain, or do not participate for any other reason.

6. Onset of RA

Questions used to code RA onset are presented in Table A10.1.

Table A10.1: Questions used to code onset of RA

Wave	Question
1	Has a doctor ever told you that you have (or have had) any of the conditions on this card? PROBE : What others? CODE ALL THAT APPLY Chronic lung disease such as chronic bronchitis or emphysema Asthma Arthritis (including osteoarthritis , or rheumatism) Osteoporosis, sometimes called thin or brittle bones Cancer or a malignant tumour (excluding minor skin cancers) Parkinson's disease Any emotional, nervous or psychiatric problems Alzheimer's disease Dementia, organic brain syndrome, senility or any other serious memory impairment None of these
	Which type or types of arthritis do you have: (READ OUT EACH IN TURN AND CODE ALL THAT APPLY) osteoarthritis? rheumatoid arthritis? some other kind of arthritis?
	Approximately how old were you when you were first told by a doctor that you had arthritis?
2-7	Our records show that when we last interviewed you on [^date of last interview] you said that you had had (or had been told by a doctor you had had) arthritis. Yes No
	Reason why respondent disputes having had arthritis[3]. Never had No longer has Did not have previously, but has now
	Apart from what you have already told us, and thinking about what has happened since we last saw you on [^date of last interview] has a doctor told you that you have any of the conditions on this card[4] PROBE - 'What others?'···Code all that apply. Chronic lung disease such as chronic bronchitis or emphysema Asthma Arthritis (including osteoarthritis , or rheumatism) Osteoporosis, sometimes called thin or brittle bones Cancer or a malignant tumour (excluding minor skin cancers) Parkinson's disease Any emotional, nervous or psychiatric problems Alzheimer's disease Dementia, senility or another serious memory impairment None of these
	Which type or types of arthritis [^do you / does [^name]] have... code all that apply. Osteoarthritis? Rheumatoid arthritis? Some other kind of arthritis?
	Approximately how old were you when you were first told by a doctor that you had arthritis?
	When in the last two years were you first told by a doctor that you had arthritis?

[3] In wave 7, choice of answers is: Never diagnosed, No longer has, Did not have previously, but has now, Misdiagnosed.

[4] In wave 7, conditions also include Malignant blood disorder, e.g. leukaemia, Multiple Sclerosis or Motor Neurone Disease.

Seven hundred and eighty-three respondents were coded as reporting RA with a valid age of onset. This was a sub-group of the 2,467 respondents who, in at least one wave, reported a history of RA. 1,684 of these 2,467 were coded as missing for RA onset because they provided inconsistent information about RA onset or incomplete information about age of onset. Of these respondents, 55 reported a history of RA but subsequently disputed that they had ever had the condition, and never re-confirmed the diagnosis. 1,094 respondents reported a history of RA and subsequently reported a history of a different type of arthritis with no confirmatory report of a history of RA. 186 respondents reported multiple types of arthritis the first time that arthritis was reported, and as this is the time when information about age of onset is used, it was impossible to identify which type of arthritis the age given referred to. The remaining 349 respondents gave no information about age of onset.

7. Adverse exposures

Questions from the face-to-face interview and self-completion questionnaire that were used to measure adversities during childhood and adulthood are presented in Tables A10.2 and A10.3, respectively.

Table A10.2: Questions used to measure childhood adversities

Adversity	Questions	Mode
Poor amenities and/or crowding at age 10 & living in UK	We would like to find out more about where you lived when you were ten years old. Earlier you told me that when you were ten you lived at (a residence in recorded country for residence living in at 10th year of life). How many bedrooms did your household occupy in this residence? If asked: Include only bedrooms. Do not count bathrooms, kitchens, living rooms, dining rooms or any rooms your household sublet. Including yourself, how many people lived in your household at this residence when you were 10? Did this accommodation have any of the features on this card when you were aged 10? Fixed bath Cold running water supply Hot running water supply Inside toilet Central heating All of these None of these In what year did you start living in your (first / next) residence that you lived in for six months or more? Was this residence (which you started living at in (year when started living in residence)) in the UK? In what year did you stop living in this residence (which you started living at in (year when stopped living in residence))?	IV
Severe financial hardship	Have you ever experienced severe financial hardship? If so, how old were you when it first happened?	SC
Parental unemployment 6m+	When you were aged under 16, were either of your parents unemployed for more than 6 months when they wanted to be working?	SC
Early parental loss	Now I would like to ask you a few questions about your parents. Did your parents permanently separate or divorce before you were 16? By parents, I mean your natural or adoptive parents? Yes No Spontaneous only: One or both parents died before respondent was 16 (coded as yes) Spontaneous only: parents never lived together during respondent's lifetime (coded as yes) Spontaneous only: Never lived with parents / Don't know (coded as yes)	IV
Separation from mother for 6m+	Were you separated from your mother for 6 months or longer before you were 16?	IV
Parents argue often by 16	When you were aged under 16, did your parents argue or fight very often?	SC
Parent abused substances/ mental health difficulties	When you were aged under 16, did your parents drink excessively, take drugs or have mental health problems?	SC
Physically abused by parent	When you were under 16, were you physically abused by your parents?	SC
Sexually assaulted	Have you ever been a victim of sexual assault (including rape or harassment)?	SC

	If so, How old were you when it first happened?	
Had life threatening illness or injury	Have you ever had a life-threatening illness or accident? If so, How old were you when it first happened?	SC
Severe physical attack	Have you ever been a victim of serious physical attack or assault? If so, How old were you when it first happened?	SC
Witness death or serious injury	Have you ever witnessed the serious injury or death of someone in war or military action? If so, How old were you when it first happened? Other than in war or military action, have you ever witnessed an accident or violent act in which someone was killed or seriously wounded? If so, How old were you when it first happened?	SC
Lost close relative or friend	Have you ever lost a very close friend or relative in a war or military service? If so, How old were you when it first happened? Have you ever had a very close friend or relative who died or was at risk of death due to illness or serious accident? If so, How old were you when it first happened?	SC
Major natural disaster	Have you ever experienced a major fire, flood, earthquake or other natural disaster? If so, How old were you when it first happened?	SC

IV indicates fact to fact interview, SC indicates self-completion questionnaire.

Table A10.3: Questions used to measure adversities during adulthood

Adversity	Questions	Mode
Severe financial hardship	Have you ever experienced severe financial hardship? If so, How old were you when it first happened?	SC
Unemployed and searching for work	We would like to find out about the paid work that you have done. I'm going to ask you about each job you have had that lasted for 6 months or more. If you have done a series of short-term jobs for different employers that were essentially the same role then please count these as one job. Age left full time education (derived variable stored in the data archive). Have you ever done any paid work which lasted for a period of 6 months or more? If yes: Did you start your first paid job which lasted for 6 months or more straight after you left full-time education or was there more than a 3-month gap? Which of these describes the situation(s) you were in straight after you left continuous full-time education (before you started your first job?) Code all that apply. Unemployed and searching for a job Unemployed but not searching for a job Short term job (i.e. less than 6 months) Sick or disabled Looking after home or family Looking after a sick or disabled relative or friend Retired Education / Training Voluntary work Other – SPECIFY In what year did you start your (first / next) paid job which lasted for 6 months or more? In what year did you stop doing that job? Did you start your next job straight after leaving this job or was there more than a 3-month gap? Which of these describes the situation(s) you were in during the time before you started your next job? Code all that apply. Same list as above. Which of these describes the situation(s) you were in during the time after you left your last job? Code all that apply. Same list as above. Have you ever done any paid work which lasted for a period of 6 months or more? If no: Which of these describes the situation(s) you were in straight after you left continuous full-time education (before you started your first job?) Code all that apply. Same list as above. Has your situation changed since then? In what year did your situation change? Which of these describes the situation you changed to? Code all that apply.	IV

Involuntary job loss	Have you ever left a job because the company you were working for went out of business or the site closed down? If so, which job did you leave because the company you were working for went out of business or the site closed down?	
Carer as main occupation	The same occupational history questions as those used to code unemployment.	IV
Provided long term care for relative or friend	Have you ever provided long-term care to a disabled or impaired friend or relative or friend? If so, How old were you when it first happened?	SC
Partner or child addicted to a substance	Have you ever had a husband, wife, partner or child who has been addicted to drugs or alcohol? If so, How old were you when it first happened?	SC
Breakdown of cohabiting relationship	Including same sex partnerships, have you ever lived together with someone (else) as a couple or have you ever been married? Are you still living with “”? If not, why is this? Relationship breakdown (including divorce) – ONLY THIS ANSWER IS ASSIGNED A YES VALUE Widowed / partner died Partner moved into nursing or care home Other reason In what year did you stop living with “”?	IV
Moving house	In what year did you stop living in this residence (which you started living at in “”)? Ask respondent to estimate the year they stopped living in this residence. If cannot estimate, ask for decade and enter the mid year of this decade – i.e. if 1940s enter 1945.	IV
Death of cohabiting partner	Including same sex partnerships, have you ever lived together with someone (else) as a couple or have you ever been married? Are you still living with “”? If not, why is this? Relationship breakdown (including divorce) Widowed / partner died – ONLY THIS ANSWER IS ASSIGNED A YES VALUE Partner moved into nursing or care home Other reason In what year did “” die?	IV
Death of child	Based on information collected in previous waves Our records show that when we last interviewed you, you had a child called “”, whose date of birth was “”. Are these details correct? Is this child still alive? Did “” live with you for most of his/her childhood? When did “” die? New information about biological children Have you ever given birth to a(nother) baby – even one who only lived for a short time? Have you ever fathered a(nother) baby – even one who only lived for a short time? Is “” still alive? When did “” die? New information about adopted children (Apart from the adopted child you have already told me about), have you adopted any (other) children as your own? Is “” still alive?	IV

	When did “” die? Did “” live with you for most of his/her childhood?	
Stillbirth, miscarriage or abortion (female only)	Have you ever had a child that was not born alive? Include miscarriages, abortions or stillbirths. Please do not include any children mentioned already. In what year did this (your first such, your next such) pregnancy end?	IV
Death or near death of relative or close friend in peace time	Have you ever had a very close friend or relative who died or was at risk of death due to illness or serious accident? If so, How old were you when it first happened?	SC
Death of relative or close friend in war time	Have you ever lost a very close friend or relative in a war or military service? If so, How old were you when it first happened?	SC
Victim of sexual assault	Have you ever been a victim of sexual assault (including rape or harassment)? If so, How old were you when it first happened?	SC
Victim of serious physical attack	Have you ever been a victim of serious physical attack or assault? If so, How old were you when it first happened?	SC
Life threatening illness or accident	Have you ever had a life-threatening illness or accident? If so, How old were you when it first happened?	SC
Active combat	Have you ever fired a weapon in combat or been fired upon? If so, How old were you when it first happened?	SC
Witnessed serious injury or death	Have you ever witnessed the serious injury or death of someone in war or military action? If so, How old were you when it first happened? Other than in war or military action, have you ever witnessed an accident or violent act in which someone was killed or seriously wounded? If so, How old were you when it first happened?	SC
Natural disaster	Have you ever experienced a major fire, flood, earthquake or other natural disaster? If so, How old were you when it first happened?	SC

Note: IV indicates fact to fact interview, SC indicates self-completion questionnaire.

Information about life events was collected in the self-completion questionnaire using pairs of questions; the first asked whether the event had ever occurred, and the second, which was only asked if the event was reported, asked for the year when it first happened. Indicators of life events reported (for the first time) during each life stage were created as follows. If respondents reported that they had never experienced the event, the variable is assigned zero for all life stages. If they reported the event, the variable is given a value of one for the life stage in which it was first experienced, and a zero for earlier life stages, if applicable. For subsequent life stages, no information is available about the event, and so the value assigned for each subsequent life stage is equal to the proportion of respondents who reported the same exposure for the first time during that life stage. For example, 510 respondents reported experiencing severe financial hardship for the first time during transition (ages 16-29). These respondents are assigned a value of one for the variable indicating severe financial hardship during transition, and zero for financial hardship during childhood. For the variable indicating financial hardship during early adulthood, they are all assigned a value of 0.018; this is the proportion of respondents who reported severe financial hardship for the first time during early adulthood.

Theories of stress proliferation (Pearlin et al. 1997) and cumulative disadvantage (Dannefer 2003) predict that adversities are more likely to occur among respondents who have already been exposed. Therefore, assigning values to respondents who have already been exposed that are mean values for those who have not already been exposed is likely to underestimate true values. Since adversities during each life stage are uncommon, assignment of underestimated values is associated with underestimated variance. This would result in conservative estimates of associations, which means that we can have more confidence in the robustness of any associations found.

Poor housing amenities and/or overcrowding during childhood is coded using retrospective information about housing conditions at age 10. The variable indicates both provision of shelter, which is a basic human need, and economic status. The latter depends on context. Consequently, this variable is coded as missing for respondents living outside the UK at age 10; for those living in the UK, the criteria for a yes value change over time. The criteria are designed to reflect relative level of amenities, with similar proportions of each cohort assigned a yes value (reflecting poor amenities) for this variable. See Table A10.4.

Table A10.4: Criteria for poor housing amenities/overcrowding at age 10 for UK residents

Born	Criteria
1907-1919	No fixed bath, no hot running water, no inside toilet and more than two people to each bedroom
1920-1929	No fixed bath, no hot running water, no inside toilet and more than two people to each bedroom
1930-1939	None/one of fixed bath, hot running water, inside toilet and > two people to each bedroom
1940-1949	Up to two of fixed bath, hot running water, inside toilet and > two people to each bedroom
1950-1959	More than two people to each bedroom
1960-1969	More than two people to each bedroom
1970-1979	More than two people to each bedroom
1980-1989	More than two people to each bedroom

For child death, children included are respondents' biological children, and non-biological children who spent most of their childhood with the respondent. In LIFE, information is collected about children in three stages: (1) confirmation or correction of information provided in previous waves of data collection, (2) additional information about respondents' biological children who hadn't been mentioned previously, (3) additional information about respondents' adopted children who hadn't been mentioned previously. Respondents reported for each child their year of birth, whether they were still living, and their year of death. This information is used to calculate the age of the respondent in the year that their child died. More than one age is calculated for respondents reported losing more than one child.

Variables indicating house moves take three values; no or few moves, a moderate number of moves, and many moves. Because moving is more frequent during some life stages than others, the distributions of the number of moves reported during each life stage were divided into terciles, with approximately one third of respondents falling into each tercile. Numbers of moves associated with each tercile are reported in Table A10.5. For indices of adversity, a binary indicator of many moves is used.

Table A10.5: Moving house

Life stage	No or few moves	Moderate moves	Lots of moves
Youth (ages 16-30)	0-4	5,6	7-13
Early adulthood (ages 31-44)	0-2	3	4-9
Mid-adulthood (ages 45-59)	0-1	2	3-7
Youth and early adulthood (ages16-44)	0-4	5-7	8-18
Youth to mid-adulthood (ages 16-59)	0-5	6-8	9-19

I considered using additional information to code material adversity, but decided that the information available was insufficient. HMRC records from 1948 have been linked to the records of ELSA respondents (Bozio et al. 2010). National Insurance contributions are included in these records. Since these are means tested, I considered using non-payment of National Insurance as an indicator of financial hardship. However, reflecting an apparently regressive rule, National Insurance contributions are not paid by some wealthy members of society as well as the poorer ones, as all those who are not working do not contribute, regardless of income and assets. I therefore decided that this indicator of material adversity was not sufficiently precise.

I also considered using information about low pay. During the LIFE face to face interview, respondents provided retrospective information about pay. 4,865 respondents gave information about gross pay and 2,385 gave information about net pay. This information could be used in conjunction with national records of mean income levels year on year to

identify those whose pay fell below a poverty line. However, as information about outgoings is very limited, net pay would have to be used, and this information is available for relatively few respondents. Moreover, there are gaps in the information due not only to missing information but also to questionnaire design; respondents were asked about pay only when they started employment in a new job. Further, recall of pay may not be accurate.

Other authors have measured material adversity during childhood using similar information to that used in this paper. For example, Tampubolon (2015) used housing amenities and self-reported financial hardship during childhood as indicators of "childhood material lack".

8. Resources

Variables that I thought might buffer impacts of adversity on the development of RA were parenting, cultural capital during childhood, and education. Tests were conducted to estimate whether interactions of each variable with adversity predicted risk of RA onset.

Parent-child relationships were assessed retrospectively using a reduced form of the Parental Bonding Instrument (PBI, Parker et al. 1979) that was administered in the self-completion questionnaire. The PBI has two scales for each parent, one measuring care and the other over-protection, which are currently used (Karukivi et al. 2014, Enokido et al. 2014). The shortened version has good psychometric properties (Todd et al. 1994). It has seven items relating to each parent, listed in Table A10.6.

Table A10.6: Items used to measure parent-child relationships

Item	Care	Overprotective
Mother let me do the things I like doing*		X
Mother appeared to understand my problems and worries	X	
Mother liked me to make my own decisions*		X
Mother seemed emotionally cold to me*	X	
Mother made me feel I was not wanted*	X	
Mother tried to make me dependent on her/him		X
Mother was overprotective of me		X

1=”very unlike” 2=”moderately unlike” 3=”moderately like” 4=”very like”
* Reverse coded. The same questions are asked about the respondent’s father

Using the approach suggested by Parker et al. (2014), scores for care and over-protectiveness were calculated by summing item values for each scale, separately for maternal and paternal parenting. Four variables were created for each respondent.

I experimented with other measures of parenting, based on these scores. The first assigned respondents to one of four groups depending upon whether their scores on each dimension of parenting fell above or below cut points. Parker et al. (2014) describe the four groups and suggest scores for cut points, which were used. The four groups are optimal parenting (high care, low overprotection), affectionate constraint (high care and high overprotection), neglectful parenting (low care, low overprotection) and affectionless control (low care, high overprotection). Respondents were assigned a value for two variables, one relating to maternal and the other relating to paternal parenting.

Second, a classification of parenting was created in which respondents were assigned to one of the four groups on the basis of the closest-to-optimal parenting that they received, regardless of which parent provided this parenting and whether one or both parents parented in this way. This created a single variable that measured quality of parenting. This approach assumes that positive experiences of parenting from either parent figure buffer the impacts of adversity, an argument put forward by Shonkoff et al. 2012.

Continuous and binary measures were created for each measure of parenting.

Cultural capital during childhood was indicated by whether or not respondents reported having enough books to fill two shelves in their home when they were aged 10. Education was measured using their highest qualification at the time of the LIFE interview.

Variables measuring parenting, cultural capital during childhood, and education are derived from the original dataset using the sub-sample with complete data about RA onset and each variable. Summary statistics are presented in Table A10.7.

Table A10.7: Summary statistics of possible resources

	Binary			Continuous				
Variable	Obs	%=yes	No.=yes	No.=no	Mean	S.D.	Min	Max
Maternal caring	4,915	88.5%	4340	4,915	9.93	1.85	3	12
Maternal overprotection	4,915	28.3%	1391	4,915	7.67	1.96	4	16
Fathering caring	4,915	85.8%	4217	4,915	9.56	1.88	3	12
Fathering overprotection	4,915	25.8%	1268	4,915	7.54	1.88	4	16
Maternal optimal	4,915	68.3%	3357					
Mat. affectionate constraint	4,915	20.4%	1003					
Maternal neglectful	4,915	3.5%	172					
Maternal affectionless control	4,915	7.9%	388					
Fathering optimal	4,915	68.6%	3372					
Fath. affectionate constraint	4,915	17.2%	845					
Fathering neglectful	4,915	5.8%	285					
Fathering affectionless control	4,915	8.4%	413					
Best parenting available								
Optimal	4,915	80.2%	3942					
Affectionate constraint	4,915	14.8%	727					
Neglectful	4,915	2.2%	108					
Affectionless control	4,915	2.8%	138					
Cultural capital in childhood								
At least 2 shelves books at 10	6,449	18.6%	1,199					
Education								
Highest qualification in 2006				6,233	2.47	1.89	0	5
No qualifications or Level 1	6,233	31.8%	1,982					
Level 4 or above	6,233	37.9%	2,362					
Interactions between each variable and total level of adversity								
Maternal caring (linear measures)				3,336	8.30	9.65	0	36
Maternal overprotection				3,336	6.70	8.28	0	42
Fathering caring				3,336	7.90	9.18	0	36
Fathering overprotection				3,336	6.63	8.20	0	48
Maternal caring (binary measures)				3,336	0.73	0.94	0	3
Maternal overprotection				3,336	0.27	0.70	0	3
Fathering caring				3,336	0.69	0.92	0	3
Fathering overprotection				3,336	0.24	0.67	0	3
Maternal optimal				3,336	0.54	0.86	0	3
Mat. affectionate constraint				3,336	0.19	0.58	0	3
Maternal neglectful				3,336	0.05	0.32	0	3
Maternal affectionless control				3,336	0.08	0.43	0	3
Fathering optimal				3,336	0.54	0.86	0	3
Fath. affectionate constraint				3,336	0.15	0.51	0	3
Fathering neglectful				3,336	0.07	0.40	0	3
Fathering affectionless control				3,336	0.09	0.46	0	3
Best parenting available							0	
Optimal				3,336	0.67	0.93	0	3
Affectionate constraint				3,336	0.14	0.51	0	3

Neglectful		3,336	0.02	0.24	0	3
Affectionless control		3,336	0.03	0.25	0	3
Cultural capital during childhood						
At least 2 shelves books at 10		3,639	0.15	0.53	0	3
Education and life course adversity up to age 44						
Highest qualification in 2006		3,323	4.04	5.35	0	25
No qualifications or Level 1		3,323	0.43	0.96	0	5
Level 4 or above		3,323	0.64	1.16	0	5
Education and life course adversity up to age 59						
Highest qualification in 2006		3,286	4.74	5.93	0	25
No qualifications or Level 1		3,286	0.49	1.07	0	5
Level 4 or above		3,286	0.75	1.30	0	5

Sample is LIFE with information about RA onset. Parenting & cultural capital interacted with childhood adversity.

The importance of each variable as a resource was assessed using models that include as predictors of RA onset total life course adversity, one hypothesised resource, and the interaction term that combines adversity and the resource. The variable is considered a resource if the interaction term is negative and statistically significant at the 95% level of confidence. This is a strict test, as I wished to include in models only those variables that affected associations between adversities and RA onset.

Parenting models include gender. This is because ratings of parenting may differ by gender. Some studies report that compared with men, women rate their parents as more caring (Mackinnon et al. 1989, Cubis et al. 1989), and that both genders rate fathers as more overprotective than mothers (Brewin et al. 1992, Richman et al. 1990). Furthermore, the impacts of parenting on later life outcomes may differ by the offspring's gender (Pearce et al. 1995, Richman et al. 1990). The results are presented in Table A10.8.

The high number of statistical tests (108 in total) means that one should be cautious about interpreting low p-values as evidence of associations in the wider population. There is no evidence that cultural capital or education confers protection against impacts of adversity

on the risk of RA onset, and so they are not included as resources in the models of changing RA risk with age.

There is weak evidence that maternal overprotection is associated with a lower risk of developing RA from ages 45 and 60 (for the binary measure HR=0.702, 95%CI 0.536-0.920, p=0.010; HR=0.688, 95%CI 0.486-0.974, p=0.035, respectively) and that in the context of high levels of adversity, maternal overprotection is associated with a higher hazard of developing the condition from age 60 (increase in HR with each additional adversity=1.149, 95%CI 1.008-1.310, p=0.038). There is no evidence of an interaction effect when the binary measure of maternal overprotection is used, and coupled with the high number of tests, I did not consider this sufficient evidence to include parenting as a resource in the models.

Table A10.8: Hazard ratios for RA onset contingent upon hypothesised resources and their interactions with adversity

	RA onset from 45			RA onset from 60		
	HR	95% ci	p-val	HR	95% ci	p-val
Model 1: Care and overprotection from each parent (binary measures)						
Female	1.141	0.759-1.714	0.526	1.156	0.679-1.967	0.594
Maternal care	0.758	0.155-3.702	0.732	0.693	0.103-4.683	0.707
Maternal overprotection	**0.332**	**0.111-0.991**	**0.048**	0.253	0.056-1.154	0.076
Paternal care	1.527	0.359-6.493	0.566	0.941	0.177-4.998	0.943
Paternal overprotection	1.901	0.771-4.690	0.163	1.347	0.384-4.720	0.642
Adversity	1.160	0.587-2.294	0.669	0.881	0.540-1.437	0.611
Adv*maternal care	1.076	0.615-1.883	0.797	1.264	0.625-2.557	0.515
Adv*mat. overprotection	1.201	0.798-1.807	0.379	1.313	0.765-2.255	0.324
Adv*paternal care	1.012	0.588-1.741	0.966	1.102	0.575-2.111	0.770
Adv*pat. overprotection	0.830	0.575-1.198	0.320	0.882	0.531-1.464	0.627
N	3363			2619		
Model 2: Care and overprotection for each parent (linear measures)						
Female	1.122	0.743-1.693	0.584	1.125	0.657-1.924	0.668
Maternal care	0.825	0.630-1.081	0.163	0.840	0.597-1.182	0.317
Maternal overprotection	**0.702**	**0.536-0.920**	**0.010**	**0.688**	**0.486-0.975**	**0.035**
Paternal care	1.077	0.820-1.416	0.592	1.168	0.827-1.650	0.377
Paternal overprotection	1.290	0.990-1.680	0.059	1.186	0.840-1.676	0.332
Adversity	0.674	0.117-3.882	0.659	0.880	0.506-1.530	0.650
Adv*maternal care	1.061	0.954-1.180	0.276	1.060	0.934-1.204	0.369
Adv*mat. overprotection	1.092	0.979-1.219	0.116	**1.149**	**1.008-1.310**	**0.038**
Adv*paternal care	1.002	0.897-1.119	0.972	0.961	0.845-1.093	0.545
Adv*pat. overprotection	0.915	0.818-1.024	0.123	0.883	0.768-1.017	0.084
N	3363			2619		
Model 3: Closest-to-optimal parenting from either parent						
Female	1.150	0.779-1.696	0.482	1.078	0.650-1.787	0.771
Optimal	reference			reference		
Affectionate constraint	0.506	0.152-1.683	0.267	0.324	0.057-1.831	0.202

Neglect	0.000	0.000	1.000	0.000	0.000	1.000
Affectionless control	2.017	0.209-19.424	0.544	0.817	0.020-33.003	0.915
Adversity	**1.237**	**1.070-1.430**	**0.004**	1.161	0.971-1.389	0.102
Adv*optimal	reference			reference		
Adv*affection constraint	1.106	0.707-1.730	0.658	1.260	0.674-2.358	0.469
Adv*neglect	0.812	0.000	1.000	0.869	0.000	1.000
Adv*affectionless control	0.540	0.166-1.760	0.307	0.833	0.174-3.984	0.819
N	3604			2825		
Model 4: Four types of parenting from each parent (binary measures)						
Female	1.140	0.759-1.713	0.529	1.115	0.658-1.891	0.685
Maternal: optimal	reference					
Affectionate constraint	0.321	0.096-1.077	0.066	0.155	0.023-1.053	0.057
Neglect	0.910	0.057-14.661	0.947	0.000	0.000-0.000	
Affectionless control	0.555	0.092-3.341	0.521	0.744	0.084-6.563	0.790
Paternal: optimal	reference					
Affectionate constraint	1.663	0.623-4.438	0.310	1.144	0.266-4.925	0.857
Neglect	0.176	0.005-5.942	0.333	0.772	0.020-29.916	0.890
Affectionless control	1.758	0.402-7.681	0.453	1.708	0.278-10.489	0.563
Adversity	**1.269**	**1.071-1.505**	**0.006**	1.181	0.965-1.445	0.107
Maternal adv*optimal	reference					
Adv*affection constraint	1.169	0.738-1.851	0.505	1.450	0.753-2.791	0.267
Adv*neglect	0.916	0.352-2.383	0.857	0.259	0.259-0.259	
Adv*affectionless control	1.104	0.580-2.101	0.763	0.994	0.404-2.446	0.989
Paternal adv*optimal	reference					
Adv*affection constraint	0.843	0.563-1.265	0.410	0.864	0.464-1.608	0.644
Adv*neglect	1.334	0.452-3.934	0.602	0.763	0.163-3.568	0.731
Adv*affectionless control	0.778	0.428-1.414	0.411	0.883	0.420-1.857	0.742
N	3363			2619		
Model 5: Cultural capital during childhood						
Books	0.697	0.272-1.782	0.451	0.772	0.219-2.724	0.688
Adversity	**1.242**	**1.078-1.430**	**0.003**	1.175	0.986-1.400	0.071
Adv*books	0.992	0.666-1.479	0.969	0.935	0.553-1.580	0.802
N	3668			2876		
Model 6: Highest qualification in 2006 (linear measure)						
Highest qualification	0.945	0.789-1.132	0.542	0.922	0.721-1.178	0.515
Adversity	**1.370**	**1.120-1.676**	**0.002**	1.205	0.932-1.558	0.154
Adv*highest qualification	0.972	0.902-1.046	0.444	1.006	0.916-1.104	0.902
N	3396			2632		
Model 7: Highest qualification in 2006 Level 4 or above						
Level 4 or above	1.271	0.638-2.533	0.496	1.444	0.574-3.636	0.435
Adversity	**1.267**	**1.054-1.523**	**0.012**	1.257	0.990-1.598	0.061
Adv*Level 4 or above	1.044	0.786-1.386	0.768	0.929	0.647-1.333	0.690
N	3396			2632		
Model 8: Highest qualification in 2006 below Level 1						
Below Level 1	0.795	0.375-1.686	0.550	0.745	0.265-2.094	0.577
Adversity	**1.332**	**1.131-1.569**	**0.001**	1.204	0.972-1.491	0.089
Adv*below Level 1	0.891	0.649-1.222	0.473	1.035	0.700-1.530	0.864
N	3396			2632		

These are results from 16 models, 8 for RA with onset from 45 and 8 for RA with onset from 60. Adversity is total exposure up to age 44 for RA with onset from 45, and up to age 59 for RA with onset from 60. Analyses are run on sub-samples with complete information about all variables in each model. Optimal parenting is high care, low overprotection. Neglect is low care and low overprotection. Affectionless control is low care, high overprotection. Affectionate control is high care and high overprotection.

9. Factors to condition upon

Model specification is improved by including factors that are associated with both adversity and RA onset (Greenland et al. 1999). Based on evidence summarised in the introduction, factors thought to predict RA onset were measured and correlations tested between each and RA onset. Once the variables that predicted RA onset had been identified, additional tests were conducted to test whether these variables were also associated with adversity.

Variables considered were qualifications in 2006 and measures relating to sex hormones. LIFE includes comprehensive fertility histories as well as information about use of hormonal contraceptives, ages of menarche and menopause, and removal of ovaries and hysterectomies. Summary statistics of the variables coded are presented in Table A10.9. These are drawn from the original dataset, excluding respondents who did not participate in LIFE or for whom information is missing about RA status or age of onset.

Table A10.9: Summary statistics for female sex hormone variables

Variable	Obs	%=yes /Mean	No.=yes /S.D.	Min	Max
Any live births	3,707	85.8%	3181	0	1
Any pregnancies lasting at least 8 months	3,707	85.9%	3184	0	1
Menarche by age 12	3,707	37.6%	1394	0	1
Menarche after age 14	3,707	18.5%	684	0	1
Last period after age 52	3,707	20.7%	769	0	1
Years between menarche and menopause	2,883	36.56	4.71	23	50
Oral contraception/injection/implant by 59	3,562	48.2%	1718	0	1
HRT use by age 59	2,856	18.8%	538	0	1
Hysterectomy by 44	3,693	11.5%	423	0	1
Hysterectomy by 59	3,693	20.5%	756	0	1
Removal of ovaries by 44	3,681	3.6%	134	0	1
Removal of ovaries by 59	3,681	8.9%	328	0	1
Hysterectomy or removal of ovaries by 44	3,685	11.9%	437	0	1
Hysterectomy or removal of ovaries by 59	3,689	21.1%	780	0	1

Based on the female respondents who participated in LIFE and provided sufficient information to code age of RA onset

Cox regression models were estimated of RA onset contingent upon measures of education and each sex hormone variable in separate bi-variate regressions. The proportional hazards assumption was also tested for each variable.

The results, which are presented in Table A10.10, provide no evidence of associations between any sex hormone related variable and RA onset. Consequently, we do not condition the analyses on these sex hormone variables.

Table A10.10: Hazard ratios and p-values from PH tests for RA onset contingent upon female sex hormones and education in 2006

	RA onset from 45				RA onset from 60			
	HR	95% c.i.	p-val	PH test p-val	HR	95% c.i.	p-val	PH test p-val
Any live births	1.437	0.809-2.552	0.216	0.162	1.617	0.742-3.524	0.227	0.067
Any pregnancies[1]	1.414	0.796-2.511	0.237	0.170	1.584	0.727-3.451	0.247	0.070
Menarche by age 12	0.977	0.693-1.378	0.895	0.831	0.891	0.564-1.408	0.622	0.646
Menarche after age 14	1.327	0.885-1.992	0.171	0.927	1.223	0.719-2.080	0.458	0.302
Last period after age 52	0.803	0.514-1.253	0.333	0.611	0.846	0.480-1.492	0.564	0.735
Menarche-menopause (years)	1.021	0.980-1.063	0.317	0.332	1.040	0.988-1.095	0.133	0.365
Oral contraception[2] by 44	0.229	0.023-2.273	0.208	0.146				
Oral contraception[2] by 59					0.802	0.343-1.877	0.611	0.608
HRT use by age 59	1.710	0.907-3.223	0.097	0.582	0.729	0.093-5.691	0.763	0.827
Hysterectomy by 44	1.188	0.712-1.981	0.509	0.666	1.084	0.539-2.177	0.822	0.741
Hysterectomy by 59	1.113	0.734-1.686	0.615	0.980	0.950	0.538-1.676	0.858	0.117
Removal of ovaries by 44	1.056	0.431-2.584	0.905	0.663	1.101	0.346-3.501	0.870	0.779
Removal of ovaries by 59	1.103	0.608-2.001	0.747	0.691	0.802	0.323-1.991	0.635	0.158
Hysterectomy[3] by 44	1.235	0.750-2.036	0.407	0.547	1.064	0.529-2.139	0.863	0.774
Hysterectomy[3] by 59	1.125	0.746-1.696	0.575	0.845	0.921	0.522-1.626	0.778	0.114
Highest qualification in 2006	**0.878**	**0.813-0.950**	**0.001**	0.658	**0.881**	**0.795-0.975**	**0.014**	0.181
Below Level 1 in 2006	**1.479**	**1.110-1.969**	**0.007**	0.817	**1.544**	**1.066-2.236**	**0.021**	0.091
Level 4 or above in 2006	**0.623**	**0.446-0.872**	**0.006**	0.476	0.674	0.435-1.044	0.078	0.439

These are results of 34 bi-variate Cox regression analyses of each variable on RA onset. 17 regressions were estimated for RA onset from ages 45 and 60. PH tests were conducted separately for each variable, so that 34 tests were conducted. P-values below 0.05 for the PH tests suggest that the PH assumption may be violated.

1. Pregnancy lasting at least eight months
2. Oral contraception or injection or implant
3. Hysterectomy or removal of ovaries

In contrast, associations were found between education in 2006 and RA onset. Additional analyses were therefore conducted to test for associations between education and

adversity. Associations were tested with the various indices of adversity used to address different research questions. This was necessary because in the interests of parsimony, analyses should condition on education only when it is associated with both RA onset and the measure of adversity used. Results presented in Table A10.11 using the continuous measure of education indicate that education at the time of the LIFE interview is not associated with childhood adversity, is positively associated with adversity during transition and early adulthood, and is negatively associated with adversity during mid-adulthood.

To inform the decision about which measure of education to use in the analyses, bi-variate associations with adversity were estimated using different measures of education (Table A10.11). There is no theoretical reason to choose one measure of education over another. The continuous measure of education usefully summarises all available information but its distribution is far from normal (Figure A10.1), so a binary indicator of Level 2 qualifications and above is used.

Table A10.11: Evidence of associations between education at time of LIFE interview and both adversity and RA onset

Highest qualification at time of LIFE interview	Indices of adversity: Birth to 44 Beta	Birth to 44 95% ci	Birth to 44 p-value	Birth to 59 Beta	Birth to 59 95% ci	Birth to 59 p-value	Childhood (birth to 16) Beta	Childhood (birth to 16) 95% ci	Childhood (birth to 16) p-value
Linear measure	**0.042**	**0.012-0.073**	**0.006**	0.019	-0.013-0.052	0.242	-0.004	-0.020-0.013	0.667
Dummies									
No qualifications	Reference								
Level 1	-0.006	-0.292-0.280	0.968	-0.005	-0.305-0.295	0.973	0.044	-0.114-0.201	0.587
Level 2	0.013	-0.155-0.182	0.877	-0.086	-0.266-0.094	0.350	-0.019	-0.110-0.073	0.690
Level 3	**0.359**	**0.131-0.586**	**0.002**	**0.271**	**0.025-0.516**	**0.031**	-0.066	-0.190-0.058	0.295
HE but below L4	0.025	-0.153-0.204	0.781	0.002	-0.188-0.192	0.985	-0.044	-0.141-0.053	0.375
Level 4 and above	**0.241**	**0.075-0.407**	**0.005**	0.089	-0.088-0.266	0.325	0.003	-0.087-0.094	0.942
Binary measures									
No qualifications	-0.123	-0.254-0.008	0.066	-0.033	-0.172-0.107	0.647	0.019	-0.052-0.091	0.593
Level 1 and below	**-0.133**	**-0.258--0.008**	**0.037**	-0.036	-0.169-0.096	0.593	0.030	-0.038-0.098	0.381
Level 2 and below	**-0.179**	**-0.295--0.064**	**0.002**	-0.123	-0.246-0.000	0.050	0.022	-0.040-0.085	0.486
Level 3 and below	-0.092	-0.210-0.026	0.127	-0.044	-0.170-0.082	0.494	0.005	-0.059-0.069	0.881
Below Level 4	**-0.193**	**-0.332--0.054**	**0.007**	-0.084	-0.232-0.065	0.270	-0.023	-0.098-0.053	0.554

Highest qualification at time of LIFE interview	Indices of adversity: Youth (17-29) Beta	Youth (17-29) 95% ci	Youth (17-29) p-value	Early adulthood (30-44) Beta	Early adulthood (30-44) 95% ci	Early adulthood (30-44) p-value	Mid-adulthood (45-59) Beta	Mid-adulthood (45-59) 95% ci	Mid-adulthood (45-59) p-value
Linear measure	**0.031**	**0.018-0.044**	**0.000**	**0.018**	**0.005-0.030**	**0.005**	**-0.021**	**-0.033--0.009**	**0.001**
Dummies									
No qualifications									
Level 1	-0.053	-0.175-0.069	0.392	-0.024	-0.140-0.091	0.681	-0.066	-0.178-0.045	0.243
Level 2	0.009	-0.063-0.081	0.805	0.087	0.019-0.155	0.012	-0.043	-0.110-0.024	0.212
Level 3	**0.224**	**0.127-0.321**	**0.000**	**0.171**	**0.079-0.263**	**0.000**	0.029	-0.062-0.121	0.532
HE but below L4	0.071	-0.005-0.148	0.067	0.057	-0.016-0.129	0.124	-0.062	-0.133-0.009	0.088
Level 4 and above	**0.152**	**0.080-0.224**	**0.000**	**0.088**	**0.020-0.157**	**0.012**	**-0.131**	**-0.198--0.063**	**0.000**
Binary measures									
No qualifications	**-0.086**	**-0.141--0.030**	**0.002**	**-0.083**	**-0.135--0.030**	**0.002**	**0.065**	**0.014-0.117**	**0.013**
Level 1 and below	**-0.104**	**-0.157--0.051**	**0.000**	**-0.094**	**-0.144--0.044**	**0.000**	**0.055**	**0.006-0.104**	**0.028**
Level 2 and below	**-0.137**	**-0.187--0.087**	**0.000**	**-0.060**	**-0.108--0.013**	**0.013**	**0.053**	**0.006-0.100**	**0.026**
Level 3 and below	**-0.086**	**-0.137--0.034**	**0.001**	-0.023	-0.072-0.026	0.355	**0.083**	**0.035-0.131**	**0.001**
Below Level 4	**-0.113**	**-0.175--0.052**	**0.000**	-0.036	-0.095-0.023	0.227	**0.105**	**0.047-0.163**	**0.000**

Highest qualification at time of LIFE interview	RA onset from 45 HR	95% ci	p-value	RA onset from 59 HR	95% ci	p-value
Linear measure	**0.878**	**0.813-0.950**	**0.001**	**0.881**	**0.795-0.975**	**0.014**
Dummies						
No qualifications						
Level 1	0.901	0.493-1.649	0.736	0.893	0.427-1.869	0.764
Level 2	0.854	0.581-1.254	0.420	0.768	0.457-1.292	0.320
Level 3	0.648	0.353-1.188	0.161	0.501	0.201-1.251	0.139
HE but below L4	0.658	0.420-1.029	0.066	0.683	0.387-1.206	0.189
Level 4 and above	**0.482**	**0.295-0.788**	**0.004**	**0.507**	**0.265-0.968**	**0.040**
Binary measures						
No qualifications	**1.453**	**1.089-1.937**	**0.011**	**1.503**	**1.042-2.166**	**0.029**
Level 1 and below	**1.479**	**1.110-1.969**	**0.007**	**1.544**	**1.066-2.236**	**0.021**
Level 2 and below	**1.622**	**1.188-2.214**	**0.002**	**1.601**	**1.060-2.419**	**0.025**
Level 3 and below	**1.604**	**1.147-2.243**	**0.006**	1.483	0.957-2.296	0.078
Below Level 4	**1.781**	**1.119-2.833**	**0.015**	1.669	0.896-3.111	0.107

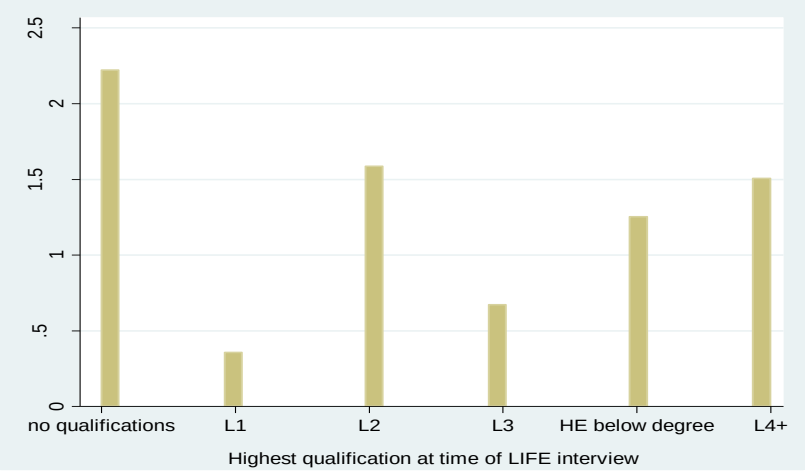


Figure A10.1: Highest level of qualification at time of LIFE interview

10. Smoking

The questions used to measure smoking history are presented in Table A10.12. They elicit information about the years in which the respondent started and ended smoking and the total duration of smoking.

Table A10.12: Questions used to measure smoking history

Question	Answers provided
Have you ever smoked cigarettes?	Yes / No
In what year did you first smoke daily?	Open answer
How old do you think you were when you first smoked daily? (Asked if cannot provide year)	11 years or less / 12 to 15 years / 16 to 29 years / 30 to 39 years / 40 to 49 years / 50 to 59 years / 60 to 69 years / 70 to 79 years / 80 years or over
Do you smoke cigarettes at all nowadays?	Yes / No
In what year did you last smoke a cigarette?	Open answer
How old do you think you were when you last smoked? (Asked if cannot provide year)	11 years or less / 12 to 15 years / 16 to 29 years / 30 to 39 years / 40 to 49 years / 50 to 59 years / 60 to 69 years / 70 to 79 years / 80 years or over
For approximately how many years regularly?	Less than 5 years / 5 to 9 years / 10 to 14 years / 15 to 19 years / 20 years or more

Some respondents reported smoking regularly for fewer years than the number of years between their reports of when they started and stopped smoking. Presumably, these respondents stopped smoking and then took it up again over this period. In order to create variables that measure years of smoking during pre-specified life stages, I assume that for these respondents, the rate of smoking is the same across time.

I exclude smoking before age 16 because it will not help to answer RQ5. RQ5 asks whether any associations found between childhood adversity and RA onset are mediated by smoking.

Smoking is measured during transition, early and mid-adulthood. Three variables are created for each life stage and for combinations of life stages, one measuring the total

number of years smoked, the second indicating whether the respondent smoked at all, and the third indicating smoking every year during the life stage. Summary statistics are presented in Table A10.13.

Table A10.13: Summary statistics of smoking variables

Measure of smoking	Obs.	Mean/%=yes	S.D./No.=yes
Years smoked at least one a day 16-29	7542	5.997	6.091
Smoked at least one year 16-29	7539	54.8%	4134
Smoked every year 16-29	7542	22.0%	1657
Years smoked at least one a day 16-44	7247	11.573	12.374
Smoked at least one year 16-44	7246	55.2%	4003
Smoked every year 16-44	7247	16.9%	1222
Years smoked at least one a day 30-44	7460	5.621	6.861
Smoked at least one year 30-44	7455	44.6%	3323
Smoked every year 30-44	7460	31.0%	2310
Years smoked at least one a day 16-59	6954	14.816	17.322
Smoked at least one year 16-59	6954	53.7%	3736
Smoked every year 16-59	6954	25.1%	1743
Years smoked at least one a day 30-59	7167	8.958	12.196
Smoked at least one year 30-59	7161	42.7%	3056
Smoked every year 30-59	7167	15.5%	1110
Years smoked at least one a day45-59	7505	3.502	5.846
Smoked at least one year 45-59	7498	30.0%	2253
Smoked every year 45-59	7505	15.4%	1158

Separate Cox regressions were run of RA onset on each smoking variable. I conditioned on gender because both smoking behaviours and risk RA onset differ between men and women. The results are presented in the Table A10.14.

Number of years smoked during each life stage was selected to measure smoking behaviour because this predicts RA onset as well as the other types of measure and summarises more information.

Table A10.14: Hazard ratios of RA onset contingent upon smoking behaviours

	RA onset 45+			RA onset 60+			RA onset 45-59		
	HR	95%CI	p-val	HR	95%CI	p-val	HR	95% CI	p-val
Years smoked 16-29	1.021	0.998-1.045	0.079	1.010	0.980-1.042	0.509	1.023	0.985-1.063	0.233
Smoked at all 16-29	1.243	0.931-1.659	0.140	1.070	0.732-1.565	0.727	1.325	0.824-2.130	0.246
Smoked every year 16-29	**1.531**	**1.122-2.087**	**0.007**	1.312	0.859-2.002	0.209	1.638	0.987-2.719	0.056
Years smoked 30-44	**1.023**	**1.003-1.044**	**0.023**	1.019	0.993-1.046	0.158	1.013	0.979-1.049	0.452
Smoked at all 30-44	**1.398**	**1.052-1.857**	**0.021**	1.359	0.938-1.970	0.105	1.176	0.728-1.901	0.507
Smoked every year 30-44	**1.379**	**1.034-1.839**	**0.029**	1.323	0.911-1.921	0.141	1.112	0.668-1.852	0.683
Years smoked 45-59				**1.031**	**1.003-1.059**	**0.028**	1.001	0.962-1.042	0.947
Smoked at all 45-59				**1.536**	**1.056-2.234**	**0.025**	1.029	0.616-1.716	0.914
Smoked every year 45-59				1.490	0.993-2.236	0.054	0.909	0.465-1.776	0.780
Years smoked 16-44	**1.012**	**1.000-1.024**	**0.041**	1.010	0.995-1.025	0.183	1.006	0.986-1.025	0.575
Smoked at all 16-44	1.306	0.971-1.757	0.078	1.211	0.823-1.783	0.331	1.249	0.761-2.051	0.379
Smoked every year 16-44	**1.727**	**1.242-2.402**	**0.001**	1.674	1.088-2.576	0.019	1.548	0.867-2.763	0.139
Years smoked 16-59				1.008	0.998-1.019	0.127	1.001	0.987-1.016	0.861
Smoked at all 16-59				1.124	0.757-1.669	0.563	1.154	0.693-1.923	0.582
Smoked every year 16-59				1.347	0.899-2.018	0.149	0.994	0.554-1.781	0.983
Years smoked 30-59				1.013	0.998-1.027	0.085	1.004	0.984-1.024	0.683
Smoked at all 30-59				1.263	0.862-1.851	0.230	1.070	0.647-1.768	0.792
Smoked every year 30-59				1.339	0.879-2.040	0.174	0.900	0.444-1.823	0.770

These are results of 36 separate Cox regressions of RA onset on each measure of smoking, conditioning on gender.

11. Variables used in sensitivity analyses

These variables were measured in wave 3 of data collection.

Cognitive function was measured during the face-to-face interview with no interruptions and nobody present apart from the interviewer and respondent. Both memory and executive function were measured.

One of the measures of memory function is a delayed recall test. In this test, a list of ten words was read to respondents. They were immediately asked to recall as many words as they could, generating a score between 0 and 10. After performing several unrelated tasks, they were once again asked to recall as many of the ten words as they could. The score for delayed recall (0-10) is used, because scores from the same test predicted accuracy of data recalled in another large British dataset (Brown 2013).

Depressive symptoms were measured by summing scores of eight items of the Centre for Epidemiological Studies Depression scale (CESD). These items are presented in Table A10.15.

Table A10.15: Items used to measure depressive symptoms

Item	Response	Score
Now think about the past week and the feelings you have experienced. Please tell me if each of the following was true for you much of the time during the past week.		
Much of the time during the past week, you felt depressed?	Yes	1
	No	0
Much of the time during the past week, you felt that everything you did was an effort?	Yes	1
	No	0
Much of the time during the past week, your sleep was restless?	Yes	1
	No	0
Much of the time during the past week, you were happy?	Yes	0
	No	1
Much of the time during the past week, you felt lonely?	Yes	1
	No	0
Much of the time during the past week, you enjoyed life?	Yes	0
	No	1
Much of the time during the past week, you felt sad?	Yes	1
	No	0
Much of the time during the past week, you could not get going?	Yes	1

	No	0

Pain was measured using the questions presented in Table A10.16

Table A10.16: Questions used to measure pain

Are you often troubled with pain?	Yes / No
How bad is the pain most of the time? Is it…	Mild Moderate Severe

Appendix 11: Choice of model for survival analyses

Table A11.1 presents p-values from tests of the proportional hazards assumption for variables used in the analyses in relation to RA onset from ages 16, 45, and 60.

Table A11.1: P-values from tests of the proportional hazards assumption for variables included in the analyses

	RA with onset from age		
	16	45	60
Total childhood adversity (to age 16)	0.534	0.997	0.871
Total life course adversity (0-44)		0.913	0.849
Cumulative life course adversity (0-44)		0.869	0.852
Total life course adversity (0-59)			0.965
Cumulative life course adversity (0-59)			0.680
Total years smoking 30-44		0.311	0.547
Total years smoking 45-59			0.385
Female	0.058	0.119	0.590
Cohort of birth	0.149	0.112	0.285
Level 2 qualification or higher in 2006	0.930	0.948	0.222

Notes: These are results of tests of the proportional hazards (PH) assumption following separate Cox regressions of RA onset on each variable. P-value<0.05 suggests violation of the PH assumption. The sample is participants of LIFE who provided complete information about the predictor and RA onset. All models include one predictor and the hazard function, except for cohort of birth, which is estimated using five dummy variables indicating birth during different periods. Measures of gender and education are binary and measures of smoking and adversity are continuous. Total adversity indicates the total number of adversities during the life stage or stages. Cumulative level indicates the number of life stages in which at least one adversity was reported.

Appendix 12: How multiple imputed datasets were created

Missing values were imputed in 20 datasets using Stata version 14 (StataCorp. 2015). No assumptions were made about patterns of missingness and an imputation strategy referred to as the chained approach (Van Buuren 2007) was used.

The variables imputed were those used in the analyses, referred to as variables of interest, and auxiliary variables. Analyses used as the outcome the hazard function for RA onset, which is derived from time to censoring or RA onset, and whether or not RA onset occurred. Missing values were not imputed for these two variables because Stata 14 does not support survival analysis using outcome variables for which missing values have been imputed using multiple imputation. However, both variables were included in imputation models for the other variables of interest.

Multiple imputation assumes that data are missing at random conditional upon a set of conditioning, or auxiliary, variables (Goldstein 2009). Imputation models included as many auxiliary variables as possible, as this is recommended by Rubin (1996), and has been found to increase efficiency and reduce bias (Collins et al. 2001). Auxiliary variables were selected from a larger group, referred to as auxiliary candidates, which were chosen because they had below 10% missing values and were thought to be associated with the values and missingness of the variables of interest. The initial selection of auxiliary candidates was informed by existing evidence about determinants of (1) variables of interest and (2) participation in ELSA (Hancock et al. 2016).

In order to select auxiliary variables from auxiliary candidates, correlations were estimated with values and missingness for each variable of interest, and a scoring system was devised to summarise the results.

Some auxiliary candidates were conceptually similar, likely to be highly correlated and to have similar relationships with variables of interest. An example is home ownership status and socio-economic status, both measured in wave 3. As this could cause problems with convergence, just one was selected as an auxiliary variable, based on the scoring system described above.

Auxiliary variables chosen were number of sweeps in which the respondent had participated, being a core or core partner sample member, having had a wave 3 interview concurrent with the partner's interview, participant in HSE 2003, living with a partner, depression score using the Centre for Epidemiological Studies Depression (CESD) scale in wave 3, memory score from cognitive function test in wave 3, limiting longstanding illness in wave 3, poor or very poor self-rated health in wave 3, self-rated dental health in wave 3, car owner in wave 3, home owner in wave 3, ever pregnant in wave 3, last period after the age of 52, having had a hysterectomy or removal of ovaries by age 44, and use of hormonal contraception by age 59.

Multiple imputation using all chosen auxiliary variables failed to converge. In order to achieve convergence, specific variables were omitted from each imputation model. A strategy was devised to guide decisions about the order in which variables were omitted. The first variables omitted were auxiliary variables that had weakest correlations with values and missingness for the imputed variable. Second, variables of interest were omitted for which there was least evidence for associations with values and missingness of the imputed variable. Finally, highly correlated variables were omitted, as these variables were likely to cause problems with convergence.

Although the main analyses are conducted using imputed datasets that include only participants in the LIFE interview who provided full information about RA onset, multiple imputation used all available data, regardless of participation in LIFE. The only respondents excluded from imputation models were those for whom information was missing about RA onset, gender, or date of birth.

Table A12.1 presents summary statistics for variables of interest using the original dataset with missing values and the multiple datasets with missing values imputed.

Using the multiple datasets with imputed values for missing data, estimated mean values of adversity are generally higher than those reported by respondents who provided complete information. Differences are particularly striking when adversities are summed over longer periods of time, e.g. from birth to age 59. This suggests that respondents who did not provide complete information about adversity tended to have experienced more adversities over their lives than those who provided complete information. The exception is that respondents who provided complete information tended to report at least one adversity during more life stages.

Compared against estimates using the imputed datasets, respondents who provided complete information tended to smoke during more years between the ages of 30 and 44, and for fewer years between 45 and 59.

Table A12.1: Summary statistics using the original and twenty imputed datasets

			Original sample			Multiple samples (n=6,624)		
Variable	Type	Values	Obs	Mean %=yes	SD N=yes	Mean	95%ci	
Childhood adversity	terciles	0	3580	45.9	1643	43.9	41.9	45.9
		1	3580	29.9	1069	29.6	27.9	31.4
		2+	**3580**	**24.2**	**868**	**26.4**	**24.9**	**28.0**
	binary		3580	54.1	1937	56.1	54.1	58.1
	dummies	0	3580	45.9	1643	43.9	41.9	45.9
		1	3580	29.9	1069	29.6	27.9	31.4
		2	3580	14.3	513	15.1	13.9	16.3
		3+	**3580**	**9.9**	**355**	**11.4**	**10.2**	**12.5**
Adversity 0-44	terciles	**0-1**	**3428**	**43.3**	**1485**	**36.4**	**35.0**	**37.8**
		2-3	3428	37.8	1297	37.5	36.1	38.9
		4+	**3428**	**18.8**	**646**	**26.1**	**24.8**	**27.5**
	continuous	**0-6+**	**3428**	**2.050**	**1.624**	**2.398**	**2.345**	**2.452**
	dummies	**0**	**3428**	**18.6**	**637**	**15.1**	**14.1**	**16.1**
		1	**3428**	**24.7**	**848**	**21.3**	**20.1**	**22.4**
		2	3428	21.6	742	20.4	19.2	21.6
		3	3428	16.2	555	17.1	15.8	18.4
		4	**3428**	**9.7**	**332**	**11.6**	**10.7**	**12.5**
		5	**3428**	**5.3**	**180**	**7.2**	**6.4**	**8.0**
		6+	**3428**	**3.9**	**134**	**7.4**	**6.4**	**8.3**
Adversity 0-59	terciles	**0-1**	**3214**	**34.5**	**1108**	**27.3**	**26.0**	**28.6**
		2-3	**3214**	**38.0**	**1220**	**36.2**	**34.8**	**37.5**
		4+	**3214**	**27.6**	**886**	**36.6**	**35.2**	**37.9**
	continuous	**0-7+**	**3214**	**2.503**	**1.825**	**2.966**	**2.909**	**3.022**
	dummies	**0**	**3214**	**13.2**	**425**	**9.9**	**9.1**	**10.8**
		1	**3214**	**21.3**	**683**	**17.3**	**16.3**	**18.4**
		2	**3214**	**20.4**	**656**	**18.6**	**17.5**	**19.8**
		3	3214	17.5	564	17.5	16.5	18.6
		4	3214	13.4	431	14.2	13.1	15.2
		5	**3214**	**6.7**	**215**	**9.1**	**8.3**	**9.9**
		6	**3214**	**3.8**	**121**	**5.9**	**5.2**	**6.7**
		7+	**3214**	**3.7**	**119**	**7.4**	**6.5**	**8.2**
Cumulative adversity 0-44								
	dummies	**0**	**4998**	**12.7**	**637**	**15.1**	**14.1**	**16.1**
		1	**4998**	**32.7**	**1636**	**34.4**	**33.0**	**35.9**
		2	4998	35.2	1761	34.0	32.7	35.3
		3	**4998**	**19.3**	**964**	**16.4**	**15.3**	**17.6**
	continuous	**0-3**	**4998**	**1.611**	**0.937**	**1.518**	**1.489**	**1.547**
Cumulative adversity 0-59								
	dummies	0	4640	9.2	425	9.9	9.1	10.8
		1	**4640**	**25.4**	**1178**	**26.7**	**25.5**	**27.9**
		2	4640	33.9	1573	33.4	32.1	34.8
		3	4640	22.9	1062	22.5	21.3	23.6
		4	**4640**	**8.7**	**402**	**7.5**	**6.6**	**8.3**
	continuous	0-4	4640	1.965	1.093	1.908	1.878	1.939

Youth adversity	binary		5145	50.1	2579	51.0	49.7	52.2
	dummies	0	5145	49.9	2566	49.0	47.8	50.3
		1	5145	29.3	1506	29.2	28.0	30.5
		2	5145	13.0	667	13.1	12.1	14.0
		3+	5145	7.9	406	8.7	7.9	9.4
Early adulthood adversity								
	binary		4999	43.4	2170	44.8	43.4	46.1
	dummies	0	4999	56.6	2829	55.2	53.9	56.6
		1	4999	26.3	1313	26.4	25.2	27.6
		2	4999	11.2	561	11.7	10.8	12.6
		3+	4999	5.9	296	6.6	5.9	7.4
Mid-adulthood adversity								
	binary		4644	38.3	1778	39.0	37.7	40.4
	dummies	0	4644	61.7	2866	61.0	59.6	62.3
		1	4644	24.7	1147	24.8	23.6	26.0
		2	4644	8.9	413	9.1	8.3	10.0
		3+	4644	4.7	218	5.1	4.5	5.7
Adversities from histories during:								
childhood	binary		4971	43.6	2168	44.3	43.0	45.6
youth	binary		6540	36.9	2414	36.9	35.7	38.0
early adulthood	binary		6540	38.0	2483	38.0	36.8	39.1
mid-adulthood	binary		6540	30.3	1980	30.3	29.2	31.4
Material adversity during:								
childhood	binary		**4178**	**16.7**	**699**	**18.3**	**16.8**	**19.8**
youth	binary		**5435**	**11.4**	**619**	**12.6**	**11.7**	**13.5**
0-29	binary		**4161**	**19.5**	**812**	**27.8**	**26.5**	**29.1**
0-44	binary		**4161**	**22.1**	**918**	**33.1**	**31.7**	**34.4**
0-59	binary		**4161**	**25.0**	**1040**	**37.5**	**36.2**	**38.9**
childhood	dummies	**0**	**4178**	**83.3**	**3479**	**81.7**	**80.2**	**83.2**
		1	4178	14.9	622	16.1	14.7	17.4
		2+	4178	1.8	77	2.2	1.8	2.7
youth	dummies	**0**	**5435**	**88.6**	**4816**	**87.4**	**86.5**	**88.3**
		1	5435	9.8	534	10.6	9.7	11.4
		2+	5435	1.6	85	2.0	1.6	2.5
0-29	dummies	**0**	**4161**	**80.5**	**3349**	**72.2**	**70.9**	**73.5**
		1	**4161**	**16.5**	**688**	**21.6**	**20.3**	**22.9**
		2+	**4161**	**3.0**	**124**	**6.1**	**5.2**	**7.0**
0-44	dummies	**0**	**4161**	**77.9**	**3243**	**66.9**	**65.6**	**68.3**
		1	**4161**	**17.6**	**733**	**23.5**	**22.3**	**24.8**
		2+	**4161**	**4.4**	**185**	**9.5**	**8.5**	**10.5**
0-59	dummies	**0**	**4161**	**75.0**	**3121**	**62.5**	**61.1**	**63.8**
		1	**4161**	**18.3**	**762**	**24.3**	**23.1**	**25.6**
		2	**4161**	**4.6**	**193**	**8.1**	**7.2**	**9.0**
		3+	**4161**	**2.0**	**85**	**5.1**	**4.4**	**5.8**
Social adversity during:								
childhood	continuous	**0-3+**	**4568**	**0.715**	**0.799**	**0.750**	**0.728**	**0.772**
youth	continuous	**0-3+**	**5211**	**0.548**	**0.702**	**0.571**	**0.553**	**0.589**
0-29	continuous	**0-3+**	**4499**	**1.256**	**1.093**	**1.320**	**1.290**	**1.350**
0-44	continuous	**0,1-2,3-5,6+**	**4368**	**1.089**	**0.787**	**1.149**	**1.128**	**1.170**
0-59	continuous	**0,1-2,3+**	**4368**	**1.234**	**0.714**	**1.245**	**1.227**	**1.264**

childhood	dummies	**0**	**4568**	**50.3**	**2296**	**48.2**	**46.8**	**49.6**
		1	4568	28.0	1280	28.6	27.4	29.8
		2	**4568**	**13.3**	**609**	**14.3**	**13.4**	**15.2**
		3	4568	5.5	249	5.8	5.2	6.4
		4+	4568	2.9	134	3.1	2.6	3.6
youth	dummies	0	5211	57.4	2990	56.1	54.8	57.4
		1	5211	30.4	1584	30.7	29.5	31.9
		2	5211	10.3	538	11.0	10.2	11.8
		3+	5211	1.9	99	2.2	1.8	2.6
0-29	dummies	**0**	**4499**	**31.6**	**1423**	**29.3**	**28.1**	**30.4**
		1	4499	29.8	1340	29.8	28.6	31.0
		2	4499	20.0	899	20.6	19.5	21.7
		3	4499	10.2	457	11.0	10.1	11.9
		4	4499	5.1	230	5.6	4.9	6.2
		5+	4499	3.3	150	3.8	3.3	4.3
0-44	dummies	**0**	**4368**	**23.2**	**1013**	**20.7**	**19.6**	**21.8**
		1	4368	26.4	1154	25.7	24.6	26.8
		2	4368	22.0	959	22.1	21.0	23.3
		3	**4368**	**12.9**	**563**	**14.1**	**13.2**	**15.1**
		4	**4368**	**7.7**	**337**	**8.6**	**7.8**	**9.4**
		5	4368	4.1	181	4.7	4.1	5.3
		6+	4368	3.7	161	4.1	3.5	4.7
0-59	dummies	**0**	**4059**	**17.8**	**723**	**15.1**	**14.2**	**16.1**
		1	**4059**	**25.0**	**1016**	**23.4**	**22.3**	**24.5**
		2	4059	21.8	885	21.8	20.6	23.0
		3	4059	15.3	620	16.1	15.1	17.1
		4	**4059**	**9.0**	**366**	**10.2**	**9.4**	**11.0**
		5	**4059**	**5.2**	**213**	**6.3**	**5.6**	**7.0**
		6	**4059**	**2.7**	**109**	**3.4**	**2.9**	**3.9**
		7+	**4059**	**3.1**	**127**	**3.6**	**3.1**	**4.2**
Family adversity during:								
childhood	binary	0-2+	5364	35.8	1922	36.2	34.9	37.5
youth	binary	0,1+	5427	31.5	1709	32.2	31.1	33.4
0-29	continuous	0,1-2,3+	5288	0.633	0.643	0.648	0.631	0.665
0-44	continuous	**0,1-2,3+**	**5137**	**0.829**	**0.701**	**0.861**	**0.844**	**0.879**
0-59	continuous	**0.1-3,4+**	**4773**	**0.824**	**0.612**	**0.867**	**0.851**	**0.884**
childhood	dummies	0	5364	64.2	3442	63.8	62.5	65.1
		1	5364	23.1	1240	23.1	22.1	24.2
		2	5364	9.0	484	9.2	8.4	10.0
		3	5364	2.6	137	2.7	2.2	3.1
		4+	5364	1.1	61	1.2	0.9	1.5
youth	dummies	0	5427	68.5	3718	67.8	66.6	68.9
		1	5427	23.7	1286	23.9	22.8	24.9
		2+	5427	7.8	423	8.4	7.7	9.1
0-29	dummies	0	5288	45.7	2419	44.9	43.5	46.2
		1	5288	30.2	1595	30.1	28.8	31.3
		2	5288	15.0	794	15.4	14.4	16.3
		3	5288	5.9	313	6.2	5.6	6.8
		4+	5288	3.2	167	3.5	3.0	4.0

0-44	dummies	**0**	**5137**	**34.6**	**1775**	**32.9**	**31.7**	**34.1**
		1	5137	29.3	1505	29.0	27.7	30.2
		2	5137	18.6	958	19.1	18.1	20.2
		3	5137	9.7	497	10.3	9.5	11.1
		4	5137	5.0	257	5.5	4.9	6.1
		5+	5137	2.8	145	3.2	2.8	3.7
0-59	dummies	**0**	**4773**	**29.0**	**1385**	**26.6**	**25.5**	**27.7**
		1	4773	27.6	1319	27.2	26.0	28.3
		2	4773	21.0	1001	20.9	19.9	22.0
		3	**4773**	**10.9**	**521**	**11.9**	**11.0**	**12.8**
		4	**4773**	**6.1**	**292**	**7.1**	**6.4**	**7.8**
		5	**4773**	**2.8**	**133**	**3.4**	**2.9**	**3.9**
		6+	4773	2.6	122	2.9	2.4	3.3
Traumatic adversity during:								
childhood	continuous	0-2+	4662	0.326	0.564	0.338	0.318	0.357
youth	binary	0,1+	5294	17.7	938	18.6	17.5	19.8
0-29	binary	0,1+	4654	39.6	1842	41.0	39.3	42.6
0-44	binary	0,1+	4654	43.4	2019	44.8	43.2	46.4
0-59	binary	0,1+	4654	48.1	2237	49.5	47.9	51.0
childhood	dummies	0	4662	72.4	3373	71.6	70.2	73.1
		1	4662	22.7	1060	23.0	21.7	24.2
		2+	4662	4.9	229	5.4	4.6	6.2
youth	dummies	0	5294	82.3	4356	81.4	80.2	82.5
		1+	5294	17.7	938	18.6	17.5	19.8
0-29	dummies	0	4654	60.4	2812	59.0	57.4	60.7
		1	4654	30.0	1396	30.7	29.3	32.1
		2+	4654	9.6	446	10.3	9.3	11.3
0-44	dummies	0	4654	56.6	2635	55.2	53.6	56.8
		1	4654	31.3	1457	32.0	30.7	33.4
		2+	4654	12.1	562	12.8	11.7	13.9
0-59	dummies	0	4654	51.9	2417	50.5	49.0	52.1
		1	4654	33.9	1580	34.4	33.0	35.8
		2	4654	11.5	535	12.2	11.2	13.1
		3+	4654	2.6	122	2.9	2.4	3.4
Chronic adversity during:								
youth	binary	0,1+	5422	13.1	711	14.0	13.1	14.9
16-44	binary	0,1+	5422	28.0	1516	29.2	28.0	30.5
16-59	binary	0,1+	5422	39.2	2127	40.5	39.2	41.8
youth	dummies	0	5422	86.9	4711	86.0	85.1	86.9
		1	5422	12.1	658	12.7	11.7	13.6
		2+	5422	1.0	53	1.3	1.0	1.7
16-44	dummies	0	5422	72.0	3906	70.8	69.5	72.0
		1	5422	21.8	1180	22.4	21.2	23.5
		2+	5422	6.2	336	6.8	6.1	7.5
16-59	dummies	0	5422	60.8	3295	59.5	58.2	60.8
		1	5422	28.5	1544	28.8	27.6	30.0
		2	5422	8.2	445	8.7	7.9	9.4
		3+	**5422**	**2.5**	**138**	**3.1**	**2.6**	**3.6**
Acute adversity during:								
youth	binary		5356	11.2	602	11.9	11.0	12.8

16-44	binary		5356	15.1	809	16.0	15.1	17.0
16-59	binary		**5356**	**18.0**	**962**	**19.2**	**18.1**	**20.3**
youth	dummies	0	5356	88.8	4754	88.1	87.2	89.0
		1	5356	9.9	528	10.1	9.2	10.9
		2+	5356	1.4	74	1.8	1.4	2.2
16-44	dummies	0	5356	84.9	4547	84.0	83.0	84.9
		1	5356	13.0	695	13.3	12.3	14.2
		2+	**5356**	**2.1**	**114**	**2.8**	**2.2**	**3.3**
16-59	dummies	**0**	**5356**	**82.0**	**4394**	**80.8**	**79.7**	**81.9**
		1	5356	15.3	820	15.7	14.6	16.7
		2+	**5356**	**2.7**	**142**	**3.6**	**2.9**	**4.2**
Female gender	binary		6624	54.7	3626	54.7	53.5	55.9
Level 2+ in 2006	binary		6109	68.4	4179	67.7	66.5	68.9
Born by 1920	binary		6624	3.7	247	3.7	3.3	4.2
Born 1921-1930	binary		6624	12.9	854	12.9	12.1	13.7
Born 1931-1940	binary		6624	23.8	1579	23.8	22.8	24.9
Born 1941-1950	binary		6624	34.7	2297	34.7	33.5	35.8
Born 1951 or after	binary		6624	24.9	1647	24.9	23.8	25.9
Years smoked 30-44	continuous		**6272**	**5.553**	**6.843**	**5.372**	**5.208**	**5.537**
Years smoked 45-59	continuous		6337	3.383	5.758	3.602	3.459	3.745

The original sample includes all participants in LIFE who provided information about RA status, gender, and date of birth.

Appendix 13: Descriptive statistics

Table A13.1 presents lifetime prevalence and incidence rates of RA for the unweighted and weighted samples that participated in the LIFE interview, and that participated in at least one sweep of ELSA regardless of participation in LIFE. Numbers in the weighted samples are smaller than in the unweighted samples because weights are available only for those who participated in LIFE, or in the first seven waves of ELSA. The results suggest that adults with RA were more likely than those without RA to participate in ELSA, but less likely to participate in the LIFE interview.

Table A13.1: Lifetime prevalence and incidence rates of RA in weighted and unweighted samples

		Number of respondents	Lifetime prevalence 95% confidence interval		Incidence per 100 per year 95% confidence interval	
LIFE	Unweighted	6,626	3.92%	3.46%-4.39%	0.054	0.047-0.060
	Weighted	5,889	4.37%	3.80%-4.92%	0.058	0.051-0.067
ELSA	Unweighted	16,118	4.72%	4.39%-5.04%	0.068	0.063-0.073
	Weighted	3,303	3.90%	3.17%-4.63%	0.051	0.042-0.062

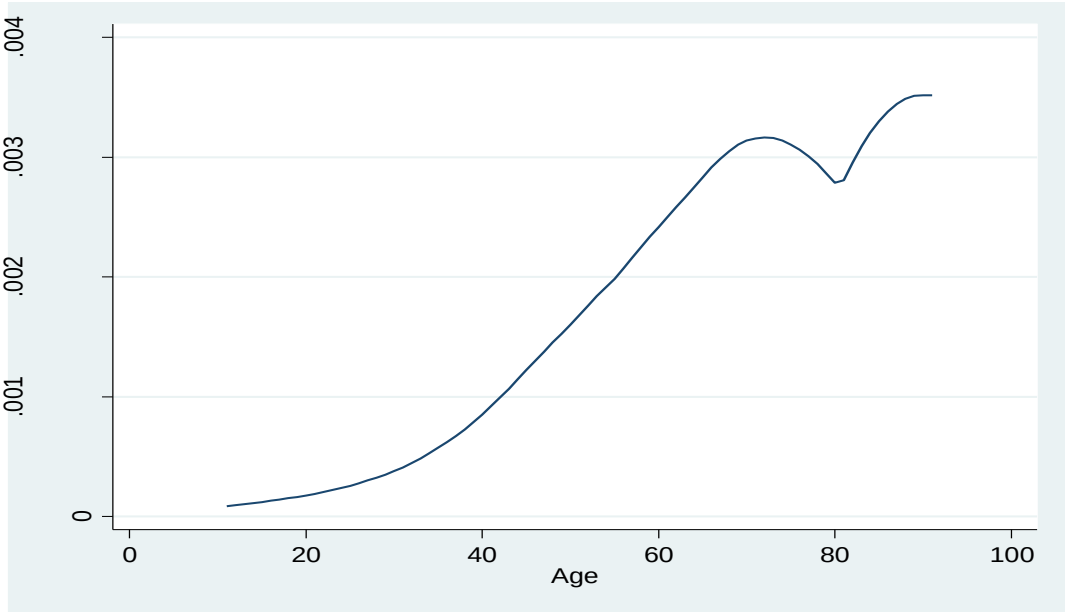
RA onset before age 16 is classified as juvenile, not rheumatoid, arthritis.

In the main text, Figure 3.3 presents the hazard function for RA onset adjusted for birth cohort for the LIFE sample. Figure A13.1 presents the equivalent hazard function using the whole ELSA sample.

Figure A13.1 shows that up to age 80, the baseline hazard function for the total ELSA sample is very similar to that for the respondents who participated in LIFE (Figure 3.3). Only 16 of the respondents who participated in the LIFE interview reported RA onset after age 80, and so the smoothed hazard function ends at about age 80 for this sub-sample. Amongst the total ELSA sample, 31 respondents reported RA onset after age 80, and the curve changes direction with a second peak of relatively high incidence at just over the age of 90. The

increased risk of RA onset in very late life may reflect attrition from the sample due to death as well as an increased likelihood of developing a chronic illness amongst those who remain.

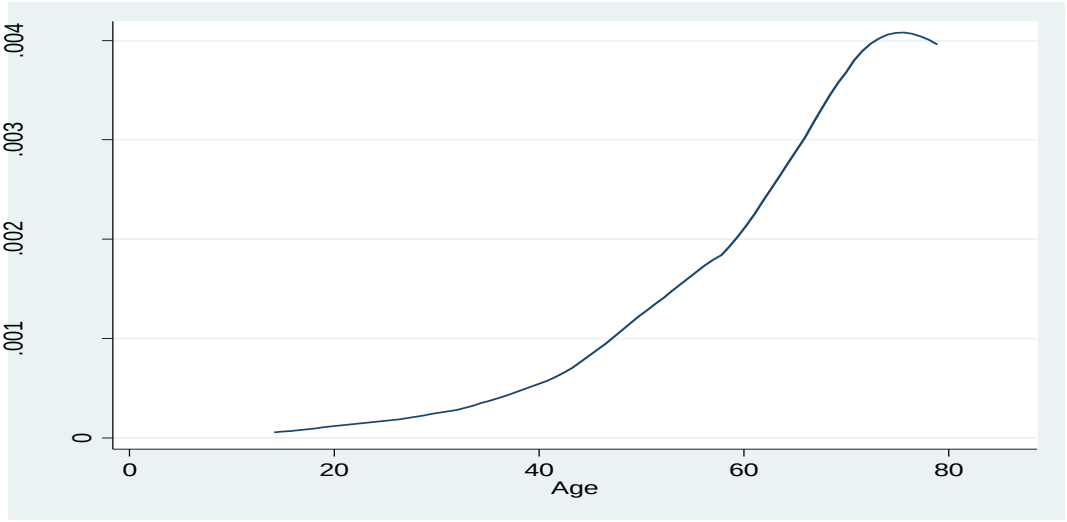
Figure A13.1: Hazard function for RA onset adjusted for birth cohort using the whole ELSA sample



This figure uses a base of 16,118 respondents who participated in at least one sweep of ELSA, of whom 760 reported RA onset.

Figure A13.2 presents the equivalent hazard function using the weighted LIFE sample, which is also very similar to Figure 3.3.

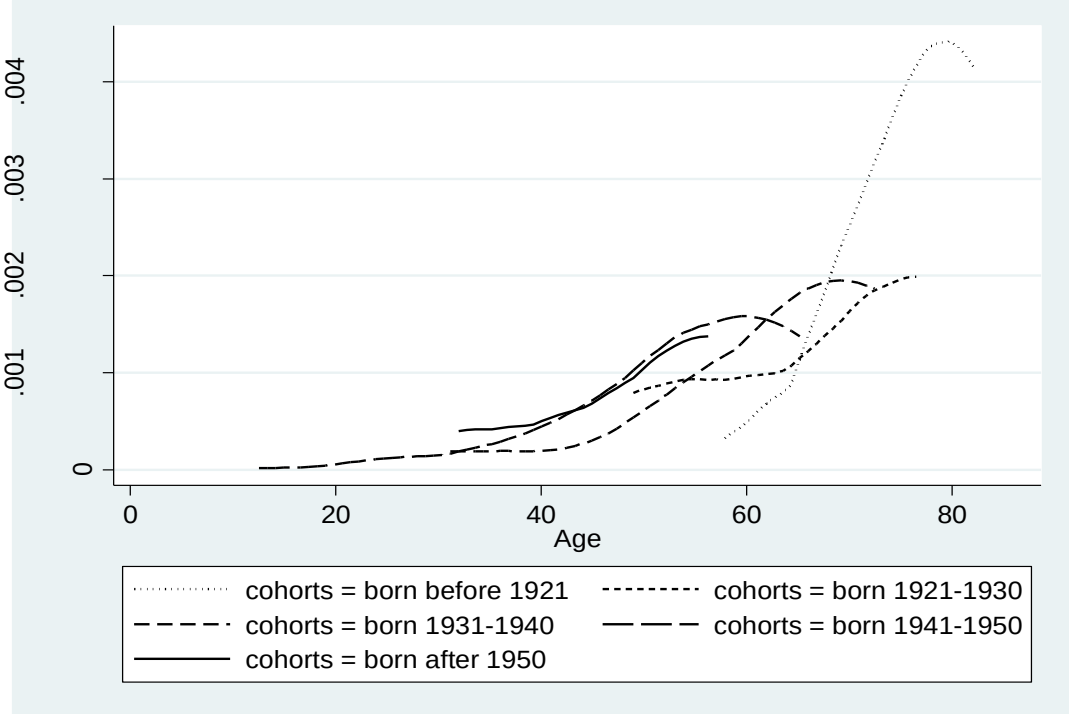
Figure A13.2: Hazard function for RA onset adjusted for birth cohort using weighted sample of LIFE participants



Figures A13.3, A13.4, and A13.5 present hazard functions for RA onset using the weighted LIFE sample for each birth cohort, for men and women, and for respondents with different socio-economic backgrounds, respectively.

The results are similar to those using the unweighted LIFE sample. As for Figure3. 4, which used the unweighted LIFE sample, Figure A13.3 illustrates that RA onset was diagnosed earlier in the life course for younger cohorts. In the weighted sample, mean age of RA onset is 49 for those born after 1950, 54 for those born between 1941 and 1950, 63 for those born between 1931 and 1940, 68 for those born between 1921 and 1930, and 77 for those born before 1921.

Figure A13.3: Hazard functions for RA onset for each birth cohort using weighted sample of LIFE participants



As with the unweighted sample, Figure A13.4 suggests a gender difference in RA onset that turns out not to be statistically significant. The hazard ratio for RA onset of women compared against men is 1.048, 95%CI=0.806-1.363, p=0.727. Figure A13.5 suggests a small difference between those growing up with a main carer whose main occupation was routine or manual, but the difference is statistically significant; HR=1.652, 95%CI=1.228-2.223, p=0.001.

Figure A13.4: Hazard functions for RA o Hazard functions for RA onset for men and women adjusted for birth cohort, using weighted sample of LIFE participants

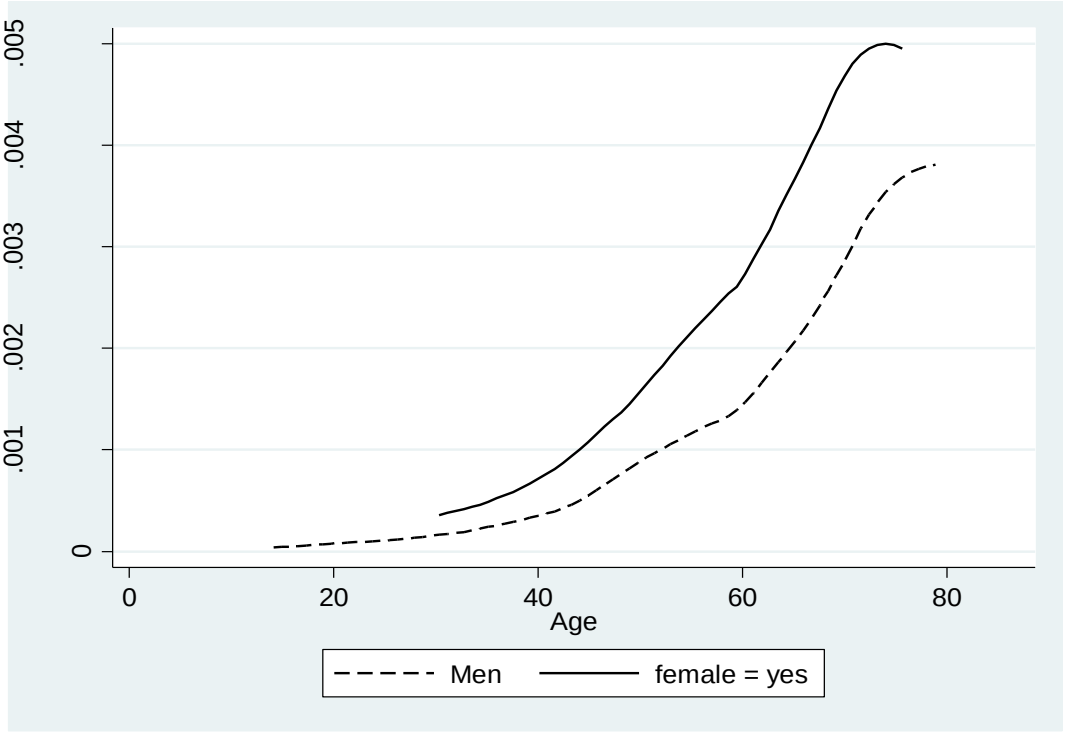
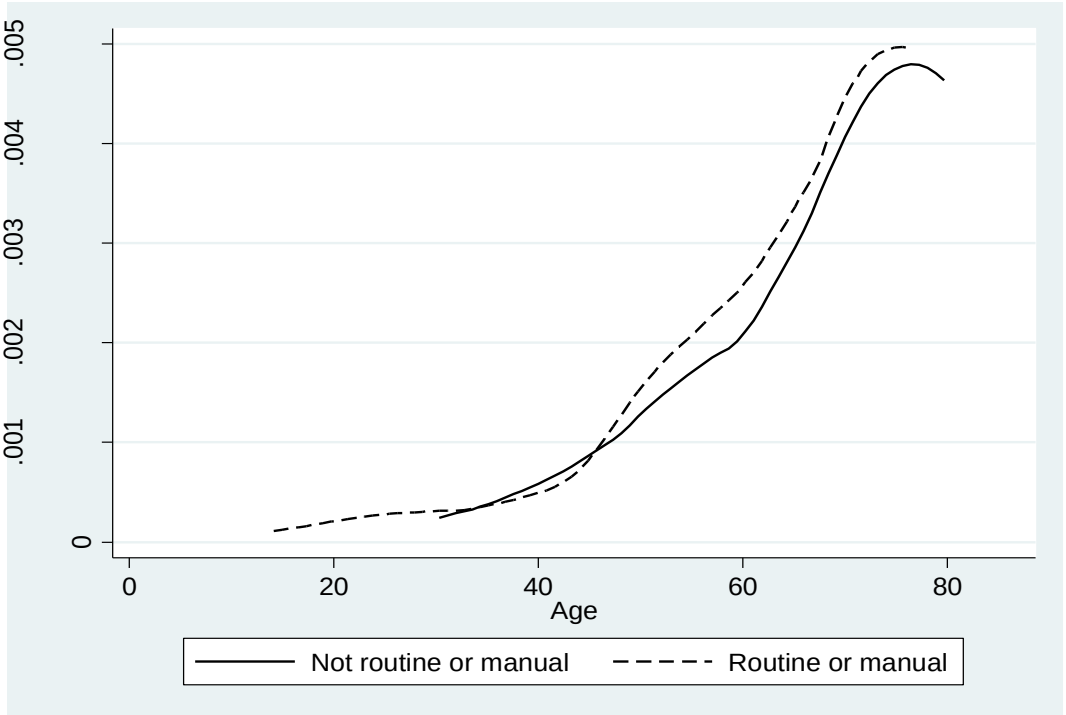


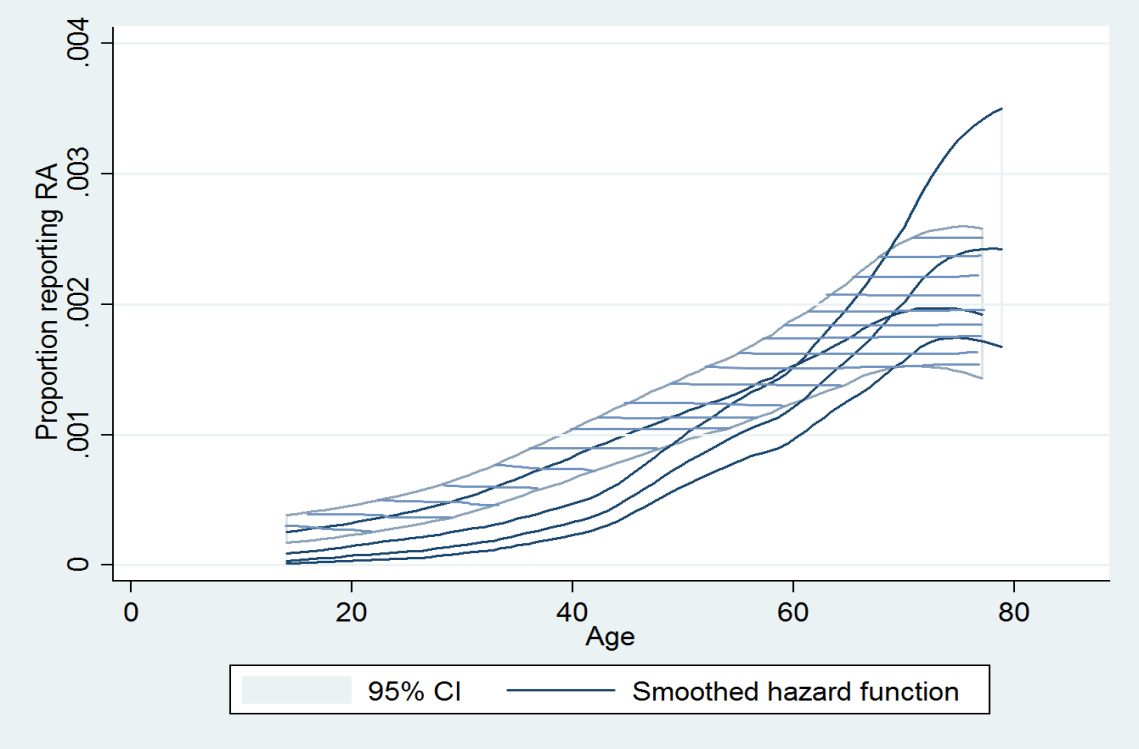
Figure A13.5: Hazard functions for RA onset by socio-economic background, adjusted for birth cohort and using weighted sample of LIFE participants



Note: Socio-economic background is measured by whether the respondent reported that their father had a manual or routine occupation when they were 14 years old.

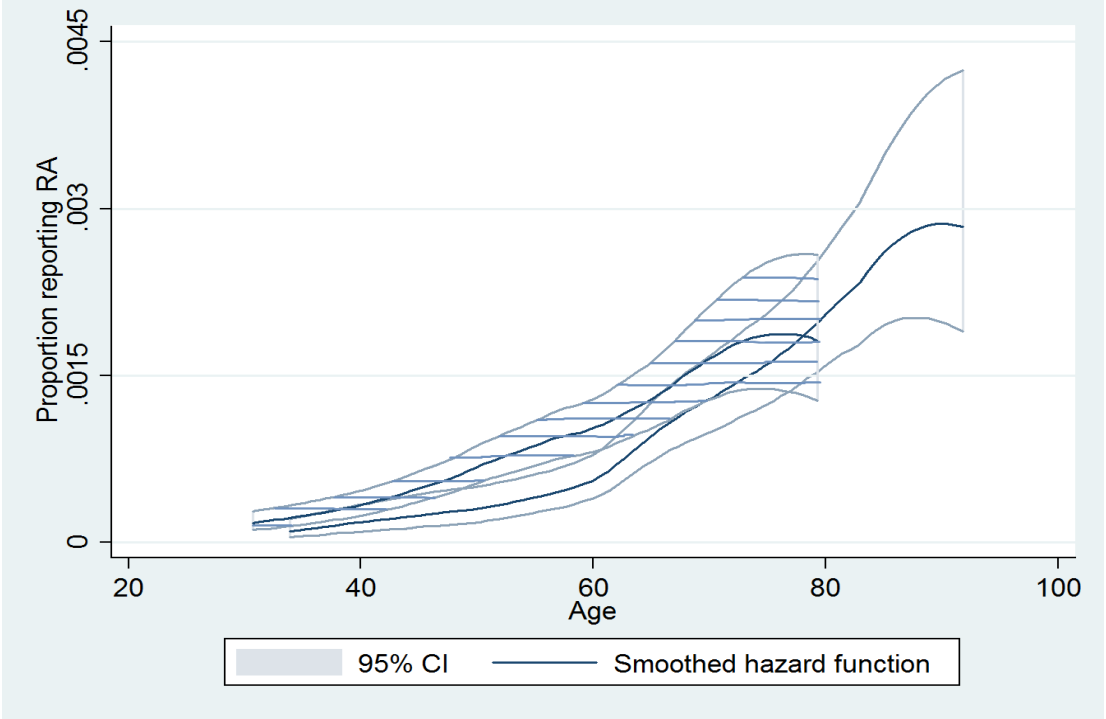
Figures A13.6 and A13.7 present hazard functions with confidence intervals for men and women, and respondents growing up with a main carer whose occupation was routine/manual or not. There is no adjustment for birth cohort, as Stata does not support inclusion of confidence intervals for adjusted hazard functions. The unadjusted hazard ratios for RA onset by gender and socioeconomic background are 1.079, 95%CI=0.845-1.378, p=0.542 and 1.684, 95%CI=1.280-2.216, p=0.000, respectively.

Figure A13.6: Unadjusted hazard functions with confidence intervals for men and women who participated in LIFE



Hazard functions with confidence intervals are striped for women and blank for men.

Figure A13.7: Unadjusted hazard functions with confidence intervals by socio-economic background for LIFE participants



Hazard functions with confidence intervals are striped for those whose main carer during childhood had a routine or manual occupation and blank for those whose was not.

For all groups, confidence intervals increase with age, probably because a higher proportion of respondents have been censored.

Figure A13.6 shows that up to about age 50, more women than men develop RA, but thereafter, the confidence intervals for women and men overlap substantially. Figure A13.7 shows a more consistent relationship between those who grew up in more and less socio-economically advantaged families, with those from more disadvantages families developing the condition sooner and more frequently. Although the confidence intervals for the two groups overlap a little for most of the life course, it is only late in life – at about age 65 – that the confidence intervals between the two groups overlap substantially. RA risk increases amongst those from socio-economically advantaged backgrounds after age 80, but there are

no observations from the disadvantaged group at this age, possibly reflecting the socio-economic gradient in life expectancy (Office for National Statistics 2015).

Table A13.2 presents summary statistics for all variables used in the analyses, including those used in the appendices, for men and women using the imputed datasets. Means are estimated and have confidence intervals, and gender differences are indicated when these confidence intervals do not overlap.

Table A13.2: Summary statistics for men and women separately

			Men (n=2,998)		Women (n=3,626)	
Variable	Type		Mean/%	95%CI	Mean	95%CI
Childhood adversity	terciles	0	44.3	41.6-46.9	43.7	41.2-46.2
		1	29.7	27.5-31.9	29.5	27.4-31.7
		2+	26.0	23.9-28.2	26.8	24.7-28.8
	binary		55.7	53.1-58.4	56.3	53.8-58.8
	dummies	0	44.3	41.6-46.9	43.7	41.2-46.2
		1	29.7	27.5-31.9	29.5	27.4-31.7
		2	15.4	13.7-17.2	14.8	13.3-16.4
		3+	10.6	9.1-12.1	12.0	10.3-13.6
Adversity 0-44	terciles	0-1	37.4	35.4-39.4	35.5	33.7-37.3
		2-3	37.0	35.0-39.0	37.9	36.0-39.8
		4+	25.6	23.6-27.6	26.6	24.8-28.4
	continuous	0-6+	2.362	2.285-2.440	2.428	2.360-2.496
	dummies	0	15.5	13.9-17.1	14.8	13.5-16.1
		1	21.9	20.3-23.5	20.7	19.2-22.3
		2	20.1	18.3-21.9	20.7	19.0-22.3
		3	16.9	15.1-18.8	17.2	15.7-18.8
		4	11.6	10.2-13.0	11.6	10.3-13.0
		5	7.1	6.0-8.3	7.2	6.1-8.2
		6+	6.9	5.6-8.2	7.8	6.6-9.0
Adversity 0-59	terciles	0-1	27.7	25.9-29.5	26.9	25.2-28.6
		2-3	35.7	33.7-37.7	36.5	34.7-38.3
		4+	36.6	34.5-38.7	36.5	34.7-38.4
	continuous	0-7+	2.940	2.852-3.027	2.987	2.912-3.061
	dummies	0	10.2	9.0-11.4	9.7	8.6-10.8
		1	17.5	16.0-19.0	17.2	15.7-18.7
		2	18.8	17.0-20.7	18.5	17.0-19.9
		3	16.9	15.2-18.6	18.1	16.6-19.5
		4	14.4	13.0-15.8	14.0	12.4-15.5
		5	9.3	8.0-10.7	8.9	7.7-10.0
		6	6.0	4.9-7.1	5.9	4.8-6.9
		7+	6.8	5.7-8.0	7.8	6.7-9.0
Cumulative adversity 0-44	dummies	0	15.5	13.9-17.1	14.8	13.5-16.1
		1	35.1	33.1-37.2	33.9	32.0-35.8
		2	33.8	31.9-35.7	34.3	32.4-36.1
		3	15.6	13.9-17.3	17.1	15.5-18.7

	continuous	0-3	1.495	1.453-1.537	1.537	1.499-1.575
Cumulative adversity 0-59	dummies	0	10.2	9.0-11.4	9.7	8.6-10.8
		1	26.9	25.2-28.7	26.5	24.8-28.2
		2	33.8	31.9-35.7	33.1	31.1-35.0
		3	22.0	20.3-23.7	22.9	21.2-24.5
		4	7.0	5.9-8.2	7.8	6.6-9.0
	continuous	0-4	1.887	1.841-1.934	1.925	1.883-1.967
Youth adversity	binary		50.7	48.6-52.7	51.2	49.5-52.9
	dummies	0	49.3	47.3-51.4	48.8	47.1-50.5
		1	28.7	26.8-30.6	29.7	28.0-31.3
		2	13.5	12.1-14.8	12.8	11.5-14.0
		3+	8.5	7.4-9.5	8.8	7.8-9.8
Early adulthood adversity	binary		**43.1**	**41.0-45.1**	**46.1**	**44.3-48.0**
	dummies	0	**56.9**	**54.9-59.0**	**53.9**	**52.0-55.7**
		1	**25.3**	**23.5-27.1**	**27.4**	**25.8-29.0**
		2	11.2	10.0-12.4	12.1	10.8-13.3
		3+	6.6	5.5-7.7	6.7	5.7-7.7
Mid-adulthood adversity	binary		39.3	37.0-41.5	38.8	37.1-40.6
	dummies	0	60.7	58.5-63.0	61.2	59.4-62.9
		1	24.5	22.7-26.3	25.0	23.5-26.6
		2	9.2	8.0-10.4	9.1	8.0-10.1
		3+	5.5	4.5-6.6	4.7	3.9-5.5
Histories childhood	binary		**42.9**	**41.0-44.8**	**45.4**	**43.6-47.2**
Histories youth	binary		**30.4**	**28.8-32.1**	**42.2**	**40.6-43.8**
Histories early adulthood	binary		**36.4**	**34.7-38.2**	**39.2**	**37.6-40.8**
Histories mid-adulthood	binary		30.4	28.8-32.1	30.2	28.7-31.8
Material adversity childhood	binary		17.7	15.8-19.7	18.8	16.9-20.6
Material adversity youth	binary		12.7	11.4-14.1	12.5	11.3-13.7
Material adversity 0-29	binary		27.2	25.3-29.2	28.2	26.5-29.9
Material adversity 0-44	binary		33.4	31.4-35.4	32.8	31.0-34.5
Material adversity 0-59	binary		**39.0**	**37.0-40.9**	**36.3**	**34.6-38.1**
Material adversity childhood	dummies	0	82.3	80.3-84.2	81.2	79.4-83.1
		1	15.8	14.0-17.6	16.3	14.6-18.0
		2+	1.9	1.3-2.6	2.5	1.9-3.2
Material adversity youth	dummies	0	87.3	85.9-88.6	87.5	86.3-88.7
		1	10.6	9.4-11.8	10.5	9.3-11.7
		2+	2.1	1.5-2.7	2.0	1.5-2.5
Material adversity 0-29	dummies	0	72.8	70.8-74.7	71.8	70.1-73.5
		1	21.4	19.6-23.2	21.8	20.1-23.6
		2+	5.8	4.7-7.0	6.4	5.3-7.5
Material adversity 0-44	dummies	0	66.6	64.6-68.6	67.2	65.5-69.0
		1	23.6	21.8-25.4	23.5	21.8-25.2
		2+	9.8	8.4-11.2	9.3	8.0-10.6
Material adversity 0-59	dummies	0	**61.0**	**59.1-63.0**	**63.7**	**61.9-65.4**
		1	24.3	22.5-26.0	24.4	22.6-26.1
		2	8.6	7.4-9.9	7.7	6.5-8.8
		3+	**6.1**	**4.9-7.2**	**4.3**	**3.4-5.1**
Social adv. childhood	continuous	0-3+	0.758	0.725-0.791	0.743	0.713-0.773
Social adversity youth	continuous	0-3+	**0.529**	**0.502-0.555**	**0.606**	**0.581-0.631**
Social adversity 0-29	continuous	0-3+	**1.293**	**1.250-1.337**	**1.342**	**1.303-1.381**
Social adversity 0-44	cont.	0,1-2,3-5,6+	**1.110**	**1.080-1.139**	**1.181**	**1.153-1.210**
Social adversity 0-59	Cont.	0,1-2,3+	**1.209**	**1.182-1.235**	**1.276**	**1.250-1.301**
Social adv. childhood	dummies	0	47.6	45.6-49.7	48.7	46.8-50.6

		1	28.9	27.2-30.6	28.3	26.6-30.0
		2	**15.3**	**13.9-16.8**	**13.4**	**12.2-14.7**
		3	5.6	4.6-6.5	6.0	5.1-6.8
		4+	**2.5**	**1.8-3.2**	**3.6**	**2.9-4.2**
Social adversity youth	dummies	0	**57.6**	**55.6-59.5**	**54.9**	**53.1-56.6**
		1	**32.0**	**30.1-33.9**	**29.7**	**28.1-31.3**
		2	**8.7**	**7.6-9.8**	**12.9**	**11.7-14.0**
		3+	**1.7**	**1.2-2.2**	**2.6**	**2.0-3.2**
Social adversity 0-29	dummies	0	29.7	27.9-31.5	28.9	27.3-30.5
		1	30.1	28.2-32.0	29.5	28.0-31.1
		2	21.4	19.7-23.0	20.0	18.6-21.4
		3	10.8	9.4-12.1	11.1	10.0-12.3
		4	**5.0**	**4.0-5.9**	**6.1**	**5.2-6.9**
		5+	**3.1**	**2.4-3.8**	**4.3**	**3.6-5.1**
Social adversity 0-44	dummies	0	21.6	20.0-23.3	20.0	18.5-21.4
		1	26.6	24.8-28.3	24.9	23.5-26.4
		2	22.4	20.8-24.1	21.8	20.3-23.4
		3	14.0	12.6-15.4	14.2	13.0-15.5
		4	**7.9**	**6.8-9.0**	**9.2**	**8.1-10.2**
		5	4.2	3.4-5.0	5.1	4.25.9
		6+	**3.2**	**2.5-4.0**	**4.8**	**4.0-5.6**
Social adversity 0-59	dummies	0	**16.1**	**14.7-17.6**	**14.3**	**13.0-15.6**
		1	**24.4**	**22.7-26.2**	**22.5**	**21.1-24.0**
		2	22.5	20.7-24.3	21.2	19.7-22.8
		3	15.7	14.2-17.2	16.5	15.2-17.8
		4	10.1	8.8-11.3	10.4	9.2-11.5
		5	**5.3**	**4.4-6.3**	**7.1**	**6.1-8.0**
		6	3.0	2.2-3.7	3.8	3.0-4.5
		7+	**2.9**	**2.2-3.6**	**4.2**	**3.4-5.0**
Family adversity childhood	binary	0-2+	35.2	33.2-37.2	37.0	35.3-38.8
Family adversity youth	binary	0,1+	**23.5**	**21.9-25.0**	**39.5**	**37.8-41.2**
Family adversity 0-29	continuous	0,1-2,3+	**0.557**	**0.532-0.582**	**0.724**	**0.701-0.747**
Family adversity 0-44	continuous	0,1-2,3+	**0.758**	**0.731-0.785**	**0.947**	**0.923-0.971**
Family adversity 0-59	Continuous	0,1-3,4+	**0.771**	**0.747-0.795**	**0.947**	**0.926-0.968**
Family adversity childhood	dummies	0	64.8	62.8-66.8	63.0	61.2-64.7
		1	23.2	21.6-24.9	23.1	21.6-24.6
		2	8.7	7.6-9.7	9.7	8.6-10.8
		3	2.4	1.7-3.0	2.9	2.3-3.5
		4+	**0.9**	**0.5-1.3**	**1.4**	**1.0-1.8**
Family adversity youth	dummies	0	**76.5**	**75.0-78.1**	**60.5**	**58.8-62.2**
		1	**19.0**	**17.6-20.5**	**27.9**	**26.3-29.4**
		2+	**4.5**	**3.7-5.2**	**11.6**	**10.5-12.7**
Family adversity 0-29	dummies	0	**51.5**	**49.5-53.4**	**39.4**	**37.7-41.1**
		1	**27.8**	**26.0-29.6**	**31.9**	**30.2-33.5**
		2	**13.4**	**12.1-14.8**	**17.0**	**15.7-18.3**
		3	**4.9**	**4.1-5.8**	**7.3**	**6.4-8.2**
		4+	**2.3**	**1.7-2.9**	**4.5**	**3.7-5.2**
Family adversity 0-44	dummies	0	**39.0**	**37.1-40.8**	**27.8**	**26.3-29.4**
		1	**28.8**	**26.9-30.6**	**29.2**	**27.5-30.8**
		2	**17.5**	**16.0-19.0**	**20.5**	**19.1-21.9**
		3	**8.5**	**7.3-9.7**	**11.8**	**10.7-12.9**
		4	**4.2**	**3.4-5.0**	**6.5**	**5.6-7.4**
		5+	**2.0**	**1.4-2.6**	**4.2**	**3.5-4.9**
Family adversity 0-59	dummies	0	**32.9**	**31.1-34.7**	**21.4**	**20.0-22.8**
		1	27.5	25.7-29.3	26.9	25.3-28.4
		2	**19.7**	**18.2-21.3**	**21.9**	**20.4-23.4**
		3	**9.8**	**8.6-11.1**	**13.7**	**12.4-14.9**
		4	**5.7**	**4.8-6.7**	**8.2**	**7.3-9.2**

		5	**2.4**	**1.8-3.0**	**4.2**	**3.4-5.1**
		6+	**1.9**	**1.4-2.4**	**3.7**	**3.0-4.3**
Traumatic adv. childhood	continuous	0-2+	**0.360**	**0.333-0.387**	**0.319**	**0.296-0.343**
Traumatic adversity youth	binary	0,1+	**26.6**	**24.8-28.5**	**12.1**	**10.8-13.3**
Traumatic adversity 0-29	binary	0,1+	**48.2**	**46.0-50.3**	**35.0**	**33.0-37.0**
Traumatic adversity 0-44	binary	0,1+	**52.0**	**49.9-54.2**	**38.9**	**36.9-40.8**
Traumatic adversity 0-59	binary	0,1+	**57.5**	**55.4-59.6**	**42.8**	**40.8-44.8**
Traumatic adv. childhood	dummies	0	**69.8**	**67.8-71.8**	**73.2**	**71.3-75.0**
		1	**24.4**	**22.7-26.2**	**21.8**	**20.1-23.5**
		2+	5.8	4.7-6.9	5.1	4.2-6.0
Traumatic adversity youth	dummies	0	**73.4**	**71.5-75.2**	**87.9**	**86.7-89.2**
		1+	**26.6**	**24.8-28.5**	**12.1**	**10.8-13.3**
Traumatic adversity 0-29	dummies	0	**51.8**	**49.7-54.0**	**65.0**	**63.0-67.0**
		1	**35.2**	**33.2-37.1**	**27.0**	**25.2-28.7**
		2+	**13.0**	**11.4-14.6**	**8.1**	**7.0-9.2**
Traumatic adversity 0-44	dummies	0	**48.0**	**45.8-50.1**	**61.1**	**59.2-63.1**
		1	**36.1**	**34.1-38.1**	**28.7**	**27.0-30.4**
		2+	**15.9**	**14.2-17.7**	**10.2**	**8.9-11.4**
Traumatic adversity 0-59	dummies	0	**42.5**	**40.4-44.6**	**57.2**	**55.2-59.2**
		1	**38.5**	**36.4-40.6**	**31.0**	**29.3-32.8**
		2	**15.3**	**13.7-16.9**	**9.5**	**8.4-10.7**
		3+	**3.7**	**2.9-4.5**	**2.3**	**1.7-2.8**
Chronic adversity youth	binary	0,1+	**10.5**	**9.2-11.8**	**16.8**	**15.5-18.1**
Chronic adversity 16-44	binary	0,1+	**25.0**	**23.2-26.8**	**32.7**	**31.1-34.3**
Chronic adversity 16-59	binary	0,1+	**34.9**	**33.0-36.8**	**45.2**	**43.4-46.9**
Chronic adversity youth	dummies	0	**89.5**	**88.2-90.8**	**83.2**	**81.9-84.5**
		1	**10.0**	**8.7-11.3**	**14.8**	**13.5-16.1**
		2+	**0.5**	**0.2-0.9**	**2.0**	**1.4-2.5**
Chronic adversity 16-44	dummies	0	**75.0**	**73.2-76.8**	**67.3**	**65.7-68.9**
		1	**20.4**	**18.7-22.1**	**24.0**	**22.5-25.5**
		2+	**4.6**	**3.7-5.5**	**8.7**	**7.6-9.7**
Chronic adversity 16-59	dummies	0	**65.1**	**63.2-67.0**	**54.8**	**53.1-56.6**
		1	**26.3**	**24.6-28.1**	**30.8**	**29.1-32.4**
		2	**6.7**	**5.7-7.6**	**10.3**	**9.2-11.4**
		3+	**1.9**	**1.2-2.5**	**4.1**	**3.4-4.9**
Acute adversity youth	binary		**16.0**	**14.5-17.5**	**8.5**	**7.5-9.5**
Acute adversity 16-44	binary		**20.7**	**19.1-22.3**	**12.2**	**11.1-13.3**
Acute adversity 16-59	binary		**24.6**	**22.8-26.4**	**14.8**	**13.5-16.1**
Acute adversity youth	dummies	0	**84.0**	**82.5-85.5**	**91.5**	**90.5-92.5**
		1	**13.7**	**12.3-15.1**	**7.1**	**6.2-8.0**
		2+	**2.3**	**1.6-2.9**	**1.4**	**0.9-1.9**
Acute adversity 16-44	dummies	0	**79.3**	**77.7-80.9**	**87.8**	**86.7-88.9**
		1	**17.2**	**15.7-18.8**	**10.0**	**8.9-11.0**
		2+	**3.4**	**2.6-4.3**	**2.2**	**1.6-2.8**
Acute adversity 16-59	dummies	0	**75.4**	**73.6-77.2**	**85.2**	**83.9-86.5**
		1	**20.1**	**18.4-21.7**	**12.0**	**10.8-13.2**
		2+	**4.5**	**3.6-5.5**	**2.8**	**2.0-3.5**
Level 2+ quals in 2006	binary		**70.5**	**68.8-72.2**	**65.3**	**63.7-67.0**
Born by 1920	binary		**3.0**	**2.4-3.6**	**4.4**	**3.7-5.0**
Born 1921-1930	binary		13.3	12.1-14.6	12.5	11.4-13.6
Born 1931-1940	binary		**25.3**	**23.8-26.9**	**22.6**	**21.3-24.0**
Born 1941-1950	binary		**36.9**	**35.2-38.7**	**32.8**	**31.3-34.3**
Born 1951 or after	binary		**21.4**	**20.0-22.9**	**27.7**	**26.2-29.1**

Years smoked 30-44	continuous	**6.223**	**5.973-6.474**	**4.669**	**4.452-4.885**
Years smoked 45-59	continuous	**3.956**	**3.735-4.177**	**3.309**	**3.120-3.498**

The sample is all participants of LIFE who provided information about RA onset, date of birth, and gender. Missing values on all variables have been imputed. Bold font indicates gender differences that are statistically significant at $p<0.05$.

Table A13.3 presents summary statistics for each adversity reported during each life stage using the original dataset.

Table A13.3: Summary statistics for exposures to each adversity, using the original dataset

Adversity	Obs	%=yes	N=yes
Childhood (up to 15)			
poor amenities and/or crowding at age 10 & living in UK	6,370	12.5%	796
severe financial hardship	4,611	3.0%	139
parental unemployment 6m+	5,450	5.6%	305
early parental loss	6,754	12.1%	819
separation from mother for 6m+	6,745	14.0%	947
parents argue often	5,525	19.8%	1092
parent drank, drugs, mental health	5,589	6.3%	350
parent physically abused respondent	5,601	3.5%	194
sexually assaulted	5,600	3.7%	208
major natural disaster	5,560	3.2%	176
had life threatening illness or injury	5,463	7.6%	415
severe physical attack	5,554	1.3%	72
witness death or serious injury	5,453	3.4%	188
lost close relative or friend	5,097	14.7%	749
Youth (16-29)			
first experienced severe financial hardship	5,577	7.6%	424
any period of unemployment searching for work	6,755	4.3%	291
job loss resulting from company closing	6,718	5.8%	391
stillbirth, miscarriage or abortion	6,740	9.1%	610
first provided long-term care for relative or friend	5,565	2.0%	111
main occupation carer of first time cared	5,570	2.8%	155
first had partner or child addicted	5,612	1.8%	102
breakdown of cohabiting partnership	6,758	10.4%	706
house moves	6,732	47.3%	3184
death of cohabiting partner	6,758	0.5%	35
death of child when respondent	6,759	2.0%	135
stillbirth, miscarriage or abortion	6,740	9.1%	610
first death of close friend/relative not in war	5,525	16.9%	934
first death or risk of death of close friend/relative in war	5,581	5.0%	278
death of close friend or relative	5,494	21.0%	1154
first victim of sexual assault	5,600	1.7%	94
first victim of serious physical attack	5,597	2.1%	118
first life threatening illness or accident	5,580	3.7%	209
first fired weapon or been fired upon	5,619	4.3%	244
first witnessed serious injury or death not in war	5,571	6.3%	349
first witnessed serious injury or death in war	5,604	3.9%	219
witnessed serious injury or death	5,557	9.6%	533
first experienced natural disaster	5,589	3.1%	173
Early adulthood (30-44)			
first experienced severe financial hardship	5,577	3.2%	179
any period of unemployment searching for work	6,755	4.9%	330
job loss resulting from company closing	6,718	7.5%	505
stillbirth, miscarriage or abortion	6,740	5.3%	358
first provided long-term care for relative or friend	5,565	4.4%	243
main occupation carer of first time cared	5,583	5.7%	321
first had partner or child addicted	5,612	1.1%	63
breakdown of cohabiting partnership	6,758	15.0%	1016
house moves	6,732	49.9%	3360
death of cohabiting partner	6,758	1.7%	117
death of child when respondent	6,759	1.6%	107
stillbirth, miscarriage or abortion	6,740	5.3%	358
first death of close friend/relative not in war	5,525	12.1%	667

first death or risk of death of close friend/relative in war	5,581	0.3%	18
death of close friend or relative	5,481	12.5%	684
first victim of sexual assault	5,600	0.2%	13
first victim of serious physical attack	5,597	1.0%	55
first life threatening illness or accident	5,580	2.7%	151
first fired weapon or been fired upon	5,619	0.2%	10
first witnessed serious injury or death not in war	5,571	2.0%	110
first witnessed serious injury or death in war	5,604	0.2%	13
witnessed serious injury or death	5,551	2.1%	117
first experienced natural disaster	5,589	1.6%	89
Mid-adulthood (45-59)			
first experienced severe financial hardship	5,577	2.2%	124
any period of unemployment searching for work	6,755	5.7%	386
job loss resulting from company closing	6,718	9.1%	611
stillbirth, miscarriage or abortion	6,740	0.2%	15
first provided long-term care for relative or friend	5,565	9.0%	501
main occupation carer of first time cared	5,595	11.3%	631
first had partner or child addicted	5,612	0.9%	48
breakdown of cohabiting partnership	6,758	7.2%	487
house moves	6,732	47.7%	3210
death of cohabiting partner	6,758	5.6%	380
death of child when respondent	6,759	1.3%	87
stillbirth, miscarriage or abortion	6,740	0.2%	15
first death of close friend/relative not in war	5,525	12.7%	699
first death or risk of death of close friend/relative in war	5,581	0.2%	10
death of close friend or relative	5,486	12.9%	708
first victim of sexual assault	5,600	0.1%	4
first victim of serious physical attack	5,597	0.7%	39
first life threatening illness or accident	5,580	5.0%	279
first fired weapon or been fired upon	5,619	0.0%	1
first witnessed serious injury or death not in war	5,571	1.2%	67
first witnessed serious injury or death in war	5,604	0.1%	3
witnessed serious injury or death	5,551	1.3%	70
first experienced natural disaster	5,589	1.6%	90

Appendix 14: Do adversities predict RA onset? Additional results.

Table A14.1 presents results of models of RA onset on single adversities with mutual adjustment, using the observed sample. They indicate that childhood housing amenities and crowding are an important predictor of RA onset.

Table A14.1: Associations between RA onset and single adversities during each life stage with mutual adjustment

	RA onset from 45 (n=3,256)			RA onset from 60 (n=2,586)		
Childhood adversity	HR	95%ci	p-val	HR	95%ci	p-val
Poor housing amenities/crowding	**1.924**	**1.167-3.175**	**0.010**	**2.707**	**1.457-5.027**	**0.002**
Financial hardship	0.636	0.147-2.745	0.544	0.590	0.077-4.521	0.612
Parental unemployment 6m+	0.700	0.249-1.965	0.498	0.969	0.296-3.170	0.958
Parental loss	0.833	0.384-1.807	0.644	1.070	0.397-2.882	0.893
Maternal separation 6m+	0.718	0.347-1.487	0.372	0.754	0.306-1.861	0.540
Parents often argue	1.280	0.734-2.231	0.385	1.430	0.684-2.987	0.341
Par. substance abuse/mental illness	1.987	0.933-4.231	0.075	0.703	0.161-3.059	0.638
Physical abuse by parent	2.071	0.706-6.072	0.185	2.312	0.523-10.214	0.269
Sexual assault	0.459	0.063-3.354	0.443			
Major natural disaster	1.094	0.341-3.512	0.880	1.215	0.288-5.119	0.791
Life threatening illness/injury	0.905	0.394-2.083	0.815	1.352	0.533-3.427	0.526
Physical attack	1.448	0.194-10.779	0.718			
Witness death/serious injury	1.801	0.713-4.549	0.214	1.182	0.277-5.040	0.822
Loss of close relative/friend	1.274	0.732-2.219	0.391	1.294	0.622-2.693	0.490

	RA onset from age 45 (n=3,239)			RA onset from 60 (n=2,570)		
Transition adversity	HR	95%ci	p-val	HR	95%ci	p-val
Financial hardship						
Unemployment, searching for work	1.606	0.581-4.441	0.361	0.785	0.105-5.845	0.813
Involuntary job loss	1.691	0.775-3.691	0.187	1.349	0.415-4.392	0.619
Caring role	3.932	0.851-18.174	0.080			
House moves	**0.638**	**0.440-0.924**	**0.017**	**0.422**	**0.233-0.766**	**0.005**
Death of partner	1.715	0.223-13.202	0.604	2.786	0.313-24.780	0.358
Death of child	1.694	0.527-5.445	0.376	2.907	0.878-9.625	0.081
Stillbirth, miscarriage, abortion	1.699	0.837-3.451	0.142	1.710	0.636-4.598	0.288
Partnership breakdown	1.329	0.563-3.138	0.516	**4.020**	**1.637-9.871**	**0.002**
Partner or child addicted						
Sexual assault						
Physical attack	0.621	0.079-4.857	0.650			
Life threatening illness/injury	2.204	0.996-4.875	0.051	**3.733**	**1.543-9.028**	**0.003**
Witness death/serious injury	1.033	0.492-2.172	0.931	0.945	0.359-2.486	0.908
Major natural disaster	1.784	0.710-4.482	0.218	1.953	0.566-6.742	0.290
Active combat	1.316	0.525-3.298	0.558	0.756	0.203-2.814	0.676

	RA onset from age 45 (n=3,319)			RA onset from age 60 (n=2,571)		
Early adulthood adversity	HR	95%ci	p-val	HR	95%ci	p-val
Financial hardship						
Unemployment, searching for work	1.129	0.400-3.186	0.818	1.081	0.244-4.781	0.918
Involuntary job loss	1.062	0.478-2.356	0.883	1.481	0.569-3.858	0.421
Caring role	0.704	0.218-2.269	0.556	0.000	0.000-0.000	
House moves	0.778	0.569-1.063	0.115	0.775	0.515-1.167	0.222
Death of partner	1.183	0.288-4.862	0.816	0.000	0.000-0.000	
Death of child	0.748	0.104-5.401	0.773	0.000	0.000-0.000	
Stillbirth, miscarriage, abortion	0.991	0.353-2.779	0.986	0.871	0.204-3.716	0.852
Partnership breakdown	1.053	0.534-2.074	0.882	1.350	0.565-3.226	0.500

Partner or child addicted						
Sexual assault						
Physical attack	1.294	0.173-9.683	0.802			
Life threatening illness/injury	0.453	0.063-3.263	0.432	0.926	0.126-6.777	0.940
Witness death/serious injury	1.537	0.374-6.325	0.551	1.533	0.208-11.332	0.675
Major natural disaster						
Active combat						

	RA onset from age 60 (n=2,743)		
Mid-adulthood adversity	HR	95%ci	p-val
Financial hardship			
Unemployment, searching for work	0.427	0.057-3.171	0.405
Involuntary job loss	0.740	0.265-2.068	0.566
Caring role	0.802	0.286-2.251	0.676
House moves	1.121	0.758-1.657	0.566
Death of partner	1.420	0.550-3.669	0.469
Death of child	1.214	0.166-8.857	0.848
Stillbirth, miscarriage, abortion			
Partnership breakdown	1.005	0.299-3.376	0.993
Partner or child addicted			
Sexual assault			
Physical attack			
Life threatening illness/injury	0.456	0.062-3.339	0.440
Witness death/serious injury			
Major natural disaster			
Active combat			

These are results from seven models. Each model includes mutual adjustment for each adversity, total adversity within each life stage for which single adversities are not included, birth cohort, gender and Level 2+ qualifications at the time of LIFE. Childhood is up to age 15, youth is 16-29, early adulthood is 30-44, mid-adulthood is 45-59.

Appendix 15: How do adversities over the life course combine to predict RA onset? Additional results.

12. Does the life stage during which one is exposed matter? What is the relative importance for RA onset of adversities during childhood, youth, early and mid-adulthood?

It is possible that findings, reported in the main text, about the salience for RA onset of childhood and youth adversity reflect reporting bias in questions that ask about the first time that events were experienced. I therefore conducted sensitivity analyses using indices that exclude adversities reported using this type of question. These constitute about half the childhood and adult adversities reported; 7 out of 14, and 8 out of 15, respectively. I expected the reduced index to capture adversity less comprehensively, resulting in greater measurement error and weaker evidence for associations, regardless of any bias resulting from using the "first time" questions. Bias would be indicated if the pattern of results, that is the relative importance for RA onset of childhood and transition adversity reported in the main analyses, were not evident when the reduced index was used.

The results are presented in Table A15.1. As predicted, the evidence for associations between RA onset and youth adversity is slightly weaker, although the results for childhood adversity are almost identical. The pattern of findings is very similar to that presented in the main text; adversities during childhood and youth appear particularly salient for RA onset.

Table A15.1: Associations between adversity during each life stage and RA onset, excluding adversities reported using questions about first experiences

Adversity during each life stage	RA onset from age 45 (n=6,560)			RA onset from age 60 (n=5,525)		
	HR	95%CI	p-value	HR	95%CI	p-value
Childhood	**1.375**	**1.035-1.827**	**0.028**	1.326	0.914-1.922	0.137
Youth	**1.500**	**1.138-1.977**	**0.004**	**1.775**	**1.252-2.515**	**0.001**
Early adulthood	1.097	0.828-1.453	0.518	0.978	0.678-1.409	0.904

Mid-adulthood	1.170	0.820-1.671	0.387

These are results from two models, each adjusted for birth cohort, gender, and level of education at the time of LIFE. HR is hazard ratio, and 95%CI is 95% confidence interval. Childhood is ages 0-15, youth 16-29, early adulthood 30-44, and mid-adulthood 45-59. The measures for adversity during each life stage are indicators of exposure to one or more adversity.

Additional sensitivity analyses were conducted using a smaller dataset that excluded respondents who, in wave 3, reported moderate or severe pain or depression, or who performed poorly on a memory recall task. Details are given in Appendix 18. Using this sample to test for the salience of adversity during any particular life stage provided different results, presented in Tables A18.4 and A18.5. Because results of analyses examining the salience of adversity during particular life stages were unreliable, no further tests to examine life course patterns of adversity as predictors of RA onset were conducted.

To examine gender differences in the main sample, Cox regression analyses were estimated for RA onset on the number of life stages during which at least one adversity was reported for men and women separately. The results are presented in Table A15.2. They provide no evidence of gender differences in the relationship between cumulative life course adversity and RA onset.

Table A15.2: Cumulative life course adversity and RA onset among men and women

		RA onset from 45					
		Men (n=2,975)			Women (n=3,585)		
Measure		HR	95%CI	p-value	HR	95%CI	p-value
Dummies	0						
	1	2.630	0.896-7.724	0.078	1.416	0.622-3.220	0.407
	2	**3.937**	**1.387-11.175**	**0.010**	1.961	0.860-4.470	0.109
	3	**3.294**	**1.091-9.945**	**0.035**	2.275	0.931-5.559	0.071
	Wald test			**0.050**			0.201
Linear		**1.372**	**1.079-1.745**	**0.010**	**1.311**	**1.030-1.668**	**0.028**
		RA onset from 60					
		Men (n=2,593)			Women (n=2,932)		
Measure	Values	HR	95%CI	p-value	HR	95%CI	p-value
Dummies	0						
	1	3.087	0.427-22.339	0.264	1.912	0.507-7.209	0.339
	2	**6.666**	**1.052-42.224**	**0.044**	2.193	0.648-7.419	0.207
	3	6.389	0.964-42.346	0.055	2.841	0.828-9.748	0.097
	4	5.608	0.692-45.425	0.106	2.854	0.552-14.768	0.211

Wald test			0.116			0.606
Linear	**1.375**	**1.086-1.741**	**0.008**	1.250	0.974-1.604	0.080

Results from four models, each adjusted for birth cohort and education. HR is hazard ratio, 95%CI 95% confidence interval.

Appendix 16: Do material, psychosocial and behavioural factors independently predict RA onset? Additional results.

13. Do material and social adversities independently predict RA onset?

To examine whether relationships between adversity and RA onset are graded, associations were estimated using sets of dummies. Results are presented in Table A16.1. They suggest that relationships between RA onset and material adversities are likely to be threshold effects of one or more material adversities, and that that relationships with social adversities are likely to be graded.

Table A16.1: HRs for RA onset contingent upon material and social adversities using sets of dummies

Childhood		RA onset from age 16 (n=6,623)			RA onset from age 45 (n=6,560)			RA onset from age 60 (n=5,525)		
Type of adversity		HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Material	0	Reference								
	1	1.376	0.961-1.971	0.081	1.332	0.906-1.958	0.145	1.519	0.944-2.446	0.085
	2+	0.907	0.304-2.705	0.860	0.959	0.327-2.817	0.940	1.272	0.407-3.974	0.679
Social	0	Reference								
	1	1.181	0.860-1.624	0.304	1.194	0.845-1.687	0.316	1.238	0.821-1.867	0.308
	2	1.365	0.927-2.009	0.115	1.446	0.955-2.189	0.081	1.262	0.734-2.170	0.399
	3	1.351	0.767-2.378	0.297	1.368	0.741-2.527	0.317	1.060	0.450-2.498	0.894
	4+	1.660	0.823-3.348	0.157	1.682	0.789-3.584	0.178	0.987	0.250-3.890	0.985

Birth to 44		RA onset from age 45 (n=6,560)		
Type of adversity		HR	95%CI	p-val
	0	Reference		
Material	1	1.242	0.862-1.790	0.245
	2+	1.278	0.762-2.145	0.353
Social	0			
	1	**1.647**	**1.029-2.636**	**0.038**
	2	1.483	0.913-2.410	0.111
	3	**1.993**	**1.176-3.376**	**0.010**
	4	**2.191**	**1.224-3.923**	**0.008**
	5	1.167	0.398-3.421	0.778
	6+	**2.892**	**1.380-6.060**	**0.005**

Birth to 59		RA onset from age 60 (n=5,525)		
Type of adversity		HR	95%CI	p-val
Material	0			
	1	1.471	0.958-2.260	0.078
	2	1.412	0.608-3.275	0.422
	3+	1.882	0.750-4.723	0.178
Social	0			
	1	**2.319**	**1.075-5.001**	**0.032**
	2	**2.492**	**1.170-5.305**	**0.018**
	3	**2.894**	**1.275-6.570**	**0.011**
	4	**2.550**	**1.037-6.270**	**0.041**
	5	1.974	0.615-6.331	0.253
	6	0.099		
	7+	3.255	0.994-10.662	0.051

These are results from ten models estimated using twenty samples with imputed values of respondents who participated in LIFE. Each model includes a set of dummies for one type of adversity and a single continuous measure for the other type of adversity, so that there is mutual adjustment for material and social adversity. Models are also adjusted for birth cohort, gender and qualifications at Level 2 or above in 2006 and total adversity during the life stages in which material and social adversities are not included. Childhood is 0-15. Bold font indicates associations that are statistically significant at $p<0.05$.

14. Are any associations found explained by health behaviours?

Table A16.2 presents results of models of RA onset on material and social adversities with and without smoking.

Table A16.2: HRs for RA onset contingent upon material and social adversities with adjustment for smoking

	RA onset from age 45 (n=6,560)			RA onset from age 60 (n=5,525)		
	HR	95%CI	p-value	HR	95%CI	p-value
Material adversity birth to 29	1.284	0.925-1.781	0.135	**1.540**	**1.021-2.323**	**0.039**
Social adversity birth to 29	**1.229**	**1.077-1.402**	**0.002**	**1.194**	**1.005-1.418**	**0.043**
Material adversity birth to 29	1.275	0.919-1.770	0.146	**1.531**	**1.014-2.311**	**0.043**
Social adversity birth to 29	**1.224**	**1.073-1.397**	**0.003**	1.187	0.999-1.411	0.052
Smoking during early adulthood	1.012	0.993-1.032	0.225	0.980	0.929-1.034	0.454
Smoking during mid- adulthood				1.055	0.999-1.114	0.056

These are HRs for four models, each adjusted for birth cohort, gender and education. Smoking is the number of years smoked. Early adulthood is 30-44, mid-adulthood is 45-59. HRs for material adversities refer to one or more adversity as opposed to none. HRs for social adversities refer to each additional adversity, up to a maximum of three or more. Bold font indicates associations that are statistically significant at $p<0.05$.

Additional models estimated associations between smoking and RA onset with adjustment only for gender. These found evidence of correlations between smoking and RA onset. For example, the HR for each additional year of smoking between ages 16 and 44 for RA onset from age 45 is 1.01 (95%CI=1.00-1.02, p=0.041) and for each additional year of smoking between 45 and 59 for RA onset from age 60 is 1.03 (95%CI=1.00-1.06, p=0.028).

15. How do the answers to these questions vary by gender?

Table A16.3 presents results of models of RA onset on material and social adversities for men and women separately.

Table A16.3: HRs for RA onset contingent upon material and social adversities for men and women

Men

	RA onset from age 16 (n=2,997)			RA onset from age 45 (n=2,975)			RA onset from age 60 (n=2,593)		
Adversity	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Childhood									
Material	1.529	0.927-2.520	0.096	1.559	0.924-2.630	0.096	**1.887**	**1.015-3.507**	**0.045**
Social	1.135	0.883-1.460	0.321	1.156	0.884-1.511	0.289	1.242	0.890-1.734	0.202
Birth to 44									
Material				**1.589**	**1.018-2.480**	**0.041**	**1.865**	**1.067-3.258**	**0.029**
Social				**1.355**	**1.025-1.790**	**0.033**	**1.442**	**1.001-2.077**	**0.049**
Birth to 59									
Material							**1.912**	**1.123-3.255**	**0.017**
Social							**1.549**	**1.025-2.341**	**0.038**

Women

	RA onset from age 16 (n=3,626)			RA onset from age 45 (n=3,585)			RA onset from age 60 (n=2,932)		
Adversity	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Childhood									
Material	1.166	0.699-1.945	0.556	1.081	0.617-1.895	0.785	1.153	0.590-2.253	0.678
Social	1.220	0.969-1.535	0.090	1.254	0.971-1.619	0.083	0.981	0.699-1.376	0.910
Birth to 44									
Material				0.995	0.626-1.580	0.982	1.114	0.617-2.010	0.721
Social				**1.389**	**1.084-1.780**	**0.009**	1.195	0.857-1.667	0.293
Birth to 59									
Material							1.153	0.669-1.988	0.607
Social							1.207	0.832-1.753	0.322

These are results from six models for men and six models for women, all with adjustment for birth cohort and qualifications of Level 2+ at time of LIFE, and with mutual adjustment for material and social adversities. Models that include childhood material and social adversities adjusts also for total adversity between 16 until RA onset is measured, and the model that includes material and social adversities to age 44 as predictors of RA onset from age 60 includes adjustment for total adversity between 45 and 59. Material adversity is measured using an indicator of one or more adversity. Social adversities are measured using continuous variables with the following values: childhood 0,1,2,3+; birth to 44 0,1-2,3-5,6+; birth to age 59 0,1-2,3+.

When interaction terms are included in analyses using the whole sample, there is no evidence of gender differences. P-values for the interaction terms are presented in Table A16.4.

Table A16.4: P-values for interaction terms of gender with material and social adversities

		RA onset from age		
Life stage	Type	16	45	60
Childhood	Material	0.506	0.353	0.336
	Social	0.396	0.500	0.609
Childhood	Material		0.451	0.509
	Social		0.665	0.375
Youth	Material		0.837	0.453
	Social		0.779	0.844
Childhood and youth	Material		0.257	0.263
	Social		0.772	0.406
Birth to 44	Material		0.282	0.217
	Social		0.981	0.338
Birth to 59	Material			0.290
	Social			0.178

P-values are from ten models, each with mutual adjustment for material and social adversities, birth cohort, Level 2 qualifications at the time of LIFE and gender. For models with material and social adversity during childhood and youth, there is also adjustment for total adversity during subsequent life stages. Childhood is 0-15, youth is 16-29.

Table A16.5 presents the HRs for RA onset contingent upon material and social adversities with and without smoking behaviour, for men and women separately.

Table A16.5: HRs for RA onset contingent upon material and social adversities with adjustment for smoking for men and women

Men

	RA onset from age 45 (n=2,975)			RA onset from age 60 (n=2,593)		
	HR	95%CI	p-val	HR	95%CI	p-val
Material adversity birth to 29	**1.590**	**1.007-2.511**	**0.047**	**1.932**	**1.101-3.389**	**0.022**
Social adversity birth to 29	**1.231**	**1.010-1.500**	**0.039**	**1.313**	**1.024-1.682**	**0.032**
Material adversity birth to 29	1.566	0.989-2.480	0.056	**1.909**	**1.075-3.389**	**0.027**
Social adversity birth to 29	**1.227**	**1.007-1.496**	**0.042**	**1.307**	**1.016-1.681**	**0.037**
Smoking 30-44	1.022	0.993-1.053	0.142	0.966	0.894-1.043	0.377
Smoking 45-59				**1.084**	**1.004-1.171**	**0.039**

Women

	RA onset from age 45 (n=3,585)			RA onset from age 45 (n=2,932)		
	HR	95%CI	p-val	HR	95%CI	p-val
Material adversity birth to 29	1.059	0.652-1.719	0.818	1.208	0.651-2.243	0.549
Social adversity birth to 29	**1.219**	**1.010-1.472**	**0.040**	1.082	0.845-1.384	0.533
Material adversity birth to 29	1.057	0.651-1.716	0.823	1.205	0.650-2.234	0.554
Social adversity birth to 29	**1.217**	**1.008-1.470**	**0.042**	1.075	0.840-1.377	0.566
Smoking during 30-44	1.003	0.977-1.031	0.807	1.002	0.928-1.081	0.965
Smoking during 45-59				1.019	0.941-1.104	0.646

These are HRs for eight models, four for men and four for women. Smoking is the number of years smoked. Childhood is 0-15, youth is 16-29, early adulthood is 30-44, mid- adulthood is 45-59.

Appendix 17: Are some types of social adversity more salient predictors of RA onset than others?

16. Comparison of adversities in different life domains: relationship-related and traumatic adversities

In order to examine whether relationships between family and traumatic adversities and RA onset are graded, associations were tested with sets of dummies. The results are presented in Table A17.1.

The results suggest that any relationships between RA onset and family-related adversities during childhood and youth are likely to be threshold effects of one or more adversities, but during longer period (from birth to 29, 44, and 59) are likely to be graded. Any relationships between RA onset and traumatic adversity are likely to be threshold effects of one or more trauma, except in childhood, where the relationship appears graded with a maximum of two or more traumas.

Consequently, continuous measures of family adversity were created for adversity from birth to age 29 (no adversities, one or two adversities, and three or more adversities), from birth to age 44 (no adversities, one or two adversities, three or more adversities), and from birth to age 59 (no adversities, one to three adversities, four or more adversities). During childhood and youth, measures of family adversity are binary indicators of one or more adversity. Binary indicators were created for trauma for all periods except for during childhood, for which the measure of trauma is continuous (zero, one, or two traumatic adversities).

Table A17.1: HRs for RA onset contingent upon relationship-related and traumatic adversities using sets of dummies

Childhood		RA onset from age 16 (n=6,623)			RA onset from age 45 (n=6,560)			RA onset from age 60 (n=5,525)		
Type of adversity	Values	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Relationship-related	0									
	1	1.044	0.754-1.444	0.796	1.115	0.788-1.578	0.537	1.106	0.715-1.711	0.649
	2	1.295	0.854-1.963	0.224	1.399	0.899-2.177	0.137	0.944	0.488-1.825	0.863
	3	1.048	0.451-2.438	0.913	1.069	0.423-2.700	0.888	0.871	0.227-3.344	0.840
	4+	0.916	0.226-3.719	0.902	1.056	0.259-4.312	0.940	1.002	0.135-7.455	0.998
Trauma	0									
	1	1.224	0.889-1.687	0.215	1.162	0.823-1.641	0.392	1.155	0.739-1.807	0.527
	2+	**1.748**	**1.029-2.970**	**0.039**	1.702	0.963-3.008	0.067	1.463	0.646-3.316	0.362

Birth to 44		RA onset from age 45 (6,560)		
Type of adversity	Values	HR	95%CI	p-value
Relationship-related	0			
	1	1.378	0.936-2.028	0.104
	2	1.302	0.849-1.997	0.226
	3	**1.757**	**1.073-2.877**	**0.025**
	4	1.518	0.776-2.970	0.223
	5+	1.760	0.727-4.257	0.210
Trauma	0			
	1	1.331	0.957-1.851	0.090
	2+	1.225	0.766-1.959	0.396

Birth to age 59		RA onset from age 60 (5,525)		
Type of adversity	Values	HR	95%CI	p-value
Relationship-related	0			
	1	**1.733**	**1.019-2.948**	**0.042**
	2	1.713	0.973-3.016	0.062
	3	1.631	0.816-3.259	0.166

	4		1.973	0.876-4.446	0.101
	5		0.101		1.000
	6+		1.719	0.424-6.964	0.448
Trauma	0				
	1		1.235	0.801-1.904	0.339
	2		1.074	0.557-2.069	0.831
	3+		0.977	0.237-4.029	0.974

These are results from ten models. Each model includes a set of dummies for one type of adversity (relationship-related or trauma), a continuous measure for the other type of social adversity and a binary indicator of one or more material adversities. Models are also adjusted for birth cohort, gender, Level 2 or higher qualifications at time of LIFE and total adversity during the life stages in which relationship-related and traumatic adversities are not included. Childhood is 0-15.

17. Comparison of chronic and acute adversities

To examine whether relationships between chronic and acute adversities and RA onset are graded, associations were tested with sets of dummies. Results are presented in Table A17.2.

Results indicate that any relationships between RA onset and both chronic and acute adversities are likely to reflect threshold effects of one or more adversity.

Table A17.2: HRs for RA onset contingent upon chronic and acute adversities using sets of dummies

16 to 29		RA onset from age 30 (6,613)			RA onset from age 45 (6,560)			RA onset from age 59 (5,525)		
Type of adversity	Values	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Chronic	0	Reference			Reference			Reference		
	1	**1.548**	**1.048-2.287**	**0.028**	**1.695**	**1.114-2.580**	**0.014**	**2.429**	**1.462-4.036**	**0.001**
	2+	1.047	0.181-6.057	0.959	1.324	0.203-8.640	0.769	2.291	0.312-16.832	0.415
Acute	0	Reference			Reference			Reference		
	1	0.819	0.493-1.362	0.442	0.822	0.473-1.427	0.486	0.884	0.437-1.789	0.733
	2+	0.686	0.165-2.858	0.605	0.765	0.181-3.231	0.715	0.730	0.103-5.175	0.753

16 to 44			RA onset from age 45 (6,560)			RA onset from age 59 (5,525)		
Chronic	0		Reference			Reference		
	1		**1.484**	**1.062-2.073**	**0.021**	**1.649**	**1.076-2.527**	**0.022**
	2+		1.289	0.663-2.506	0.455	1.577	0.661-3.764	0.305
Acute	0		Reference			Reference		
	1		0.850	0.500-1.446	0.550	0.694	0.331-1.457	0.335
	2+		0.882	0.323-2.412	0.807	1.070	0.335-3.419	0.909

16 to 59					RA onset from age 60 (5,525)		
Chronic	0				Reference		
	1				1.345	0.892-2.029	0.157
	2				1.509	0.734-3.103	0.263
	3+				1.265	0.304-5.254	0.747
Acute	0				Reference		
	1				0.729	0.386-1.374	0.328
	2+				0.897	0.283-2.839	0.853

These are results from 12 models. Each model includes a set of dummies for one type of adversity (chronic or acute), an indicator of one or more adversities not classified as chronic or acute, an indicator of one or more childhood adversities, birth cohort, gender, and qualifications at Level 2 or above at the time of LIFE.

These results are based on small numbers and could be a quirk of the data. Whilst further evidence should be collected to test the reliability of these findings, it is informative to know how many respondents reported adversities classified as chronic and acute and also reported a history of RA. Table A17.3 presents this information. As predicted, the numbers are small, signalling the importance of testing the reliability of these findings using other datasets. Nevertheless, the statistical significance of associations between RA onset and chronic adversities (reported in the main text) reflects a high degree of consistency.

Table A17.3: Numbers of respondents with one or more adversity who reported RA onset.

	RA onset from age 30		RA onset from age 45		RA onset from age 60	
Adversity	Number	95%CI	Number	95%CI	Number	95%CI
Chronic during:						
16-29	42	30-54	38	26-49	24	15-33
16-44			72	58-87	42	31-53
16-59					53	41-64
Acute during:						
16-29	24	13-34	21	11-30	12	5-19
16-44			30	18-41	16	7-24
16-59					19	10-28

18. How do the answers to these questions vary by gender?

Table A17.4 presents results of models of RA onset on family and traumatic adversities for men and women separately. They provide weak evidence of gender differences but suggest that, especially for RA onset from 45, traumas are relatively important for men and relationship-related adversities are relatively important for women.

Table A17.4: HRs for RA onset contingent upon relationship-related and traumatic adversities for men and women separately

Men

Adversity		RA onset from age 16 (n=2,997)			RA onset from age 45 (n=2,975)			RA onset from age 60 (n=2,593)		
Life stage	Type	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Childhood	Relationship-related	0.986	0.655-1.483	0.944	0.996	0.637-1.558	0.987	1.161	0.677-1.991	0.587
	Trauma	1.248	0.888-1.755	0.202	1.239	0.868-1.768	0.238	1.325	0.868-2.021	0.192
Birth to 44	Relationship-related				1.124	0.828-1.526	0.454	1.138	0.774-1.673	0.510
	Trauma				1.462	0.935-2.287	0.096	1.555	0.892-2.713	0.120
Birth to 59	Relationship-related							1.306	0.851-2.003	0.222
	Trauma							1.581	0.898-2.785	0.113

Women

Adversity		RA onset from age 16 (n=3,626)			RA onset from age 45 (n=3,585)			RA onset from age 60 (n=2,932)		
Life stage	Type	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Childhood	Relationship-related	1.191	0.810-1.750	0.375	1.346	0.877-2.064	0.174	0.937	0.522-1.680	0.826
	Trauma	1.328	0.986-1.788	0.062	1.277	0.919-1.774	0.145	1.071	0.650-1.765	0.787
Birth to 44	Relationship-related				**1.465**	**1.096-1.957**	**0.010**	1.364	0.920-2.021	0.122
	Trauma				1.184	0.784-1.788	0.422	0.896	0.495-1.620	0.715
Birth to 59	Relationship-related							1.359	0.873-2.117	0.175
	Trauma							0.909	0.510-1.622	0.747

These are results from six models for men, and eight for women, all with adjustment for birth cohort, gender, and qualifications of Level 2 or above at time of LIFE, and with mutual adjustment for relationship-related and traumatic adversities. Models also adjust for material adversity during the period in which relationship-related and traumatic adversities are included, and for childhood adversity, as appropriate. Relationship-related adversity during childhood is measured using an indicator of one or more adversities, and during other periods using continuous variables with values for birth to age 44 of 0, 1-2, and 3+ and for birth to age 59 of 0,1-3,4+. Traumatic adversities are measured using indicators of one or more trauma during all periods except for childhood, when the variable takes values of 0,1,2+.

Table A17.5 presents results of models of RA onset on chronic and acute adversities for men and women separately.

There is some indication that HRs for RA onset from age 45 are higher and more consistent amongst men than women in relation to chronic adversity. However, tests with interaction terms of chronic adversity provide no evidence that the gender differences are statistically significant. The p-values for the interaction terms are 0.372 for chronic adversity between 16 and 29, and 0.556 for chronic adversity between 16 and 44.

Whilst there is no evidence of associations between acute adversity and RA onset for either men or women, HRs for women are consistently below one. No results are presented for associations between acute adversity and RA onset from age 60 among women because although 53 women reported RA onset from 60, none also reported acute adversities. Whilst there is no evidence that acute adversities are protective for RA onset amongst women, numbers are small, and the results suggest that an association might be found if a larger sample were used.

Table A17.5: HRs for RA onset contingent upon chronic and acute adversities for men and women separately

Men

Adversity Life stage	Type	RA onset from age 30 (n=2,995) HR	95%CI	p-value	RA onset from age 45 (n=2,975) HR	95%CI	p-value	RA onset from age 60 (n=2,593) HR	95%CI	p-value
Youth	Chronic	**1.936**	**1.106-3.389**	**0.021**	**2.041**	**1.102-3.779**	**0.023**	**2.378**	**1.116-5.068**	**0.025**
	Acute	0.997	0.554-1.794	0.993	1.042	0.569-1.909	0.895	1.246	0.624-2.488	0.534
Youth to 44	Chronic				**2.112**	**1.225-3.643**	**0.007**	1.649	0.908-2.994	0.100
	Acute				1.307	0.759-2.251	0.335	1.125	0.570-2.220	0.734
Youth to 59	Chronic							**2.059**	**1.092-3.880**	**0.026**
	Acute							1.262	0.685-2.326	0.455

Women

Adversity Life stage	Type	RA onset form age 30 (n=3,618) HR	95%CI	p-value	RA onset from age 45 (n=3,585) HR	95%CI	p-value	RA onset from age 60 (n=2,932) HR	95%CI	p-value
Youth	Chronic	1.320	0.812-2.143	0.262	1.487	0.874-2.531	0.144	**2.455**	**1.271-4.743**	**0.008**
	Acute	0.524	0.196-1.397	0.196	0.481	0.148-1.569	0.225			
Youth to 44	Chronic				1.564	0.965-2.537	0.070	1.671	0.971-2.877	0.064
	Acute				0.523	0.196-1.402	0.198			
Youth to 59	Chronic							1.442	0.790-2.631	0.233
	Acute									

These are results from six models for men and six for women, all adjusted for birth cohort, gender, and qualifications of Level 2 or above in 2006, and with mutual adjustment for chronic and acute adversities. Models also adjust adversities that were not easily classified as chronic or acute, and childhood adversity measured using a binary indicator of one or more adversities. Models with chronic and acute adversities during youth are also adjusted for total adversity during subsequent life stages, using continuous measures. Chronic adversities are main occupation as carer and/or reporting being a carer, having a partner or child who is addicted to alcohol or drugs, and breaking up with a cohabiting partner. Acute adversities are being a victim of sexual assault, being a victim of a serious physical attack, witnessing a death or serious injury, or a major natural disaster. All measures of chronic and acute adversity are indicators of one or more adversity.

Appendix 18: Sensitivity analyses excluding those who reported pain or depression, or performed poorly on a memory test at the time of LIFE

Sensitivity analyses were conducted using LIFE participants except for those with incomplete information about RA onset, gender or date of birth, and further excluding those who in the Wave 3 main interview reported pain or depression or scored poorly on a memory test.

People with RA are relatively likely to report pain and depression (Covic et al. 2012), and each of these has been associated with biased recall of (increased) childhood adversity (Raphael et al. 2001, Widom & Morris 1997). It is possible that associations found between life course adversity and subsequent RA onset results from recall bias due to the symptoms of RA, such as pain, and its comorbidity with depression. If this were the case, pain and depression at the time of recall would confound associations reported between life course adversity and RA onset and excluding groups who reported pain and depression from the analyses would reduce the magnitude and consistency of associations.

Members of the NCDS who scored poorly on a memory test similar to that used in ELSA had particularly poor recall of childhood conditions (Brown 2013). Excluding these participants reduces power but is likely to increase the accuracy of measures based on recall. Reducing power is likely to reduce the statistical significance of any associations found; increasing accuracy is likely to increase it, if the associations found are not simply a coincidental effect of measurement error.

One set of sensitivity analyses was conducted, excluding respondents who reported pain or depression or whose recall scores were low.

Pain was measured using self-report and was classified as none, mild, moderate, or severe. 1,524 respondents who reported moderate or severe pain were excluded.

Depression was measured using the CESD 8-item scale with a cut point of 3 indicating depression. This cut point has been used before (White et al. 2017), and has been validated against depression diagnosed amongst older adults using standard psychiatric interviews (Turvey et al. 1999). 1,330 respondents who reported depression according to this criterion were excluded.

The test used to assess memory function involves the interviewer reading a list of 10 words to the participant, who is then asked to recall as many words as he or she can remember. Brown (2013) used data from the 1958 British birth cohort study to compare accounts of living conditions during childhood (number of rooms and number of people in the household) collected in the 1960s with retrospective accounts of the same childhood conditions among the same sample when they were aged 50, in 2008. Cohort members whose retrospective account of childhood living conditions matched the 1960s information scored higher on a memory test, which, like the test used in ELSA, involved recall of 10 words. Among those with well-matched accounts, the mean number of words recalled was 5.58 with a standard deviation of 1.80. Among those with poorly matched accounts, the mean score was 4.97 with a standard deviation of 1.98. In the ELSA sample, 2,805 respondents scored below 5, 1,654 scored below 4, and 916 scored below 3. I excluded from the sensitivity analyses the 1,654 respondents who scored below 4.

Some of the respondents were excluded because they fell into more than one excluded group. In total, 3,173 respondents were excluded from the sensitivity analyses, leaving a

sample of 3,451. Of these, 102 reported RA from age 16, 85 from age 45, and 53 from age 60.

Summary statistics are presented in Table A18.1.

Table A18.1: Summary statistics

Variable	Measure	Values	Mean/ %=yes	95% CI
Childhood adversity	Terciles	0	45.5	43.1-47.9
		1	29.5	27.5-31.5
		2+	25.0	23.1-26.8
	Binary	1+	54.5	52.1-56.9
Adversity 0-44	Terciles	0-1	37.7	35.8-39.6
		2-3	38.2	36.2-40.2
		4+	24.1	22.3-26.0
	Continuous	0-6+	2.315	2.245-2.384
Adversity 0-59	Terciles	0-1	28.6	26.8-30.3
		2-3	37.3	35.4-39.3
		4+	34.1	32.3-36.0
	Continuous	0-7+	2.842	2.767-2.918
Cumulative adversity 0-44	Dummies	0	15.5	14.1-16.9
		1	35.3	33.4-37.3
		2	34.1	32.2-36.1
		3	15.1	13.6-16.6
	Continuous	0-3	1.488	1.451-1.525
Cumulative adversity 0-59	Dummies	0	10.3	9.2-11.5
		1	27.6	25.9-29.2
		2	34.2	32.4-36.0
		3	22.0	20.4-23.6
		4	5.9	4.9-6.8
	Continuous	0-4	1.855	1.815-1.896
Youth adversity	Binary	1+	50.1	48.3-51.9
Early adulthood adversity	Binary	1+	44.2	42.3-46.1
Mid-adulthood adversity	Binary	1+	36.8	34.9-38.6
Material adversity during childhood	Binary	1+	14.3	12.9-15.7
Material adversity during youth	Binary	1+	9.0	8.0-10.0
Material adversity 0-29	Binary	1+	17.0	15.5-18.5
Material adversity 0-44	Binary	1+	19.6	18.0-21.2
Material adversity 0-59	Binary	1+	23.1	21.4-24.8
Social adversity during childhood	Continuous	0-3+	0.700	0.670-0.731
Social adversity during youth	Continuous	0-3+	0.553	0.526-0.579
Social adversity 0-29	Continuous	0-3+	1.246	1.203-1.288
Social adversity 0-44	Continuous	0-6+[1]	1.082	1.052-1.113
Social adversity 0-59	Continuous	0-3+[2]	1.227	1.199-1.255

Relationship adversity during childhood	Binary	1+	33.5	31.8-35.2
Relationship adversity during youth	Binary	1+	32.9	31.2-34.6
Relationship adversity 0-29	Continuous	0-3+[2]	0.6	0.6-0.6
Relationship adversity 0-44	Continuous	0-3+[2]	0.8	0.8-0.8
Relationship adversity 0-59	Continuous	0-4+[3]	0.8	0.8-0.8
Traumatic adversity during childhood	Continuous	0-2+	0.3	0.3-0.4
Traumatic adversity during youth	Binary	1+	16.4	15.0-17.7
Traumatic adversity 0-29	Binary	1+	39.1	37.2-41.0
Traumatic adversity 0-44	Binary	1+	43.2	41.3-45.2
Traumatic adversity 0-59	Binary	1+	48.3	46.3-50.2
Chronic adversity during youth	Binary	1+	13.8	12.5-15.1
Chronic adversity 16-44	Binary	1+	28.1	26.4-29.7
Chronic adversity 16-59	Binary	1+	39.3	37.5-41.1
Acute adversity during youth	Binary	1+	11.3	10.2-12.5
Acute adversity 16-44	Binary	1+	15.4	14.1-16.7
Acute adversity 16-59	Binary	1+	18.5	17.1-20.0
Female gender	Binary		53.7	52.1-55.4
Level 2+ qualifications at time of LIFE	Binary		78.9	77.5-80.4
Born by 1920	Binary		1.4	1.0-1.7
Born 1921-1930	Binary		7.5	6.7-8.4
Born 1931-1940	Binary		21.6	20.2-23.0
Born 1941-1950	Binary		39.7	38.0-41.3
Born 1951 or after	Binary		29.8	28.3-31.3
Years smoked during early adulthood	Continuous		4.8	4.5-5.0
Years smoked during mid-adulthood	Continuous		2.7	2.5-2.9

Summary statistics refer to the 3,451 respondents in imputed datasets who participated in LIFE and provided information about RA onset, gender and date of birth, who did not report pain or depression and scored above 3 on the word recall test during wave 3. One participant, who reported RA with onset before age 16, is excluded. Childhood is 0-15, youth 15-29, early adulthood 30-44, mid-adulthood 45-59.

1. Social adversity between birth and 44 is a continuous variable with values of 0,1-2,3-5,6+.
2. These variables have values of 0,1-2,3+.
3. Relationship-related adversity from birth to age 59 has values of 0,1-3,4+.

Results of Cox regression analyses used to address RQ1 are presented in Table A18.2.

Results reflect the loss of power due to the smaller sample size, but are otherwise similar to those presented in the main text.

Table A18.2: Associations between total exposure to adversity and risk of RA onset

Adversity Childhood Measure		RA onset from 16 Men and women (n=3,451) HR	95%CI	p-val	Men (n=1,597) HR	95%CI	p-val	Women (n=1,854) HR	95%CI	p-val
Terciles	0	Reference			Reference			Reference		
	1	**2.000**	**1.142-3.503**	**0.015**	1.833	0.815-4.134	0.143	2.171	0.988-4.770	0.053
	2+	**2.263**	**1.216-4.209**	**0.010**	1.841	0.679-4.993	0.230	**2.673**	**1.196-5.971**	**0.017**
Wald test				**0.016**			0.313			**0.040**
Binary	0	Reference								
	1+	**2.126**	**1.261-3.582**	**0.005**	1.852	0.845-4.057	0.124	**2.411**	**1.186-4.901**	**0.015**
		RA onset from 45								
Birth to 44 Measure		Men and women (n=3,420) HR	95%CI	p-val	Men (n=1,586) HR	95%CI	p-val	Women (n=1,834) HR	95%CI	p-val
Terciles	0-1	Reference			Reference			Reference		
	2-3	**1.844**	**1.020-3.331**	**0.043**	1.685	0.761-3.728	0.198	2.045	0.813-5.146	0.128
	4-11	**2.573**	**1.299-5.097**	**0.007**	1.887	0.716-4.974	0.199	**3.409**	**1.315-8.834**	**0.012**
Wald test				**0.020**						**0.035**
Continuous		**1.225**	**1.070-1.403**	**0.003**	1.120	0.920-1.364	0.259	**1.326**	**1.100-1.597**	**0.003**
		RA onset from 60								
Birth to 59 Measure		Men and women (n=2,799) HR	95%CI	p-val	Men (n=1,350) HR	95%CI	p-val	Women (n=1,449) HR	95%CI	p-val
Terciles	0-1	Reference			Reference			Reference		
	2-3	1.924	0.796-4.651	0.146	2.663	0.815-8.704	0.105	1.304	0.329-5.176	0.706
	4-12	**2.441**	**1.049-5.683**	**0.038**	2.017	0.587-6.928	0.265	3.055	0.917-10.175	0.069
Wald test				0.137			0.263			0.115
Continuous		**1.189**	**1.027-1.377**	**0.020**	1.134	0.927-1.388	0.220	**1.258**	**1.016-1.557**	**0.035**

All models are adjusted for birth cohort and qualifications at Level 2 or above at time of LIFE. The model for men and women together is also adjusted for gender. Continuous measures have maximum values of 6 (or more) for adversities between birth and 44, and of 7 (or more) for adversities between birth and 59. HR is hazard ratio, 95% ci is 95% confidence interval.

Results of Cox regression models of RA onset on cumulative levels of adversity over the life course are presented in Table A18.3, and the results are similar to those presented in the main text.

Table A18.3: Associations between cumulative exposure to adversity and risk of RA onset

Number of life stages exposed to adversity Measure	Values	RA onset from age 45 (n=3,420) HR	95%CI	p-value	RA onset from age 60 (n=2,799) HR	95%CI	p-value
Dummies	0	Reference			Reference		
	1	2.090	0.643-6.785	0.220	3.526	0.463-26.885	0.224
	2	**3.288**	**1.140-9.483**	**0.028**	5.111	0.718-36.408	0.103
	3	**3.774**	**1.208-11.793**	**0.022**	6.280	0.882-44.736	0.067
	4				6.914	0.882-44.736	0.091
Wald test				0.061			0.355
Continuous		**1.479**	**1.145-1.910**	**0.003**	**1.401**	**1.070-1.835**	**0.014**

Models are adjusted for birth cohort, gender, and qualifications of Level 2 or above at time of LIFE. HR is hazard ratio, 95% ci is 95% confidence interval.

Results of Cox regression models of RA onset on adversity during each life stage with mutual adjustment are presented in Table A18.4. The results differ from those presented in the main text. Using this sample, whilst adversity at each life stage is related to increased risk of RA onset (HRs are all over 1), only childhood adversity appears salient for RA onset later in life. Consequently, additional sensitivity analyses were conducted using the smaller sample and indices of adversities measured using the occupational, housing, fertility and partnership histories but excluding life events. The results, presented in Table A18.5 differ from those presented in Table A18.4; adversity during early adulthood is the most salient. The inconsistent results mean that no conclusions are drawn about whether one life stage is more important than another for RA onset.

Table A18.4: Associations between RA onset and adversity during each life stage, with mutual adjustment

	RA onset from age 45 (n=6,560)			RA onset from age 60 (n=5,525)		
Adversity during each life stage	HR	95%CI	p-value	HR	95%CI	p-value
Childhood	**2.043**	**1.172-3.563**	**0.012**	**2.518**	**1.234-5.136**	**0.011**
Youth	1.243	0.791-1.953	0.346	1.178	0.666-2.084	0.574
Early adulthood	1.344	0.832-2.171	0.227	1.450	0.792-2.653	0.228
Mid-adulthood				1.028	0.567-1.864	0.929

These are results from two models, each adjusted for birth cohort, gender, and qualifications at Level 2 and above at time of LIFE. HR is hazard ratio, and 95%CI is 95% confidence interval. Childhood is 0-15, youth 16-29, early adulthood 30-44, mid-adulthood 45-59. Measures of adversity at each life stage indicate one or more adversity.

Table A18.5: Associations between adversity during each life stage and RA onset, excluding adversities reported using questions about first experiences

	RA onset from age 45 (n=3,420)			RA onset from age 60 (n=2,799)		
Adversity during each life stage	HR	95%CI	p-value	HR	95%CI	p-value
Childhood	1.495	0.950-2.354	0.082	1.387	0.758-2.538	0.289
Youth	1.468	0.942-2.288	0.090	1.395	0.792-2.459	0.249
Early adulthood	**1.594**	**1.029-2.470**	**0.037**	**1.924**	**1.102-3.359**	**0.021**
Mid-adulthood				0.926	0.515-1.666	0.798

These are results from two models, each adjusted for birth cohort, gender, and qualifications at Level 2 and above at time of LIFE. HR is hazard ratio, and 95%CI is 95% confidence interval. Childhood is 0-15, youth 16-29, early adulthood 30-44, mid-adulthood 45-59. Measures of adversity at each life stage indicate one or more adversity.

Table A18.6 presents results of Cox regression models of RA onset on adversities classified as material and social. As for the results in the main analyses, hazard ratios for each type of adversity are greater than one in all models. Evidence for associations with social adversities is weaker, probably reflecting loss of power due to the smaller sample size. In contrast, evidence for the importance of material adversity appears stronger. This means that amongst respondents excluded in these sensitivity analyses because they are likely to provide inaccurate information, those with a history of RA under-reported material adversity more than those without RA. It is possible that people with RA tend to under-report material adversity earlier in their lives, but only if their recall is poor or if they have co-morbid pain or depression.

Table A18.6: HRs for RA onset contingent upon material and social adversities

Life stage and type of adversity	**RA onset from age 16** (n=3,451)			RA onset from age 45 (n=3,420)			RA onset from age 60 (n=2,799)		
	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Childhood									
Material	**1.849**	**1.138-3.002**	**0.013**	**1.921**	**1.140-3.236**	**0.014**	**2.461**	**1.307-4.635**	**0.005**
Social	1.247	0.966-1.608	0.090	1.309	0.993-1.724	0.056	1.184	0.829-1.691	0.352
Birth to 44									
Material				1.557	0.967-2.508	0.069			
Social				**1.557**	**1.160-2.089**	**0.003**			
Birth to 59									
Material							1.674	0.933-3.003	0.084
Social							**1.632**	**1.012-2.633**	**0.045**

These are results of five models with mutual adjustment for material and social adversities and total adversity during other life stages, birth cohort, gender and Level 2+ qualifications at time of LIFE. Material adversity is measured using an indicator of one or more adversity. Social adversities are measured using continuous variables with values as follows: childhood 0,1,2,3+; birth to 44 0,1-2,3-5,6+; birth to 59 0,1-2,3+.

As reported in the main analyses, there is no evidence that smoking mediates associations between adversity and RA onset. Results are presented in Table A18.7.

Table A18.7: HRs for RA onset contingent upon material and social adversities with and without smoking

	RA onset from age 45 (n=3,420)			RA onset from age 60 (n=2,799)		
	HR	95%CI	p-value	HR	95%CI	p-value
Material adversity birth to 29	1.636	0.998-2.681	0.051	**2.164**	**1.190-3.936**	**0.011**
Social adversity birth to 29	**1.243**	**1.010-1.530**	**0.040**	1.162	0.890-1.518	0.270
Material adversity birth to 29	1.636	0.998-2.684	0.051	**2.129**	**1.171-3.874**	**0.013**
Social adversity birth to 29	**1.244**	**1.010-1.530**	**0.040**	1.147	0.876-1.502	0.317
Smoking during early adulthood	0.999	0.967-1.033	0.975	0.944	0.857-1.039	0.236
Smoking during mid- adulthood				1.095	0.992-1.208	0.071

These are HRs for four models, each adjusted for birth cohort, gender and education. Smoking is the number of years smoked. Childhood is 0-15, youth is 16-29, early adulthood is 30-44, mid-adulthood is 45-59. HRs for material adversities refer to one or more adversity as opposed to none. HRs for social adversities refer to each additional adversity, up to a maximum of three or more. Bold font indicates associations that are statistically significant at $p<0.05$.

Tables A18.8 and A18.9 present results from sensitivity analyses that compare relationships between RA onset and adversities of different types; family-related vs. traumatic, and chronic vs. acute. Findings are similar to those reported in the main text, although the smaller sample size means that they are not as striking.

Table A18.8: HRs for RA onset contingent upon relationship-related and traumatic adversities

Life stage & type of adversity	RA onset from age 16 (n=3,451) HR	95%CI	p-val	RA onset from age 45 (n=3,420) HR	95%CI	p-val	RA onset from age 60 (n=2,799) HR	95%CI	p-val
Childhood									
Relations	1.104	0.716-1.702	0.654	1.136	0.711-1.813	0.594	0.969	0.530-1.770	0.918
Trauma	1.360	0.987-1.875	0.060	1.396	0.985-1.980	0.061	1.331	0.852-2.081	0.209
Birth to 44									
Relations				**1.583**	**1.144-2.191**	**0.006**			
Trauma				1.273	0.801-2.024	0.307			
Birth to 59									
Relations							**1.659**	**1.007-2.733**	**0.047**
Trauma							1.043	0.580-1.877	0.888

These are results from five models, each adjusted for birth cohort, gender, and Level 2+ qualifications at time of LIFE with mutual adjustment for relationship-related and traumatic adversities, material adversity during the life stage in which relationship-related and traumatic adversities are included, and total adversity during other life stages. Childhood relationship-related adversity is measured using an indicator of 1+ adversities. Family adversity during other periods is measured using continuous variables with values for birth-44 of 0,1-2,3+ adversities and for birth-59 of 0,1-3,4 adversities. Traumatic adversities are measured using indicators of 1+ during all periods except childhood, when the variable takes values of 0,1,2+.

Table A18.9: HRs for RA onset contingent upon chronic and acute adversities

Life stage & type	RA onset from age 30 (n=3,446) HR	95%CI	p-val	RA onset from age 45 (n=3,420) HR	95%CI	p-val	RA onset from age 60 (n=2,799) HR	95%CI	p-val
16-29									
Chronic	1.492	0.805-2.764	0.204	1.485	0.764-2.884	0.243	2.153	0.964-4.808	0.062
Acute	1.070	0.543-2.108	0.845	0.928	0.441-1.953	0.843	0.962	0.371-2.494	0.937
16 to 44									
Chronic				1.538	0.947-2.498	0.082	**1.946**	**1.053-3.597**	**0.034**
Acute				0.824	0.414-1.642	0.583	0.797	0.332-1.911	0.611
16 to 59									
Chronic							1.623	0.894-2.946	0.112
Acute							0.686	0.299-1.570	0.372

These are results from six models, each with mutual adjustment for chronic and acute adversities, and adjustment for adversities not classified as chronic or acute, childhood adversity measured using an indicator of one or more adversities, birth cohort, gender and qualifications of Level 2 or above at the time of LIFE. Chronic adversities are main occupation as carer and/or reporting being a carer, having a partner or child who is addicted to alcohol or drugs and breaking up with a cohabiting partner. Acute adversities are being a victim of sexual assault, being a victim of a serious physical attack, witnessing a death or serious injury, or a major natural disaster. Measures of chronic and acute adversity and of adversities not classified as chronic or acute are indicators of one or more adversity.

Appendix 19: Sensitivity analyses using alternative multiple imputed datasets

Using multiple imputation, missing values are imputed for indices of adversity rather than for individual adversities. Most analyses use indices of adversity and so it is appropriate to impute missing values for them. This was just as well since it proved impossible to impute missing values for individual adversities as imputation models would not converge.

Many respondents provided information about some but not all adversities, and so, for many indices of exposure, partial but not complete information is available. The main analyses use indices of adversity that were calculated only for respondents who provided complete information about the relevant adversities. All other respondents were assigned missing values for the index, even if they had provided partial information. Values from the complete cases were then used to impute missing values for all other respondents, using the technique of multiple imputation.

The drawback with this method is that it does not use all available information because some respondents provided partial information about the adversities that contribute to each index. In these sensitivity analyses, indices were created in the original dataset that included values for respondents who provided information about at least half the adversities measured in each index. Index values were the number of adversities reported, not scaled up. These were used to create multiple imputed datasets so that sensitivity analyses could be conducted.

Summary statistics for the main variables used are presented in Table A19.1.

Compared against the summary statistics using the other multiple imputed datasets (Table 3.7), reported levels of adversities are slightly higher. The exceptions are that levels of material adversity during transition and of traumatic adversities throughout the life course are slightly lower in these datasets.

Table A19.1: Summary statistics

		Observed dataset						Imputed datasets derived from indices using partial information	
		Indices using complete information			Indices using partial information				
Variable and measure	Values	N	Mean %=y	SD / no.=y	N	Mean %=y	SD / no.=y	Mean %=y	95% CI
Adversity 0-15									
terciles	0	3580	45.9	1643	5491	42.5	2334	42.5	41.2-43.8
	1	3580	29.9	1069	5491	29.6	1624	29.5	28.2-30.7
	2+	3580	24.2	868	5491	27.9	1533	28.0	26.8-29.3
binary	1+	3580	54.1	1937	5491	57.5	3157	57.5	56.2-58.8
Adversity 0-44									
Terciles	0-1	3428	43.3	1485	5284	37.9	2000	36.2	34.9-37.4
	2-3	3428	37.8	1297	5284	37.5	1983	37.0	35.7-38.3
	4+	3428	18.8	646	5284	24.6	1301	26.8	25.7-28.0
Continuous	0-6+	3428	2.050	1.624	5284	2.322	1.734	2.423	2.375-2.471
Adversity 0-59									
Terciles	0-1	3214	34.5	1108	5280	28.0	1480	26.4	25.3-27.6
	2-3	3214	38.0	1220	5280	36.8	1944	36.0	34.8-37.2
	4+	3214	27.6	886	5280	35.2	1856	37.6	36.3-38.8
Continuous	0-7+	3214	2.503	1.825	5280	2.908	1.975	3.023	2.970-3.075
Cumulative 0-44									
Dummies	0	4998	12.7	637	5296	15.6	826	14.8	13.8-15.7
	1	4998	32.7	1636	5296	34.9	1849	34.3	33.0-35.5
	2	4998	35.2	1761	5296	33.9	1793	34.4	33.2-35.6
	3	4998	19.3	964	5296	15.6	828	16.5	15.5-17.5
Continuous	0-3	4998	1.611	0.937	5296	1.495	0.935	1.527	1.503-1.552
Cumulative 0-59									
Dummies	0	4640	9.2	425	5292	10.0	531	9.4	8.6-10.2
	1	4640	25.4	1178	5292	26.7	1411	25.9	24.8-27.0
	2	4640	33.9	1573	5292	33.6	1779	33.7	32.5-35.0
	3	4640	22.9	1062	5292	22.2	1177	23.0	21.9-24.1
	4	4640	8.7	402	5292	07.4	394	8.0	7.3-8.7
Continuous	0-4	4640	1.965	1.093	5292	1.904	1.086	1.942	1.914-1.970
15-29 (binary)	1+	5145	50.1	2579	5319	50.0	2660	50.6	49.3-51.9
30-44 (binary)	1+	4999	43.4	2170	5447	43.6	2373	44.6	43.3-46.0
45-59 (binary)	1+	4644	38.3	1778	5489	40.8	2241	41.5	40.2-42.8
Material adversity during:									
0-15 (binary)	1+	4178	16.7	699	6516	17.0	1106	17.0	16.1-17.9
0-29 (binary)	1+	4161	19.5	812	6481	25.2	1633	25.2	24.1-26.3
0-44 (binary)	1+	4161	22.1	918	6481	29.9	1940	29.9	28.8-31.0
0-59 (binary)	1+	4161	25.0	1040	6481	33.9	2195	33.9	32.7-35.0
Social adversity during:									
0-15 (continuous)	0-3+	4568	0.715	0.799	5355	0.731	0.804	0.731	0.710-0.753
0-29 (continuous)	0-3+	4499	1.256	1.093	5246	1.263	1.091	1.263	1.234-1.293
0-44 (continuous)	0-6+[1]	4368	1.089	0.787	5237	1.116	0.790	1.116	1.094-1.137
0-59 (continuous)	0-3+[2]	4368	1.234	0.714	5237	1.227	0.699	1.227	1.208-1.246

Relationship adversity during:									
0-15 (binary)	1+	5364	35.8	1922	6620	34.3	2269	34.3	33.1-35.4
0-29 (continuous)	0-3+[2]	5288	0.633	0.643	6603	0.632	0.650	0.632	0.616-0.648
0-44 (continuous)	0-3+[2]	5137	0.829	0.701	6597	0.851	0.711	0.851	0.834-0.868
0-59 (continuous)	0-4+[3]	4773	0.824	0.612	6586	0.868	0.620	0.868	0.853-0.883
Trauma during:									
0-15 (continuous)	0-2+	4662	0.326	0.564	5355	0.318	0.560	0.318	0.303-0.333
0-29 (binary)	1+	4654	39.6	1842	5249	37.9	1989	37.9	36.6-39.2
0-44 (binary)	1+	4654	43.4	2019	5246	41.7	2187	41.7	40.4-43.0
0-59 (binary)	1+	4654	48.1	2237	5246	46.5	2442	46.5	45.2-47.9
Chronic adversity during:									
16-29 (binary)	1+	5422	13.1	711	5524	0.132	728	0.137	0.127-0.146
16-44 (binary)	1+	5422	28.0	1516	5522	0.279	1539	0.286	0.275-0.298
16-59 (binary)	1+	5422	39.2	2127	5424	0.393	2129	0.393	0.381-0.406
Acute adversity during:									
16-29 (binary)	1+	5356	11.2	602	5503	0.113	620	0.113	0.104-0.121
16-44 (binary)	1+	5356	15.1	809	5503	0.151	832	0.151	0.142-0.161
16-59 (binary)	1+	5356	18.0	962	5503	0.180	989	0.177	0.166-0.187
Female (binary)		6624	54.7	3626	6624	54.7	3626	54.7	53.5-55.9
Level 2+ (binary)		6109	68.4	4179	6109	68.4	4179	67.7	66.5-68.9
Born by 1920 (binary)		6624	3.7	247	6624	3.7	247	3.7	3.3-4.2
Born 1921-30 (binary)		6624	12.9	854	6624	12.9	854	12.9	12.1-13.7
Born 1931-40 (binary)		6624	23.8	1579	6624	23.8	1579	23.8	22.8-24.9
Born 1941-50 (binary)		6624	34.7	2297	6624	34.7	2297	34.7	33.5-35.8
Born 1951+ (binary)		6624	24.9	1647	6624	24.9	1647	24.9	23.8-25.9
Years smoked 30-44 (cont.)		6272	5.553	6.843	6272	5.553	6.843	5.553	5.384-5.723
Years smoked 45-59 (cont.)		6337	3.383	5.758	6337	3.383	5.758	3.383	3.242-3.525
RA from 16 (binary)		260			260			260	
RA from 45 (binary)		221			221			221	
RA from 60 (binary)		137			137			137	

Summary statistics refer to the 6,623 respondents who participated in LIFE and provided information about RA onset, gender and date of birth. One participant, who reported RA with onset before age 16, is excluded. Childhood is 0-15, youth 15-29, early adulthood 30-44, mid-adulthood 45-59.

1. Social adversity between birth and 44 is a continuous variable with values of 0,1-2,3-5,6+.
2. These continuous variables have values of 0,1-2,3+.
3. Relationship-related adversity from birth to age 59 has values of0,1-3,4+.

The results of Cox regression analyses used to address RQ1 are presented in Table A19.2. They are very similar to those presented in the main text. The only difference is that the magnitude of association with childhood adversity is very slightly reduced.

Table A19.2: Associations between total exposure to adversity and risk of RA onset

Adversity 0-15	RA onset from 16								
	Men and women (n=6,623)			Men (n=2,997)			Women (n=3,626)		
	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Terciles 0	Reference			Reference			Reference		
1	**1.378**	**1.003-1.892**	**0.048**	1.357	0.842-2.187	0.210	1.395	0.904-2.152	0.132
2+	**1.460**	**1.056-2.017**	**0.022**	1.367	0.851-2.196	0.196	1.524	0.970-2.396	0.068
Wald test			**0.044**			0.333			0.143
Binary 1+	**1.418**	**1.076-1.870**	**0.013**	1.363	0.906-2.051	0.137	1.460	0.992-2.148	0.055

0-44	RA onset from 45								
	Men and women (n=6,560)			Men (n=2,975)			Women (n=3,585)		
Measure	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Terc. 0-1	Reference			Reference			Reference		
2-3	1.397	0.958-2.037	0.082	1.621	0.950-2.767	0.077	1.225	0.737-2.037	0.434
4-11	**1.890**	**1.318-2.709**	**0.001**	**2.049**	**1.206-3.481**	**0.008**	**1.750**	**1.066-2.873**	**0.027**
Wald test			**0.004**			**0.034**			0.093
Cont.	**1.143**	**1.057-1.236**	**0.001**	**1.163**	**1.040-1.301**	**0.008**	**1.123**	**1.005-1.255**	**0.041**

0-59	RA onset from 60								
	Men and women (n=5,525)			Men (n=2,593)			Women (n=2,932)		
Measure	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
Terc. 0-1	Reference								
2-3	1.607	0.962-2.686	0.070	**2.939**	**1.220-7.080**	**0.016**	1.064	0.550-2.058	0.853
4-12	**1.980**	**1.187-3.304**	**0.009**	**3.672**	**1.545-8.725**	**0.003**	1.273	0.651-2.488	0.480
Wald test			**0.030**			**0.012**			0.747
Cont.	**1.121**	**1.025-1.227**	**0.012**	**1.196**	**1.060-1.350**	**0.004**	1.048	0.917-1.199	0.489

Models are adjusted for birth cohort and Level 2 qualifications or higher at time of LIFE. The model for men and women together is adjusted for gender. Continuous measures have maximum values of 6 for adversities between birth and age 44 and of 7 for adversities between birth and age 59. HR is hazard ratio, 95% ci is 95% confidence interval.

Results of Cox regression models of RA onset on cumulative levels of adversity over the life course are presented in Table A19.3. They are very similar to those presented in the main text.

Table A19.3: Associations between cumulative exposure to adversity and risk of RA onset

Number of life stages exposed to adversity		RA onset from age 45 (n=3,420)			RA onset from age 60 (n=2,799)		
Measure	Values	HR	95%CI	p-val	HR	95%CI	p-val
Dummies	0	Reference			Reference		
	1	1.754	0.994-3.095	0.053	2.200	0.812-5.964	0.121
	2	**2.273**	**1.295-3.988**	**0.004**	**2.932**	**1.121-7.671**	**0.028**
	3	**2.473**	**1.349-4.535**	**0.003**	**3.679**	**1.374-9.854**	**0.010**
	4				3.074	1.374-9.854	0.052
	Wald test			**0.011**			0.054
Continuous		**1.301**	**1.116-1.516**	**0.001**	**1.275**	**1.084-1.501**	**0.003**

Models are adjusted for birth cohort, gender and Level 2 or higher qualifications at time of LIFE. HR is hazard ratio, 95% ci is 95% confidence interval.

Results of Cox regression models of RA onset on adversity during each life stage with mutual adjustment are presented in Table A19.4. The results are very similar to those presented in the main text.

Table A19.4: Associations between RA onset and adversity during each life stage, with mutual adjustment

Adversity during each life stage	RA onset from age 45 (n=6,560)				RA onset from age 60 (n=5,525)			
	HR	95%CI		p-value	HR	95%CI		p-value
Childhood	**1.410**	**1.040**	**1.912**	**0.027**	1.446	0.981	2.132	0.062
Youth	**1.529**	**1.149**	**2.034**	**0.004**	**1.808**	**1.259**	**2.596**	**0.001**
Early adulthood	1.025	0.757	1.390	0.872	0.875	0.600	1.276	0.488
Mid-adulthood					1.176	0.814	1.701	0.388

These are results from two models, each adjusted for birth cohort, gender and Level 2 or higher qualifications at time of LIFE. HR is hazard ratio, and 95%CI is 95% confidence interval. Childhood is ages 0-15, youth 16-29, early adulthood 30-44, mid-adulthood 45-59. Measures of adversity at each life stage are binary indicators of one or more adversities.

Table A19.5 presents results of Cox regression models of RA onset on adversities classified as material and social. The results are very similar to those reported in the main text.

Table A19.5: HRs for RA onset contingent upon material and social adversities

Life stage & type	RA onset from age 16 (n=6,623)			RA onset from age 45 (n=6,560)			RA onset from age 60 (n=5,525)		
	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
0-15									
Material	**1.375**	**1.028-1.841**	**0.032**	1.325	0.964-1.821	0.083	**1.509**	**1.021-2.232**	**0.039**
Social	**1.192**	**1.018-1.395**	**0.029**	**1.215**	**1.023-1.444**	**0.027**	1.102	0.883-1.377	0.390
0-44									
Material				1.267	0.955-1.681	0.101	**1.498**	**1.051-2.135**	0.026
Social				**1.386**	**1.163-1.652**	**0.000**	**1.294**	**1.027-1.630**	**0.029**
0-59									
Material							**1.626**	**1.151-2.297**	**0.006**
Social							1.281	0.983-1.669	**0.067**

These are results of six models with mutual adjustment for material and social adversities and total adversity during other life stages, birth cohort, gender and Level 2+ qualifications at time of LIFE. Material adversity is measured using an indicator of one or more adversity. Social adversities are measured using continuous variables with values of 0,1,2,3+ between 0&15; 0,1-2,3-5,6+ between 0-44, 0,1-2,3+ between 0&59.

As reported in the main analyses, there is no evidence that smoking mediates associations between adversity and RA onset. Results are presented in Table A19.6.

Table A19.6: HRs for RA onset contingent upon material and social adversities with adjustment for smoking

	RA onset from age 45 (n=6,560)			RA onset from age 60 (n=5,525)		
	HR	95%CI	p-value	HR	95%CI	p-value
Material adversity 0-29	1.303	0.975-1.743	0.074	**1.536**	**1.070-2.204**	**0.020**
Social adversity 0-29	**1.261**	**1.107-1.436**	**0.000**	**1.217**	**1.032-1.436**	**0.020**
Material adversity 0-29	1.296	0.969-1.733	0.081	**1.534**	**1.069-2.202**	**0.020**
Social adversity 0-29	**1.255**	**1.101-1.429**	**0.001**	**1.210**	**1.026-1.427**	**0.024**
Smoking 30-44	1.013	0.993-1.033	0.204	0.982	0.932-1.035	0.506
Smoking 45-59				1.052	0.996-1.110	0.067

These are results for four models. Smoking is the number of years smoked. Childhood is 0-15, youth is 16-29, early adulthood is 30-44, mid-adulthood is 45-59.

Tables A19.7 and A19.8 present results from comparisons of relationships between RA onset and adversities of different types; family-related vs. traumatic, and chronic vs. acute. The results are similar to those reported in the main text.

Table A19.7: HRs for RA onset contingent upon relationship-related and traumatic adversities

Life stage	RA onset from age 16 (n=3,451)			RA onset from age 45 (n=3,420)			RA onset from age 60 (n=2,799)		
and type	HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
0-15									
Relations	1.106	0.857-1.426	0.438	1.205	0.915-1.587	0.184	1.071	0.752-1.525	0.703
Trauma	**1.277**	**1.022-1.597**	**0.032**	1.224	0.957-1.564	0.107	1.151	0.834-1.589	0.393
0-44									
Relations				**1.290**	**1.062-1.567**	**0.010**	1.220	0.948-1.569	0.122
Trauma				1.327	0.981-1.794	0.066	1.152	0.778-1.707	0.480
0-59									
Relations							1.218	0.914-1.623	0.178
Trauma							1.185	0.801-1.751	0.395

These are results from six models, each adjusted for birth cohort, gender, and Level 2+ qualifications at time of LIFE with mutual adjustment for relationship-related and traumatic adversities, material adversity during the life stage in which relationship-related and traumatic adversities are included, and total adversity during other life stages. Childhood relationship-related adversity is measured using an indicator of 1+ adversities. Family adversity during other periods is measured using continuous variables with values for 0-44 of 0, 1-2, 3+ adversities and for 0-59 of 0, 1-3, 4 adversities. Traumatic adversities are measured using indicators of 1+ during all periods except childhood, when the variable takes values of 0, 1, 2+.

Table A19.8: Hazard ratios for RA onset contingent upon chronic and acute adversities

Life stage & type	RA onset from age 30 (n=6,613) HR	95%CI	p-val	RA onset from age 45 (n=6,560) HR	95%CI	p-val	RA onset from age 60 (n=5,525) HR	95%CI	p-val
16-29									
Chronic	**1.661**	**1.123-2.457**	**0.011**	**1.773**	**1.174-2.677**	**0.006**	**2.674**	**1.630-4.384**	**0.000**
Acute	0.761	0.468-1.238	0.271	0.756	0.453-1.262	0.285	0.800	0.424-1.507	0.490
16-44									
Chronic				**1.561**	**1.139-2.140**	**0.006**	**1.814**	**1.220-2.697**	**0.003**
Acute				0.834	0.543-1.281	0.407	0.745	0.419-1.325	0.316
16-59									
Chronic							1.371	0.940-2.001	0.102
Acute							0.723	0.418-1.253	0.248

These are results from six models, each with mutual adjustment for chronic and acute adversities, and adjustment for adversities not classified as chronic or acute, childhood adversity measured using an indicator of one or more adversities, birth cohort, gender and qualifications of Level 2 or above at the time of LIFE. Chronic adversities are main occupation as carer and/or reporting being a carer, having a partner or child who is addicted to alcohol or drugs and breaking up with a cohabiting partner. Acute adversities are being a victim of sexual assault, being a victim of a serious physical attack, witnessing a death or serious injury, or a major natural disaster. Measures of chronic and acute adversity and of adversities not classified as chronic or acute are indicators of one or more adversity.

Appendix 20: Detailed information about data and measures

19. Dataset

The ELSA sample consists of core members and their cohabiting partners. Original core members were participants in HSE in 1998, 1999, or 2001, and in the first wave of ELSA data collection between 2002 and 2003. Refreshment samples of new core members were added in waves 3,4, and 6 to maintain numbers and the age distribution as the original core members aged. Participants of HSE between 2001 and 2004 who were aged 50-53 at the time of data collection were included in wave 3. In wave 4, participants of HSE 2006 who were aged 50-74 at the time of data collection were interviewed. In wave 6, the refreshment sample included respondents from HSE 2009-2011 aged 50-55.

ELSA Life history data were collected in a separate interview in wave 3, between 2006 and 2007. Retrospective information was collected from participants who not only provided interviews at wave 3 but also consented to providing information about their lives so far in an additional interview. The exception is that participants who did not provide a wave 3 interview were invited to participate in the life history interview if their cohabiting partner had agreed to provide life history data. Those whose wave 3 main interview was conducted late (after April 19th, 2007) were excluded.

20. Measures

<u>Depressive symptoms</u>

The 8-item version of the Centre for Epidemiology depression scale (CESD) was administered in each wave of data collection during the psychosocial module of the main interview. The items are set out in Table A20.1.

Table A20.1: Items used to measure depressive symptoms

Item	Response	Score
Now think about the past week and the feelings you have experienced. Please tell me if each of the following was true for you much of the time during the past week.		
Much of the time during the past week, you felt depressed?	Yes No	1 0
Much of the time during the past week, you felt that everything you did was an effort?	Yes No	1 0
Much of the time during the past week, your sleep was restless?	Yes No	1 0
Much of the time during the past week, you were happy?	Yes No	0 1
Much of the time during the past week, you felt lonely?	Yes No	1 0
Much of the time during the past week, you enjoyed life?	Yes No	0 1
Much of the time during the past week, you felt sad?	Yes No	1 0
Much of the time during the past week, you could not get going?	Yes No	1 0

These items are asked in the psychosocial module of the main interview in each wave or data collection

Hypothesised confounders and mediators

Socio-economic factors

All available information was used to create measures of socio-economic factors. For childhood SEP, information was used from the earliest wave in which it was available. The only exception to this was if a respondent classified their main carer's occupation as unemployed or in casual work and later classified their occupation differently; in this situation, the latter information was used instead of the classification as unemployed or in casual work. If information provided in different waves differed by more than two categories, then a missing value was assigned to the variable. That is, if the main carer's occupation was described in one wave as professional/managerial and in another as semi-skilled or routine/manual, or if the main carer's occupation was described in one wave as professional/managerial or skilled in one wave and routine/manual in another.

For accumulated wealth and qualifications, information collected in wave 2 was used in the first instance. If the information was missing in wave 2, information was used from wave 1, and if this information was missing also, information was used from waves 3, 4, 5 and 6, in that order. Thus, although the variables are referred to as qualifications below Level 2 in 2004 and low wealth in 2004, the date is an approximation.

Stable psychological factors

Stable psychological factors were measured in a self-completion questionnaire administered during wave 5. Items and which dimension they refer to are listed in Table A20.2. Following guidelines (Lachman & Weaver 1997), all scores were reverse coded except for the items relating to calm and careless, and the mean for each dimension was calculated. If values were provided for at least half the items for a dimension, that dimension was assigned a score based on the mean of the values provided. If more than half the items for a dimension had missing values, the dimension was not assigned a value.

Table A20.2: Items used to measure stable psychological factors and their factor loadings

	Agreeable	Open	Extravert	Conscientious	Neurotic
During the past 30 days, to what degree did you feel:					
Outgoing			Y		
Please indicate how well each of the following describes you:					
Helpful	Y				
Moody					Y
Organised				Y	
Friendly			Y		
Warm	Y				
Worrying					Y
Responsible				Y	
Lively			Y		
Caring	Y				
Nervous					Y
Creative		Y			
Hardworking				Y	
Imaginative		Y			
Soft-hearted	Y				
Calm					Y
Intelligent		Y			
Curious		Y			
Active			Y		
Careless				Y	
Broad-minded		Y			
Sympathetic	Y				
Talkative			Y		
Sophisticated		Y			
Adventurous		Y			
Thorough				Y	

Respondents were asked to tick one of the following responses for each item: A lot / Some / A little / Not at all. Calm and careless are reverse coded.

Childhood adversity

The questions used to measure childhood adversities are presented in Table A20.3. Criteria for poor housing amenities have changed over time. Details about how these were defined are given in Appendix 10.

Table A20.3: Questions used to measure childhood adversities

Adversity	Question/s	Mode
Poor amenities and/or crowding at age 10 & living in UK	We would like to find out more about where you lived when you were ten years old. Earlier you told me that when you were ten you lived at (a residence in recorded country for residence living in at 10th year of life). How many bedrooms did your household occupy in this residence? If asked: Include only bedrooms. Do not count bathrooms, kitchens, living rooms, dining rooms or any rooms your household sublet. Including yourself, how many people lived in your household at this residence when you were 10? Did this accommodation have any of the features on this card when you were aged 10? Fixed bath Cold running water supply Hot running water supply Inside toilet Central heating All of these None of these In what year did you start living in your (first/next) residence that you lived in for six months or more? Was this residence (which you started living at in (year when started living in residence)) in the UK? In what year did you stop living in this residence (which you started living at in (year when stopped living in residence))?	IV
Severe financial hardship	Have you ever experienced severe financial hardship? If so, how old were you when it first happened?	SC
Parental unemployment 6m+	When you were aged under 16, were either of your parents unemployed for more than 6 months when they wanted to be working?	SC
Early parental loss	Now I would like to ask you a few questions about your parents. Did your parents permanently separate or divorce before you were 16? By parents, I mean your natural or adoptive parents? Yes No Spontaneous only: One or both parents died before respondent was 16 (yes) Spontaneous only: Parents never lived together during respondent's lifetime (coded as yes) Spontaneous only: Never lived with parents / Don't know (coded as yes)	IV
Separation from mother for 6m+	Were you separated from your mother for 6 months or longer before you were 16?	IV
Parents argued often	When you were aged under 16, did your parents argue or fight very often?	SC
Parent abused substances/ mental health difficulties	When you were aged under 16, did your parents drink excessively, take drugs or have mental health problems?	SC
Physically abused by parent	When you were under 16, were you physically abused by your parents?	SC
Sexually assaulted	Have you ever been a victim of sexual assault (including rape or harassment)? If so, How old were you when it first happened?	SC
Had life threatening illness or injury	Have you ever had a life-threatening illness or accident? If so, How old were you when it first happened?	SC
Severe physical attack	Have you ever been a victim of serious physical attack or assault? If so, How old were you when it first happened?	SC
Witness death or serious injury	Have you ever witnessed the serious injury or death of someone in war or military action? If so, How old were you when it first happened? Other than in war or military action, have you ever witnessed an accident or violent act in which someone was killed or seriously wounded? If so, How old were you when it first happened?	SC

Lost close relative or friend	Have you ever lost a very close friend or relative in a war or military service? If so, How old were you when it first happened? Have you ever had a very close friend or relative who died or was at risk of death due to illness or serious accident? If so, How old were you when it first happened?	SC
Major natural disaster	Have you ever experienced a major fire, flood, earthquake or other natural disaster? If so, How old were you when it first happened?	SC

All questions were asked during the life history interview in wave 3. IV indicates face to face interview, SC indicates self-completion questionnaire.

Medication use

Participants taking medications that might affect depressive symptoms and/or inflammation were identified using detailed information from wave 0 and the wave 6 nurse interview. The detailed information provided information about all prescribed medications and whether they had been taken during the previous 7 days. Each medication was coded using the British National Formulary classification codes set out in 1997, 1998, 2000 and 2011. For wave 0, the classification codes that indicated a yes value were all those beginning with 2 or 4, 3.2, 6.1, 6.3, 6.4.1, 7.3.1, 7.3.2, 8.2, 8.3, 10.1, 11.4. The same codes were used for wave 6 and in addition 1.5.2 and 1.5.3. This information was supplemented by information provided during the health module of the main interviews. The questions asked are presented in Table A20.4.

Table A20.4: Questions asked to elicit information about use of pharmaceutical medication

	Drugs that are likely to influence depressive symptoms	Interview
1	I have some questions about any treatment you may have had for your depression. Did a doctor or nurse suggest that you take medication, or see a mental health professional for counselling? This may include a psychiatrist, psychologist, or social worker for counselling or psychotherapy. Responses: Medication, Counselling, Both medication and counselling, None.	Main 24
2	Did you start [taking medication/seeing a mental health professional/taking medication and seeing a mental health professional] within two weeks of being offered this treatment?	Main 4
3	Did you feel better within 6 weeks after [medication/seeing a mental health professional/medication and seeing a mental health professional]?	Main 2
	Drugs that are likely to influence inflammation	
4	Are you currently taking any medication, tablets or pills for high blood pressure?	Main 2-6
5	Can I just check, are you taking any medication which prevents you from getting high blood pressure?	Main 3-6
6	Are you currently taking any tablets, pills or other medication that you swallow for diabetes?	Main 2-6
7	Are you currently taking any medication to lower cholesterol level?	Main 3-6
8	Can I just check, are you currently taking medication which prevents you from getting high cholesterol any more?	Main 3-6
9	Are you taking statins (drugs to lower cholesterol) bought over the counter from a pharmacist, without prescription from a doctor? Here are some examples of common statins, which may be bought over the counter: Atorvastatin (Lipitor), Fluvastatin (Lescol, Lescol XL), Pravastatin (Lipostat), Rosuvastatin (Crestor) and Simvastatin (Zocor)	Nurse 6
10	Are you currently taking medication to thin your blood like Warfarin, Asparin, Plavix, Ticlid or other medication to thin the blood?	Main 2-6
11	I would like to check whether any of the medications you are taking are on this list of beta-blockers. Could you show me the medications, or the repeat prescription list for any medications, that you have been taking over the past week? Responses: Taking beta-blocker, Not taking beta-blocker, Taking other beta-blocker not on the showcard.	Main 25
12	I would like to check whether any of the medications you are taking are on this list of ACE inhibitors or A2 receptor blockers. Could you show me the medications, or the repeat prescription list of any medications, that you have been taking over the past week? Responses: Taking ACE inhibitor or A2 receptor blocker, Not taking ACE inhibitor or A3 receptor blocker, Taking other ACE inhibitor not on showcard	Main 2-6

Medication for depression is indicated if responses to Q1 is “medication” and to Q2 and/or Q3 is yes. Medication likely to influence inflammation is indicated by a positive response to any of Q4-Q12.

Psychosocial factors

The questions used to measure psychosocial factors in adulthood are presented in Table A20.5.

Table A20.5: Questions used to measure psychosocial factors.

Variable	Questions	Wave
Perceived strain	We should like to know how your health has been in general over the past few weeks. Have you recently… … felt constantly under strain? Not at all, No more than usual, Rather more than usual, Much more than usual (GHQ item)	13 SC
Belonging and relationships		
Loneliness	1 How often do you feel you lack companionship? 2 How often do you feel left out? 3 How often do you feel isolated from others? 4 How often do you feel in tune with the people around you? 5 How often do you feel lonely Hardly ever or never, Some of the time, Often	W2:1-4 W3-6: 1-5 SC
Got partner since last wave Lost partner since last wave	Do you have a husband, wife or partner with whom you live?	1-6 SC
Stressful relationships with: Partner Child Other family Friend	1 How much do they really understand the way you feel about things? 2 How much can you rely on them if you have a serious problem? 3 How much can you open up to them if you need to talk about your worries? 4 How much do they criticise you? 5 How much do they let you down when you are counting on them? 6 How much do they get on your nerves? A lot, some, a little, not at all	1-6 SC
Community stress	How do you feel about your local area, that is everywhere within a 20 minute walk or about a mile of your home? Please tick one box on each line. The closer your tick is to a statement the more strongly you agree with it. Tick one box on each line (1 is closest to first statement, 7 closest to second statement) I really feel part of this area vs I feel that I don't belong in this area Vandalism and graffiti are a big problem in this area vs There is no problem with vandalism and graffiti in this area I often feel lonely living in this area vs I have never felt lonely living in this area Most people in this area can be trusted vs Most people in this area can't be trusted	13 SC

	People would be afraid to walk alone in this area after dark	vs	People feel safe walking alone in this area after dark	
	Most people in this area are friendly	vs	Most people in this area are unfriendly	
	People in this area will take advantage of you	vs	People in this area will always treat you fairly	
	This area is kept very clean	vs	This area is always full of litter and rubbish	
	If you were in trouble, there are lots of people in this area who would help you	vs	If you were in trouble, there is nobody in this area who would help you	
Occupation-related stress				
In control generally High demands generally	Here are some questions about how you feel about your life in general. Please say how much you agree or disagree with the following statements. 1 At home, I feel I have control over what happens in most situations 2 At work, I feel I have control over what happens in most situations 3 I feel that what happens in my life is often determined by factors beyond my control 4 In general, I have different demands that I think are hard to combine 5 In general, I have enough time to do everything 6 Considering the things I have to do at work, I have to work very fast 7 Considering the things I have to do at home, I have to work very fast Strongly agree, Moderately agree, Slightly agree, Slightly disagree, Moderately disagree, Strongly disagree			1-6 SC
Work effort:reward Items 1-7,9,10,12 Low work control Items 8,11 Job insecurity Item 6	Here are some statements people might use to describe their work. We would like to know how strongly you think these apply to the paid employment you did in the last month. 1 All things considered I am satisfied with my job 2 My job is physically demanding 3 I receive the recognition I deserve for my work 4 My salary is adequate 5 My job promotion prospects are poor 6 My job security is poor 7 I am under constant time pressure due to a heavy workload 8 I have very little freedom to decide how I do my work 9 I have the opportunity to develop new skills 10 I receive adequate support in difficult situations 11 At work, I feel I have control over what happens in most situations 12 Considering the things I have to do at work, I have to work very fast Strongly agree, Agree, Disagree, Strongly disagree			2-6 SC
Status				
Feels worse off than: Neighbours Friends	Compared to the financial situation of [other people living around here/most of your friends], would you say your household is:...			2-5 IV

Colleagues	Much worse off, A bit worse off, About the same, A bit better off, Much better off? And how does your financial situation compare to most of your close work colleagues? Would you say your household is: Much worse off, A bit worse off, About the same, A bit better off, Much better off?	
Subjective social status	Think of this ladder as representing where people stand in our society. At the top of the ladder are the people who are the best off – those who have the most money, most education and best jobs. At the bottom are the people who are the worst off – who have the least money, least education, and the worst jobs or no jobs. The higher up you are on this ladder, the closer you are to the people at the very top and the lower you are, the closer you are to the people at the very bottom. Please mark a cross on the rung on the ladder where you would you place yourself.	1-6 SC
Financial strain		
Can't buy some important things	Does having too little money stop you from doing any of the following things? (Can select any number) Buy your first choices of food items Have family and friends round for a drink or meal Have an outfit to wear for social or family occasions Keep your home in a reasonable state of decoration Replace or repair broken electrical goods Pay for fares or other transport costs to get to and from places you want to go Buy presents for friends or family once a year Take the sorts of holidays you want Treat yourself from time to time None of these	2-6 IV
Perceived financial strain	Which of the phrases on the card best describes how [you/you and your husband/wife/partner] are getting along financially these days? Manage very well, Manage quite well, Get by alright, Don't manage very well, Have some financial difficulties, Have severe financial difficulties	1-6 IV
Social withdrawal	<u>Engagement</u> Which of these statements apply to you? Tick <u>all</u> that apply I read a daily newspaper I have a hobby or pastime I have taken a holiday in the UK in the last 12 months I have taken a holiday abroad in the last 12 months I have gone on a daytrip or outing in the last 12 months I use the internet and/or email I own a mobile phone None of these statements apply to me <u>Participation</u> Are you a member of any of these organisations, clubs or societies? Tick <u>all</u> that apply Political party, trade union or environmental groups Tenants groups, resident groups or Neighbourhood Watch	1-6 SC

	Church or other religious groups Charitable associations Education, arts or music groups or evening classes Social clubs Sports clubs, gyms, exercise classes Any other organisations, clubs or societies No, I am not a member of any organisations, clubs or societies <u>Social activity</u> Now some questions about your social activities. How often, if at all, do you do any of the following activities? (Twice a month or more/About once a month/Every few months/About once or twice a year/Less than once a year/Never) Go to the cinema Eat out of the house Go to an art gallery or museum Go to the theatre, a concert or opera	

SC self-completion, IV main interview.

Measures for loneliness, stressful relationships, and community stress are based on multiple items. For these measures, some items were reverse coded so that item values were aligned, and then the values were summed. For example, the fourth item for loneliness was reverse coded, and then added to the sum of the remaining items (3 for wave 2, and 4 for subsequent waves). Respondents with missing values for no more than half the items were assigned values based on the information provided, and these values were scaled up to match values for respondents who answered all the items.

Low control generally was measured by taking the mean of items in Table A20.5 that indicate control at home (items 1, and 3 reverse coded), and then taking the mean of this measure with the item that indicates control at work (item 2). Respondents with missing values for items 1 or 3 (but not both) were included. High demands was measured by combining items 4-7, after reverse coding items 4,6, and 7.

Previous studies using ELSA data to measure work stress include measures of effort reward imbalance and low control at work (Dragano et al. 2011, Lunau et al. 2013). As described by Dragano et al (2011), items 8 and 11 were used to measure job control. These items are similar to items in the Job Content Questionnaire (Karasek et al. 1998). Item 8 was reverse coded and the mean of the two items was calculated. Again, following Dragano et al. (2011), the remaining 10 items were included in a factor analysis (using the maximum likelihood method of estimation, two factors, followed by a promax rotation that allows correlation between the factors). Based on the results, reward was measured using items 1,3,4,5,6,9,and 10, with half weights assigned to items 5 and 6, to calculate a mean value. Effort was measured by taking the mean of items 7 and 12. Effort reward imbalance was calculated by dividing reward by effort.

Item 6 (reverse coded) was used to measure job insecurity.

Social withdrawal is calculated by assigning participants to a tercile for each of engagement, participation (excluding sports clubs, gyms or exercise classes) and activity, and calculating the mean.

Health behaviours

The measure of alcohol consumption was chosen because this is the only measure that is consistent across all waves. Respondents were asked whether they drank alcohol every day of the week, or almost daily, and a variable was constructed to indicate this frequency of drinking.

Three questions were used to measure physical activity. Respondents were asked to rate how often they took part in sports of activities that involve vigorous, moderate, and mild

levels of activity. How this information was used to code a single variable is summarised in Table A20.6. The resulting variable has four values; high, moderate, low, and sedentary.

Table A20.6: Classification of physical activity as high, moderate, or low

		Q2 (moderate)			
Q3 (mild)	Q1 (vigorous)	>1/week	1/week	1-3/month	Hardly ever/never
>1/week	>1/week	H	H	H	H
	1/week	H	M	M	M
	1-3/month	H	M	M	M
	Hardly ever/never	M	M	L	L
1/week	>1/week	H	H	H	H
	1/week	H	M	M	M
	1-3/month	H	M	L	L
	Hardly ever/never	M	L	L	L
1-3/month	>1/week	H	H	H	H
	1/week	H	M	M	M
	1-3/month	M	L	L	L
	Hardly ever/never	M	L	L	S
Hardly ever/never	>1/week	H	H	H	H
	1/week	H	M	M	M
	1-3/month	M	L	L	L
	Hardly ever/never	M	L	L	S

H is high, M is moderate, L is low, S is sedentary.
Q1 asks, "We would like to know the type and amount of physical activity involved in your daily life. Do you take part in sports or activities that are vigorous: more than once a week, once a week, one to three times a month, hardly ever, or never?"
Q2 asks, "And do you take part in sports or activities that are moderately energetic: more than once a week, once a week, one to three times a month, hardly ever, or never?"
Q3 asks, "And do you take part in sports or activities that are mildly energetic: more than once a week, once a week, one to three times a month, hardly ever, or never?"

Metabolic biomarkers

All respondents who were not pregnant were eligible to have their blood pressure measured. In waves 2, 4, and 6, nurses measured systolic and diastolic blood pressures three times at one-minute intervals using an Omron HEM-907 machine. The average values of the three measures were used. Blood pressures were taken while respondents were sitting, and after they had been resting for at least 5 minutes. Nurses measured the room temperature, and if this was outside the range of 15-20'C, they attempted to alter it by opening or closing doors and windows.

Moderators

Questions used to measure each health status were asked during the health modules of the main interviews in all waves. See Table A20.7.

Table A20.7: Questions used to measure health status

Variable	Questions	Waves
RA, asthma	Has a doctor ever told you that you have (or have had) any of the conditions on this card? PROBE : What others? CODE ALL THAT APPLY Chronic lung disease such as chronic bronchitis or emphysema Asthma Arthritis (including osteoarthritis , or rheumatism) Osteoporosis, sometimes called thin or brittle bones Cancer or a malignant tumour (excluding minor skin cancers) Parkinson's disease Any emotional, nervous or psychiatric problems Alzheimer's disease Dementia, organic brain syndrome, senility or any other serious memory impairment None of these Which type or types of arthritis do you have: READ OUT EACH IN TURN AND CODE ALL THAT APPLY Osteoarthritis? Rheumatoid arthritis? Some other kind of arthritis? Approximately how old were you when you were first told by a doctor that you had arthritis?	1
RA	Our records show that when we last interviewed you on [date of last interview] you said that you had had (or had been told by a doctor you had had) arthritis. Reason why respondent disputes having had arthritis: Never had No longer has Did not have previously, but has now Misdiagnosed	2-6
Asthma	Our records show that when we last interviewed you on [date of last interview] you said that you had had (or had been told by a doctor you had had) asthma. Reason why respondent disputes having had asthma. Never had No longer has Did not have previously, but has now Misdiagnosed	2-6
RA, asthma	Apart from what you have already told us, and thinking about what has happened since we last saw you on [date of last interview] has a doctor told you that you have any of the conditions on this card PROBE - 'What others?'···CODE ALL THAT APPLY. Chronic lung disease such as chronic bronchitis or emphysema Asthma Arthritis (including osteoarthritis , or rheumatism) Osteoporosis, sometimes called thin or brittle bones Cancer or a malignant tumour (excluding minor skin cancers) Parkinson's disease Any emotional, nervous or psychiatric problems Alzheimer's disease Dementia, senility or another serious memory impairment None of these Which type or types of arthritis [do you / does [name]] have...	2

	CODE ALL THAT APPLY. Osteoarthritis? Rheumatoid arthritis? Some other kind of arthritis? Approximately how old were you when you were first told by a doctor that you had arthritis?	
RA, asthma	Apart from what you have already told us, and thinking about what has happened since we last saw you on [^date of last interview] has a doctor told you that you have any of the conditions on this card PROBE - 'What others?'···CODE ALL THAT APPLY. Chronic lung disease such as chronic bronchitis or emphysema Asthma Arthritis (including osteoarthritis , or rheumatism) Osteoporosis, sometimes called thin or brittle bones Cancer or a malignant tumour (excluding minor skin cancers) Parkinson's disease Any emotional, nervous or psychiatric problems Alzheimer's disease Dementia, senility or another serious memory impairment Malignant blood disorder, e.g. leukaemia or lymphoma None of these Which type or types of arthritis [do you / does [name]] have... CODE ALL THAT APPLY. Osteoarthritis? Rheumatoid arthritis? Some other kind of arthritis? Approximately how old were you when you were first told by a doctor that you had arthritis?	3-6
Active asthma	Have you had attacks of wheezing or whistling in your chest at any time in the last 12 months? If has ever had attacks of shortness of breath with wheezing: Is/Was your breathing absolutely normal between attacks?	1-5

Appendix 21: Additional information about analyses

I considered including age squared in the models used to address the first three RQs because the relationship between age and depressive symptoms over the life course is known to be a function of both age and age squared (Kessler et al. 1992). Studies have found that prevalence of depressive symptoms decreases from childhood up to about age 50, after which prevalence rates increase. Most respondents in ELSA are aged over 50, so it was not clear whether age squared should be included in specifications. Analyses using RE models were therefore conducted to assess whether specifications including age squared predict inflammation and depressive symptoms more accurately than models without age squared. The results are presented in Table A21.1. After including gender and age, age squared predicts both depressive symptoms and Ln(CRP), although effect sizes are negligible. The increase in R-square between the two specifications is negligible in relation to Ln(CRP), but substantial in relation to depressive symptoms (R^2=0.018 without age^2, and R^2=0.023 with age^2). Based on these considerations, I decided to include age squared in all specifications.

Table A21.1: Changes in depressive symptoms and inflammation with age.

	Model 1: Outcome is standardised Ln(CRP)					Model 2: Outcome is depressive symptoms				
	beta	95%CI	p-val	Rsq	N	beta	95%CI	p-val	Rsq	N
Model 1										
Female	0.082	0.045-0.119	0.000	0.013	17211	0.490	0.433-0.547	0.000	0.018	29635
Age	0.011	0.009-0.012	0.000			0.007	0.004-0.009	0.000		
Model 2										
Female	0.084	0.047-0.121	0.000	0.013	17211	0.464	0.407-0.521	0.000	0.023	29635
Age	0.039	0.019-0.059	0.000			-0.135	-0.160-0.109	0.000		
Age squared	0.000	0.000-0.000	0.005			0.001	0.001-0.001	0.000		

These are results of random effects models. No additional variables are included.

Appendix 22: Additional results

Sensitivity analyses were conducted in relation to RQ1 using an alternative measure of depressive symptoms with three categories; no, one and two or more depressive symptoms. For specifications in which depressive symptoms was the outcome, ordered probits were used. Using this measure, the results were very similar to those reported in the main text. Each SD increase in Ln(CRP) predicted an increase in depressive symptoms four years later (range 0-2) of 0.030 units (95%ci=0.010-0.066, p=0.008, N=7,829). There was no evidence that depressive symptoms predicted Ln(CRP) four years later (β=0.014, 95%ci=-0.011-0.039, p=0.262, N=5,869).

Results using this three category measure of depressive symptoms by gender, health status and age category are presented in Tables A22.1 and A22.2. They are similar to those presented in the main text using a continuous measure of depressive symptoms.

Table A22.1: Associations between inflammation and depressive symptoms four years later by gender, age category and health status.

	Whole sample				Men				Women			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	0.033	-0.008-0.075	0.118	7829	0.028	-0.015-0.070	0.202	3596	**0.047**	**0.010-0.084**	**0.013**	**4233**
Gender	**0.198**	**0.143-0.253**	**0.000**									
Gender*Ln(CRP)(t-1)	0.008	-0.047-0.063	0.773									

	Whole sample				Aged under 70				Aged 70 plus			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	**0.038**	**0.006-0.071**	**0.020**	7830	**0.036**	**0.004-0.069**	**0.030**	**5485**	**0.074**	**0.021-0.127**	**0.006**	**2345**
70 plus(t-1)	**0.174**	**0.114-0.234**	**0.000**									
70 plus(t-1)*Ln(CRP)(t-1)	0.030	-0.031-0.091	0.340									

	Whole sample				No longstanding illness				With longstanding illness			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	0.017	-0.024-0.057	0.425	7829	0.026	-0.015-0.067	0.215	3685	**0.051**	**0.013-0.089**	**0.009**	**4144**
Longstanding illness(t-1)	**0.258**	**0.201-0.314**	**0.000**									
Longstanding illness(t-1)*Ln(CRP)(t-1)	0.040	-0.015-0.095	0.154									

	Whole sample				With RA			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	**0.038**	**0.008-0.068**	**0.014**	6962	0.028	-0.170-0.226	0.782	165
RA(t-1)	**0.365**	**0.173-0.558**	**0.000**					
RA(t-1)*Ln(CRP)(t-1)	0.012	-0.180-0.204	0.901					

	Whole sample				With history of asthma			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	0.028	-0.002-0.059	0.066	7788	0.063	-0.010-0.135	0.089	1200
Asthma(t-1)	**0.291**	**0.208-0.374**	**0.000**					
Asthma(t-1)*Ln(CRP)(t-1)	0.041	-0.035-0.118	0.290					

	Whole sample				With active asthma			
Outcome is depressive symptoms at t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Ln(CRP)(t-1)	**0.038**	**0.009-0.066**	**0.010**	7825	0.040	-0.082-0.162	0.517	472
Active asthma(t-1)	**0.375**	**0.254-0.496**	**0.000**					
Active asthma(t-1)*Ln(CRP)(t-1)	0.026	-0.094-0.146	0.667					

These are results from 15 random effects models using linear regressions and depressive symptoms as a continuous variable, adjusted for depressive symptoms at time t-1, age and age squared at time t, gender, medication for inflammation or depression at time t, qualifications below Level 2 in 2004 and wealth in 2004. The first two sets of models are also adjusted for longstanding illness at time t-1. The model that includes the indicator of age 70 and over does not include additional adjustment for age, and the specifications for sub-samples aged below 70 and 70+ adjust for age but not age squared. Measures of Ln(CRP) and depressive symptoms are standardised. Bold font indicates associations with p-values below 0.05.

Table A22.2: Associations between depressive symptoms and Ln(CRP) four years later by gender, age category and health status.

	Whole sample				Men				Women			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.017	-0.014-0.048	0.279	5869	0.006	-0.034-0.046	0.769	2659	0.020	-0.012-0.052	0.221	3210
Gender	0.042	-0.004-0.088	0.074									
Gender*Depr(t-1)	-0.006	-0.041-0.030	0.755									

	Whole sample				Aged below 70				Aged 70+			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.018	-0.009-0.045	0.192	5870	0.013	-0.016-0.041	0.391	4265	0.037	-0.011-0.084	0.130	1605
70+(t-1)	0.028	-0.021-0.077	0.258									
70+(t-1)*Depr(t-1)	0.007	-0.039-0.053	0.766									

	Whole sample				No longstanding illness				With longstanding illness			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.025	-0.005-0.056	0.101	5869	0.033	-0.002-0.067	0.067	2828	-0.004	-0.039-0.031	0.831	3041
Longstanding illness(t-1)	**0.045**	**0.002-0.087**	**0.039**									
Longstanding illness(t-1)*Depr(t-1)	-0.022	-0.056-0.012	0.207									

	Whole sample				With RA			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.010	-0.016-0.037	0.447	5240	-0.043	-0.217-0.132	0.630	114
RA(t-1)	0.075	-0.080-0.230	0.345					
RA(t-1)*Depr(t-1)	-0.055	-0.200-0.090	0.457					

	Whole sample				With history of asthma			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.013	-0.013-0.039	0.341	5837	0.001	-0.064-0.066	0.971	870
Asthma(t-1)	**0.101**	**0.034-0.167**	**0.003**					
Asthma(t-1)Depr(t-1)	0.009	-0.042-0.060	0.731					

	Whole sample				With active asthma			
Outcome is Ln(CRP) at time t	beta	95%CI	p_val	N	beta	95%CI	p_val	N
Depr(t-1)	0.010	-0.016-0.035	0.457	5866	0.063	-0.041-0.168	0.236	346
Active asthma(t-1)	**0.109**	**0.020-0.198**	**0.016**					
Active asthma(t-1)*Depr(t-1)	0.067	-0.006-0.139	0.071					

These are results from 15 random effects models, with Ln(CRP) at time t as the outcome and adjusted for Ln(CRP) at time t-1, age and age squared at time t, gender, medication for inflammation or depression at time t, qualifications below Level 2 in 2004, and wealth in 2004. The first two sets of models are also adjusted for longstanding illness at time t-1. The model that includes the indicator of age 70+ does not include additional adjustment for age, and the specifications for sub-samples above and below 70 adjust for age but not age squared. Measures of Ln(CRP) and depressive symptoms are standardised. Bold font indicates associations with p-values below 0.05.

Pairwise correlations between variables used in the SEMs are presented in Table A22.3. Auto-correlations between waves are high, but otherwise variables are not highly correlated.

Table A22.3: Pairwise correlations between variables used in the SEM.

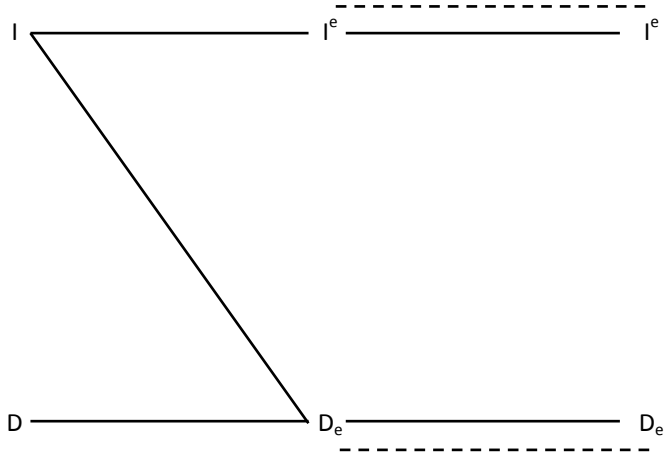
	Fem.	Age	SEP	LLI	Meds	$(crp)_2$	$(crp)_4$	$(crp)_6$	Dep_2	Dep_4	Dep_6	$Obes_3$	$Obes_5$	$Inact_3$	$Inact_5$	$Pain_3$	$Pain_5$	$Strss_3$	$Strss_5$
Female	1																		
Age	-0.01	1																	
SEP	0.05	0.08	1																
LLI	0.03	**0.42**	0.17	1															
Meds	0.03	0.26	0.12	0.23	1														
$Ln(CRP)_2$	0.05	0.11	0.18	0.16	0.16	1													
$Ln(CRP)_4$	0.04	0.09	0.14	0.11	0.12	***0.65***	1												
$Ln(CRP)_6$	0.06	0.12	0.13	0.13	0.12	***0.60***	***0.66***	1											
$Depress_2$	0.13	0.07	0.23	0.29	0.13	0.09	0.08	0.07	1										
$Depress_4$	0.14	0.07	0.20	0.23	0.13	0.11	0.07	0.08	***0.50***	1									
$Depress_6$	0.13	0.08	0.18	0.20	0.13	0.11	0.08	0.09	**0.44**	***0.50***	1								
$Obesity_3$	0.10	0.01	0.12	0.12	0.14	*0.32*	*0.33*	0.28	0.08	0.08	0.07	1							
$Obesity_5$	0.11	0.05	0.12	0.13	0.17	*0.32*	*0.34*	*0.33*	0.09	0.08	0.07	***0.90***	1						
$Inactivity_3$	0.06	*0.32*	0.29	*0.33*	0.20	0.18	0.17	0.18	0.24	0.24	0.22	0.15	0.16	1					
$Inactivity_5$	0.08	*0.34*	0.24	*0.32*	0.17	0.19	0.16	0.18	0.23	0.25	0.25	0.16	0.16	***0.54***	1				
$Pain_3$	0.08	0.09	0.18	*0.36*	0.15	0.15	0.15	0.14	0.29	*0.31*	0.29	0.14	0.14	0.27	0.25	1			
$Pain_5$	0.11	0.09	0.18	*0.32*	0.16	0.12	0.14	0.13	0.27	0.28	0.27	0.16	0.15	0.24	0.27	***0.50***	1		
$Stress_3$	0.03	0.10	**0.46**	0.21	0.16	0.17	0.14	0.17	*0.32*	*0.31*	0.29	0.11	0.12	0.30	0.28	0.25	0.23	1	
$Stress_5$	0.05	0.09	**0.44**	0.18	0.15	0.16	0.11	0.14	*0.32*	*0.33*	*0.32*	0.11	0.12	0.29	0.30	0.24	0.25	0.72	1

Age measured in 2004 (wave 2), SEP measured using low accumulated wealth in 2004, LLI is limiting longstanding illness by 2004, meds is use of medication between waves 0 and 6 that may affect inflammation and/or depressive symptoms. Stress is an index comprised of low self-efficacy, low subjective social status, financial strain and social withdrawal. Ln(CRP) and depressive symptoms are standardised and measured in waves 2,4and6. Obesity is waist circumference of 88cms+ for women and 102cms+ for men. Inactivity refers to lack of physical exercise. Subtext numbers refer to waves of data collection, which are two years apart. Italicised and bold font indicate strong correlations

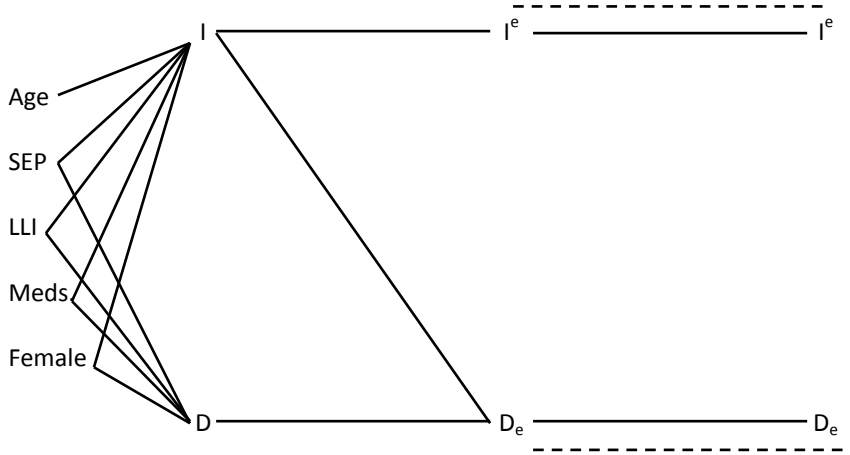
The SEM was built in stages and results are presented in Figure A22.1. Results are consistent with those of the final model, reported in Figure 4.3.

Figure A22.1: Building the SEM in stages (n=11,986 except in Stage 1)

Stage 1: Inflammation and depressive symptoms (n=10,835)

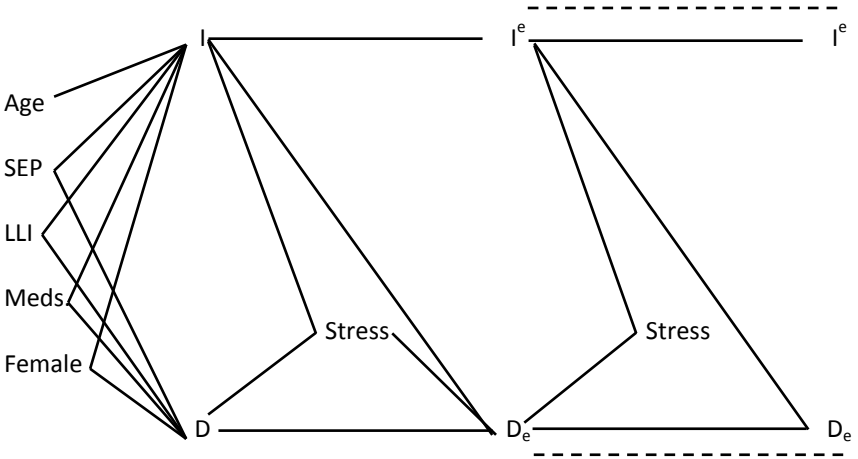


Stage 2: Stage 1 + time-invariant confounders

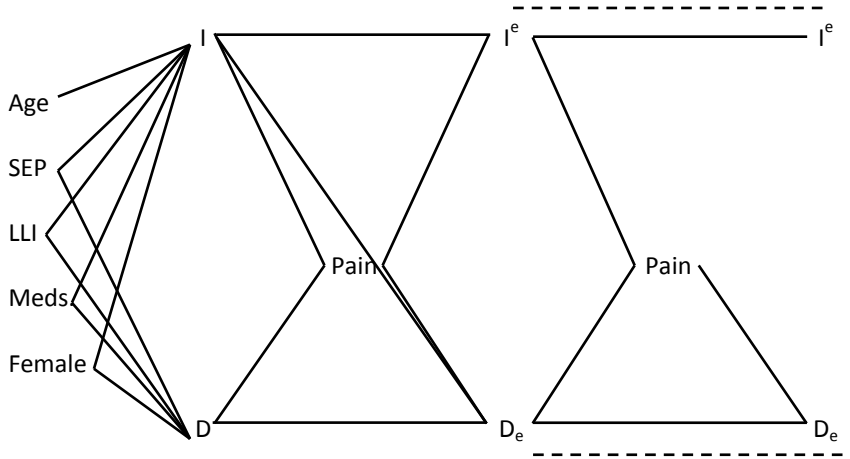


Dashed lines indicate inverse correlations

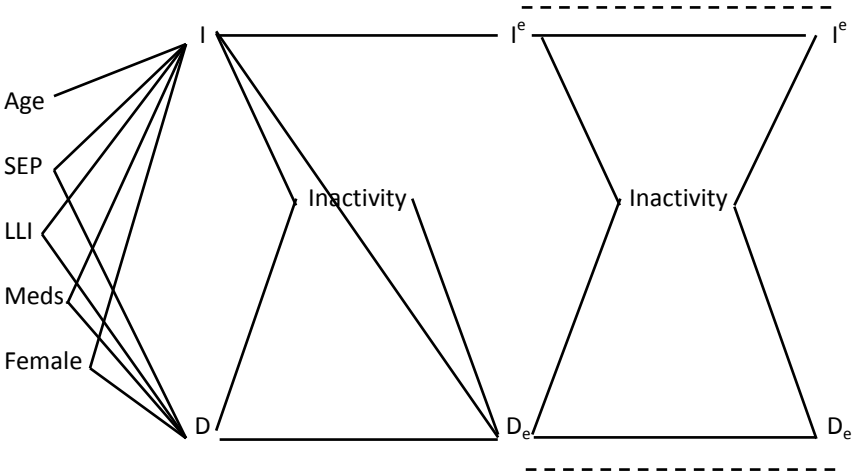
Stage 3: Stage 2 + one mediator



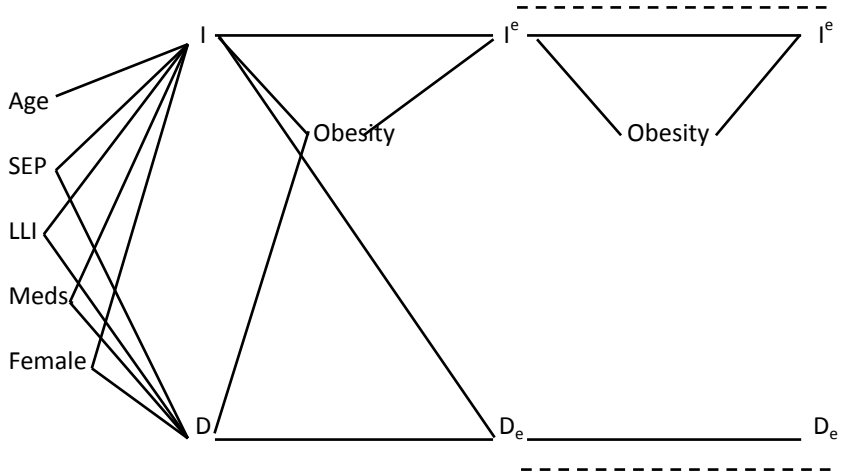
Stage 3: Stage 2 + one mediator



Stage 3: Stage 2 + one mediator

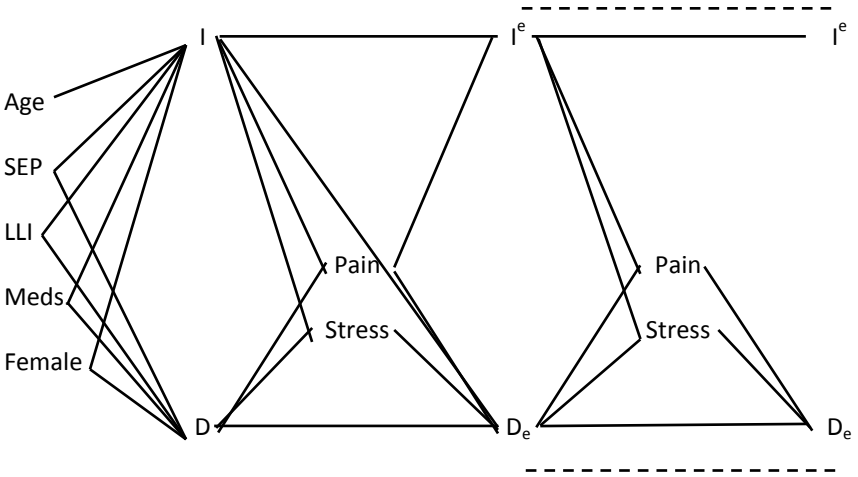


Stage 3: Stage 2 + one mediator

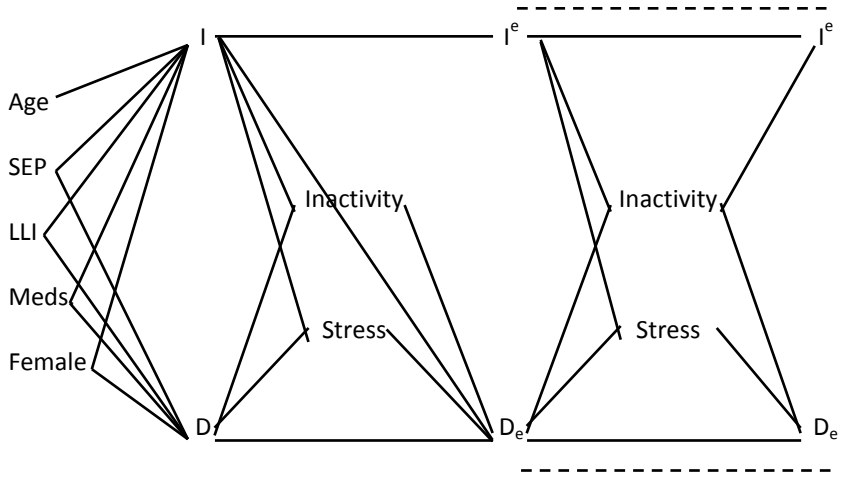


All mediators are auto-correlated over time and inter-correlated in wave 3

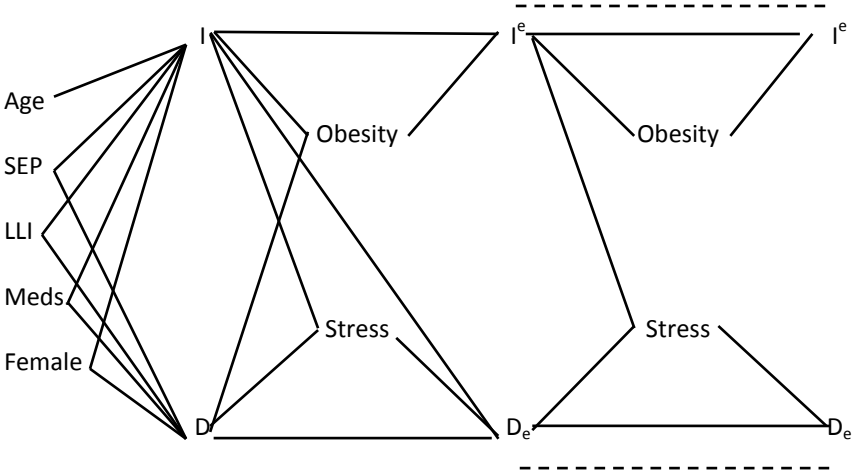
Stage 4: Stage 2 + two mediators



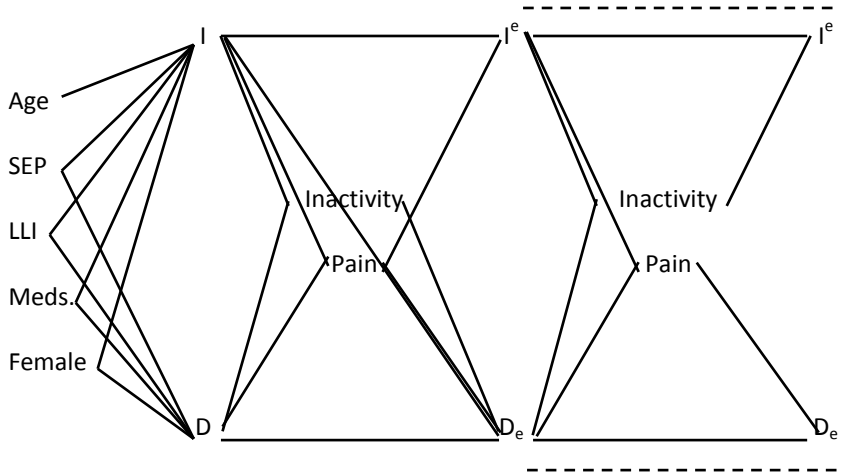
Stage 4: Stage 2 + two mediators



Stage 4: Stage 2 + two mediators

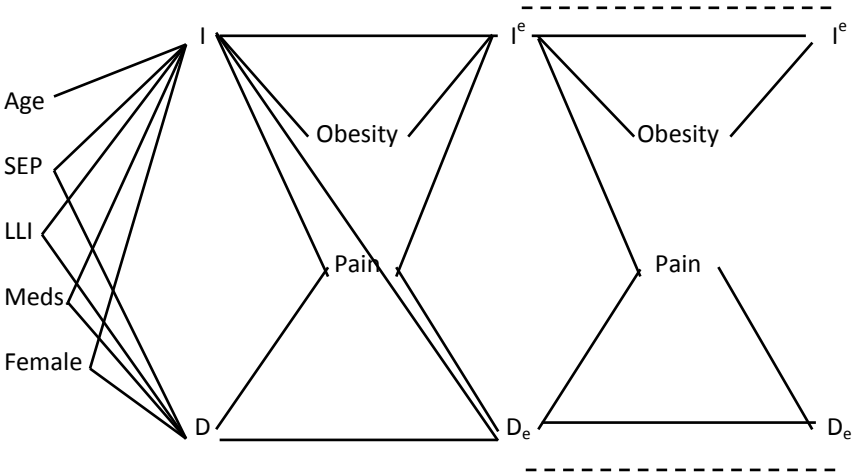


Stage 4: Stage 2 + two mediators

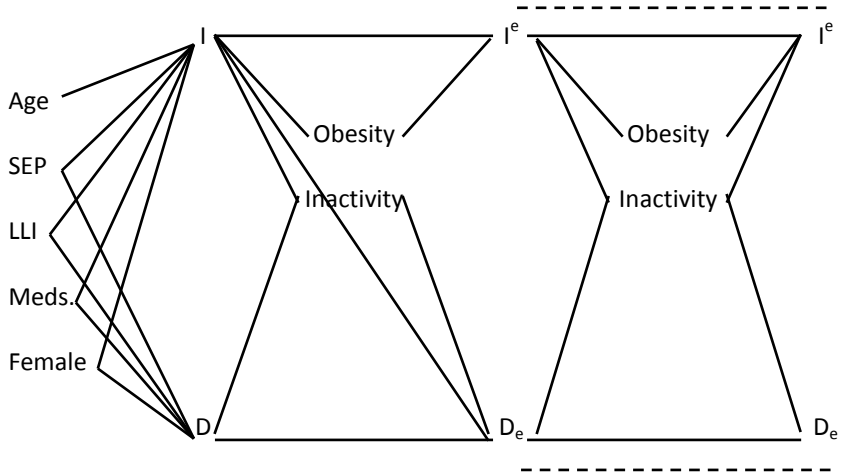


All mediators are auto-correlated over time and inter-correlated in wave 3

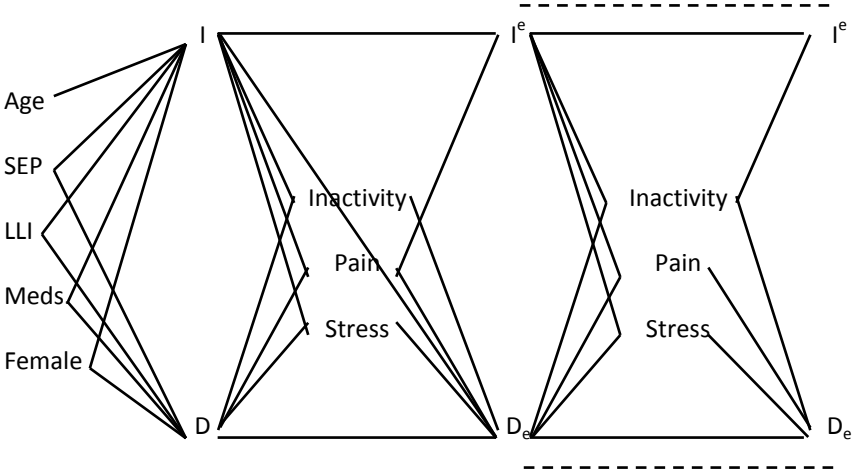
Stage 4: Stage 2 + two mediators



Stage 4: Stage 2 + two mediators

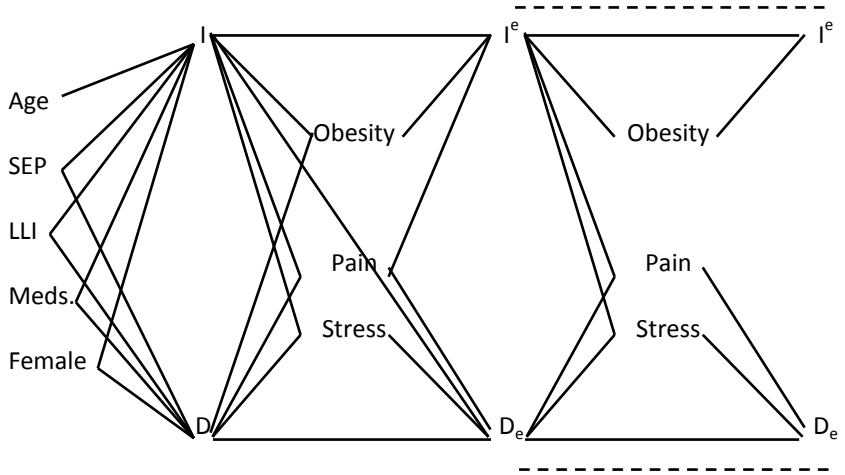


Stage 5: Stage 2 + three mediators



All mediators inter-correlated in wave 3

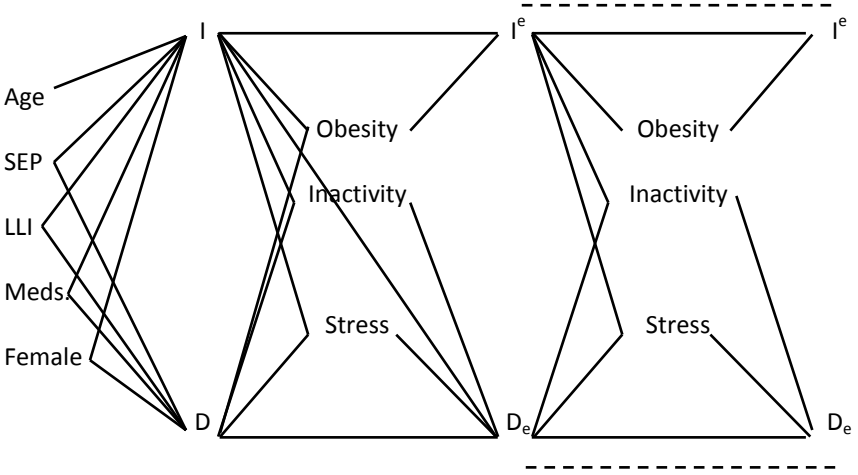
Stage 5: Stage 2 + three mediators



Pain correlated with (1) obesity (2) stress in wave 3

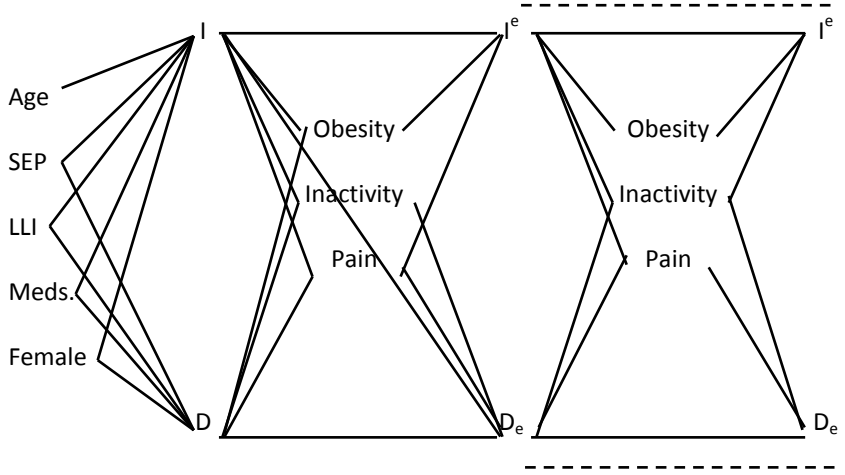
Mediators are auto-correlated over time in all models

Stage 5: Stage 2 + three mediators



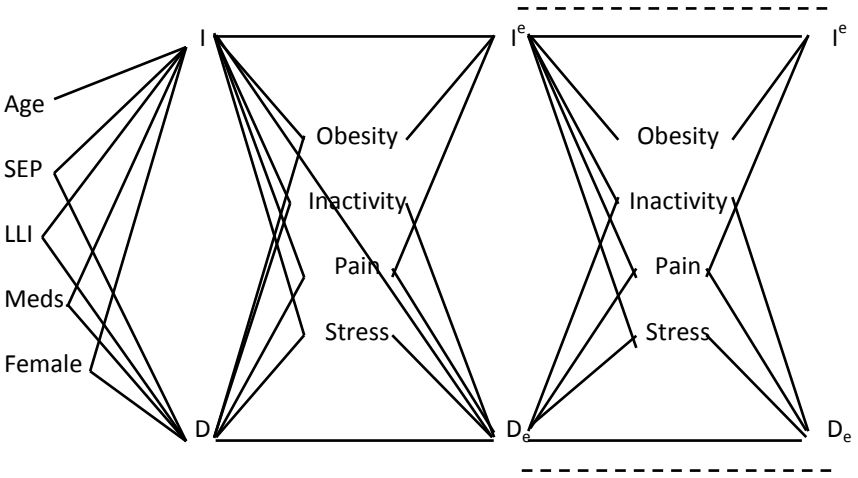
Inactivity correlated with (1) obesity (2) stress in wave 3

Stage 5: Stage 2 + three mediators



All mediators inter-correlated in wave 3

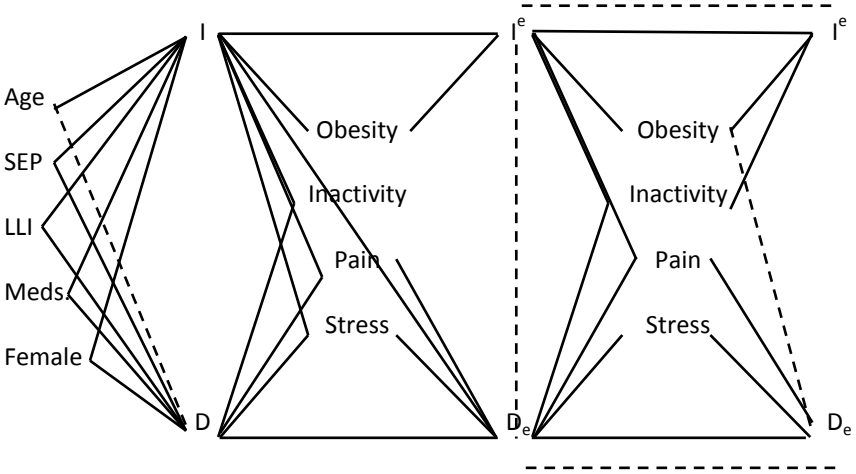
Final specification



Results of additional sensitivity analyses are presented in Figure A22.2, which contains eleven illustrations. The first illustration uses the ADF method of estimation, which uses less available data but makes no assumptions about the distributions of variables. Mediated associations reported in the main analyses are no longer statistically significant when using ADF, reflecting the lack of power; the MLMV estimation uses 11,986 observations whereas the ADF estimation uses 1,762. Smaller sample size may also result in fitting difficulties, as negative correlations are found between inflammation and depressive symptoms during wave 4, and between depressive symptoms and obesity.

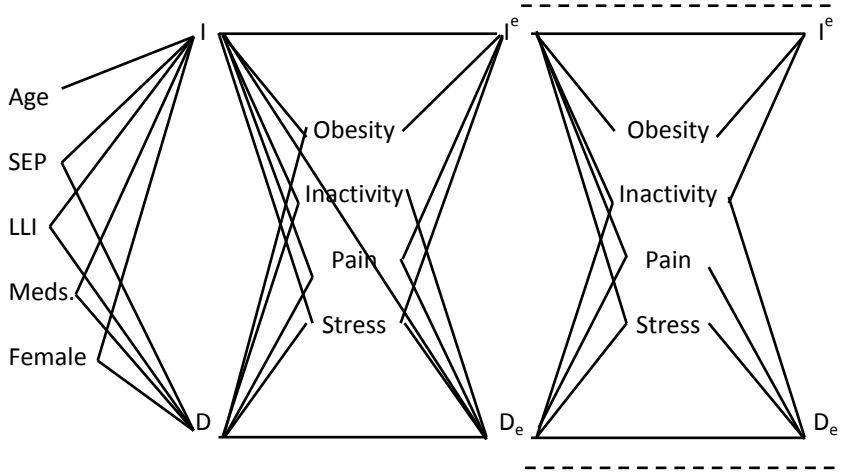
Figure A22.2: Additional robustness checks (n=11,986 except for ADF estimation)

1. ADF estimation (n=1,762)



Inactivity correlated with (1) obesity (2) stress in wave 3

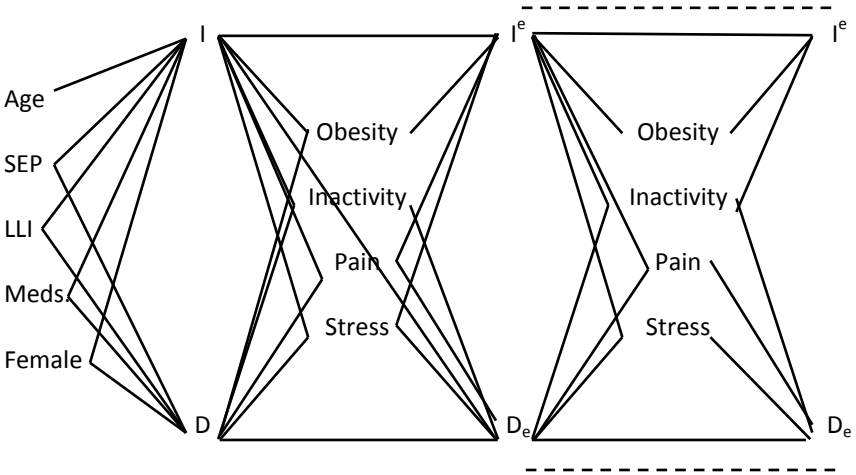
2. Stress/social withdrawal index excludes subjective social status



All wave 3 mediators inter-correlated except stress and obesity

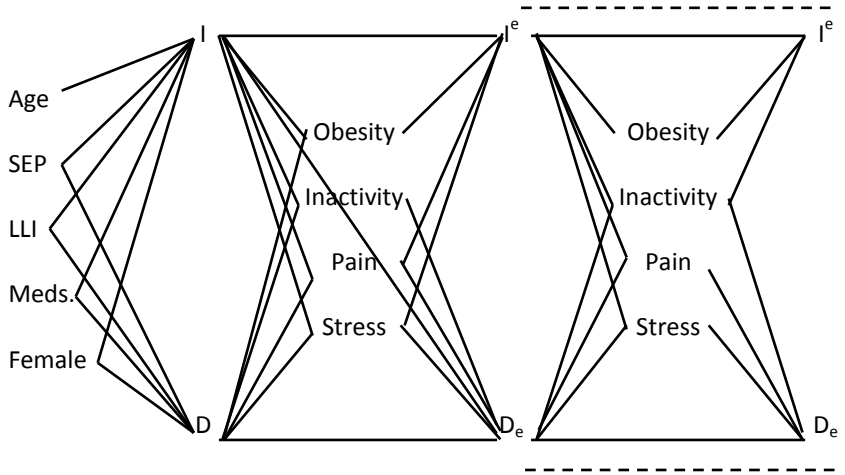
Mediators are auto-correlated over time in all models

3. Stress/social withdrawal index excludes financial strain



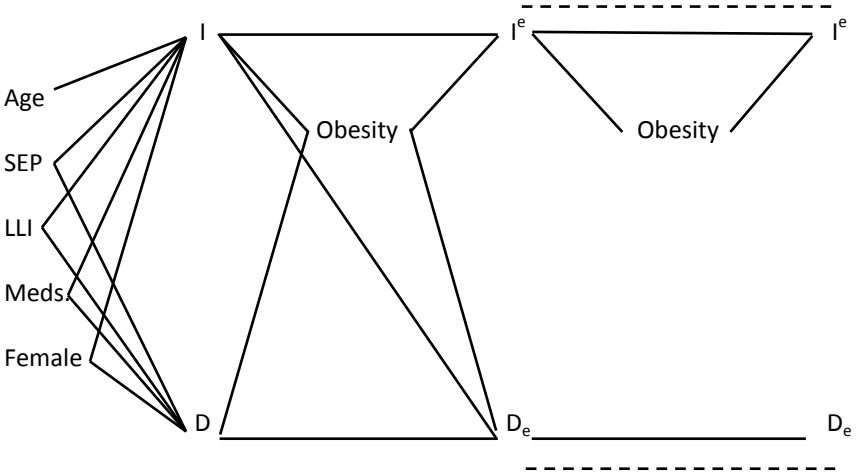
Inactivity correlated with (1) obesity (2) stress in wave 3

4. Stress index excludes social withdrawal



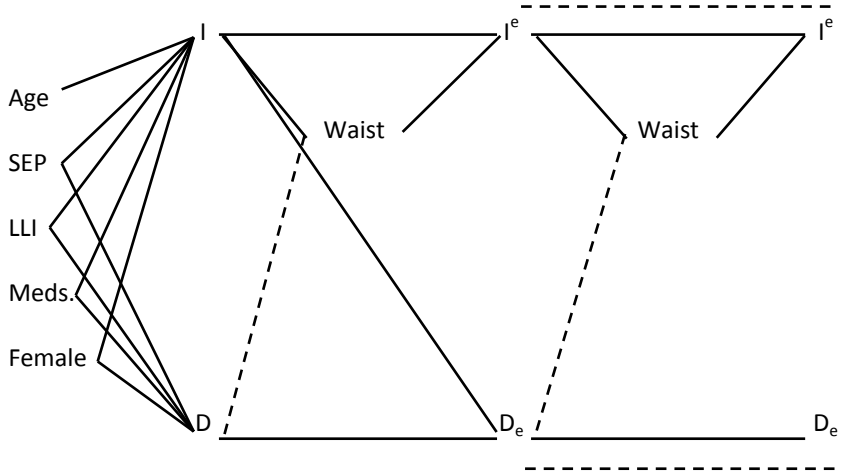
All mediators inter-correlated in wave 3

5. Obesity measured using BMI of 30+



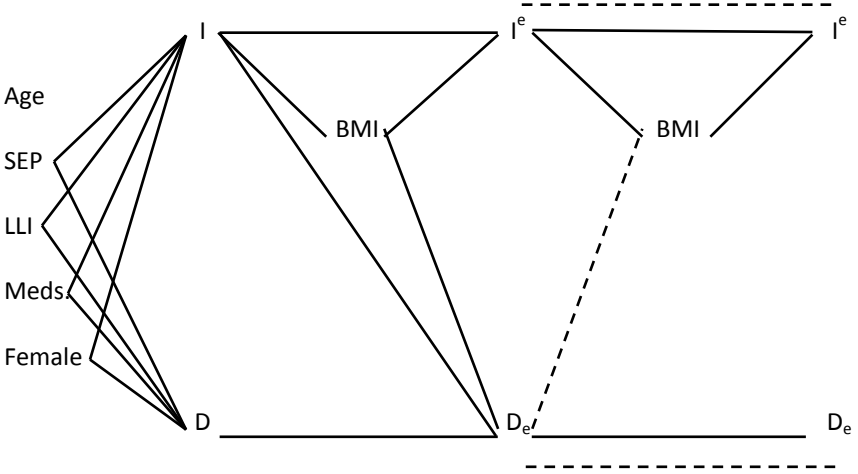
Obesity auto-correlated over time

6. Waist measurement instead of obesity



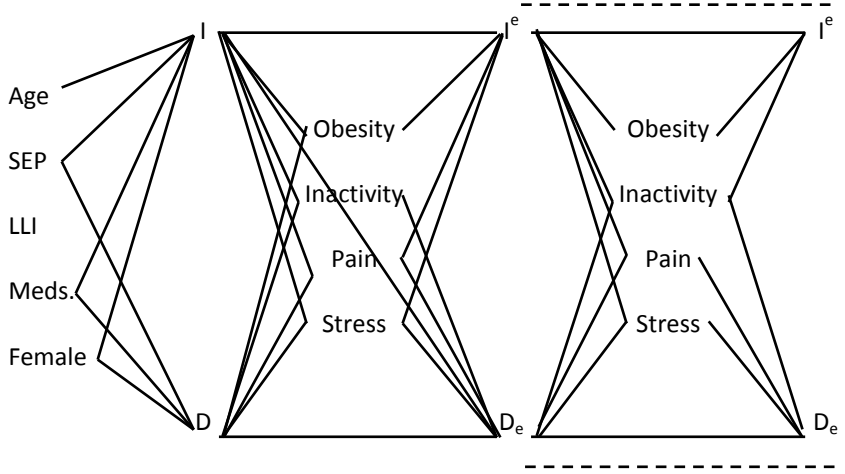
Waist auto-correlated over time

7. BMI values (Kg/m^2) instead of obesity



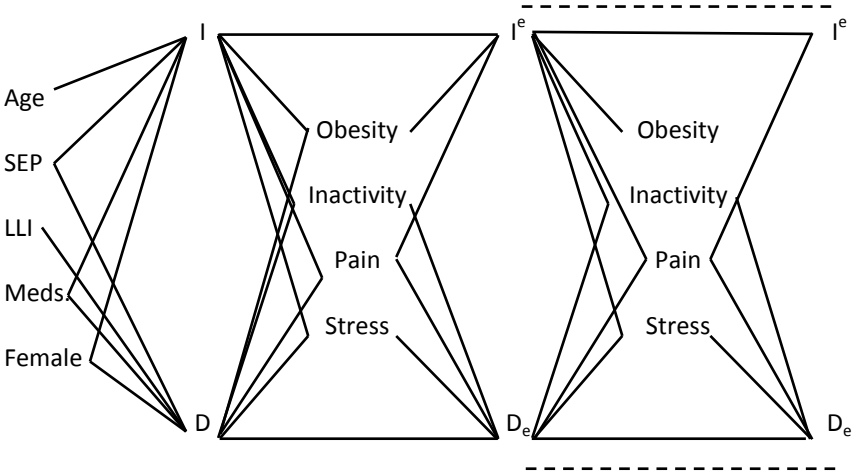
BMI is auto-correlated over time

8. Pain in hips, knees, feet or mouth (excludes back pain)



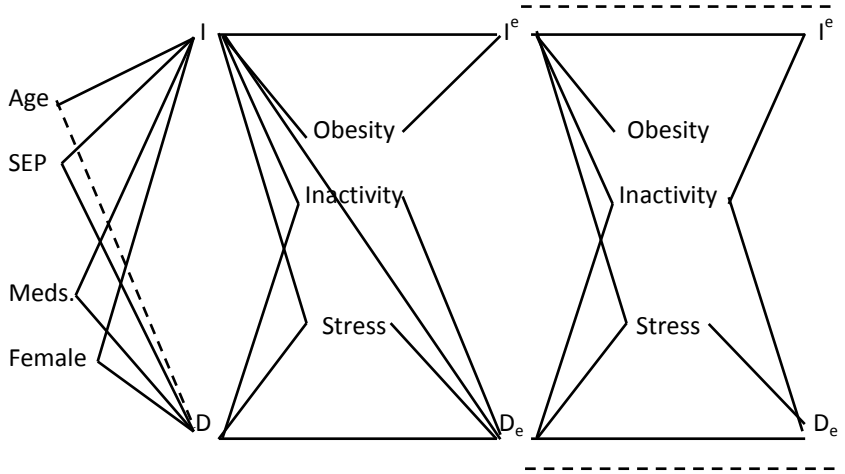
All mediators auto-correlated and inter-correlated in wave 3 except obesity and stress

9. Respondents with main and nurse interviews up to two months apart



N=2,638. Wave 3 mediators inter-correlated except obesity and stress

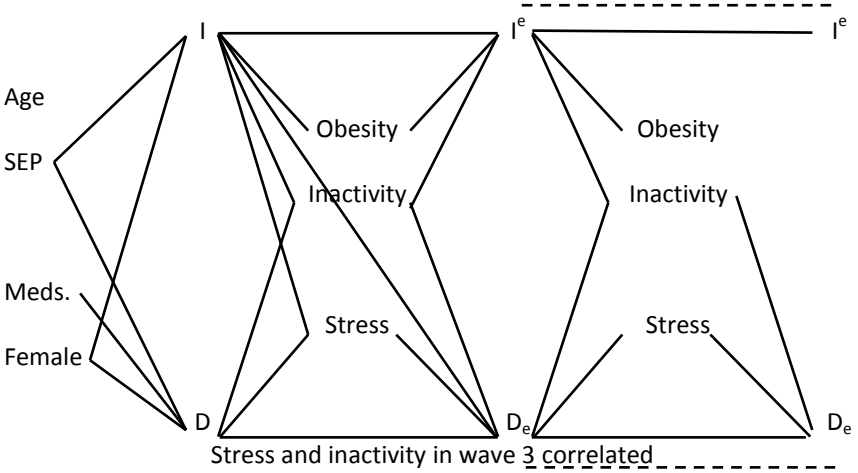
10. Respondents with history of asthma, excluding pain (n=2,935)



All mediators inter-correlated in wave 3 except obesity and stress

All mediators are auto-correlated over time

11. Respondents with current asthma, excluding pain (n=1,949)



Stress and inactivity in wave 3 correlated

Illustrations 2-8 include alternative measures of mediating factors. Summary statistics for these measures are presented in Table A22.4. Illustrations 2-4 and 8 indicate that using alternative measures of stress and pain (excluding back pain) does not change the results.

Table A22.4: Summary statistics for alternative and additional measures in the SEMs

	Wave 3					Wave 5				
Variable	Mean /%=y	SD/ N=y	Min	Max	N	Mean /%=y	SD/ N=y	Min	Max	N
Stress and social withdrawal index, excluding:										
Subj. social status	0.581	0.127	0.25	1.000	6915	0.563	0.128	0.25	1.000	7235
Financial strain	0.555	0.120	0.183	0.967	6892	0.539	0.121	0.183	0.956	7209
Social withdrawal	0.468	0.123	0.139	0.967	6897	0.461	0.125	0.139	0.967	7204
Alternative measures of obesity:										
BMI 30 plus	31.0	46.2	0	1	8507	31.5	46.5	0	1	7999
Waist in cms	96.7	13.3	58.2	171.6	8612	96.9	13.5	58.0	155.2	8097
BMI in Kg/m^2	28.3	5.07	14.9	59.9	8507	28.4	5.20	15.1	66.7	7999
Alternative measure of pain, excluding back pain										
Pain in limbs	24.0	42.7	0	1	7873	24.2	42.8	0	1	7791

Based on the sample used to estimate SEMs, includes respondents who provided complete information about gender, age, accumulated wealth in 2004, limiting longstanding illness by wave 2 and medication use.

Illustrations 5-7 show that relationships between obesity and both depressive symptoms and inflammation were the same, regardless of whether obesity was measured using a cutpoint of high waist circumference or high BMI (30+). However, depressive symptoms in wave 4 predicted lower continuous values of BMI and waist circumference in wave 5. Additional models estimated for men and women separately (not illustrated here) found a positive association between depressive symptoms in wave 4 and waist circumference in wave 5 among men and a negative one among women.

Illustration 9 shows that excluding respondents whose main and nurse interviews were more than two months apart does not affect the results.

Illustrations 10 and 11 present results of SEMs for respondents with asthma that exclude pain as a hypothesised mediator, since pain is not associated with asthma.

Detailed results of the SEM using the MLMV method for the whole sample are presented in Table A22.5.

Table A22.5: Results of SEM for whole sample with MLMV estimation method (n=11,986)

Model	Coefficient	95% confidence interval		p-value
Outcome is Ln(CRP) in wave 2				
Female	0.080	0.032	0.128	0.001
Age in 2004	0.009	0.006	0.012	0.000
Low wealth in 2004	0.249	0.219	0.280	0.000
Limiting longstanding illness by wave 2	0.161	0.131	0.190	0.000
Medication by use by wave 6	0.368	0.299	0.438	0.000
Outcome is depressive symptoms in wave 2				
Female	0.240	0.200	0.280	0.000
Age in 2004	-0.001	-0.003	0.001	0.313
Low wealth in 2004	0.234	0.209	0.259	0.000
Limiting longstanding illness by wave 2	0.295	0.270	0.319	0.000
Medication by use by wave 6	0.129	0.068	0.189	0.000
Outcome is psychological stress in wave 3				
Ln(CRP) in wave 2	0.024	0.021	0.027	0.000
Depressive symptoms in wave 2	0.039	0.037	0.042	0.000
Outcome is obesity in wave 3				
Ln(CRP) in wave 2	0.157	0.146	0.168	0.000
Depressive symptoms in wave 2	0.020	0.009	0.030	0.000
Outcome is physical inactivity in wave 3				
Ln(CRP) in wave 2	0.072	0.065	0.079	0.000
Depressive symptoms in wave 2	0.069	0.062	0.076	0.000
Outcome is pain in wave 3				
Ln(CRP) in wave 2	0.056	0.047	0.064	0.000
Depressive symptoms in wave 2	0.097	0.089	0.104	0.000
Outcome is Ln(CRP) in wave 4				
Ln(CRP) in wave 2	0.609	0.584	0.635	0.000
Depressive symptoms in wave 2	-0.006	-0.031	0.020	0.659
Psychological stress in wave 3	0.092	-0.123	0.307	0.402
Pain in wave 3	0.087	0.015	0.160	0.018
Obesity in wave 3	0.214	0.163	0.264	0.000
Physical inactivity in wave 3	0.016	-0.073	0.105	0.723
Outcome is depressive symptoms in wave 4				
Depressive symptoms in wave 2	0.413	0.392	0.434	0.000
Ln(CRP) in wave 2	0.041	0.008	0.075	0.016
Ln(CRP) in wave 4	-0.022	-0.057	0.012	0.204
Psychological stress in wave 3	0.937	0.758	1.117	0.000

Pain in wave 3	0.389	0.330	0.448	0.000
Obesity in wave 3	0.003	-0.041	0.047	0.878
Physical inactivity in wave 3	0.190	0.119	0.260	0.000
Outcome is psychological stress in wave 5				
Psychological stress in wave 3	0.690	0.672	0.708	0.000
Ln(CRP) in wave 4	0.004	0.002	0.006	0.001
Depressive symptoms in wave 4	0.015	0.012	0.017	0.000
Outcome is obesity in wave 5				
Obesity in wave 3	0.876	0.866	0.887	0.000
Ln(CRP) in wave 4	0.020	0.014	0.026	0.000
Depressive symptoms in wave 4	0.001	-0.005	0.006	0.802
Outcome is physical inactivity in wave 5				
Physical inactivity in wave 3	0.518	0.496	0.540	0.000
Ln(CRP) in wave 4	0.035	0.027	0.042	0.000
Depressive symptoms in wave 4	0.043	0.036	0.049	0.000
Outcome is pain in wave 5				
Pain in wave 3	0.451	0.429	0.473	0.000
Ln(CRP) in wave 4	0.034	0.026	0.042	0.000
Depressive symptoms in wave 4	0.052	0.044	0.059	0.000
Outcome is Ln(CRP) in wave 6				
Ln(CRP) in wave 4	0.864	0.817	0.910	0.000
Depressive symptoms in wave 4	0.006	-0.021	0.034	0.651
Psychological stress in wave 5	0.028	-0.192	0.247	0.804
Pain in wave 5	-0.022	-0.097	0.054	0.574
Obesity in wave 5	0.069	0.011	0.126	0.020
Physical inacitivity in wave 5	0.094	0.005	0.182	0.038
Outcome is depressive symptoms in wave 6				
Depressive symptoms in wave 4	0.755	0.705	0.805	0.000
Ln(CRP) in wave 4	-0.007	-0.044	0.030	0.703
Ln(CRP) in wave 6	0.013	-0.022	0.048	0.483
Psychological stress in wave 5	0.375	0.766	0.000	0.000
Pain in wave 5	0.106	0.230	0.000	0.000
Obesity in wave 5	-0.085	0.009	0.118	0.110
Physical inactivity in wave 5	0.143	0.286	0.000	0.000
Co-variances between error terms				
Psychological stress in wave 3 * pain in wave 3	0.006	0.005	0.006	0.000
Psychological stress in wave 3 * obesity in wave 3	0.001	0.000	0.002	0.134
Psychological stress in wave 3 * physical inactivity in wave 3	0.007	0.006	0.008	0.000
Pain in wave 3 * obesity in wave 3	0.010	0.006	0.013	0.000
Pain in wave 3 * physical inactivity in wave 3	0.017	0.015	0.019	0.000
Obesity in wave 3 * physical inactivity in wave 3	0.008	0.005	0.011	0.000
Ln(CRP) in wave 4 * Ln(CRP) in wave 6	-0.207	-0.243	-0.171	0.000
Depressive symptoms wave 4 * depressive symptoms wave 6	-0.289	-0.327	-0.251	0.000

11,986 observations. Depressive symptoms and Ln(CRP) are standardised, and measures in waves 3 and 5 are scaled to have values between zero and one.

Chapter 6: Appendix 23: Discussion of relationships between obesity, inflammation and depressive symptoms found using Structural Equation Models

Results of the Structural Equation Model presented in Figure 4.3 include evidence that obesity, measured by high waist circumference, predicted and was predicted by chronic inflammation. The magnitude of the latter association is non-trivial; a large waist is associated with 6.2% SDs of Ln(CRP) two years later, which is equivalent to just over 1mg/L of CRP. It is thought that obesity is linked to chronic low-grade inflammation through pathways involving white adipose tissue in the abdominal region and gut microbiota (Capuron et al. 2017, Castanon et al. 2014, Penninx et al. 2013, Kumari & Kozyrskyj 2017).

High waist circumference did not mediate the prospective association between CRP and depressive symptoms because it did not predict depressive symptoms. This finding contrasts with existing evidence that obesity predicts depressive symptoms (Daly 2013, Luppino et al. 2010) and attenuates the prospective association between inflammation and depression (Chocano-Bedoya et al. 2014). The different results probably reflect the inclusion in this study of different co-variates, such as physical inactivity and pain.

The main analyses using high waist circumference to indicate obesity and sensitivity analyses that used high BMI (30+) to indicate obesity each found that depressive symptoms in wave 2 predicted obesity two years later. This is consistent with results of a meta-analysis of 15 prospective studies, which reports associations between depression and onset of obesity (Luppino et al. 2010). However, the SEMs adjust for earlier measures of depressive symptoms and obesity, and after these adjustments, depressive symptoms (in wave 4) did not predict obesity (in wave 5).

Sensitivity analyses of SEM using raw values of waist circumference and BMI found that depressive symptoms predicted lower values two years later, even between waves 4 and 5. The finding resonates with recent findings that British adults who are unemployed are more likely than other working-age adults to be underweight (Hughes & Kumari 2017). It indicates the importance of examining relationships not only with obesity but also with being underweight.

Together with evidence reported above about relationships between depressive symptoms and obesity, this suggests that relationships between depressive symptoms and subsequent weight change vary depending upon the individual's initial weight. Consistent with this, Luppino's meta-analysis finds no evidence of a prospective association between depressive symptoms and overweight (BMI=25-29.99), but reports a positive association with obesity (BMI>=30, Luppino et al. 2010).

Relationships between overweight, obesity, inflammation, depressive symptoms and depression appear complex. Tully et al. (2015) report prospective associations between chronic low-grade inflammation and depressive symptoms among non-obese adults but not among adults who are obese. Thus, obesity may moderate rather than mediate the prospective relationship between chronic inflammation and depressive symptoms, although this possibility was not tested here.