Risk of depression and cardiovascular disease across the lifespan: the role of systemic inflammation

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Summary

Both depression and cardiovascular disease (CVD) affect millions of people worldwide and account for considerable mortality. In adults, comorbidity between these conditions is common, suggesting that shared pathophysiological mechanisms, such as systemic inflammation, may be involved. However, the direction of association between depression and CVD risk in young people remains unclear. Gaps also remain in our understanding of the role of different immune components in these relationships across the lifespan.

The purpose of this thesis was two-fold. First, to investigate the association between CVD risk (as defined by systolic blood pressure, total cholesterol, low-density lipoprotein, high-density lipoprotein, high body mass index, and smoking status) and depressive symptoms in young people. Second, to test the convergence of evidence for systemic inflammation as a shared mechanism for depression and CVD across the lifespan.

I conducted a systematic review and meta-analysis of longitudinal studies of CVD risk factors and subsequent depressive symptoms in young people. Then I used data from two contrasting observational studies: the Avon Longitudinal Study of Parents and Children (ALSPAC) and the United Kingdom (UK) Biobank to study associations between inflammation, depression, and CVD risk in different age groups. ALSPAC is a prospective birth cohort of 15,000 individuals born in and around Bristol in 1990/91. In contrast, UK Biobank is a long-term UK-based study of over 500,000 individuals aged 40 years old and over. I used several measures of systemic inflammation including interleukin-6 (IL-6), C-reactive protein (CRP), white blood cell count (WCC), and number of childhood infections.

Through the systematic review and meta-analysis, I highlighted that obesity and cigarette smoking are strongly associated with depressive symptoms in individuals up to age 24 years. Few longitudinal studies of young people have considered the effect of other CVD risk factors such as systolic blood pressure, total cholesterol, low-density lipoprotein, or high-density lipoprotein. I followed PRISMA guidelines when reporting these findings. Using

ALSPAC data, I revealed that CVD risk is associated with subsequent depressive symptoms but not the other way around. Obesity and cigarette smoking in particular appear to drive this association. These findings suggest that targeting smoking and obesity in young people may be important for the prevention of both depression and CVD in adults.

I also used ALSPAC to study the effects of inflammatory markers on health outcomes in young people. Specifically, I investigated the associations of childhood infections, IL-6, and CRP with depressive symptoms and psychotic experiences. I showed that a higher burden of common childhood infections is associated with depressive symptoms and psychotic experiences in early and mid-adolescence. In contrast, I discovered that childhood IL-6 and CRP were more strongly associated with subsequent CVD risk than depressive symptoms. CVD risk in adolescence appeared to mediate the relationship between childhood IL-6 or CRP and depressive symptoms in late-adolescence. These results suggest that markers of systemic inflammation in early life have differing associations with depression and CVD risk in young people.

I used the UK Biobank to investigate the potential effects of inflammatory markers on comorbid and monomorbid depression and CVD outcomes in middle-aged and older adults. I used both CRP concentration and WCC as exposures. I discovered that CRP and WCC are both associated with depression and ischaemic heart disease (IHD), as well as comorbid depression and IHD. I also showed evidence of specific association between WCC and IHD. These findings suggest that systemic inflammation is likely to be a shared mechanism for depression and IHD, but the risk of each outcome may be underpinned by distinct inflammatory pathways.

Taken together, these results indicate that the bidirectional association between CVD and depression is not present until adulthood. While the association between systemic inflammation and depression/CVD appears to be robust, pathophysiological mechanisms for depression and CVD may differ across the lifespan.

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Declaration

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the preface and specified in the text.

It is not substantially the same as any work that has already been submitted before for any degree or other qualification except as declared in the preface and specified in the text.

This dissertation contains 46,000 words excluding references, which does not exceed the prescribed word limit for the Clinical Medicine Degree Committee.

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Peer-Reviewed Publications Arising from the Work to Date

1. Chaplin AB, Jones PB, Khandaker GM. **Association between common early-childhood infection and subsequent depressive symptoms and psychotic experiences in adolescence: a population-based longitudinal birth cohort study.** Psychological Medicine. 2020 Nov; 1-11.
2. Chaplin AB, Jones PB, Khandaker GM. **Sexual and physical abuse and depressive symptoms in the UK Biobank.** BMC Psychiatry. 2021 May; 248.
3. Chaplin AB, Daniels NF, Ples D, Anderson RZ, Gregory-Jones A, Jones PB, Khandaker GM. **Longitudinal association between cardiovascular risk factors and depression in young people: a systematic review and meta-analysis of cohort studies.** Psychological Medicine. 2021 Jun; 1-11.
4. Chaplin AB, Smith N, Jones PB, Khandaker GM. **Direction of association between cardiovascular risk and depressive symptoms during the first 18 years of life: a prospective birth cohort study.** Journal of Affective Disorders. 2021 Sep; 508-516.

Abbreviations

AHA	American Heart Association
BMI	Body mass index
CRP	C-reactive protein
CI	Confidence interval
CVD	Cardiovascular disease
DAMPs	Damage-associated molecular patterns
DOHAD	Developmental origins of health and disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
HDL	High-density lipoprotein
HPA	Hypothalamic-pituitary-adrenal axis
i3C	International Childhood Cardiovascular Cohorts Consortium
ICD	International Classification of Diseases
IHD	Ischaemic heart disease
IL	Interleukin
IL-6R	Interleukin-6 receptor
IQR	Interquartile range
LDL	Low-density lipoprotein
LMICs	Low- and middle-income countries
LRT	Likelihood ratio test
MCMC	Markov Chain Monte Carlo
MDD	Major depressive disorder
NHS	National Health Service
NLR	Neutrophil to lymphocyte ratio

OR	Odds ratio
PLIKSi	Psychosis-Like Symptom Interview
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SEP	Socioeconomic position
SMD	Standardised mean difference
SMFQ	Short mood and feelings questionnaire
TNF	Tumour necrosis factor
UK	United Kingdom
WBC	White blood cell
WCC	White blood cell count
WHO	World Health Organization

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SECTION A: BACKGROUND

Chapter 1: Introduction

1.1 Rationale for Investigating Risk of Depression and Cardiovascular Disease (CVD)

Both depression and cardiovascular disease (CVD) affect millions of people worldwide (1). The risk factors for these conditions are complex, but often begin in early life and take time to develop (2,3). Once illness is established, depression and CVD can have long-term negative effects on quality of life. Despite the significant burden these conditions place on the health of individuals, they each receive less funding than neurological diseases, infection, or cancers (4). This is particularly problematic in the context of depression, given that depression remains poorly understood relative to CVD and other physical illnesses. Furthermore, these conditions appear to be related and may be risk factors for each other. Work is required to understand the relationship between depression and CVD across the lifespan and to establish shared mechanisms that may serve as robust targets for future therapeutic interventions.

This thesis is divided into seven chapters and six sections, including a section for references. Section A contains an introduction to the topic (Chapter 1, Page 18) and an overview of the analytic work presented in this thesis (Chapter 2, Page 60). In this first chapter, I present basic epidemiological information about depression and CVD. I then consider the links between depression and CVD across the lifespan, in childhood and adulthood. I approached the discussion of these possible relationships systematically, according to Paths A to F in Figure 1. I follow this with a summary of the evidence that lends support to systemic inflammation as a shared mechanism for depression and CVD before moving on to key social and demographic influences in these relationships. The breadth and depth of evidence regarding systemic inflammation, depression, and CVD is considerable. I then present the analytic work in Section B (Chapter 3, Page 74), Section C (Chapter 4, Page 110; Chapter 5, Page 144) and Section D (Chapter 6, Page 187). Section E (Chapter 7, Page 212) concludes this thesis by discussing the findings and suggesting future directions for research. Section F contains the reference list.

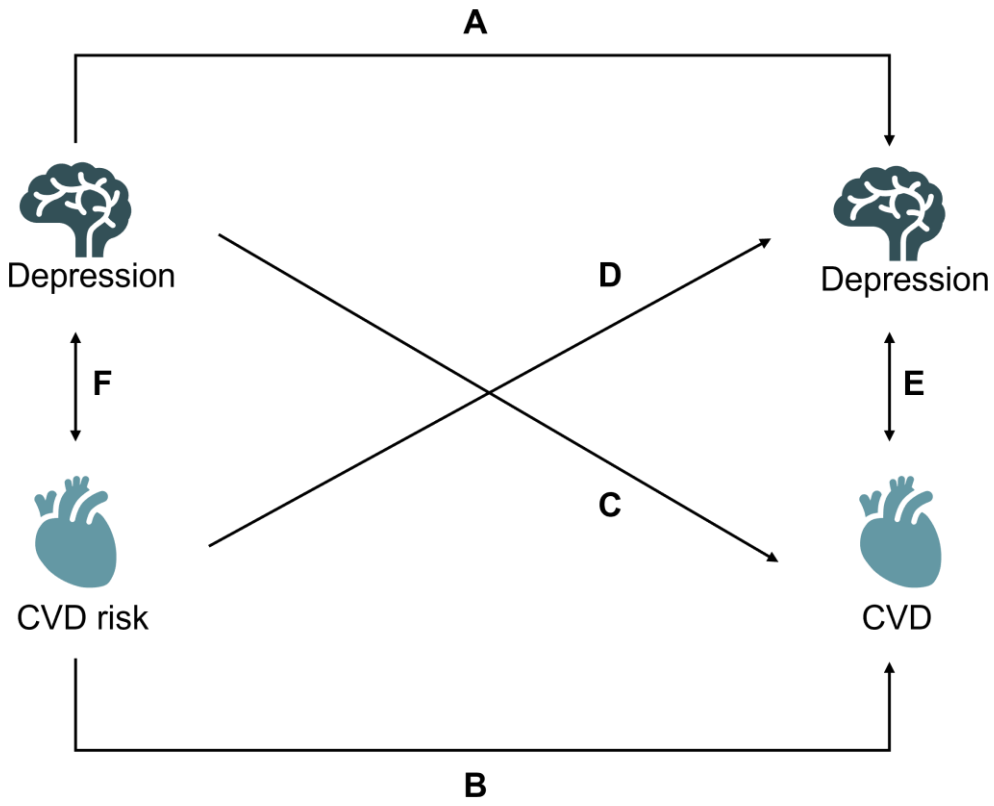


Figure 1. Temporal associations between depression and CVD risk (represented by Paths A to F) discussed in Chapter 1.

1.1.1 Characteristics and prevalence of depression

Major depressive disorder (MDD) is a common mental disorder affecting more than 163 million people globally (1). Episodes of MDD are characterised by a syndrome of emotional, behavioural, cognitive and somatic phenomena: persistent low mood, anhedonia, low self-esteem, sleep disturbance, appetite/weight changes, and concentration difficulties. According to the World Health Organisation (WHO), the lifetime prevalence of depression ranges from 20% to 25% in women and 7% to 12% in men (5). MDD is a leading cause of disability worldwide and can lead to suicide, the second leading cause of death in individuals age 15 to 29 years (1). From both the individual and societal perspective, depression is a problem of pressing importance.

MDD is particularly debilitating due to its recurrent nature, often beginning in adolescence (6). The majority of individuals who develop a lifetime episode of depression will go on to experience another (7). Each recurrence increases the risk of suicide as well as increasing the risk of another episode by approximately 16% (8). In contrast, longer duration of recovery is related to reduced risk of recurrence (7). Recurrence rates are similar among young people and adults (9). Earlier age of onset predicts longer depressive episodes and suicidal behaviour (10), while later age of onset is associated with shorter time to recurrence in adolescents (11). These findings are particularly concerning given that most depression cases are established in early life (12). Indeed, around 3% of children/adolescents in the US reported current depression in 2016 (13). The worldwide prevalence of depression in children/adolescents may be similar (14), however the global representativeness of prevalence data for depression in this age group is limited (15). Moreover, MDD has been validated in children as young as age 3 years, with anhedonia representing a particularly important clinical indicator (16). Therefore, MDD can be viewed as a long-term recurrent condition affecting individuals across the lifespan.

MDD is a highly heterogeneous condition. Depressive episodes can differ by severity, recurrence, degree of remission, and presence of psychotic features (17,18). The Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 includes a number of uncoded specifiers to categorise depressive episodes into more specific subtypes (Figure 2) (17). One such subtype is MDD with atypical features i.e. symptoms such as increased appetite/weight gain and hypersomnia (19). This atypical MDD subtype in particular may be associated with dysregulation of biological systems, such as increased inflammation and metabolic changes (20). Alteration to these biological processes may explain the comorbidity between depression and cardiometabolic conditions (20). Moreover, given the potential differences in underlying causes, distinct MDD subtypes may respond differently to antidepressants (20,21). As with most long-term physical and mental conditions, it is likely that MDD subtypes result from complex interaction of genetic and environmental factors.

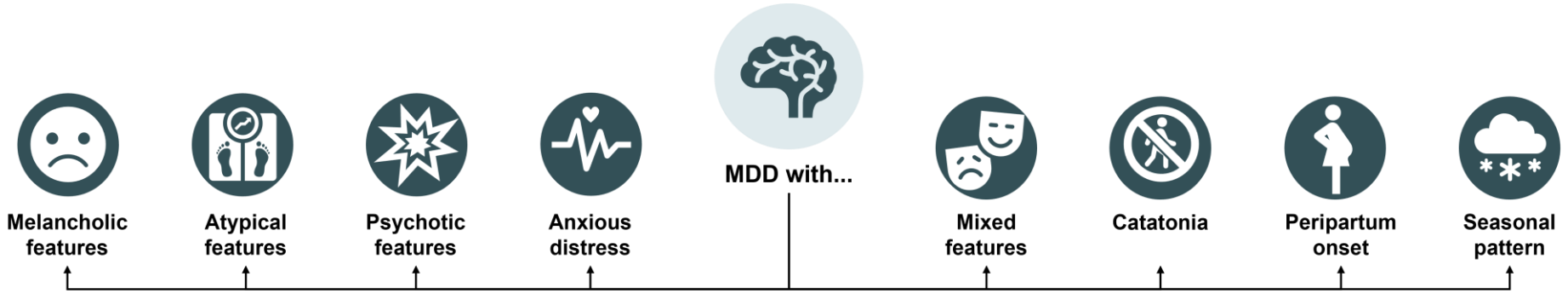


Figure 2. Subtypes of MDD, based on DSM-5 uncoded specifiers.

1.1.2 Characteristics and prevalence of CVD

CVD is the leading cause of death worldwide, causing around a third of all global deaths (1). CVD refers to a group of conditions affecting the heart and blood vessels, including ischaemic heart disease (IHD) (also called coronary artery disease or coronary heart disease), cerebrovascular disease, and peripheral vascular disease. CVD affects more than 485 million people worldwide (1). The lifetime risk of CVD is 31% in women and 46% in men after accounting for physical activity level (22). CVD mortality appears to be increasing in women age 35 to 54 years (23). IHD is responsible for around 26% of all global CVD cases, making it the most common form of CVD (1). Coordinated international effort is required to reduce the high universal prevalence of CVD.

Atherosclerosis often precedes CVD, although the clinical manifestations of distinct forms of CVD are different (24). Atherosclerosis is an inflammatory disease characterised by the build-up of fatty plaques in the blood vessels (24). Immune cells play a role in plaque formation and activation of inflammation can accelerate progression of the plaques (25). Over time, the plaque leads to narrowing and occlusion of the arteries, increasing the risk of myocardial infarction (MI) and stroke (24). Both plaque rupture and erosion can lead to cardiovascular death as material from inside the plaque becomes exposed to platelets and coagulation factors (26). This process of atherothrombosis appears to depend partly on sex. Plaque rupture is more frequent in men (27), whereas plaque erosion is more common in cases of sudden death in women (28).

Many risk factors for atherosclerosis and CVD are environmental factors that persist over an extended period of time. Smoking, high body mass index (BMI), physical inactivity, poor diet, high total cholesterol, high blood pressure, and high blood glucose are well-known risk factors for CVD (29). Adverse pregnancy outcomes such as gestational diabetes and pre-eclampsia are also associated with increased risk of subsequent CVD (23). CVD risk factors are highly prevalent in the general population. The estimated lifetime risk of developing

hypertension exceeds 90% in high-income countries (30). Over two billion people are overweight or obese worldwide (31), and almost 476 million have diabetes (1). In addition, 36% of men and 7% of women smoke cigarettes (32). Certain CVD risk factors may also cross-predict each other across the lifespan. For example, a recent meta-analysis of 21 longitudinal studies found that childhood obesity was positively associated with adult blood pressure and inversely associated with adult high-density lipoprotein (HDL) cholesterol (33). Many of the environmental factors that contribute to the pathogenesis of atherosclerosis and CVD are modifiable but may require intervention in early life.

1.1.3 Characteristics and prevalence of comorbid depression and CVD

Depression and CVD often occur together (34). Depression increases the risk of subsequent CVD outcomes and vice versa (34). Pre-existing depression in CVD patients is also related to premature cardiovascular mortality (34). The bidirectional association between the two conditions suggests shared risk factors and/or pathophysiological mechanisms. Indeed, there is an extensive body of literature exploring the epidemiology of comorbid depression and CVD, particularly in middle-aged and older adults; the key points are set out below.

The reported prevalence of comorbid depression and CVD differs between studies and contexts. A meta-analysis of 27 studies found that the prevalence of MDD among heart failure patients ranged from 9% to 60% (35). The pooled prevalence for MDD in heart failure patients was 22% (35), similar to the prevalence of 15% to 27% in IHD patients (36,37). An additional 31% to 45% of patients with IHD are estimated to have clinically significant depressive symptoms without meeting diagnostic criteria for MDD (37). Subthreshold depressive symptoms may explain why other studies have reported considerably higher prevalence. In a population-representative sample of over four million US adults with MDD, 58% of individuals had comorbid CVD (38). Another US-based study found similar results; 61% of 16,423 older adults in the community met criteria for comorbid MDD and CVD (39). Data also indicates that the prevalence of MDD in CVD patients is two to three times higher

than in the general population (40). A meta-analysis of epidemiological studies from China reported that 51% of hospitalised CVD patients have depression compared with 35% to 46% of CVD patients in the community (41). The different prevalence of comorbidity in hospital and community samples may reflect demographic differences and distinct study methodologies.

Depression appears to play a role in the onset of CVD (34). The presence of depression has been reported to almost double the risk of developing new CVD (42,43). Indeed, MDD has been described as the second greatest risk factor for CVD following older age, and as a stronger risk factor for CVD than diabetes (43). Depression has also been identified as an independent risk factor for various forms of CVD including IHD, angina, heart failure, and MI (35,42,44). However, one population representative study found that depression in young Swedish men was not associated with IHD or MI during 37 years of follow-up (45). Depression may instead contribute indirectly to CVD onset through its association with CVD risk factors, such as type II diabetes, hypertension, obesity, low levels of physical activity, and smoking (46,47). For example, a cross-sectional study of 20,093 adults age ≥45 years reported that individuals with depressive symptoms were 41% more likely to be active smokers and 38% more likely to forgo regular intense physical activity (47). In this study, depressive symptoms were also associated with worse cardiovascular health even after controlling for antidepressant medication use (47). Polygenic sharing between MDD and cardiometabolic traits may partly explain the apparent link between depression and CVD onset (48). Overall, the evidence indicates that depressive symptoms precede (and may contribute to) the development of CVD.

In addition to CVD onset, adult depression appears to predict morbidity and mortality in CVD patients (34). In hospital samples, depression is associated with worse cardiovascular outcomes. For example, IHD patients with depression have a two-fold increased risk of mortality in the two years following initial assessment, compared to those without depression (49). Depression is also associated with more than a two-fold increased risk of cardiac and

all-cause mortality among hospitalised MI patients (50,51). Increased cardiovascular mortality linked with depression exists for patients with heart failure and unstable angina as well as patients with comorbid heart failure and atrial fibrillation (52–54). There is also evidence of a dose-response relationship between depression severity and cardiovascular outcomes, such that more severe depression in CVD patients is associated with greater risk of subsequent morbidity and mortality (34). The link between depression and reduced adherence to medical and lifestyle interventions may play a role in the association between depression and adverse outcomes in CVD patients (34,55).

Adult depression also contributes to a reduced quality of life following CVD recovery. Depression in patients with MI has been linked with poorer quality of life in both the short and long term (56). Depression in patients with heart failure appears to be more strongly related to quality of life than social and demographic factors, severity of heart failure, or other comorbidities (57). In addition, more severe depressive symptoms in patients with IHD predict poorer lifestyle behaviours five years later, including less physical activity, lower medication adherence, higher BMI, worse sleep quality, and smoking (58). These lifestyle behaviours in turn may increase risk of adverse cardiovascular outcomes. Thus, depression may have a negative impact on multiple aspects of the course of cardiovascular illness including quality of life and morbidity.

CVD risk factors are associated with later depression in adulthood. A meta-analysis of 26 longitudinal studies in adults age ≥50 years reported that CVD and CVD risk factor composite score are both independently associated with subsequent depression (59). There was also a weak association between smoking and depression, but no evidence of associations between Framingham Score Risk Score, hypertension or dyslipidaemia with subsequent depression in adulthood (59). Conversely, good cardiovascular health is protective against depression in adulthood. The American Heart Association (AHA) has previously defined ideal cardiovascular health in adults according to smoking status, diet, physical activity, BMI, blood pressure, blood glucose, and total cholesterol (Figure 3) (29).

Having a higher number of AHA ideal cardiovascular health metrics is associated with a reduction in the odds of depressive symptoms (60). Participants meeting five to seven of the ideal cardiovascular health metrics have 36% decreased odds of depressive symptoms compared with those meeting zero to two ideal components (60). Smoking, high BMI, low physical activity, and poor diet were all inversely associated with the odds of depressive symptoms (60). Other studies have also reported that smokers have substantially higher lifetime prevalence of MDD than non-smokers (61,62). The evidence therefore suggests that the association between CVD and depression arises considerably earlier than CVD is detected.

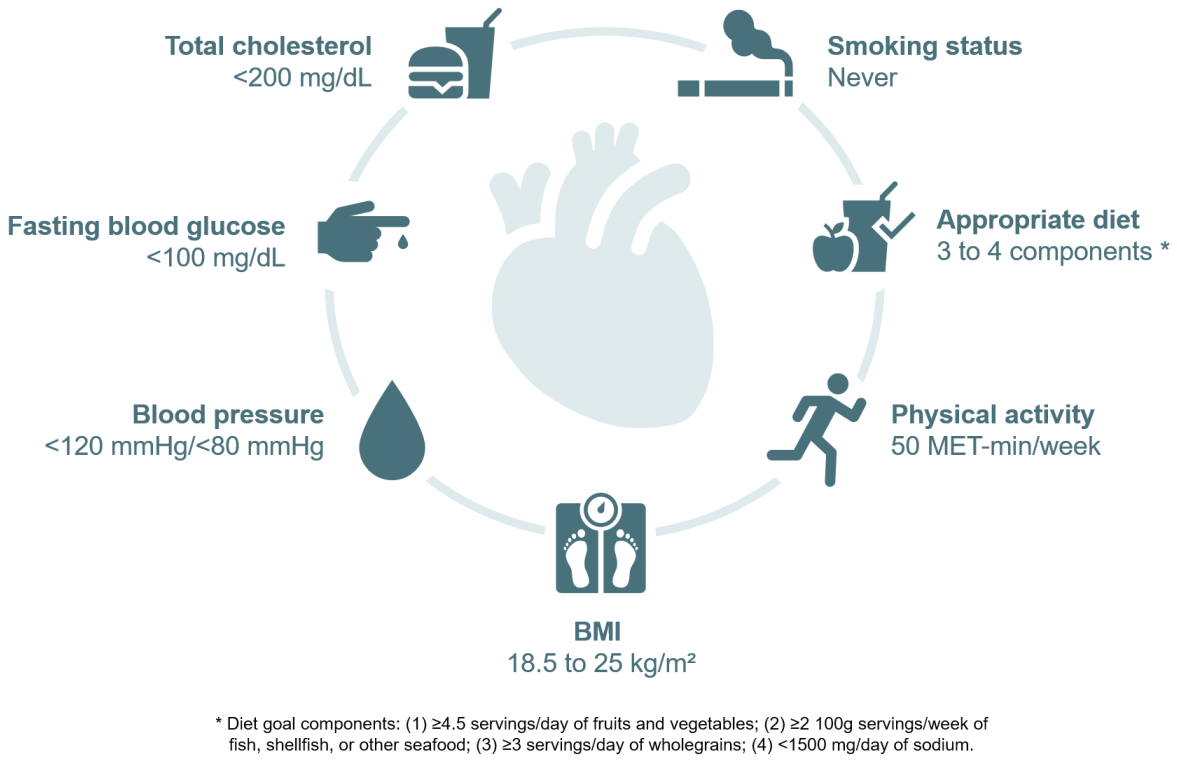


Figure 3. Ideal cardiovascular health metrics, according to the AHA.

The link between CVD and depression during adulthood may be due to shared risk factors such as systemic inflammation, which I discuss in detail in Section 1.3 (Page 37).

Alternatively, atherosclerosis may mediate the relationship between inflammation and depression. This alternative hypothesis is plausible since atherosclerosis is strongly correlated with inflammation (24,25,63). Similarly, there is a growing body of evidence linking inflammation and subsequent increased risk for depression (Section 1.3.4, Page 43).

1.2 Relationship between Depression and CVD across the Lifespan

David Barker's developmental origins of health and disease (DOHAD) hypothesis links the environmental conditions of early life with the risk of disease later in childhood and adulthood (2). The hypothesis proposes that fetal adaptations to intrauterine and maternal conditions during development shape the structure and function of organs in the body. Epigenetic processes are involved in the differentiation of cells during the early stages of development. Certain types of adverse exposures may alter long-term outcomes via these epigenetic mechanisms (64). For example, fetal exposure to tobacco smoke, antidepressant medication, and folic acid deficits have been independently associated with fetal maladaptation (64). The point in development at which exposure occurs will ultimately determine the prevalence of maladaptive alterations in the cells and tissues of the body.

Consistent with the DOHAD hypothesis is the fact that measures of depression and CVD are generally stable across the lifespan. For example, depression in childhood is strongly correlated with depression in adulthood (6). As previously mentioned in Section 1.1.3 (Page 24), depression and CVD may also cross-predict each other in a bidirectional fashion, indicating potential shared mechanisms. Understanding these conditions from the lifespan perspective may support the development of early interventions and preventative measures. Figure 1 summarises the temporal associations between depression and CVD across the lifespan. Paths A to F (Figure 1) represent these associations and are discussed in consecutive order in the subsections below.

1.2.1 Links between depression in childhood/adolescence and depression in adulthood

Path A in Figure 1 represents the association between depression in childhood/adolescence and subsequent depression in adulthood. Depression occurring in childhood/adolescence can follow homotypic continuity (i.e. similar symptoms over time) or heterotypic continuity

(i.e. change in symptoms over time) into adult life. Here, I discuss depression continuity as well as key differences in depression among different age groups.

Homotypic continuity of depressive symptoms is relatively common; an estimated 70% of children/adolescents with depression will experience recurrence of depressive symptoms within five years of a depressive episode (9,65). Evidence from clinical samples indicates that girls are more likely to have earlier recurrence of depression while boys are more likely to have persistent severe depression (66). MDD in childhood/adolescence increases the risk of MDD recurrence in adulthood as well as poor psychosocial functioning (66–68). Brain changes, particularly in the amygdala and hippocampus, may predispose to and perpetuate recurrent depression across the lifespan (69). Data from a UK-based community sample of adolescents reported that 35% experienced recurrent depressive episodes and a further 22% experienced persistent depression into adulthood (66). However, clinical samples of children/adolescents have reported higher levels of MDD recurrence in adulthood ranging from 49% to 69% (67,70,71). Given that depression begins early in life and can recur/persist, prevention and effective treatment of depression in young people remains imperative.

There is also evidence to suggest heterotypic continuity of depression across the lifespan. Psychiatric disorders in early life may influence the subsequent onset or recurrence of depressive symptoms. For example, anxiety in childhood has been shown to predict depression in adolescence (72). In addition, a US-based longitudinal study of 1,420 participants found that the relationship between depression in adolescence and young adults was entirely explained by comorbid adolescent oppositional defiant disorder, anxiety, and substance use disorders (73). These findings suggest that the relationship between child and adult depression is complex. Despite the importance of depressive episodes in early life, children and adolescents remain relatively understudied in the context of depression compared with adults.

There are a number of important differences between child/adolescent depression and adult depression. For example, biological and psychosocial risk factors may vary depending on

age of onset (74). Early childhood risk factors (e.g. neurodevelopmental problems and early life adversity) distinguish child/adolescent-onset from adult-onset depression, such that adult-onset depression is associated with low levels of childhood risk factors (74). In addition, children/adolescents and adults may present differently with depression. Children/adolescents with depression do not present with the high levels of circulating cortisol that are common in adults with depression, possibly due to the positive association between age and cortisol secretion (75). Children with depression also rarely present with sleep disturbances that are common in adolescents and adults with depression (75). Moreover, the nature of dysregulation of the serotonergic system and immune system in depression appears to vary across the lifespan (75). These distinctions may mean that depression in childhood/adolescence often goes unrecognised (and untreated) due to symptom variation from adult criteria (76).

Finally, there are differences in the efficacy of antidepressant treatments across the lifespan. For example, young people with depression do not respond to tricyclic antidepressants; this medication works in adults (75), though tricyclic drugs have largely been superseded by selective serotonin reuptake inhibitor drugs. Fluoxetine (alone or in combination with cognitive behavioural therapy) currently appears to be the best option for the treatment of MDD in children/adolescents (77). However, response to fluoxetine among adolescents with depression is heterogeneous and dependent on clinical profile (78), suggesting the need for additional effective treatment options for depression in young people. This is particularly pertinent given that young people are at increased risk of suicidal behaviours and mania following antidepressant treatment compared with adults (65,79). Thus, continued focus on the differences between child/adolescent depression and adult depression is required.

1.2.2 Links between CVD risk factors in childhood/adolescence and CVD in adulthood

Path B in Figure 1 represents the association between CVD risk factors in childhood/adolescence and subsequent CVD in adulthood. CVD outcomes (excluding congenital heart diseases) tend to develop gradually across the lifespan, first appearing in later adulthood. The presence of CVD risk factors in early life is pertinent to current cardiovascular health and future CVD in adulthood. I have given a general description of key CVD risk factors in Section 1.1.2 (Page 23).

CVD risk factors often appear in childhood/adolescence and continue into adulthood. Overweight/obesity, a key risk factor for CVD, is increasingly common in children and adolescents (80). Obesity tracks from childhood to adulthood (81). Childhood overweight/obesity is associated with higher subsequent CVD risk in adolescence (82). Parental history of CVD may influence the development of adverse CVD risk profiles in young people (82). For example, offspring of parents with early-onset IHD exhibited childhood overweight/obesity and developed higher CVD risk at a faster rate than their peers (83). Smoking is another highly prevalent CVD risk factor that begins early in life. In a study of 25,093 US participants, individuals who began smoking regularly before age 18 years were significantly less likely to intend or attempt to quit than those who began smoking at an older age (84). This has important implications for CVD risk in adulthood given that 50% of smokers in the US start before age 18 years (84). In addition, childhood blood pressure predicts adult levels, particularly for systolic blood pressure (SBP) (85). This finding suggests that hypertension is established early in life. Therefore, early identification and management of CVD risk factors may reduce CVD outcomes later in adulthood.

1.2.3 Links between depression in childhood/adolescence and CVD in adulthood

Path C in Figure 1 represents the association between depression in childhood/adolescence and CVD outcomes in adulthood. Depression in early life may predict both CVD risk factors and CVD outcomes in later life. The effect of child/adolescent depression on adult CVD

outcomes is relatively understudied compared with the effect of adult depression. I discuss the latter association in Section 1.1.3 (Page 24). In contrast, a number of studies have demonstrated links between child/adolescent depression and adult CVD risk factors, particularly obesity and smoking.

Depression in childhood and adolescence has been linked with CVD risk factors in adults. For example, depression in early life is implicated in adult obesity. A meta-analysis of six studies found that depression in adolescents was associated with a 70% increased risk of obesity in adult life (86). Both depressive symptoms and MDD diagnosis during childhood are associated with obesity in adulthood (86). The overall duration of depressive symptoms from childhood to adulthood may be particularly relevant to the strength of the relationship between depression and subsequent BMI (87). Furthermore, depression in early life is related to subsequent smoking behaviour. In a longitudinal study of 2,393 US students, depression in adolescence contributes to smoking uptake in early-adulthood and smoking modulates depressive symptoms (88). This reciprocal relationship may reinforce smoking behaviour during adulthood (88), possibly as a form of self-medication for depressive symptoms. Early adolescence appears to be the most important period in establishing the reciprocal association between depression and smoking, although associations are maintained into adulthood (89). Observational studies of MDD in early life and subsequent CVD in adulthood are relatively rare. However, large genetic studies have reported links between MDD polygenic risk score and IHD in adults (90). Depression in early life can have a range of long-term consequences on physical health in adulthood.

1.2.4 Links between CVD risk in childhood/adolescence and depression in adulthood

Path D in Figure 1 represents the association between CVD risk in childhood/adolescence and depression in adulthood. Depression in early life may predict both CVD risk factors and CVD outcomes in later life. The effect of child/adolescent depression on adult CVD

outcomes is relatively understudied compared with the effect of adult depression. I discuss the latter association in Section 1.1.3 (Page 24). In the context of adult depression, obesity is a particularly well-studied early life CVD risk factors. As such, I focus on the effect of childhood obesity on subsequent adult depression below.

Early life obesity is the most studied CVD risk factor with respect to lifetime risk of depression. A meta-analysis of six studies found that obesity in adolescents is associated with a 40% increased risk of depression in adult life (86). Another study has also reported links between overweight/obesity in childhood and increased odds of lifetime MDD (91). However, this study found no clear relationship between child/adolescent weight status and depressive symptoms in late adulthood (91), possibly due to small sample size. Similarly, a study using ALSPAC data showed that high BMI during childhood was not associated with depressive symptoms in late adolescence (92). It is possible that obesity is only relevant to risk of MDD in women. Compared to women of healthy weight, those who were overweight in adolescence are significantly more likely to experience depressive symptoms in late adulthood (93). The link between early life weight status and adult depressive symptoms is most pronounced for women who grew up in households of low socioeconomic position (SEP) (93). In contrast, no relationship was found between weight status and later depressive symptoms in men (93). The evidence suggests that the effect of child/adolescent obesity on adult depression is dependent on social and demographic factors.

The effect of other CVD risk factors in early life on depression in adulthood are less well-studied. Regarding cigarette smoking, there is some evidence that smoking in adolescence reduces depressive symptoms in early-adulthood, supporting the self-medication hypothesis (88). In contrast, a recent study using ALSPAC data revealed that there was no association between measures of insulin resistance during childhood and depressive symptoms in late adolescence (92). Studies of child/adolescent SBP or total cholesterol and subsequent risk of later depression are scarce but may offer insights into the links between depression and CVD risk across the lifespan.

1.2.5 Links between depression and CVD in adulthood

Path E in Figure 1 represents the association between depression and CVD in adulthood. I have provided an in-depth discussion of this relationship in Section 1.1.3 (Page 24). To summarise, pre-existing depression is related to CVD onset and cardiovascular mortality as well as reduced quality of life following recovery from CVD. Pre-existing CVD risk factors are also associated with depression onset. Finally, comorbid depression and CVD is relatively common, although the prevalence varies depending on the characteristics of the sample.

1.2.6 Links between depression and CVD risk in childhood/adolescence

Path F in Figure 1 represents the association between depression and CVD risk in childhood/adolescence. Depression and CVD risk factors in early life may cross-predict each other and contribute to future adverse health outcomes. Studies of CVD risk and depression in early life have generally focused on individual risk factors; the independent effects of obesity and smoking on depression (Chapter 3, Page 74) and *vice versa* are particularly well-studied. As such, I focus on the evidence for reciprocal links between depression and obesity/smoking below.

Bidirectional relationships may exist between depression and obesity/smoking in early life. Evidence is somewhat mixed for reciprocal links between obesity and depression. A meta-analysis of 22 studies representing 143,603 children reported that depression is present in 10% of children with obesity (94). In this study, obesity was associated with higher risk of depression during childhood in females, but not in males (94). Adolescent-onset MDD has also been shown to predict obesity later in adolescence (95,96). However, other epidemiological studies in adolescents have observed no associations between obesity and subsequent depression (95,97,98) or between depression and later obesity (99–101). The relationship between smoking and depression in early life appears to be clearer. In a meta-

analysis of 15 longitudinal studies of adolescents, there was evidence that depression predicts smoking, and that smoking predicts depression (102). In this meta-analysis, the studies that tested competing models directly showed that depression predicting smoking was the stronger effect (102). Exposure to second-hand smoking also appears to increase the risk of depression during adolescence (103). To confirm the potential links between depression and obesity/smoking in early life, further testing is required.

1.3 Systemic Inflammation as a Shared Mechanism for Depression and CVD

Inflammatory processes and their causes are diverse and complex (104). The physiological role of inflammation is to maintain homeostasis and promote tissue repair and recovery. Inflammation is first initiated on a cellular level and can expand to involve different inflammatory pathways and organs, resulting in systemic acute inflammation (105). Certain stimuli and unresolved inflammatory responses can promote a state of low-grade, sterile, systemic chronic inflammation, which is associated with a number of adverse health outcomes (106). From this point onwards, I will use the term systemic inflammation to refer to low-grade, sterile systemic chronic inflammation only.

1.3.1 Acute inflammatory processes usually lead to resolution of inflammation

Acute inflammation is an adaptive local response to noxious stimuli, including infection or tissue injury (107). Acute inflammation is characterised by the cardinal signs of inflammation i.e. redness, swelling, heat, and pain (104). A typical innate immune response consists of four components: inducers, sensors, mediators, and target tissues. Inflammatory inducers are classified as exogenous inducers (pathogen-associated molecular patterns, virulence factors, non-microbial inducers) and endogenous inducers (danger-associated molecular patterns (DAMPs)) (104). Inflammatory sensors, such as different pattern recognition receptors on macrophages and dendritic cells, recognise the inflammatory inducers (104,108). The sensors stimulate inflammatory mediators including vasoactive amines and peptides, fragments of complement components, lipid mediators, proteolytic enzymes, chemokines, and cytokines (e.g. interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-alpha) (104). Inflammatory mediators then act on target tissues, including local blood vessels, to induce vasodilation, extravasation of immune cells, and leakage of plasma into the infected tissue (104). IL-1, IL-6, and TNF-alpha can also have systemic effects when secreted in sufficient amounts. They induce hepatocytes to produce acute phase proteins, including C-

reactive protein (CRP), and coagulation factors (109). The immune cells that are initially recruited to the tissue, such as neutrophils, release enzymes that fight off infectious organisms and clear dead cells. This process is aided by plasma components such as antibodies and complement (104). Acute inflammatory events can also result in local transient damage such as tissue oedema, accumulation of reactive oxygen species, and intravascular thrombosis (107,108). The acute inflammatory response is usually terminated once the triggering insult is eliminated, the infection is cleared, and the damaged tissue is repaired (104). Termination of the inflammatory response and transition to the homeostatic state is an active and highly regulated process known as the resolution of inflammation (104). Resolution appears to act as a bridge between innate and adaptive immunity pathways (110).

1.3.2 Systemic inflammation can lead to damage and negative health consequences

Although acute inflammation is critical to survival following injury or infection, systemic inflammation can cause damage. A range of factors can promote systemic inflammation including chronic infections, physical inactivity, obesity, intestinal dysbiosis, diet, social isolation, psychological stress, disturbed sleep and disrupted circadian rhythm, and exposure to xenobiotics (106). Systemic inflammation is characterised by low-grade chronic inflammation occurring throughout the body (104), reflected by increased concentrations of circulating inflammatory markers in the peripheral blood such as cytokines and acute phase proteins (111). The chronic inflammatory processes underlying systemic inflammation generally develop when resolution of inflammation cannot be achieved (107,108). Resolution of inflammation can be impeded if an initial acute inflammatory response is not sufficient to eliminate noxious stimuli and/or if noxious stimuli are present for a sustained period of time; the result is persistent low levels of cell stress or dysfunction and subsequent low-grade chronic inflammatory responses (104,107,108). It is possible that systemic inflammation

reflects incomplete resolution of the initial acute response that does not fully engage an appropriate adaptive immune response that would otherwise lead to full resolution (110). The low-grade and chronic nature of systemic inflammation ultimately leads to collateral damage to tissues and organs over time (112,113).

Systemic inflammation often increases with age (114). Inflammageing, the term used to describe this age-related inflammatory state, may be partly due to cellular senescence (115). Cellular senescence is characterised by an arrest of cell proliferation and the development of a senescence-associated secretory phenotype (115). This phenotype involves increased secretion of pro-inflammatory cytokines, chemokines, and other pro-inflammatory molecules from cells (115). Senescent cells expressing this phenotype can promote various chronic health conditions and diseases (106). Inflammageing can lead to chronic low-grade activation of various immune signalling pathways, resulting in a weakened acute inflammatory response to various noxious stimuli in older adults (106); this explains why older adults with systemic inflammation are also more susceptible to viral infections and less responsive to vaccines (106). The link between age and systemic inflammation may partly explain why many non-communicable diseases are age-related.

Other than ageing, stress appears to be important in the development of systemic inflammation (106). Exposure to psychological stress early in life can result in heightened neural responses to perceived threat, which can increase inflammatory activity (116), and lead to systemic inflammation throughout the lifespan (117,118). Noradrenaline and other catecholamines are released in response to stress by the activated sympathetic nervous system and stimulate the release of myeloid cells that activate inflammatory signalling pathways following an encounter with stress-induced DAMPs (119). Evidence demonstrates that psychological stress can lead to an increase in the circulating concentrations of IL-6 and other cytokines (120). In addition, epigenetic modifications induced by parental factors during conception and maternal exposures during pregnancy (e.g. infection, diet, psychological stress, xenobiotics) may result in elevated risk of systemic inflammation during

childhood and adulthood in the offspring (106). These findings are relevant to the concept of allostatic load in which the cumulative burden of frequent/repeated exposure to stress can result in adverse health consequences (121,122).

Systemic inflammation is associated with increased risk of various diseases in adulthood, even following *in utero* or childhood exposure (106,110,112,119). Systemic inflammation can lead to changes such as breakdown of immune tolerance and impaired immune function, which can affect normal cellular physiology and contribute to the development of health conditions and disease (106). These alterations to the immune system can also increase susceptibility to infections and tumours as well as poor response to vaccines (106). Furthermore, long-term activation of the immune system is highly energy intensive and is accompanied by sickness behaviour and anorexia, which may be the result of energy shortages (123–125). Sickness behaviour and anorexia in turn can prevent adequate food intake and lead to rapid breakdown of energy reserves (123,124). Systemic inflammation can also induce blood-brain barrier changes that may contribute to sickness behaviour and anorexia through altered transport to the brain of prostaglandins, insulin, and other factors (109,126). In extreme cases, such as systemic inflammatory response syndrome and sepsis, systemic inflammation can result in multiple organ failure and death (107). Systemic inflammation can lead to physiological changes that predispose to various diseases across the lifespan.

As described above, the clinical consequences of damage caused by systemic inflammation can be severe (106). More specifically, evidence suggests that systemic inflammation is associated with increased risk of both depression (119) and CVD (112). It is possible that activation of systemic inflammatory processes may be a common link between depression and CVD. Systemic inflammation may also contribute to the high level of comorbidity between these conditions (Section 1.1.3, Page 24) (63), although it is unclear whether systemic inflammation is a risk factor or mediator for comorbid depression and CVD (63,127). Furthermore, systemic inflammation in individuals with depression and/or CVD

may be stress-induced (63), indicating a role for environmental factors in the pathogenesis of illness. Understanding how systemic inflammation may contribute to depression and CVD could result in a more nuanced understanding of these conditions as well as new targets for therapeutic interventions.

1.3.3 Markers of systemic inflammation

There are currently no standard biomarkers for indicating the presence of systemic inflammation (106), so biomarkers for acute inflammation are often used instead. Such biomarkers include those based on acute phase proteins (e.g. CRP), cytokines (e.g. IL-6), and immune cell counts. Although no biomarkers exist that can distinguish systemic inflammation from other inflammatory conditions, biomarker still offer useful information about the current inflammatory state of the individual. In addition, the presence of recurrent/persistent infection or autoimmune disease, key triggers of systemic inflammation, may be a useful supplement to these biomarkers (Figure 4).

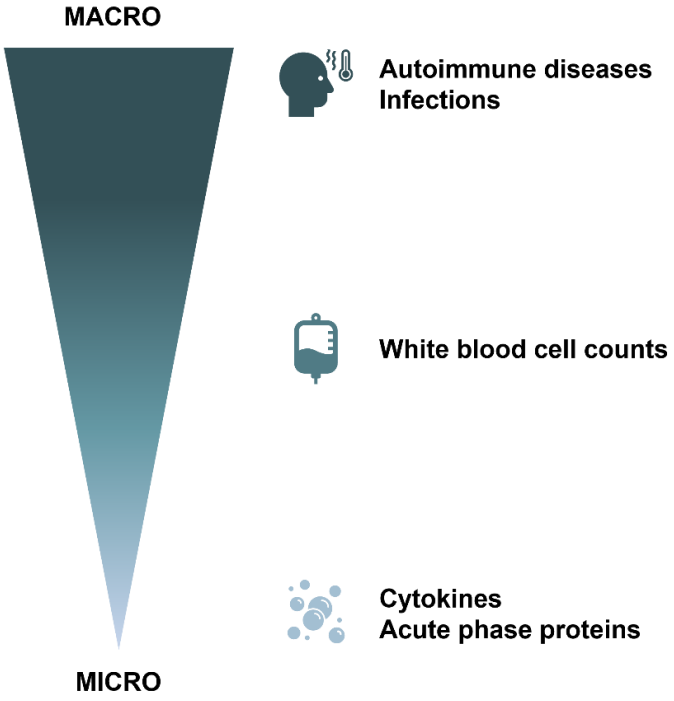


Figure 4. Macroscale to microscale markers of systemic inflammation.

Both CRP and IL-6 are widely used to assess the presence and severity of systemic inflammation (128). These measures are non-specific markers of systematic inflammation since CRP and IL-6 concentrations can be elevated in various physiological states (128,129). CRP concentration begins to increase around two hours after an acute insult (as it is downstream of IL-6), reaching its peak at 48 hours (130). CRP is synthesised primarily in hepatocytes following IL-6 stimulation as well as in smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes (131). CRP is produced as a pentameric protein, which has anti-inflammatory effects (131). At sites of inflammation and infection, pentameric CRP can irreversibly dissociate into five separate CRP monomers, which have a pro-inflammatory role in the tissue (131). Unfortunately, there are issues surrounding CRP measurement. Studies that address the stability of CRP measurements within individuals over time are conflicting, yet there is some suggestion that CRP exhibits intra-individual variability (132). CRP levels can also be affected by physiological states such as infection/fever (129), obesity (133), and exercise (134). CRP concentration at a single time point may therefore represent a state measure rather than a stable trait measure. As such, it may be problematic to rely solely on CRP values for risk prediction and therapeutic decision making in individual subjects (132).

Upstream of CRP, IL-1-beta is a potent inducer of IL-6 gene expression in various cell types (135). The IL-6 cytokine can then act through two major pathways: classic signalling and trans-signalling (Section 7.3.2, Page 225) (136,137). In classic signalling, IL-6 binds to the membrane-bound IL-6 receptor expressed on limited cell types, mainly hepatocytes and certain WBCs. Classic signalling has homeostatic functions such as cell regeneration, haematopoiesis, and release of CRP and other acute phase proteins (136). In trans-signalling, IL-6 binds to a soluble IL-6 receptor (sIL-6R) in circulation (136). The IL-6:sIL-6R complex is capable of inducing signalling on every cell type and can be inhibited by circulating soluble glycoprotein-130 (136,138). The IL-6 trans-signalling pathway promotes a

pro-inflammatory response (136,138,139) and may be an important therapeutic target for health conditions associated with inflammation. Thus, systemic inflammation may underlie elevated CRP and IL-6 concentrations although elevated levels do not necessarily indicate an inflammatory state.

There are a number of other non-specific markers for inflammation based on the levels of different white blood cells (WBC) in the blood. WBC, also called leucocytes, play an important role in the immune response. Neutrophils are the predominant WBC subset recruited to inflamed tissue by the initial innate immune response (140). Neutrophils are reactive to a wide range of potentially health-damaging stimuli and act to drive inflammation and clear pathogens (140). Other WBC subsets such as lymphocytes are involved in the slower adaptive immune response, which is responsible for long-lasting protection against recognised pathogens (141). Therefore, the neutrophil to lymphocyte ratio (NLR) can be used to assess the inflammatory state of an individual. The range for NLR in healthy non-geriatric adults may be between 0.78 and 3.58, with higher NLR values indicating higher levels of inflammation (142). In addition, WBC count (WCC) is routinely checked in clinical practice and may be used as a marker of inflammation. The normal WCC range is $5x10^9$ to $10x10^9$ cells/L (143). Inflammatory processes are indicated by a higher than normal WCC, as well as a lower count in certain cases (144). Therefore, counts of distinct WBC cell types may be useful markers for inflammation.

Here, I will discuss the associations of systemic inflammation with depression and CVD in terms of the inflammatory markers shown in Figure 4 (i.e. autoimmune diseases, infections, WCC, cytokines, and acute phase proteins).

1.3.4 Links between systemic inflammation and depression

The link between depression and autoimmune diseases is well-known. A longitudinal study of almost four million people from Denmark found that hospital contact due to autoimmune disease increased the risk of subsequent mood disorder by 45% (145). The prevalence of

MDD is substantially higher in patients with an autoimmune disease than in the general population. Specifically, the prevalence of MDD is 24% in systemic lupus erythematosus patients (146), 21% in multiple sclerosis patients (147), 19% in psoriasis patients (148), and ranges from 11% to 17% in rheumatoid arthritis patients (149,150). These autoimmune disorders may predict onset of MDD. For example, there is evidence that rheumatoid arthritis is associated with risk of first-onset depression (151), although it is unclear whether this relationship is bidirectional (151,152). Moreover, higher circulating TNF-alpha concentrations in systemic lupus erythematosus patients have been associated with MDD, severity of depressive symptoms, and poorer health-related quality of life (153,154). These findings suggest a potential role for systemic inflammation in the development of depression.

In addition to autoimmune diseases, infection is associated with depression across the lifespan. History of hospitalisation for infection has been shown to increase the risk of later mood disorder by 62% (145). This link between infection and depression appears early in life, with severe infection during childhood predicting increased odds of MDD (155). Moreover, a longitudinal study of nearly two million children from Sweden found that fetal exposure to maternal infection while hospitalised increased the risk of depression diagnosis in adulthood (156). Another longitudinal study found that maternal experiences of daily stress during pregnancy exacerbated the association between exposure to maternal infection and subsequent depressive symptoms in the adolescent offspring (157). Severe infection or exposure to infection during fetal neurodevelopment may result in subtle damage to the brain, contributing to the development of depression later in life. However, the specific infectious agent may be less relevant to the development of depression. A meta-analysis of 16 microbial infectious agents in depressed patients and non-depressed controls found that only five (31%) were associated with depression (158). It is possible that physiological changes caused by systemic inflammation (Section 1.3.2, Page 38) are responsible for the link between infection and depression.

The WCC also appears to be related to depression in adulthood. A population-based study of 3,352 adults with depression found that 22% had abnormal WCC, the majority of whom had high WCC (>10x10^9 cells/L) (159). Data indicates that elevated WCC may be particularly relevant to depression severity in men (160). Compared with controls, patients with depression have elevated counts of neutrophils and monocytes as well as reduced counts of natural killer cells (161–163). It is possible that the NLR is associated more robustly with depression than WBC subset counts (164). However, the relationship between T lymphocyte counts in depression is less clear. There is evidence to support both an increase (161,162) and decrease (163) in the levels of T lymphocytes. In addition, one study reported that increased memory CD8+ T lymphocytes and decreased natural killer cells were related to sleep disturbance in depression (162). Overall, depression is associated with WCC changes including altered levels of specific WBC subtypes.

A number of pro-inflammatory cytokines have been linked to the development of depressive symptoms. Compared with healthy controls, raised peripheral levels of IL-6, TNF-alpha, and other cytokines have been observed in MDD patients (161,165). Selective serotonin reuptake inhibitors may alleviate depressive symptoms partly by decreasing pro-inflammatory cytokine production (e.g. TNF-alpha and IL-1) and increasing anti-inflammatory cytokine production (e.g. IL-10) (166). In addition, pro-inflammatory cytokines have been shown to induce depressive symptoms in previously mentally healthy participants (166). For example, immunotherapy with interferon-alpha can lead to depressive symptoms (46). The role of IL-6 in depression is particularly well-studied. A bidirectional relationship between IL-6 and depression has been proposed, such that elevated IL-6 is associated with later depression and *vice versa* (167,168). Genetically-determined higher IL-6 concentration in childhood is also associated with increased risk of depressive symptoms in early adulthood in a linear dose-response fashion (169), suggesting that cytokines play a causal role in depression across the lifespan and that the association is unlikely to be due to residual confounding. Moreover, IL-6 signalling pathways have been implicated in MDD (169).

Cytokines may be involved in the development of depression by contributing to the dysregulation of glutamate neurotransmission, monoaminergic systems, and the hypothalamic-pituitary-adrenal (HPA) axis as well as changes to growth factors and neuropeptides, and decreased neurogenesis (170). As such, pro-inflammatory cytokines may influence genetic or environmental factors that contribute to the onset of depression.

The acute phase protein, CRP, has been widely studied in the context of depression. CRP is elevated in around 27% of patients with MDD (171). It is particularly elevated in treatment-resistant depression (172), suggesting a link between CRP and depressive symptom severity. Raised CRP concentration may be particularly important for specific symptoms of depression such as concentration difficulties, sleep disturbance, and psychomotor changes (172). CRP and depression are also related in early life. A cross-sectional study of 563 adolescent girls from Iran found significant association between serum high sensitivity CRP and depression, even after adjusting for confounders such as SEP, BMI, tobacco exposure, and recent infections (173). However, the direction of association between CRP and depression in early life remains unclear. A meta-analysis of 22 studies containing 20,791 participants age <18 years found evidence of association between CRP and future MDD but not the other way around (167). Other studies have reported the opposite; a US population-based study of 1,420 children found that depression was associated with later CRP levels but CRP was not related to later depression (174). The discrepancy between these results may be explained by genetic or environmental factors that contribute to the link between CRP and depression.

Anti-inflammatory drugs may offer new treatment options for MDD patients with signs of systemic inflammation. There are now a number of randomised controlled trials testing whether anti-inflammatory drugs as adjuvant treatment can improve outcomes in individuals with depression and raised inflammatory markers. For example, MDD patients with raised CRP may be responsive to infliximab, which inhibits TNF-alpha from stimulating CRP production (175). Statins and non-steriodal anti-inflammatory drugs may also be valuable for

treating depression (176–178). Moreover, tocilizumab, an anti-inflammatory drug that inhibits IL-6 signalling, is currently under investigation for its effect on depressive symptoms in depressed adults (179). These findings are promising, however physical comorbidities (e.g. CVD) can complicate the use of anti-inflammatory drugs with related side effects (e.g. cardiovascular morbidity/mortality) (180).

1.3.5 Links between systemic inflammation and CVD

Autoimmune diseases are associated with subsequent CVD outcomes. Type I diabetes, characterised by autoimmune destruction of pancreatic beta cells, is a well-known risk factor for CVD. Compared to their peers, individuals with type I diabetes are at substantially greater risk of IHD, MI, stroke, heart failure, atrial fibrillation, and cardiovascular mortality (181). By age 20 years, life expectancy of individuals with type I diabetes is reduced by around 12 years, with approximately 33% of the excess risk being attributable to IHD (182). Moreover, rheumatoid arthritis patients have a substantially higher risk of CVD and cardiac mortality than the general population (183,184). CVD risk factors such as insulin resistance, dyslipidaemia, and hypertension are also common is rheumatoid arthritis patients (106). There are shared inflammatory pathways between active rheumatoid arthritis and unstable plaque formation as well as links between inflammation and subclinical myocardial injury (185). These findings suggest that the excess cardiovascular risk in autoimmune diseases may be attributable to systemic inflammation.

A number of infections have been linked with CVD later in life. For example, HIV infection is an independent risk factor for ischaemic stroke, MI, and heart failure (186–188). HIV infection results in systemic inflammation and impairment of the immune system (189), which may contribute to CVD risk through altered monocyte function and subsequent progression of atherosclerotic plaque formation (190). Prolonged use of antiretroviral therapy among individuals with HIV may also increase risk of CVD through dyslipidaemia (191). Coinfection with HIV and hepatitis C virus is associated with increased risk of CVD

compared to individuals with HIV infection alone (192), perhaps suggesting a dose-response relationship between number of infections and risk of CVD outcomes. A number of clinical studies have reported a two-fold increase in risk of CVD within the first month of respiratory infection (193). For example, hospitalisation for pneumonia increases both the short-term and long-term risk of CVD (194). The evidence from studies of infection suggests a role for systemic inflammation in the development of adverse cardiovascular outcomes.

WBC are key to the formation and maintenance of atherosclerotic plaques, particularly monocyte-derived macrophages. Macrophages initiate fatty streaks at the plaque site in the blood vessel and release lytic enzymes that can leave the fibrous plaque prone to rupture or erosion. Indeed, more than half of all cells at the immediate site of plaque rupture are macrophages (195,196). Other WBC subtypes may also be associated with CVD outcomes. Regulatory T lymphocytes can have an inhibitory effect on atherosclerosis (197) whereas neutrophils can contribute to damage of blood vessel walls and destabilisation of plaques (198). Therefore, a high NLR may be a useful predictor of atherosclerosis and CVD outcomes (199). High neutrophil count (>$7.5x10^9$ cells/L) has been associated with an increase in cardiovascular mortality (200). Conversely, reduction of circulating neutrophil counts using canakinumab, a monoclonal antibody that targets IL-1-beta, has been shown to be effective at preventing CVD (201). In addition, total WCC has been reported to be a robust risk factor for fatal and non-fatal CVD (198), although it is unclear if WCC may simply reflect poor health. As with depression, CVD is associated with WCC changes including altered levels of specific WBC subtypes.

Pro-inflammatory cytokines have been implicated in atherosclerosis and CVD. Atherosclerosis is an inflammatory state; endothelial damage elicits the release of cytokines which induce a sequence of events leading to plaque formation and vascular occlusion (63). IL-1-beta is a pro-inflammatory cytokine produced by macrophages and endothelial cells at the plaque site (202,203). IL-1-beta can induce its own gene expression resulting in elevated IL-1-beta levels and maintenance of the inflammatory response at this site (203). Inhibition of

IL-1-beta appears to improve cardiovascular outcomes (203). IL-1-beta also stimulates the production of IL-6, which plays a key role in atherothrombosis (203). Observational studies have reported links between IL-6 and later CVD risk in childhood and adulthood (204,205). In addition, genetic studies support causality of IL-6 in IHD (206,207). TNF-alpha and a number of other pro-inflammatory cytokines are released by WBC in the atherosclerotic plaque which further support the maintenance of the plaque and may contribute to later CVD outcomes (202,208).

Similar to depression, CRP has been widely studied in the context of CVD. Elevated high sensitivity CRP concentration (>3 mg/L) has been linked with an increase in cardiovascular events and cardiovascular mortality in both women and men (200,209). Similarly, in a meta-analysis of 54 longitudinal studies containing 160,309 individuals, elevated circulating CRP was independently related to increased risk of IHD, stroke, and cardiovascular mortality (210). CRP concentration appears to predict CVD occurring many years in the future. For example, a study of 8,006 middle-aged men of Japanese ancestry reported that raised CRP was associated with cardiovascular events up to 15 years later (211). CRP has also been associated with adverse cardiovascular events among apparently healthy post-menopausal women (204). Finally, CRP may also be related to key CVD risk factors in children, such as BMI (205). Therefore, there is robust evidence to support a link between CRP and adverse cardiovascular outcomes.

1.4 Social and Demographic Influences on Systemic Inflammation and Depression/CVD Outcomes

In the previous section (Page 43), I presented evidence for associations of inflammatory markers with depression and CVD outcomes. It is highly likely that these relationships are influenced by a range of genetic and environmental factors. Specifically, disparities in health status and disease burden are often related to factors such as age, sex, ethnicity, and SEP, partly due to social inequalities. The link between social inequalities and differences in health outcomes is strong and persistent (212). Therefore, sociodemographic factors can affect healthcare access and quality, disease-related outcomes, and the prevalence of adverse health outcomes (212). Moreover, sociodemographic factors are also often interrelated, exacerbating existing disparities in health. The relevance of sociodemographic factors to health outcomes means that they are often included as key confounders in epidemiological studies. Here, I will discuss the influence of age, sex, ethnicity, and SEP in relation to levels of systemic inflammation and depression/CVD outcomes (Figure 5).

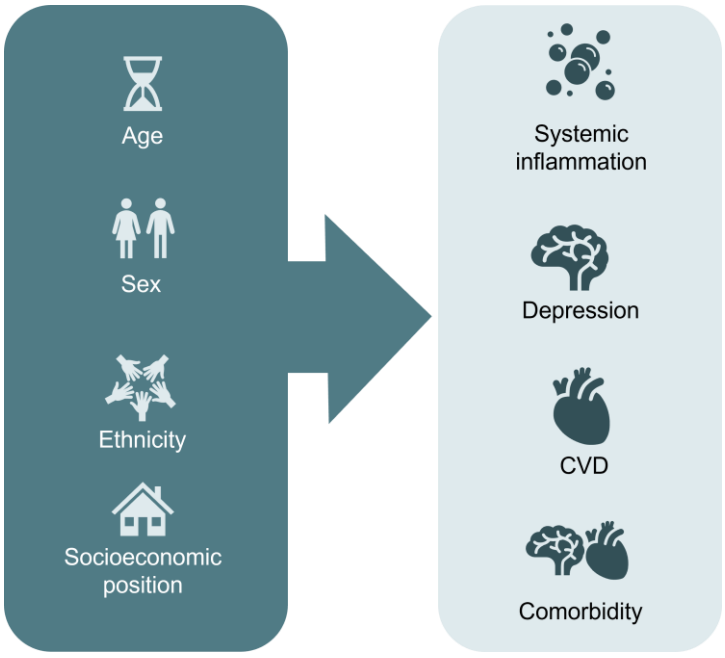


Figure 5. Social and demographic influences on systemic inflammation, depression, and CVD outcomes.

1.4.1 The role of age in systemic inflammation

Systemic inflammation is strongly associated with older age (114). As discussed in Section 1.3.2 (Page 38), the term inflammageing has been coined to describe age-related systemic inflammation, which is linked with morbidity and mortality (213). Older adults have higher circulating levels of cytokines (e.g. IL-6, IL-1, TNF-alpha), chemokines, and acute phase proteins (e.g. CRP) than younger people, as well as greater expression of genes involved in inflammation (112,114).. Ageing has long been associated with a number of changes that lead to immune system dysfunction, including cytokine dysregulation, overproduction of reactive oxygen species, slowing of autophagic processes that clear cellular waste from cells, and cellular senescence (213). In contrast, systemic inflammation in young people is rare in the absence of environmental or behavioural factors.

1.4.2 The role of age in depression and CVD outcomes

The relationship between age and the prevalence of depression is somewhat unclear. The lifetime prevalence of MDD varies widely across countries (214,215). In low- and middle-income countries (LMICs), the 12 month prevalence of MDD generally does not differ by age group (216). In high-income countries, studies have reported that the MDD 12 month prevalence decreases with age (215,216). Other research has concluded that depressive symptoms in high-income countries may follow a U-shaped pattern across adulthood, such that younger and older adults have elevated depressive symptoms compared to middle-aged adults (217). Moreover, younger women in high-income countries are more likely to have persistently high peripartum depressive symptoms in the years after birth than older women (218), perhaps due to additional confounding factors such as SEP and stress. Although the exact trajectory across the lifespan remains obscure, the association between age and MDD appears to be stronger in high-income countries than LMICs (219). In addition, genetic studies suggest that early-onset MDD is more strongly related to alleles conferring risk of bipolar disorder and schizophrenia compared to late-onset MDD (220). This may explain

partly the differences in depressive symptom profiles recorded between children/adolescents and adults with depression (221). The inconsistent findings described above suggest that the effect of age on depression may be indirect and related to other genetic and environmental factors.

In contrast to depression, there is a well-established dose-dependent relationship between older age and CVD prevalence (43). Increased age is associated with cardiovascular mortality (200). Heart attack and fatal IHD cases increases with age in both women and men (222). Data from the US national mortality data indicates that the prevalence of premature CVD mortality is 43 per 100,000 among younger adults (age 25 to 49 years) compared with a prevalence of 258 per 100,000 among middle-aged adults (age 50 to 64 years) (223). The increased risk of CVD with older age may results from the culmination of risk factors across the lifespan along with typical ageing processes that alter heart function. Since CVD is still relatively rare in young people, comorbidity between depression and CVD is more common among older people. An observational study from Taiwan reported that MI patients age ≥65 years had a substantially higher incidence of MDD compared to equivalent MI patients age <45 years (224). Therefore, there is evidence that the relationship between CVD and depression depends on age.

1.4.3 The role of sex in systemic inflammation

Sex has a somewhat complex influence on inflammatory processes. Infections are more common in males and acute inflammatory conditions in males are associated with higher risk of morbidity and mortality than in females (225). However, autoimmune disorders are more common in women and females have worse prognosis and higher mortality than males in chronic inflammatory processes (225). These findings suggest that female gender is associated with systemic inflammation, perhaps due to females having a more robust inflammatory response and higher immune reactivity than males (226). For example, a study of 2,749 participants from the US found that women have higher CRP concentrations than

men even after adjusting for oral oestrogen use, BMI, and other confounders (227). The robust inflammatory response in females is beneficial during infection but may contribute to greater severity of inflammatory diseases in females compared to males (226). Oestrogens are also known to modulate the immune response, including cytokine production and receptor expression (225). However, the role of oestrogens does fully explain the universal sex differences in inflammation found across the lifespan (225). The association of female gender and systemic inflammation is likely the result of interaction between genetic and environmental factors.

1.4.4 The role of sex in depression and CVD outcomes

Globally, depression is more common in women. Around 5% of women worldwide have depression compared to less than 4% of men (228). The prevalence of depression increases significantly from childhood to adolescence in both males and females, although the relative proportion of females reporting depressive symptoms is higher (229). Indeed, by young adolescence the reported prevalence of depression in females in approximately double that in males (229). Higher lifetime risk of depression among women is only present between puberty and menopause (230,231). This sex difference has been attributed in part to the burden of stressful reproductive events as well as the effects of hormones (230). Changes to hormone levels may increase risk of depression in women and men. Both hormone excess and hormone deficiency have been linked with increased risk of depression in women (232–234), whereas androgen deficiency has been associated with increased risk of depression in men (235). Interestingly, the risk of depression increases in boys as well as girls at the time of puberty (231), although no relationship between depression and testosterone levels has been established in adolescent males (236). Despite these findings, women with a history of depression do not differ from men with a history of depression in terms of persistence or recurrence of symptoms (231). As such, it appears that biological and social factors contribute only to the higher risk of initial depression onset among women.

On the other hand, sex differences in CVD prevalence and adverse outcomes are less clear. The typical risk factors for CVD are the same in women and men (222). Similarly, IHD is the largest contributor to cardiovascular morbidity and mortality, regardless of sex (222). However, male gender is associated with age-adjusted IHD mortality, a higher lifetime risk of CVD at age 40 years, and a higher prevalence of heart failure (200,222). In contrast, women have higher 30 day cardiovascular mortality compared with men (237,238), as well as a higher prevalence of stroke (222). The prevalence of CVD risk factors also display sex differences. Smoking, overweight/obesity, and low HDL cholesterol are more prevalent in men (239,240), whereas diabetes, high total cholesterol, and physical inactivity are more prevalent in women (239). Furthermore, there is ongoing debate about gender bias in the management of CVD (241), which may contribute to sex differences in CVD outcomes. For example, women previously experienced greater morbidity and mortality following coronary artery bypass grafting (242), but increasing use of off-pump techniques which disproportionately benefit women has narrowed the disparity in outcomes following surgery (243). Thus, it is not clear whether sex differences in CVD outcomes reflect differences in preventative care or underlying genetic vulnerability.

The literature suggests that the prevalence of comorbid depression and CVD is higher in women, although there is some evidence on the contrary. Women are more likely to have depression in the context of CVD (244,245). A study of 7,641 young adults from the US found that depression and attempted suicide was associated with increased risk of CVD mortality in both women and men, but to a substantially greater extent in women (246). Depressive symptoms in patients with IHD also appear to be most relevant in young women in terms of risk of mortality (247). Moreover, the relationship between depressive symptoms and a lack of functional improvement in cardiac patients following coronary artery bypass graft surgery is particularly pronounced among women (248). Finally, in a US study, when controlling for demographic and lifestyle risk factors, results indicated that the risk of any CVD associated with MDD was found almost exclusively among women age ≥45 years (43).

However, some studies have found that the age-adjusted prevalence of heart disease in patients with depression is similar among women and men (249), while other studies have reported that the prevalence of comorbid depression and CVD is twice as high in men compared to women (39). These differences may be due to heterogeneity within the study populations, depression/CVD measurements, or methodology.

1.4.5 The role of ethnicity in systemic inflammation

Studies considering the effect of ethnicity on systemic inflammation are largely restricted to comparison of CRP levels among the US population. In a systematic review of mainly US-based studies, 14 out of 15 relevant studies found that individuals of European origin had the lowest CRP levels while African American, Hispanic, and South Asian individuals had the highest CRP levels (250). In UK-based studies, individuals of South Asian origin have also been found to have elevated CRP relative to those of European origin (251,252). Some US studies have found Hispanic individuals have lower CRP concentrations than African Americans (253,254), while others have reported the opposite (255). In addition, US studies have demonstrated that CRP concentration is lower in East Asian individuals than European, African American or Hispanic individuals (256,257). A Canadian study also reported that East Asian participants have lower CRP concentration than European, South Asian, or Aboriginal participants (258). Moreover, Aboriginal and South Asian participants had increased WCC compared with Europeans (258). Despite these findings that suggest ethnicity influences inflammation, many US studies report no differences in CRP levels among participants of various ethnic origins (254,255,259). The discrepancy in findings regarding ethnicity and inflammation may be related to factors such as SEP, adiposity, and geographical location (257,258). Indeed, one US study observed that ethnic differences disappeared after accounting for confounders (259). It is unclear whether factors such as SEP explain the relationship between ethnicity and inflammation or whether the true effect of ethnicity is underestimated due to unintentional adjustment for mediating factors.

1.4.6 The role of ethnicity in depression and CVD outcomes

There appear to be disparities in depression and CVD outcomes according to ethnic group. In the UK, depression appears to be more prevalent among Black women than either White women or Asian women (260). The opposite was true for men in this study; depression prevalence was highest in Asian men and lowest in Black men (260). In the US, the severity of depressive symptoms in community-based older adults is higher in Hispanic and African Americans compared with European Americans (261). Disparities in depression care may partly explain ethnicity-related differences in the prevalence of depression. For example, African Americans with MDD diagnoses are 55% less likely to receive appropriate treatment for their symptoms compared with European Americans (262). Regarding CVD, African Americans have the highest age-adjusted cardiovascular mortality rates, followed by American Indian/Alaska Native, European, and Hispanic individuals (223). African American individuals are also more likely to have comorbid depression and CVD than European Americans (39). Among women, African Americans have the highest prevalence of CVD and the highest age-adjusted IHD death rate (239). In contrast, Asian American women have the lowest prevalence of IHD compared to other ethnic groups (239). These findings provide evidence that the prevalence of both depression and CVD are influenced by ethnicity.

1.4.7 The role of SEP in systemic inflammation

SEP, often characterised as income, education, or occupation, plays an important role in systemic inflammation. Low SEP, broadly defined, has been consistently associated with higher levels of systemic inflammation (250,263,264), although estimates of association between SEP and inflammatory markers vary widely across studies (263). A meta-analysis of 43 studies containing 111,156 participants reported that low SEP was associated with both elevated circulating CRP and IL-6 levels (263). In subgroup analyses, both low income and low education levels were independently related to higher CRP and IL-6 levels (263). The age at measurement of SEP and inflammatory markers did not alter the magnitude of

association between SEP and CRP/IL-6 (263), suggesting that SEP influences levels of systemic inflammation across the lifespan. Indeed, the association between lower education levels and elevated CRP is present even in older adults (259). Another recent meta-analysis containing 43,629 participants from 15 studies found that children/adolescents from the least advantaged families had 25% higher adult CRP levels compared with those from the most advantaged families (264). The association between low SEP in childhood and elevated CRP in adulthood in this study was attenuated by the inclusion of adult BMI, indicating that BMI has a strong mediating role (264). In addition to BMI, cigarette smoking may mediate the relationship between SEP and CRP. Studies that control for BMI and/or cigarette smoking have smaller associations between SEP and CRP than studies that do not control for these factors (263). However, there is no evidence that the relationship between SEP and IL-6 is influenced by BMI or cigarette smoking (263).

1.4.8 The role of SEP in depression and CVD outcomes

SEP appears to be related to the risk of depression. In high-income countries, low income is associated with a two-fold increase in odds of MDD compared to high income, whereas income does not appear to be related to MDD in LMICs (219). Childhood/adolescent depression also predicts reduced income in adulthood, indicating a reciprocal relationship between income and depression (265). In addition, the prevalence of depression in high-income countries is higher among individuals who are unemployed compared to those who are employed full-time or part-time (260). Moreover, the prevalence of peripartum depression varies depending on the SEP of the study population; a prevalence of 7% to 20% has been reported for maternal depression in high-income countries, whereas prevalence greater than 20% has been reported for LMICs (266). Low income, financial difficulties, low education levels, and unemployment have also been independently associated with peripartum depression in women, although there are some contradictory results (266).

Despite some differences in the evidence from different countries, SEP seems to play a role in the onset of depression.

Low SEP is associated with increased risk of CVD and cardiovascular mortality in high-income countries (267). Unemployment and low material amenities are both independently associated with increased risk of CVD mortality among adults from Russia, Poland, and the Czech Republic (268). Low levels of education are associated with adverse cardiovascular events worldwide (269). This finding is particularly marked in low-income countries, perhaps due the quality of medical care playing an important role in adverse CVD outcomes (269). CVD risk factors in childhood such as obesity are also more common among individuals of lower SEP (270). It is unclear whether income plays a role in CVD outcomes (82,269). Indeed, one study in Scotland found that higher deprivation levels were not associated with cardiovascular mortality (200). Finally, SEP appears to be associated with comorbid depression and CVD. Among CVD patients from a UK population representative sample, the prevalence of depression was 38% in the most deprived socioeconomic group compared with 26% in the least deprived group (271). Taken together the evidence suggests that SEP plays an important role in the onset and outcomes of both depression and CVD.

1.5 Overview of Structure and Justification of Thesis

In this chapter, I have presented the three concepts that are pertinent to this thesis. First, I discussed the associations between depression and CVD across the lifespan. Second, I addressed the evidence for systemic inflammation as a shared mechanism for depression and CVD. Finally, I highlighted the role of various social and demographic factors on systemic inflammation, depression, and CVD. In Chapter 2 (Page 60), I present the aims, objectives and methods for the current analytic work, including descriptions of the relevant datasets. Chapter 3 (Page 74), Chapter 4 (Page 110), Chapter 5 (Page 144), and Chapter 6 (Page 187) contain the analyses, themselves introduced by a visual summary (Figure 6, Figure 23, Figure 28, Figure 31). Chapter 7 (Page 212) concludes the thesis with a general discussion of the findings and suggestions for further work.

This first chapter has revealed a number of gaps in the literature regarding these three concepts. Most importantly, young people remain understudied in the context of depression and CVD risk relative to adults. The precise nature of the role of systemic inflammation in depression and CVD along with the utility of different inflammatory markers also remain unclear. The remainder of this thesis attempts to address some aspects of these gaps. My hypotheses for the analytic work in this thesis are two-fold: (i) CVD risk and depressive symptoms are bidirectionally associated in young people; and (ii) systemic inflammation is a robust shared mechanism for CVD and depression across the lifespan. The specific hypotheses I test in order to address these overall hypotheses are set out in each of the four analytic chapters.

Chapter 2: Aims and Objectives of the Thesis and Introduction to Current Analytic Work

2.1 Aims

As shown in Chapter 1, both depression and CVD are highly prevalent in the general population (Section 1.1, Page 19) and systemic inflammation may represent a shared mechanism (Section 1.3, Page 37). However, an in-depth exploration of the nuances in these relationships (Figure 1) is currently lacking. The aim of this thesis is to explore the associations between systemic inflammation, depression and CVD across the lifespan. More specifically, this thesis covers different inflammatory markers, associations of depression and CVD in childhood/adulthood, and the role of confounding demographic factors in these relationships. I have defined the age groups below (Section 2.3, Page 63). The purpose of this thesis is to shed light on the complex links between depression and CVD and to highlight potential targets for intervention.

2.2 Objectives

The objectives of this thesis are as follows:

1) Determine the direction of association between depression and CVD risk in young people.
2) Test the convergence of evidence for systemic inflammation as a shared mechanism for depression and CVD across the lifespan by:
    a) Investigating the association of various inflammatory markers with depression and CVD risk outcomes in young people.
    b) Investigating the association of various inflammatory markers with depression, CVD, and comorbid depression and CVD outcomes in adults.
    c) Investigating the specificity of association of various inflammatory markers with depression and CVD outcomes in adults.
3) Determine the effect that demographic factors have on the associations between systemic inflammation, depression and CVD across the lifespan.

The specific hypotheses tested in order to meet these objectives are set out in the subsequent chapters. Type I error (i.e. the mistaken rejection of the null hypothesis) and type II error (i.e. the mistaken acceptance of the null hypothesis) must be taken into account when attempting to accept/reject the null hypothesis.

2.3 General methods

To address the objectives of this thesis, I performed a systematic review (Objective 1) and used two different datasets for analysis: (i) the Avon Longitudinal Study of Parents and Children (ALSPAC; Objective 2a and 3); and (ii) the UK Biobank (Objective 2b and 2c). A key part of the thesis is to determine the robustness of the link between inflammation, depression, and CVD (risk) by investigating associations across the lifespan.

The age groups I refer to in throughout this thesis are defined as follows: children (age 0 to 10 years), adolescents (age 10 to 19 years), young people (age 10 to 24 years), adults (age ≥25 years), and middle-aged and older adults (age ≥40 years).

In the systematic review, associations were assessed in children and young people. Using the selected UK-based datasets, associations were assessed in children, adolescents, and middle-aged and older adults. ALSPAC was used for analysis in children/adolescents and the UK Biobank was used for analysis in adults. The specificity of association of systemic inflammation with comorbid depression and CVD (*vs* monomorbid depression or CVD) was also tested in middle-aged and older adults. Analyses were presented with and without adjustment for confounders to assess the effect of demographic factors on associations between systemic inflammation, depression, and CVD.

Various statistical methods were used including meta-analysis, regression, structural equation modelling, and imputation. I examined a range of inflammatory markers to assess convergence of the evidence for systemic inflammation as a shared mechanism for depression and CVD. The inflammatory markers used in this research include a high burden of infection, cell counts (i.e. WCC), and a high acute phase protein (i.e. CRP) or cytokine concentration (i.e. IL-6). I considered the demographic factors discussed in Section 1.4 (Page 50), namely age, sex, ethnicity, and SEP, as either key confounders or risk factors in analyses.

2.4 Description of the ALSPAC birth cohort

ALSPAC, also known as “Children of the 90s”, is a general population-based birth cohort in the former county of Avon in England. ALSPAC was established as part of an initiative by the WHO to carry out prospective birth cohorts across Europe with the purpose of studying modifiable influences on child health and development (272). Professor Jean Golding from the University of Bristol designed the methodology for ALSPAC (273). Core funding for ALSPAC is currently provided by the UK Medical Research Council, Wellcome Trust, and the University of Bristol.

The former county of Avon was located in the South West of England, comprising three UK National Health Service (NHS) administrative districts (272). In 1991, the total population in the ALSPAC catchment area was approximately 0.9 million. Avon covered both urban and rural areas, and the population was broadly representative of the rest of the UK. However, the study has a shortfall in mothers of ethnic minority origins and in less affluent families. Furthermore, there has been considerable attrition in follow-up (see Table 1, Table 6, and the text, thereafter), though the study remains a remarkable resource for research and policy planning.

Pregnant women residing in the former county of Avon with expected delivery dates between 1 April 1991 and 31 December 1992 were eligible to participate in ALSPAC. Pregnant women who migrated into the catchment area up to the point of delivery were also eligible to take part in the study. Pregnant women moving out of the catchment area prior to delivery were excluded if they had not completed the questionnaire scheduled for the third trimester of pregnancy (272). ALSPAC comprises data from the parents as well as the children and covers a wide range of phenotypic and environmental measures and biological samples.

The initial ALSPAC cohort consisted of 14,541 pregnancies which resulted in 14,062 live births. Of the live births, 13,988 infants were still alive at 12 months (272,274). Subsequent attempts to trace eligible participants who were initially missed has increased the size of the

ALSPAC cohort to 15,454 pregnancies with 14,901 infants alive at 12 months. Follow-up of the cohort until age 18 years has included 59 questionnaires, which began during pregnancy. From birth to age 7 years, the mothers answered questions about their children. From age 7 years onwards, the children attended an annual assessment clinic, during which they participate in a range of face-to-face interviews and physical tests.

2.4.1 Ethical approval and consent

Ethical approval for ALSPAC was obtained from the Local Research Ethics Committees for the three health authorities (Southmead, Frenchay, and Bristol and Weston) that formed the study's catchment area. Ethical approval for individual research studies conducted using ALSPAC data are covered under this ethical approval. The parents of participating children provided written informed consent for the use of questionnaire and clinic data in research studies approved by the ALSPAC executive committee without requiring separate consent for each study. No financial compensation was given to participants.

Detailed information about ALSPAC can be found on the study website (http://www.bristol.ac.uk/alspac). A fully searchable data dictionary is also available for information on all available ALSPAC data (http://www.bris.ac.uk/alspac/researchers/our-data).

2.4.2 Assessment of outcomes

Depressive symptoms and composite CVD risk score were the main outcomes in the studies using data from the ALSPAC cohort. Depressive symptoms were assessed by the Short Mood and Feelings Questionnaire (SMFQ) at age 10, 13, 14, 17, 18, and 19 years old. Depressive symptoms were also assessed by the Clinical Interview Schedule Revised (CISR) at age 18 years. I created the CVD risk score using age, ethnicity, maternal SEP, maternal smoking, own smoking, physical activity, BMI, SBP, LDL, HDL, and triglycerides.

Detailed information on these outcome measures as well as the other variables used in analysis (Table 1) are included as they appear in the following chapters.

Table 1. List of variables used for ALSPAC analyses.

Variable [a]	Maximum sample size	Type of variable	Measurement	Time of recording	Use in my analysis
Parental history of severe depression	7,664	Parent-based	Self-report	12 weeks gest	Confounder
Maternal smoking	10,598	Parent-based	Self-report	12 & 32 weeks gest	Exposure, Outcome
Maternal SEP	9,183	Parent-based	Self-report	32 weeks gest	Confounder, Exposure, Outcome
Maternal education	11,138	Parent-based	Self-report	32 weeks gest	Confounder
Family history of CVD	4,742	Parent-based	Self-report	Age 18	Confounder
Sex	11,786	Child-based	Self-report (by mother)	Birth	Confounder
Birthweight	11,613	Child-based	Hospital record	Birth	Confounder
Ethnicity	11,080	Child-based	Self-report	Birth	Confounder, Outcome
Number of infections	11,786	Child-based	Self-report (by mother)	Age 1.5 to 7.5	Exposure
Total difficulties score (SDQ)	8,188	Child-based	Self-report (by mother)	Age 7	Confounder
IL-6	4,626	Child-based	Biological	Age 9	Exposure
CRP	4,636	Child-based	Biological	Age 9	Exposure
BMI	4,923	Child-based	Clinic	Age 15	Exposure, Outcome
Smoking	4,757	Child-based	Self-report	Age 15	Exposure, Outcome
LDL	3,184	Child-based	Biological	Age 15	Exposure, Outcome
HDL	3,184	Child-based	Biological	Age 15	Exposure, Outcome
Triglycerides	3,184	Child-based	Biological	Age 15	Exposure, Outcome
SBP	4,831	Child-based	Biological	Age 15	Exposure, Outcome
Physical activity	4,992	Child-based	Self-report	Age 15	Exposure, Outcome
Age	5,007	Child-based	Self-report	Age 15	Confounder, Exposure, Outcome
Depressive symptoms (CISR)	4,117	Child-based	Structured interview	Age 18	Outcome
Depressive symptoms (SMFQ)	6,685 to 3,101	Child-based	Self-report	Age 10 to 19	Outcome

[a] BMI: body mass index; CISR: Clinical Interview Schedule Revised; CRP: C-reactive protein; HDL: high-density lipoprotein; CVD: cardiovascular disease; IL-6: interleukin-6; LDL: low-density lipoprotein; SBP: systolic blood pressure; SDQ: Strengths and Difficulties Questionnaire; SEP: socioeconomic position; SMFQ: Short Mood and Feelings Questionnaire.

2.4.3 Overview of analytic strategy

All studies based on ALSPAC data in the following chapters are longitudinal by design. They link a putative risk factor (i.e. the exposure) with the outcome of either depressive symptoms or CVD risk. In most cases the risk factors were continuous measures, thus I measured the change in the outcome as a function of the change in exposure. The continuous exposures were standardised to allow comparison between different exposures. This has been represented as a beta estimate. For categorical exposures, the beta estimates represent the change in outcome for the presence of the risk factor compared with its reference group. The possible contribution from factors other than the exposure of interest (i.e. confounders; alternative explanations for an apparent association) were accounted for in regression analysis.

I used multiple imputation to deal with missing values for specific confounders and exposure variables. Missing data can reduce the statistical power of a study and produce biased estimates (275). One of the assumptions of multiple imputation is that data are missing at random. A strength of multiple imputation is that, unlike complete case analysis, it incorporates the uncertainty associated with missing data. In this method, missing data are replaced with predicted values using the existing data from other variables. This process repeats a set number of times to create multiple imputed datasets, which can be analysed using standard statistical methods and the results combined using Rubin's rules.

Specifically, I used the fully conditional Markov Chain Monte Carlo (MCMC) method for multiple imputation. This method specifies a multivariate imputation model on a variable-by-variable basis by a set of conditional densities, one for each incomplete variable (276). An appropriate regression model can be selected for each variable. For example, linear regression for continuous variables and logistic regression for categorical variables (277,278). This process is repeated for each variable per iteration.

I used mediation analysis to test the indirect effect of an exposure on an outcome through an intermediate variable. Baron and Kenny were the first to describe a method for mediation analysis in which a series of regression equations were used to assess associations between: (i) exposure and outcome; (ii) exposure and mediator; and (iii) mediator and outcome (279). Significant associations are required in all of these steps to proceed with mediation modelling. This strategy has low statistical power due to multiple hypothesis tests and is no longer recommended for mediation analysis (280,281).

The pathway analysis framework based on structural equation modelling is a more appropriate method for mediation analysis (282). Simple association between the exposure and outcome is not a precondition (281), since inference about mediation is focused on the indirect effect of the exposure on the outcome. Using structural equation modelling, relationships are tested in a single analysis such that the structural equations for the direct and indirect effects are linked together and inference about them is simultaneous (282). The direct effect describes the exposure to outcome pathway controlling for the mediator whereas the indirect effect describes the exposure to outcome pathway through the mediator. The total effect is the sum of the direct and indirect effects of the exposure on the outcome (282). Inference about mediation effects is based on maximum likelihood and non-parametric bootstrapping (283). In the case of complete mediation, the pathway between exposure and outcome is eliminated by the intermediate variable. In the case of partial mediation, the pathway between exposure and outcome is attenuated.

Although mediation analysis can be useful for testing putative causal pathways for complex conditions, such as depression, it has its limitations. Associations that are considered part of the mediation model could themselves be affected by other confounders. This issue must be considered while interpreting the results of mediation analysis. Nevertheless, the issue of residual confounding is relevant to all observational investigations and is not exclusive to mediation analysis. Further description of specific statistical analyses are presented in the methods section of the relevant chapters.

2.5 Description of the UK Biobank sample

The UK Biobank is a UK-based open-access prospective study. The UK Biobank was established to allow detailed investigations of the genetic and non-genetic determinants of the diseases of middle and old age (284,285). The Science Committee for UK Biobank developed the protocol for the study. Core funding for the UK Biobank is currently provided by the Wellcome Trust, UK Medical Research Council, Cancer Research UK, and the National Institute for Health Research.

Over half a million participants age 40 to 69 years were recruited into the study. The participants were recruited from 22 assessment centres across the UK between 2006 and 2010 (286). The assessment centre sites were selected based on proximity to a sufficient population of eligible individuals and good transport links (285). The assessment centres covered various settings to provide urban-rural mix and socioeconomic and ethnic heterogeneity (286). In 2006, the total population of the UK was around 60.5 million.

The UK Biobank contains results of clinical examinations, assays of biological samples, self-reported health behaviour, genome-wide genotyping, and is supplemented by linkage with routinely available national datasets such as NHS records. At the baseline assessment, participants completed a self-report touch-screen questionnaire, a short computer-assisted interview, physical and functional measures, as well as collection of blood, urine, and saliva samples, which allow a variety of assay types (285). Follow-up is primarily conducted through linkage to electronic health-related records, although online questionnaires have also been performed. For example, an online mental health self-report questionnaire was issued in 2016.

2.5.1 Ethical approval and consent

The UK Biobank received full ethical approval from the NHS National Research Ethics Service (reference 11/NW/0382). Written informed consent was obtained from participants at

recruitment. The analyses presented in this thesis were conducted under approved UK Biobank project no. 26999.

Details of the UK Biobank resource can be found on the study website (https://www.ukbiobank.ac.uk/). A searchable showcase of UK Biobank data is also available which contains essential information, listings of database content, and access to data (https://biobank.ndph.ox.ac.uk/showcase/).

2.5.2 Summary of information used

Lifetime depression and lifetime IHD were the outcomes used in UK Biobank analysis. Depression was defined according to self-report whereas IHD was defined according to International Classification of Diseases (ICD)-10 criteria. Details of the other variables used (Table 2) in analysis are given in the relevant chapter. The data used in this particular UK Biobank study were all collected at the same time during recruitment in 2006 to 2010.

Table 2. List of variables used for UK Biobank analyses.

Variable [a]	Maximum sample size	Type of measure	Time of recording	Use in my analysis
CRP	468,553	Biological	2006 – 2010	Exposure
WCC	478,152	Biological	2006 – 2010	Exposure
IHD (diagnosis)	410,252	Clinic	2006 – 2010	Outcome
Depression (diagnosis)	410,252	Clinic	2006 – 2010	Outcome
Depression (self-report)	122,972	Self-report	2006 – 2010	Outcome
Age	502,488	Self-report	2006 – 2010	Confounder
Sex	502,488	Self-report	2006 – 2010	Confounder
Ethnicity	499,712	Self-report	2006 – 2010	Confounder
TDI	501,865	Self-report	2006 – 2010	Confounder
BMI	499,384	Clinic	2006 – 2010	Confounder
Smoking	499,540	Self-report	2006 – 2010	Confounder
Alcohol use	500,987	Self-report	2006 – 2010	Confounder
Physical activity	462,494	Self-report	2006 – 2010	Confounder
Mood disorders	410,252	Clinic	2006 – 2010	Confounder
Metabolic disorders	410,252	Clinic	2006 – 2010	Confounder
Chronic inflammatory conditions	410,252	Clinic	2006 – 2010	Confounder

Acute infections	410,252	Clinic	2006 – 2010	Confounder

[a] BMI: body mass index; CRP: C-reactive protein; ICD-10: International Classification of Diseases-10; IHD: ischaemic heart disease; TDI: Townsend deprivation index; WCC: white blood cell count.

2.5.3 Overview of analytic strategy

The study based on UK Biobank data in Chapter 6 (Page 187) is essentially cross-sectional by design due to all of the data I used being collected at the same time. The study links an exposure with the outcome of depression, IHD, or comorbid depression and IHD. The two exposures of interest were continuous measures whereas the outcomes were binary measures. As such, I have measured the presence/absence of the outcome as a function of the change in exposure. The exposures were standardised to allow comparison between different exposures. This has been represented as an OR. Effects of possible contribution from confounders were accounted for in regression analysis.

To assess the specificity of association between exposure and outcomes, I used bivariate probit regression. This is a valid method for modelling two binary outcome variables jointly as a function of an exposure.

I assessed the effect of selection bias using inverse probability weighted regression. Using this regression method is appropriate when individuals vary in their probability of having missing information, such as missing outcome data. Missing outcome data is unlikely to happen completely at random leading to biased effect estimates (287). As such, weights to account for this bias can be estimated from a logistic regression model for predicting non-response. However, the validity of the weights depend on a correctly specified model that includes all relevant exposures associated with non-response (287). This weighting method up-weights participants with missing outcome data and down-weights participants with complete outcome data. In this way, weighted analyses estimate results as if the full UK Biobank dataset were used in analyses.

Further description of statistical analyses are presented in the methods section of the relevant chapter.

SECTION B: SYSTEMATIC REVIEW

Chapter 3: A Systematic Review and Meta-analysis of Longitudinal Cohort Evidence for Association between CVD Risk Factors and Depression in Young People

3.1 Chapter Summary

AIM Quantify the association of CVD risk factors (BMI, smoking, SBP, total cholesterol, HDL) with depression in young people

METHODS

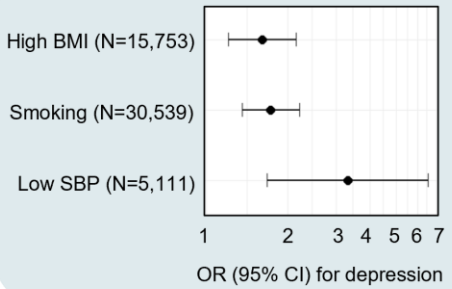
- Cohort studies of biological CVD risk factors and subsequent depression in young people
- 4,822 articles screened (Medline, Embase, PsycInfo)

INCLUDED STUDIES

Total of 23 studies included in meta-analysis

- BMI = 17 studies
- Smoking = 14 studies
- SBP = 1 study
- Total cholesterol = 0 studies
- HDL = 0 studies

RESULTS



CONCLUSIONS

- BMI and smoking are the most well-studied CVD risk factors
- BMI, smoking, and SBP are independently associated with subsequent depression
- There are a lack of studies on the effect of total cholesterol and HDL on depression in young people

Figure 6. Visual summary of Chapter 2.

3.2 Introduction

Depression is a common and serious mental illness with a lifetime risk of 10% to 20% (288). The majority of depression cases are established by age 24 years old (12); this condition is the leading cause of disability among children and young people (14). Following an initial depressive episode, the risk of recurrence is 60% (289). Therefore, early-onset depression is associated with a longer risk period for relapse as well as poor long-term outcomes (289,290). A better understanding of the aetiology of depression in young people is required to develop effective strategies for prevention and treatment (291).

CVD is a leading cause of health-related disability worldwide (292). There is evidence for bidirectional associations between CVD and depression in adults (293,294). A substantial body of literature suggests that depression is a key risk factor for CVD in adults and that it may predict poor outcomes following a cardiac event (293–298). CVD is also subsequently associated with depression in adults (34,298–300). However, studies of CVD risk and subsequent depression in young people are relatively less common. A clearer understanding of the association between CVD risk factors and depression in young people is required. Early detection and management of CVD risk factors may reduce risks for both CVD and depression subsequently during the life-course.

The WHO defines age 24 years as the upper age limit for the term young people (301). Existing studies of CVD risk and depression in young people have often focused on individual risk factors such as BMI or smoking. In the past decade, a number of systematic reviews have highlighted a longitudinal association between obesity in young people and depression across the lifespan (86,94,302,303). However, none of these studies specifically examined depression risk in young people. A recent systematic review of individuals age 14 to 35 years old reported that childhood obesity is associated with approximately 50% increased risk of depression (94). Another review reported that smoking in early life is associated with 73% increased risk of depression in young people (102). According to the

Framingham study, a gender-specific algorithm used to estimate an individual's 10 year cardiovascular risk, other established CVD risk factors for adults include SBP, total cholesterol, and HDL, in addition to smoking and BMI (304,305). These CVD risk factors are all potentially modifiable and may be important in the aetiology and prevention of depression. CVD risk factors are increasingly being examined in young people; thus, a systematic review is required to summarise these findings.

I conducted a systematic review and meta-analysis of existing studies to quantify the longitudinal association of five key CVD risk factors (BMI, smoking, SBP, total cholesterol, and HDL) and depression in young people (age ≤24 years). These CVD risk factors were chosen for a number of reasons: (i) they are part of the Framingham Cardiovascular Risk Score for adults; (ii) they are potentially modifiable; and (iii) they remain relevant in the context of young people. The outcome was depression (binary or continuous) assessed using a validated tool. I also performed a number of sensitivity analyses, for example by excluding studies that only looked at one gender or excluding studies based on quality assessment.

3.3 Hypotheses

1. High BMI is associated with depression in young people.
2. Cigarette smoking is associated with depression in young people.
3. High SBP is associated with depression in young people.
4. High total cholesterol is associated with depression in young people.
5. Low HDL is associated with depression in young people.
6. CVD risk factors are similarly associated with depression and depressive symptoms.

3.4 Methods

3.4.1 Search strategy

This study has been performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Details of the protocol were prospectively registered on PROSPERO (see: https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42020172460).

MEDLINE, EMBASE, and PsycINFO databases were searched to identify all relevant studies of the association between CVD risk factors and depression from database inception to 1 January 2020. The following keywords were used: "(*cohort OR longitudinal OR prospective OR retrospective OR follow up stud*) AND depress* AND (adolescen* OR young person OR young people OR child* OR infant OR early adult OR youth* OR teen*) AND ((cardiovascular AND risk) OR total cholesterol OR high density lipoprotein OR hdl OR smok* OR bmi OR body mass index OR adiposity OR waist circumference OR body fat distribution OR skinfold thickness OR lipid accumulation product OR systolic blood pressure OR systolic bp OR sbp) ".* The full MEDLINE search strategy is given in Figure 7**.**

3.4.2 Study selection

No language restriction was applied. The electronic search was complemented by hand-searching the reference lists of included studies. All titles and abstracts were examined to retrieve potentially relevant studies. I applied inclusion/exclusion criteria and selected the final studies for this review along with Natasha Daniels, Diana Ples, Rebecca Anderson, and Amy Gregory-Jones.

1. exp Cohort Studies/
2. (Cohort analy* or longitudinal or prospective or retrospective or ((cohort or follow up) adj (study or studies))).ti,ab.
3. 1 or 2
4. Depression/ or exp Depressive Disorder/
5. depress*.ti,ab.
6. 4 or 5
7. adolescent/ or young adult/ or exp child/ or exp infant/
8. (adolescen* or “young person” or “young people” or child or children or childhood or infant or “early adult*” or youth* or teen*).ti,ab.
9. 7 or 8
10. exp Cardiovascular Diseases/
11. cardiovascular.ti,ab.
12. 10 or 11
13. exp Risk/
14. risk.ti,ab.
15. 13 or 14
16. 12 and 15
17. ((cardiovascular or CVD or heart disease or cardiometabolic or coronary artery disease or CAD or atherosclerosis) adj3 risk).ti,ab.
18. 16 or 17
19. cholesterol/ or cholesterol, dietary/ or lipoproteins/ or exp lipoproteins, hdl/
20. (“total cholesterol” or cholesterol or “high density lipoprotein*” or hdl).ti,ab.
21. 15 or 16
22. exp Smoking/ or Smokers/ or Non-Smokers/ or Ex-Smokers/
23. smok*.ti,ab.
24. 18 or 19
25. body fat distribution/ or adiposity/ or body mass index/ or waist circumference/ or skinfold thickness/ or lipid accumulation product/
26. (BMI or “body mass index” or “body fat distribution” or adiposity or “waist circumference” or WC or “skinfold thickness” or “lipid accumulation product” or LAP).ti,ab.
27. 21 or 22
28. Blood Pressure/
29. (“systolic blood pressure” or “systolic BP” or SBP).ti,ab.
30. 24 or 25
31. 18 or 21 or 24 or 27 or 30
32. 3 and 6 and 9 and 29

Figure 7. Full search strategy for MEDLINE database.

3.4.3 Selection criteria

Studies were included that: (i) had a longitudinal population-based cohort design (prospective or retrospective); (ii) included participants with a mean age of 24 years or younger at follow-up; (iii) had at least one of the five CVD risk factors (BMI, smoking, SBP, total cholesterol, HDL) as the exposure at baseline; (iv) used a validated tool to measure depression (binary outcome or symptom score) at follow-up; and (v) reported effect estimate(s) for the association between CVD risk and subsequent depression. Studies were excluded if they did not have an unexposed group for a particular risk factor (e.g. experimental smoking used as the comparison group rather than no smoking), had depression as the exposure and the CVD risk factor as the outcome, or measured depression comorbid with another mental illness such as bipolar disorder or anxiety.

3.4.4 Data extraction

Data extraction was performed independently by me, Natasha Daniels, and Diana Ples. Any disagreements were resolved by consensus. For each included study, we extracted the following data: (i) details of the cohort (country, name/setting, design, sample size, and follow-up length); (ii) assessment of exposure and outcome; (iii) age and sex of the included participants; and (iv) results of analysis (number of participants exposed at baseline, number of participants with depression at follow-up, adjusted/unadjusted effect estimates). When studies reported various methods for assessing the exposure or repeated measures of the exposure, we used the most comprehensive measure. For example one study measured BMI eight times from birth to age 12 years (306). We chose the measure at age 7 years old as the earliest age where BMI may be an appropriate measure of central adiposity to maximise the length of follow-up. In cases where there was more than one published report from the same population, we included the study with the larger sample size (307–310). Some studies reported results where depression at baseline was adjusted for as well as analysis where baseline depression cases were removed. To minimise the possibility of

reverse causality in such cases, we included results only where baseline depression was excluded.

3.4.5 Data synthesis and meta-analysis

Separate meta-analyses were performed for BMI (Hypothesis 1, Page 78), smoking (Hypothesis 2), and SBP (Hypothesis 3). Results from studies were pooled using the inverse variance method meaning that studies with larger sample sizes were given greater weight. Results for other CVD risk factors were summarised using a narrative review (Hypothesis 4, 5). Meta-analyses were performed separately for studies that reported beta estimates i.e. for continuous depressive symptom outcomes, and odds ratios (ORs) i.e. for binary depression outcomes (Hypothesis 6). I used random-effect meta-analysis, which is appropriate where there is heterogeneity between the studies. Heterogeneity between studies was examined using the I^2 statistic.

I assessed publication bias by visual inspection of funnel plots, centred on the pooled effect estimates, and by Egger's regression test for funnel plot asymmetry (mixed-effects meta-regression model). This test indicates the existence of publication bias if the *p*-value is <0.05.

Study quality was assessed using the Newcastle-Ottawa Scale for cohort studies (311). I repeated analyses after (i) removing poor quality studies and (ii) excluding studies with only female or male participants. Meta-analyses were carried out using the "meta" package (version 4.11) in R (version 3.6.1).

3.5 Results

3.5.1 Included studies

Electronic search identified 6,617 publications (Figure 8) from which 1,795 duplicate reports were removed to leave 4,822 studies. After title and abstract screening 198 (4%) potentially eligible studies were identified, of which 29 met the inclusion criteria and were included in the systematic review (92,95–97,306–308,312–333). A total of 23 studies were included in meta-analysis. I excluded the remaining studies from meta-analysis because they were not comparable with the included studies; four studies measured BMI as a continuous variable (92,306,323,325) and three studies assessing smoking did not report comparable effect estimates (315,328,329).

Table 3 shows key characteristics of the 29 included studies. Some of these studies included effect estimates for more than one CVD risk factor. In total, there were 17 studies of BMI, 14 studies of smoking, and one study of SBP. There were no relevant studies of total cholesterol or HDL. All included studies were prospective in design, except for one which used a retrospective measure of depression at follow-up (324). The age at which CVD risk factors were measured or reported ranged from age 7 to 23 years old. The follow-up time for included studies ranged from three months to nine years. Studies of both sexes were generally well-balanced; the smallest percentage of females in a single study was 46% (330). The majority of the 29 included studies (55%) were rated as “good” quality (Table 4, Table 5). The five most commonly used confounders in adjusted analyses were: sex, age, parental education, race/ethnicity, and baseline depression (Figure 9). Only six studies (21%) did not control for or exclude baseline depression cases (Table 5).

Based on data availability, meta-analysis for BMI included 13 studies (Hypothesis 1) (95–97,314,316,318,320,321,324,326,330,332,333), and that for smoking included 11 studies (Hypothesis 2) (97,307,308,312,313,315,317,319,325,327–329,331,332). Meta-analysis for SBP included one study comprising two separate samples (Hypothesis 3) (322). As

previously mentioned, there were no studies of total cholesterol or HDL that met our inclusion criteria (Hypothesis 4, 5). Depression was the outcome in nine (69%) of the included BMI studies, eight (73%) of the smoking studies, and the SBP study (Hypothesis 6). Depressive symptoms was the outcome for five (38%) of the included BMI studies, and five (45%) of the smoking studies (Hypothesis 6).

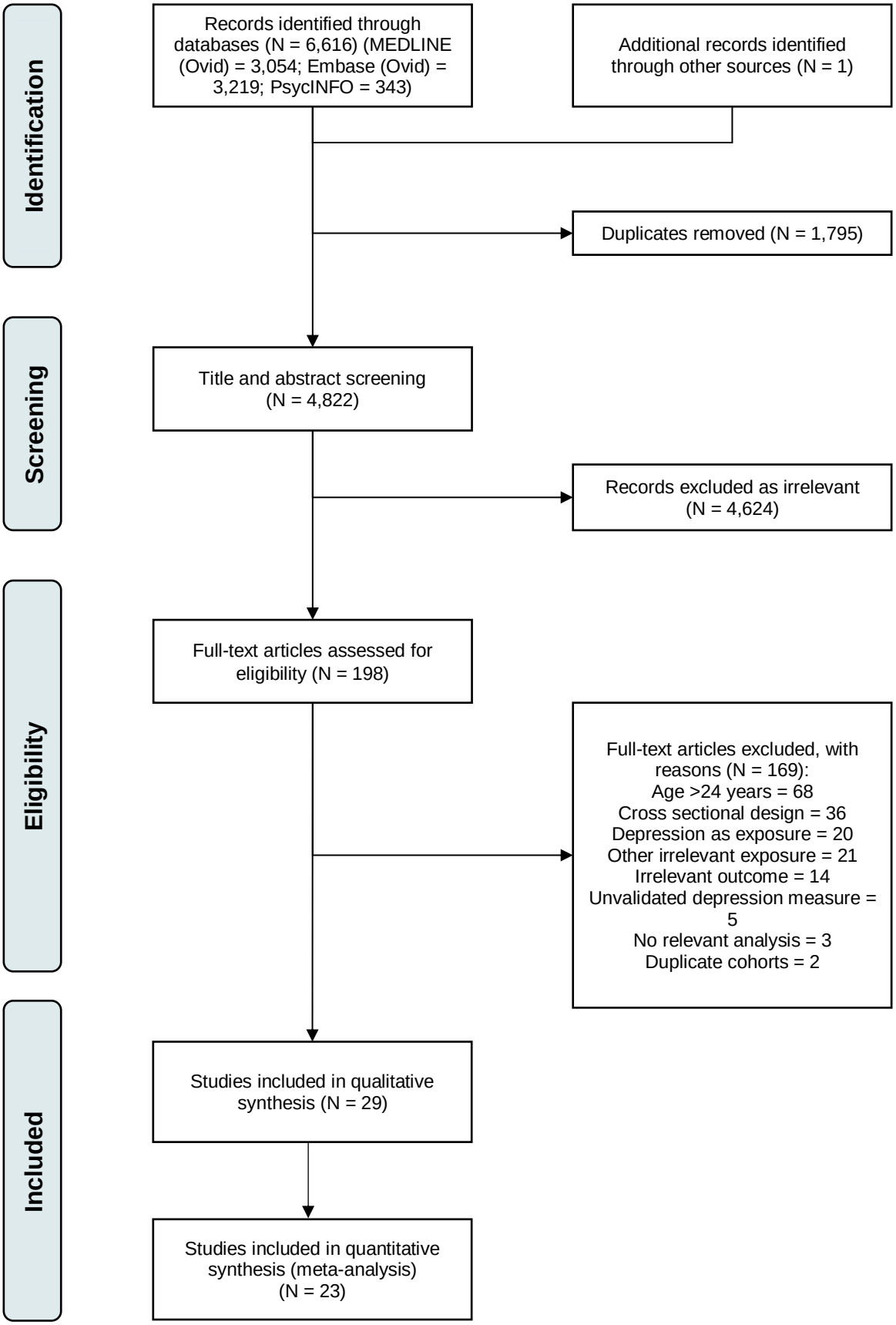


Figure 8. PRISMA flow diagram for study selection.

Table 3. Characteristics of studies included in systematic review.

Study [a]	Country	Female – no. (%)	Baseline age (years) – range or mean	Minimum follow-up (years)	Assessment of exposure	Exposed at baseline – % or mean (SD)	Assessment of depression	Depression at follow-up (%)	DSS at follow-up – mean (SD)
BMI									
Boutelle 2010	USA	495 (100) [c]	13.5	1	Obese vs healthy weight	10.7%	Structured interview (K-SADS)	1.2–3.5	1.3–1.4 (0.4)
Chang 2017	Taiwan	969 (51.2)	14.7	3	Obese vs healthy weight	F = 3.5%; M = 3.4%	Self-report (CES-DC)	-	F = 1.8 (0.5); M = 1.5 (0.4)
Clark 2007	UK	776 (51.3)	11–14	2	Obese vs healthy weight	19.6%	Self-report (SMFQ)	15.1	-
Eitle 2018	USA	AI = 308 (47.0); W = 3,403 (50.0)	12-18	1	Obese vs not obese	AI = 19.0%; W = 11.0%	Self-report (CES-D)	-	AI = 12.4 (0.6); W = 10.1 (0.2)
Frisco 2013	USA	5243 (100)	15.7	4	Consistently obese vs healthy weight	9.8%	Self-report (CES-D)	7.0	-
Gomes 2019	Brazil	NM	18	4	Obese vs not obese	6.7%	Structured interview (MINI-5)	2.9	-
Goodman 2002	USA	4718 (48.6)	<20	1	Obese vs not obese	9.7%	Self-report (CES-D)	8.9	-
Hammerton 2014 [b]	UK	EPAD = 165 (57.1); ALSPAC = 2,533 (52.1)	EPAD = 9–17; ALSPAC = 11–14	EPAD = 1.4; ALSPAC = 2	Standardised score	EPAD = 17.4%; ALSPAC = 23.7%	EPAD = Semi-structured interview (CAPA); ALSPAC = Structured interview (DAWBA)	EPAD = 8.3; ALSPAC = 1.6	EPAD F = 2.2 (NM); EPAD M = 1.6 (NM); ALSPAC = NM
Marmorstein 2014	USA	NM	11–14	6	Obese vs not obese	F = 14.7%; M = 10.7%	Structured interview (SCID)	F = 12.3; M = 7.6	-
Monshouwer 2012	Netherlands	820 (53.3)	10–12	4	Obese vs healthy weight	14.1%	Structured interview (WHO CIDI-3)	5.6	-
Perry 2020 [b]	UK	1,655 (51.6)	9	9	Raw score	17.5 (2.5)	Self-report (CIS-R)	7.0	3.1 (NM)

Piumatti 2018 [b]	Italy	178 (78.1)	21.4	1	Raw score	21.1 (2.7)	Self-report (PHQ-2)	-	1.1 (0.6)
Pryor 2016	Canada	661 (54.1)	6–12	1	Early-onset vs never overweight	11.0%	Self-report (Kovacs CDI)	-	NM
Rhew 2008	USA	206 (46.2)	12	1	Overweight vs healthy weight	F = 22.4%; M = 30.3%	Structured interview (MFQ)	-	NM
Roberts 2013	USA	2,040 (48.9) [c]	11–17	1	Obese vs healthy weight	19.7%	Structured interview (DISC IV-Y)	1.7	-
Wang 2014 [b]	Hong Kong	2,793 (48.2)	7	7	Standardised score	F = -0.03 (1.1); M = 0.3 (1.3)	Self-report (PHQ-9)	-	4.0 (NM)
Zhang 2018	Germany	1,196 (100)	21	1.4	Overweight vs healthy weight	7.2%	Structured interview (Diagnostic Interview for Mental Disorders Research Version)	6.5	-
Smoking									
Albers 2002	USA	259 (49.6) [c]	12–15	4	Ever vs never smoker	33.9%	Self-report (Kandel & Davies)	13.2	-
Bares 2014	USA	2,486 (53.0) [c]	16.6	5.5	Unit increase in cigarette use	31.3%	Self-report (CES-D)	-	4.9 (3.9)
Beal 2014	USA	262 (100)	11–20	2	Ever vs never smoker	2.9 (3.1)	Self-report (CDI/BDI)	-	46.3 (10.8)
Chaiton 2015 [b]	Canada	416 (49.7)	12–13	5	Smoking initiation vs no initiation	47.4%	Self-report (Mellinger scale)	23.8	-
Choi 1997	USA	3,215 (46.8)	12–18	4	Established vs never smoker	17.3%	Self-report (Kandel & Davies)	11.5	-
Clark 2007	UK	776 (51.3)	11–14	2	Tried/regular vs never smoker	35.2%	Self-report (SMFQ)	15.1	-
Duncan 2005	USA	6,748 (51.6)	11–21	1	Smoker vs non-smoker	F = 25.8%; M = 25.3%	Self-report (CES-D)	F = 27.0; M = 21.4	F = 13.0 (8.7); M = 10.8 (7.5)
Gage 2015	UK	NM	16	2	Unit increase in cigarette use	9.8%	Self-report (CIS-R)	7.2	-

Raffetti 2019	Sweden	1,636 (51.2)	13–14	1	Current vs non-smoker	2.0%	Self-report (CES-DC)	8.3	15.7 (NM)
Ranjit, Buchwald 2019 [b]	Finland	2,358 (50.3) [c]	14	3	Regular vs never smoker	9.1%	Self-report (GBI)	5.1 (4.9)	-
Ranjit, Korhonen 2019 [b]	Finland	2,174 (51.8) [c]	17.5	5	Ever vs never smoker	25.3%	Self-report (GBI)	4.5 (4.7)	-
Rubio 2008	USA	278 (100)	23	0.25	Smoker vs non-smoker	72.0%	Self-report (CES-D)	85.0	-
Piumatti 2018	Italy	178 (78.1)	21.4	1	Daily vs non-smokers	13.6%	Self-report (PHQ-2)	-	1.1 (0.6)
Zhang 2018	Germany	1,196 (100)	21	1.4	Current vs non-smoker	23.6%	Structured interview (Diagnostic Interview for Mental Disorders Research Version)	6.5	-
SBP									
Hammerton 2013	UK	EPAD = 164 (58.4); ALSPAC = 2,516 (52.1)	EPAD = 9–17; ALSPAC = 11–14	EPAD = 2.5; ALSPAC = 3	Standardised score	EPAD = 117.3 (13.2); ALSPAC = 111.0 (9.5)	EPAD = Semi-structured interview (CAPA); ALSPAC = Structured interview (DAWBA)	EPAD = 8.5; ALSPAC = 1.6	-

[a] ALSPAC: Avon Longitudinal Study of Parents and Children; AI: American Indian ethnicity; BDI: Beck's Depression Inventory; BMI: body mass index; CAPA: Child and Adolescent Psychiatric Assessment (Child Version); CDI: Children's Depression Inventory; CES-D: Centre for Epidemiological Studies Depression; CIS-R: Clinical Interview Schedule Revised; DAWBA: Development and Wellbeing Assessment (Child Version); DISC IV-Y: Diagnostic Interview Schedule for Children for direct administration to children or adolescents; DSM: Diagnostic and Statistical Manual of Mental Disorders; DSS: depressive symptoms score; EPAD: Early Prediction of Adolescent Depression study; F: female; GBI: General Behaviour Inventory; ICD-10: International Classification of Diseases-10; K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia; M: male; MFQ: Mood and Feelings Questionnaire; MINI-5: Mini International Neuropsychiatric Interview-5; NM: not mentioned; NS: not significant; PHQ: Patient Health Questionnaire; SBP: systolic blood pressure; SCID: Structured Clinical Interview for DSM-III-R; SD: standard deviation; SMFQ: Short Mood and Feelings Questionnaire; W: White ethnicity; WHO CIDI-3: World Health Organisation Composite International Diagnostic Interview-3.

[b] Not included in meta-analysis. The four studies not included in BMI meta-analysis were excluded because they measured BMI as a continuous variable. The three studies not included in smoking meta-analysis were excluded because they did not report effect estimates comparable with the other studies.

[c] Baseline sample only.

Table 4. Breakdown of Newcastle-Ottawa Scale (NOS) scores for included studies.

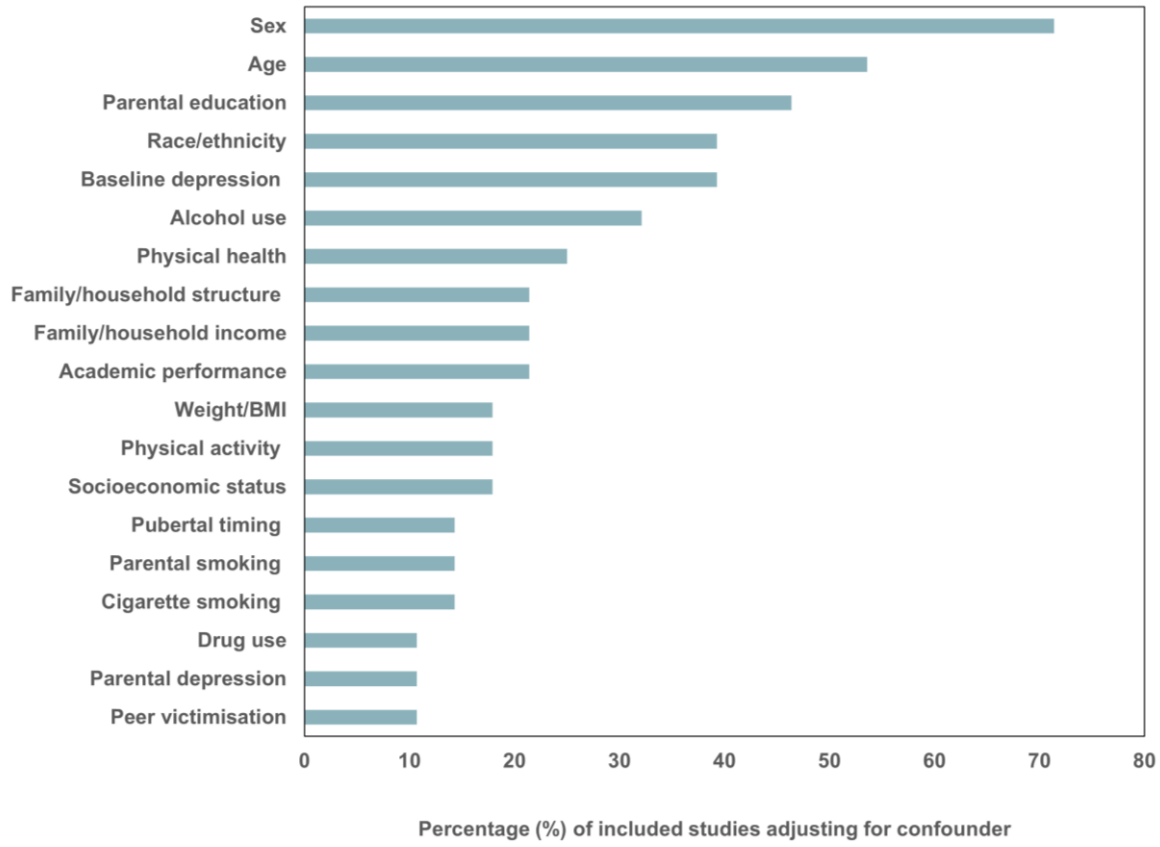
Study	Selection (out of 4)	Comparability (out of 2)	Outcome (out of 3)	Total	Rating
Albers 2002	4	2	2	8	Good
Bares 2014	3	2	2	7	Good
Beal 2014	2	2	3	7	Fair
Boutelle 2010	3	1	3	7	Good
Chaiton 2015	3	2	2	7	Good
Chang 2017	2	2	3	7	Fair
Choi 1997	3	2	3	8	Good
Clark 2007	3	2	2	7	Good
Duncan 2005	3	2	1	6	Poor
Eitle 2018	2	2	3	7	Fair
Frisco 2013	4	2	3	9	Good
Gage 2015	3	1	2	6	Good
Gomes 2019	4	1	2	7	Good
Goodman 2002	2	2	2	6	Fair
Hammerton 2014 [a]	3 / 4	0	3 / 2	6	Poor
Hammerton 2013 [a]	3 / 4	0	3 / 2	6	Poor
Marmorstein 2014	3	0	2	5	Poor
Monshouwer 2012	3	1	3	7	Good
Perry 2020	3	1	2	6	Good
Piumatti 2018	1	2	1	4	Poor
Pryor 2016	3	1	2	6	Good
Raffetti 2019	3	1	2	6	Good
Ranjit, Buchwald 2019	1	2	2	4	Poor
Ranjit, Korhonen 2019	1	2	1	5	Poor
Rhew 2008	1	1	3	5	Poor
Roberts 2013	4	2	2	8	Good
Rubio 2008	2	2	2	6	Fair
Wang 2014	3	2	2	7	Good
Zhang 2018	3	1	2	6	Good

[a] Score for EPAD study given first followed by score for ALSPAC study.

Table 5. Summary of characteristics of studies included in the systematic review.

Characteristic	Value
Cohort type – no. studies (%)	
Prospective	28 (96.6)
Retrospective	1 (3.4)
Location – no. studies (%)	
North America	15 (51.7)
Europe	11 (37.9)
Asia	2 (6.9)
South America	1 (3.4)
Sex – no. studies (%)	
Female and male	24 (82.8)
Female only	5 (17.2)
Exposure – no. studies (%) [a]	
Body mass index	17 (58.6)
Smoking	14 (48.3)
Systolic blood pressure	1 (3.4)
Total cholesterol	0 (0)
High-density lipoprotein	0 (0)
Mean (SD)	
Follow-up length (years)	2.9 (2.1)
Sample size (no. participants)	3,208 (3,004)
Baseline depression – no. studies (%)	
Controlled for / excluded	23 (79.3)
No action	6 (20.7)
Regression type – no. studies (%) [a]	
Logistic	19 (65.5)
Linear	14 (48.3)
NOS quality rating – no. studies (%)	
Good	16 (55.2)
Fair	5 (17.2)
Poor	8 (27.6)

[a] Percentages add up to more than 100% since some studies are in more than one category.



Other confounders used <2 times in included studies: family functioning, availability of social support, family economic stress, stressful life events, urban dwelling, birthplace, parenthood/ever pregnant, diet, parental BMI, maternal age, maternal mental health, mental health problems other than depression, family history of depression, alcoholic parent, cannabis use, peer smoking, impulsivity, rebelliousness, IQ, tiredness/sleep problems, interleukin-6 concentration.

Figure 9. Confounders used in adjusted analysis of included studies.

3.5.2 Meta-analysis of adjusted and unadjusted effect estimates

The analyses in this section are relevant to hypotheses 1, 2, 3, and 6 (Section 3.3, Page 78). Hypotheses 4 and 5 could not be tested due to a lack of applicable studies.

3.5.2.1 Longitudinal association between high BMI at baseline and risk of depression at follow-up

Based on seven studies reporting an adjusted OR, comprising a total of 15,753 participants, the pooled OR for depression at follow-up associated with high BMI (>25) at baseline was 1.61 (95% CI = 1.21, 2.14) (Figure 10). There was limited evidence of heterogeneity between studies (I^2 = 31%; 95% CI = 0%, 71%; Cochran's Q = 8.7; p = 0.19).

Based on six studies reporting an unadjusted OR, comprising a total of 21,025 participants, the pooled OR for depression at follow-up associated with high BMI at baseline was 1.39 (95% CI = 0.98, 1.97) (Figure 11). There was evidence of heterogeneity between studies (I^2 = 68%; 95% CI = 23%, 86%; Cochran's Q = 15.49; p <0.01).

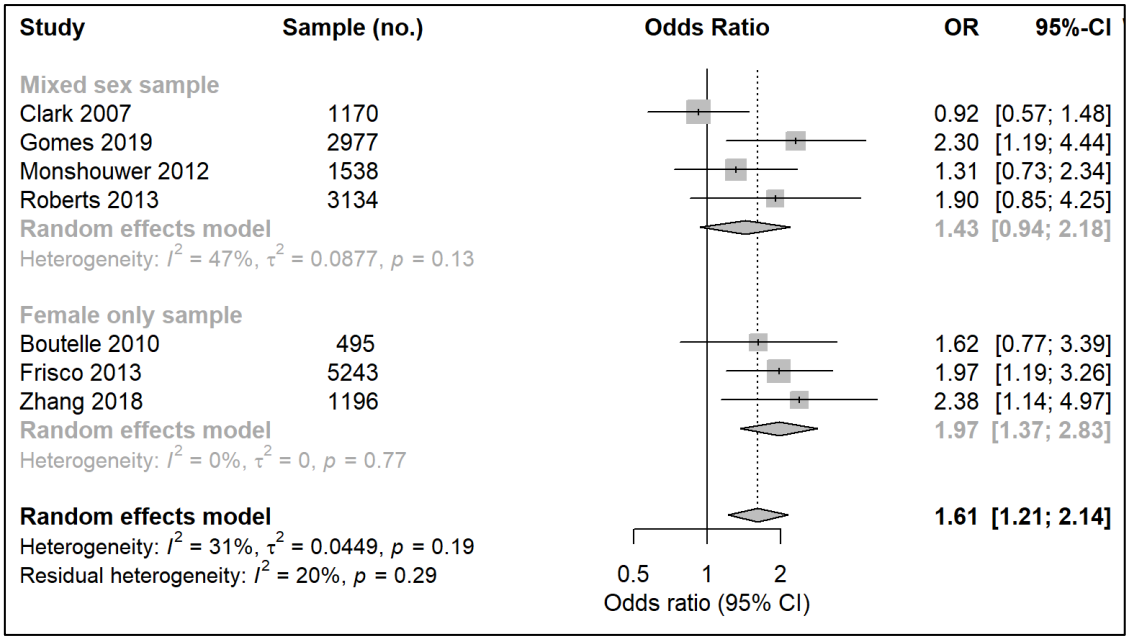


Figure 10. Meta-analysis of longitudinal association between high BMI at baseline and subsequent depression in young people (adjusted models).

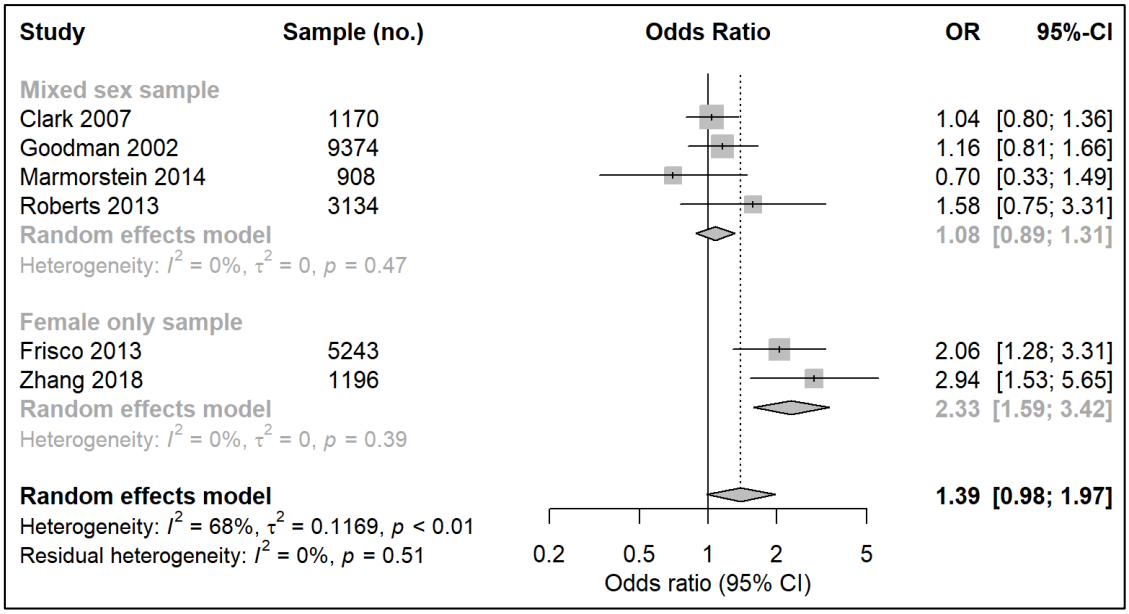


Figure 11. Meta-analysis of longitudinal association between high BMI at baseline and subsequent depression in young people (unadjusted models).

3.5.2.2 Longitudinal association between smoking at baseline and risk of depression at follow-up

Based on eight studies reporting an adjusted OR, comprising a total of 30,539 participants, the pooled OR for depression at follow-up associated with smoking at baseline was 1.73 (95% CI = 1.36, 2.20) (Figure 12). There was evidence of heterogeneity between studies (I^2 = 74%; 95% CI = 52%, 86%; Cochran's Q = 35.3; p <0.01).

Based on seven studies reporting an unadjusted OR, comprising a total of 23,398 participants, the pooled OR for depression at follow-up associated with smoking at baseline was 1.88 (95% CI = 1.42, 2.50) (Figure 13). There was evidence of heterogeneity between studies (I^2 = 84%; 95% CI = 68%, 92%; Cochran's Q = 36.75; p <0.01).

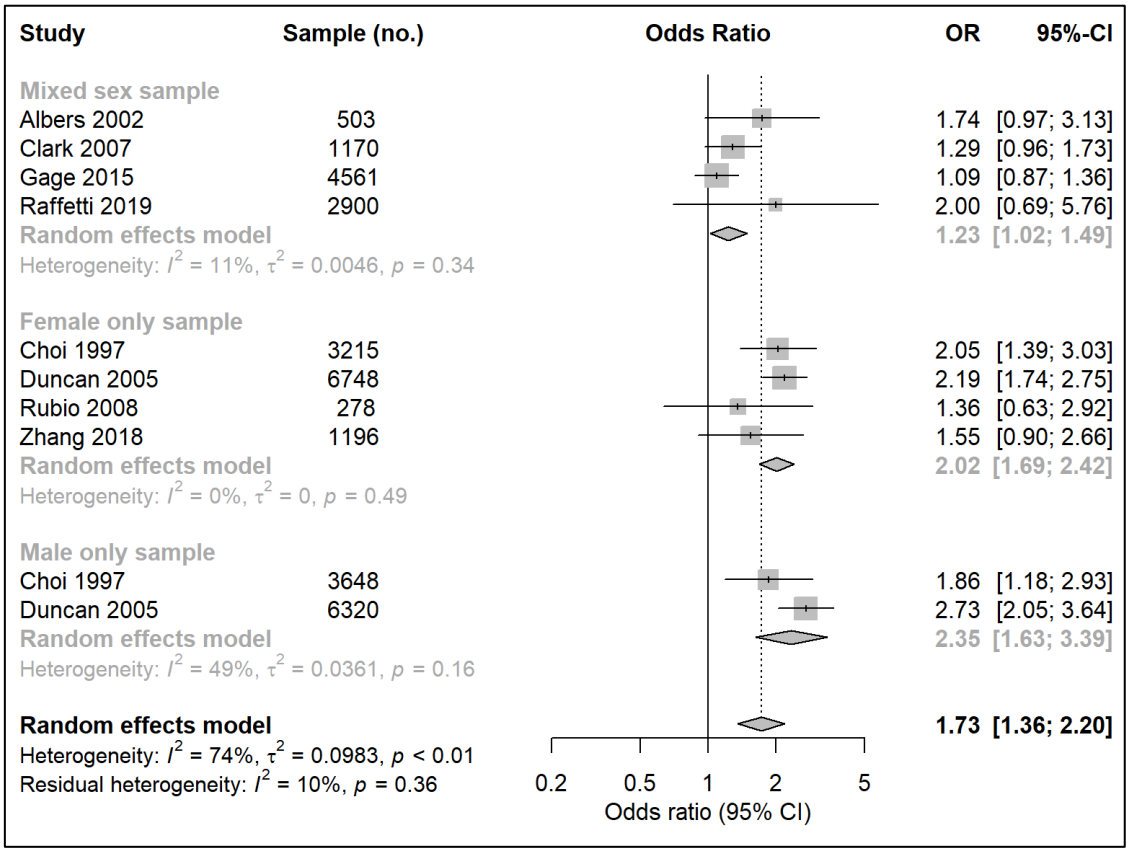


Figure 12. Meta-analysis of longitudinal association between smoking at baseline and subsequent depression in young people (adjusted models).

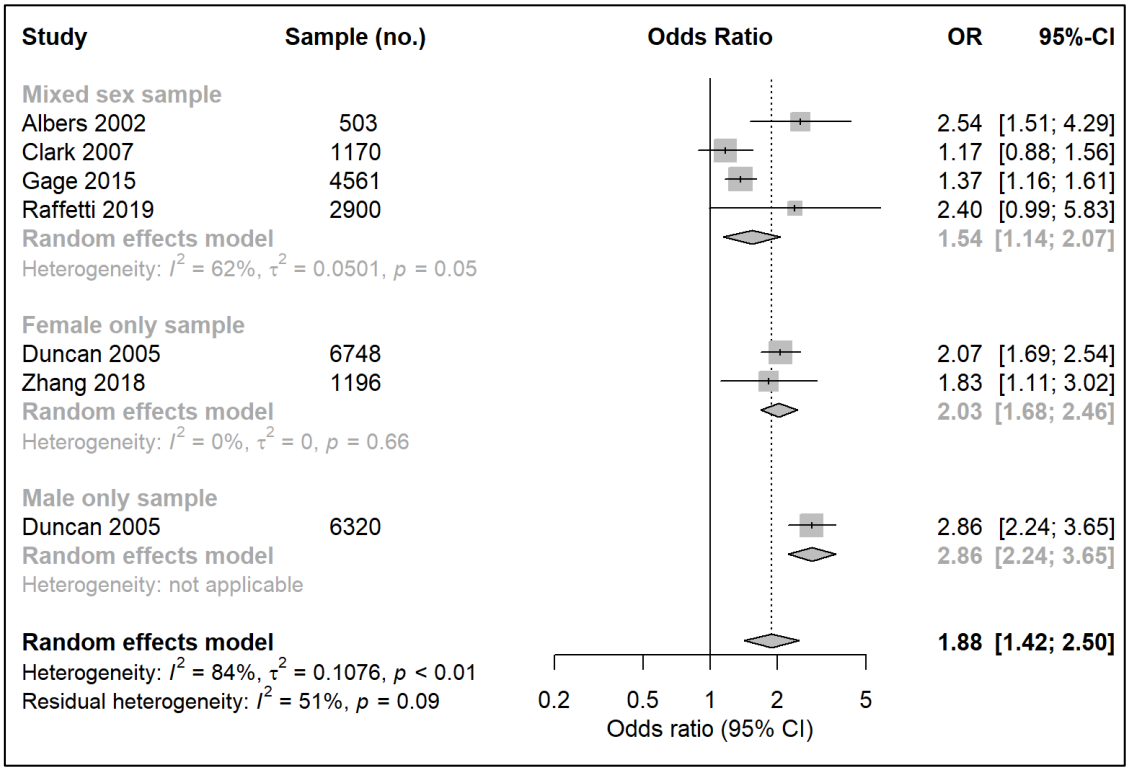
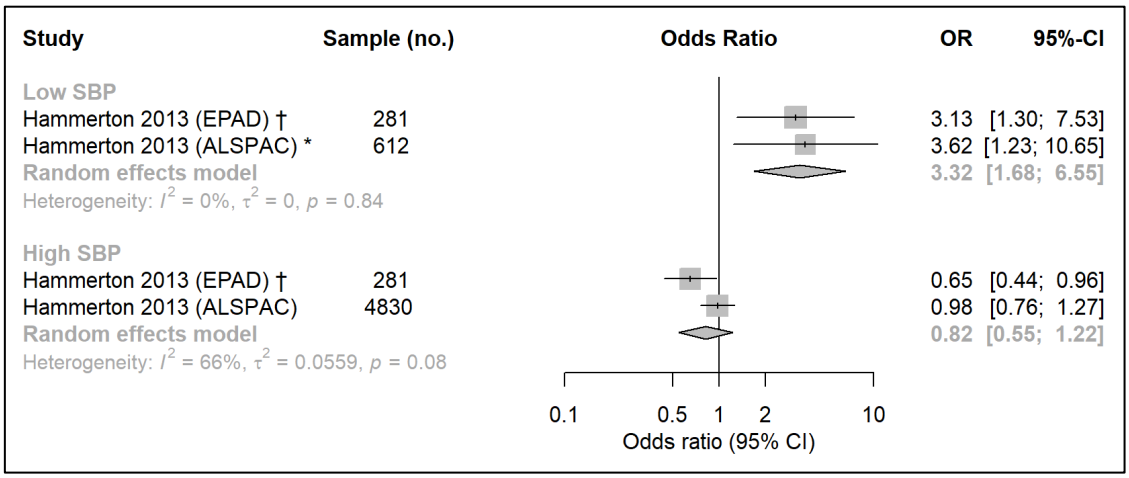


Figure 13. Meta-analysis of longitudinal association between smoking at baseline and subsequent depression in young people (unadjusted models).

3.5.2.3 Longitudinal association between SBP at baseline and risk of depression at follow-up

One study examined associations of both low and high SBP with depression in two separate samples comprising a total of 5,111 participants. Meta-analysis of these studies suggest depression at follow-up is associated with low SBP at baseline (adjusted OR = 3.32; 95% CI = 1.68, 6.55), but not with high SBP at baseline (adjusted OR = 0.82; 95% CI = 0.55, 1.22) (Figure 14). There was some evidence of heterogeneity for high SBP (I^2 = 66%; 95% CI = 0%, 92%; Cochran's Q = 3.0; p = 0.08) and little heterogeneity for low SBP (I^2 = 0%; 95% CI = 0%, 0%; Cochran's Q = 0.04; p = 0.84).



ALSPAC: Avon Longitudinal Study of Parents and Children; EPAD: Early Prediction of Adolescent Depression study; SBP: systolic blood pressure. * Subset of ALSPAC participants with mothers with recurrent depression. † EPAD participants have a mother and/or father with recurrent depression.

Figure 14. Meta-analysis of longitudinal association between SBP at baseline and subsequent depression in young people (adjusted models).

3.5.2.4 Longitudinal association between high BMI at baseline and depressive symptoms at follow-up

Based on five studies reporting an adjusted beta estimate, comprising a total of 11,516 participants, the standardised mean difference (SMD) for an increase in depressive symptoms at follow-up associated with high BMI at baseline was 0.05 (95% CI = –0.08, 0.18) (Figure 15). There was evidence of heterogeneity between studies (I^2 = 71%; 95% CI = 34%, 88%; Cochran's Q = 17.5; p <0.01).

3.5.2.5 Longitudinal association between smoking at baseline and depressive symptoms at follow-up

Based on five studies reporting an adjusted beta estimate, comprising a total of 21,490 participants, the SMD for an increase in depressive symptoms at follow-up associated with smoking at baseline was 0.37 (95% CI = 0.10, 0.64) (Figure 15). As above, there was

evidence of heterogeneity between studies (I^2 = 89%; 95% CI = 78%, 94%; Cochran's Q = 44.8; p <0.01).

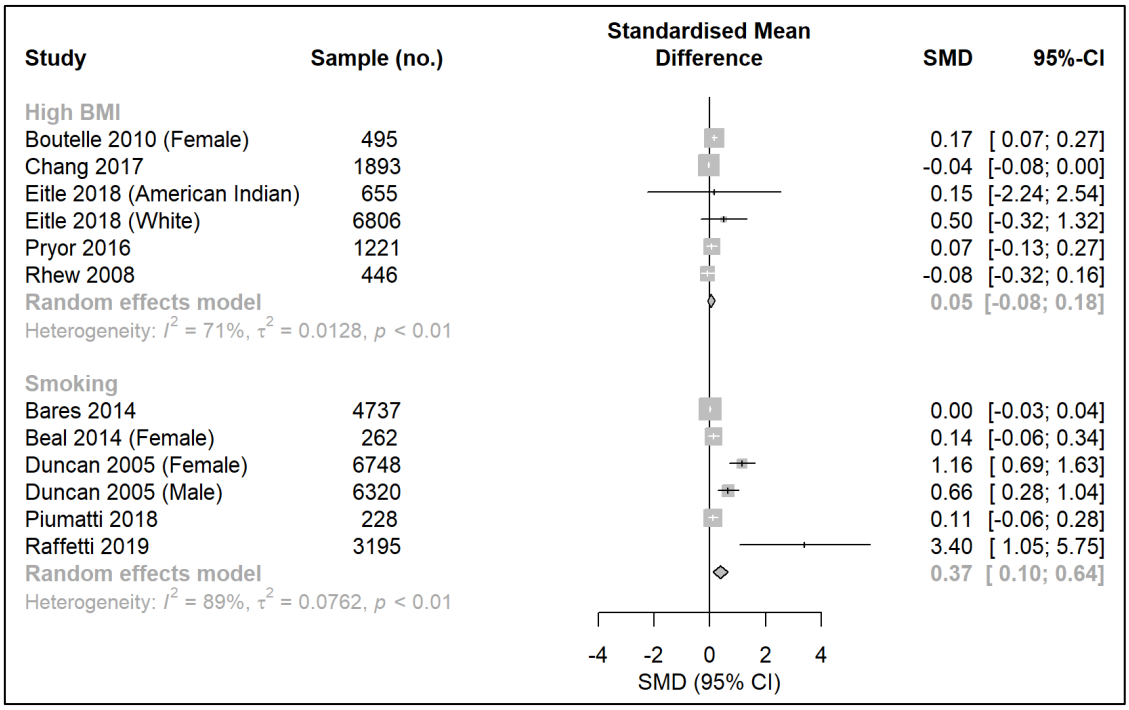


Figure 15. Meta-analysis of longitudinal association between high BMI/smoking at baseline and subsequent depressive symptoms in young people (adjusted models).

3.5.3 Results for sensitivity analysis

3.5.3.1 Longitudinal association between high BMI at baseline and risk of depression at follow-up

After excluding three studies containing only female participants (314,318,332), the adjusted pooled OR for depression at follow-up for high BMI at baseline was 1.43 (95% CI = 0.94, 2.18) (Figure 10). There was some heterogeneity between studies (I^2 = 47%; 95% CI = 0%, 83%; Cochran's Q = 5.7; p = 0.13). The adjusted pooled OR for the three female only studies was 1.97 (95% CI = 1.37, 2.83) (Figure 10). There was little heterogeneity between

studies (I^2 = 0%; 95% CI = 0%, 60%; Cochran's Q = 0.52; p = 0.77). There were no studies excluded based on quality assessment.

3.5.3.2 Longitudinal association between smoking at baseline and risk of depression at follow-up

After excluding four studies containing only female or male participants (307,317,331,332), the pooled adjusted OR for depression at follow-up for smoking at baseline was 1.23 (95% CI = 1.02, 1.49) (Figure 12). There was little heterogeneity (I^2 = 11%; 95% CI = 0%, 86%; Cochran's Q = 3.4; p = 0.34). The adjusted pooled OR for the four female only studies was 2.02 (95% CI = 1.69, 2.42) (Figure 12). There was little heterogeneity between studies (I^2 = 0%; 95% CI = 0%, 81%; Cochran's Q = 2.43; p = 0.49).

After excluding one study based on quality assessment (307), the pooled adjusted OR for depression at follow-up for smoking at baseline was 1.48 (95% CI = 1.21, 1.80) (Figure 16). There was some heterogeneity between studies (I^2 = 38%; 95% CI = 0%, 73%; Cochran's Q = 11.3; p = 0.12).

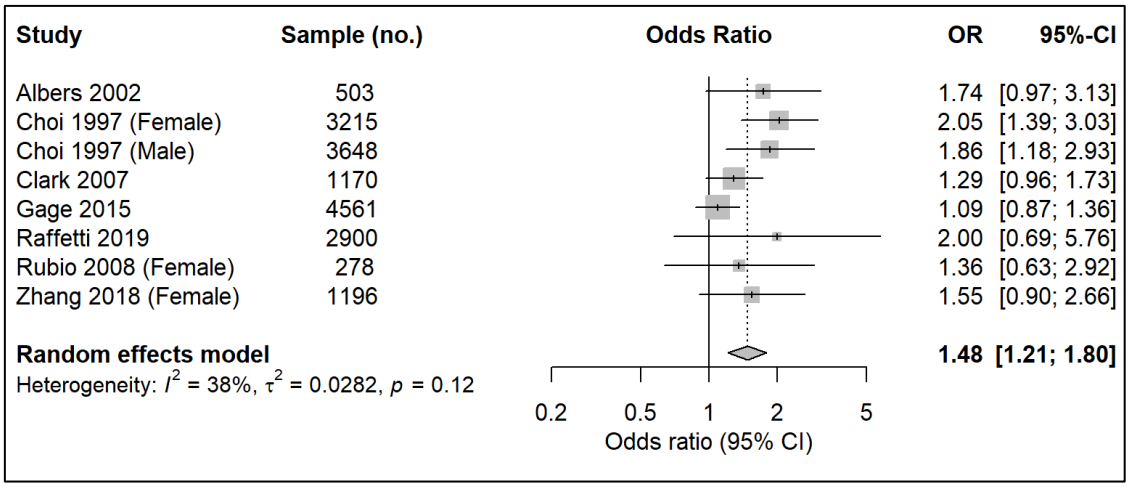


Figure 16. Meta-analysis, after studies removed based on quality assessment, of longitudinal association between smoking at baseline and subsequent depression in young people (adjusted models).

3.5.3.3 Longitudinal association between high BMI at baseline and depressive symptoms at follow-up

After excluding one study containing only female participants (314), the pooled adjusted SMD for an increase in depressive symptoms at follow-up associated with high BMI at baseline was –0.03 (95% CI = –0.07, 0.00) (Figure 17). There was no evidence of heterogeneity between studies (I^2 = 0%; 95% CI = 0%, 72%; Cochran's Q = 2.92; p = 0.57).

After excluding one study based on quality assessment (330), the pooled adjusted SMD for an increase in depressive symptoms at follow-up associated with high BMI at baseline was 0.08 (95% CI = –0.08, 0.23) (Figure 18). There was evidence of heterogeneity between studies (I^2 = 77%; 95% CI = 43%, 90%; Cochran's Q = 17.16; p <0.01).

3.5.3.4 Longitudinal association between smoking at baseline and depressive symptoms at follow-up

After excluding two studies containing only female or male participants (307,313), the pooled adjusted SMD for an increase in depressive symptoms at follow-up associated with smoking at baseline was 0.09 (95% CI = –0.16, 0.34) (Figure 17). There was evidence of heterogeneity between studies (I^2 = 79%; 95% CI = 32%, 93%; Cochran's Q = 9.37; p <0.01).

After excluding two studies based on quality assessment (307,325), the pooled adjusted SMD for an increase in depressive symptoms at follow-up associated with smoking at baseline was 0.11 (95% CI = –0.18, 0.40) (Figure 18). There was evidence of heterogeneity between studies (I^2 = 80%; 95 CI = 35%, 94%; Cochran's Q = 9.77; p <0.01).

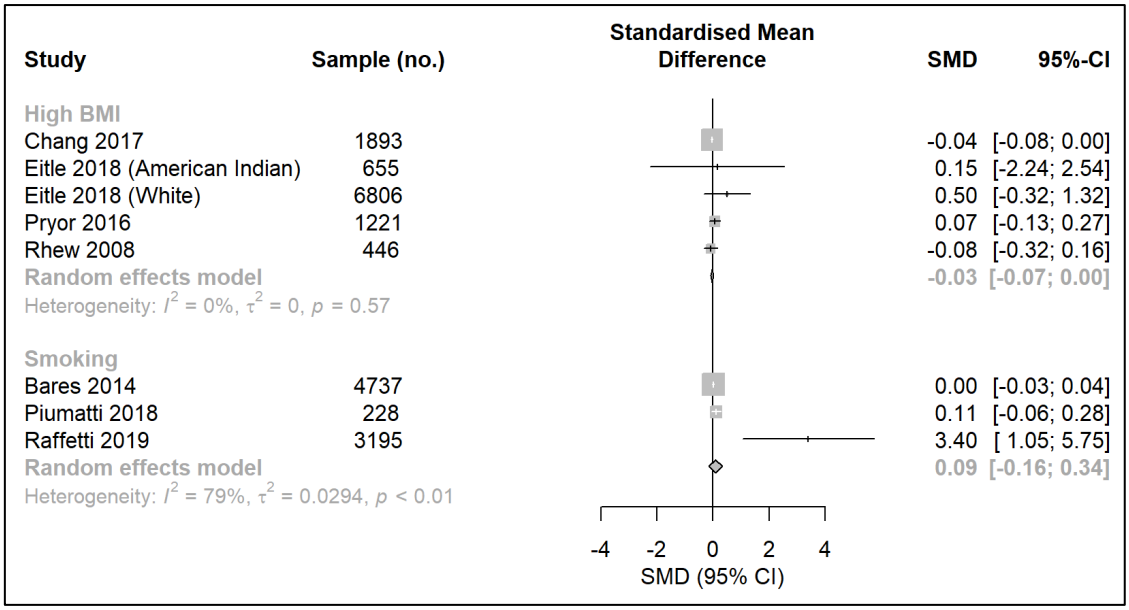


Figure 17. Meta-analysis, after female or male only studies removed, of longitudinal association between high BMI/smoking at baseline and subsequent depressive symptoms in young people (adjusted models).

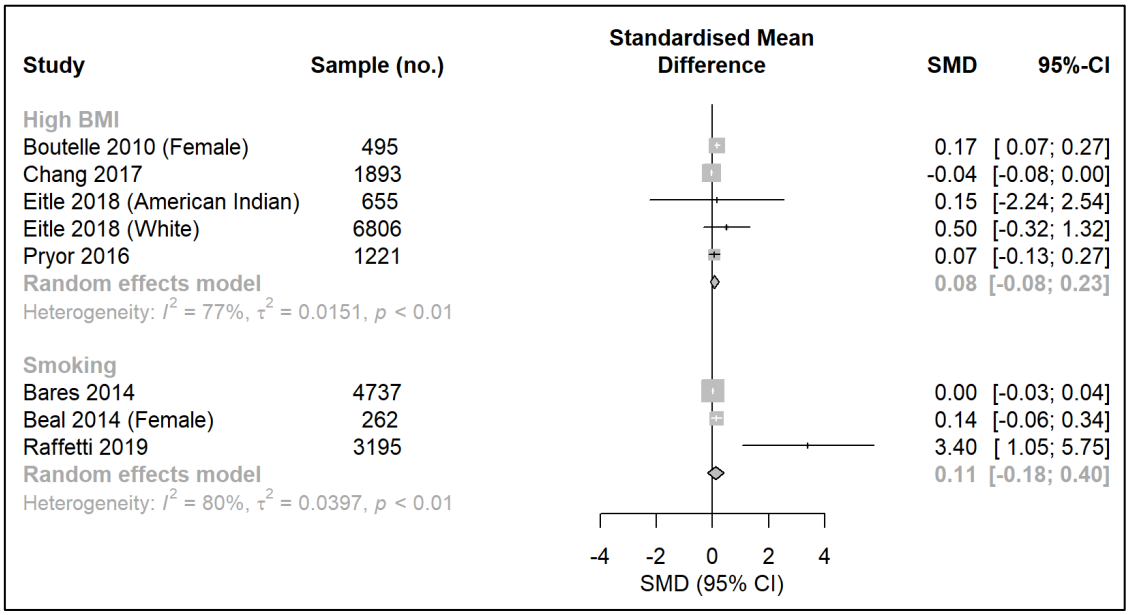


Figure 18. Meta-analysis, after studies removed based on quality assessment, of longitudinal association between high BMI/smoking at baseline and subsequent depressive symptoms in young people (adjusted models).

3.5.5 Publication bias

Based on Egger's test and funnel plots, evidence for publication bias was not present for studies reporting adjusted association between high BMI and depression (Egger's test p = 0.17 (Figure 19), smoking and depression (Egger's test p = 0.80) (Figure 20) or high BMI and depressive symptoms (Egger's test p = 0.35) (Figure 21). Evidence for publication bias was present for studies reporting the adjusted association between smoking and depressive symptoms (Egger's test p = 0.01) (Figure 22).

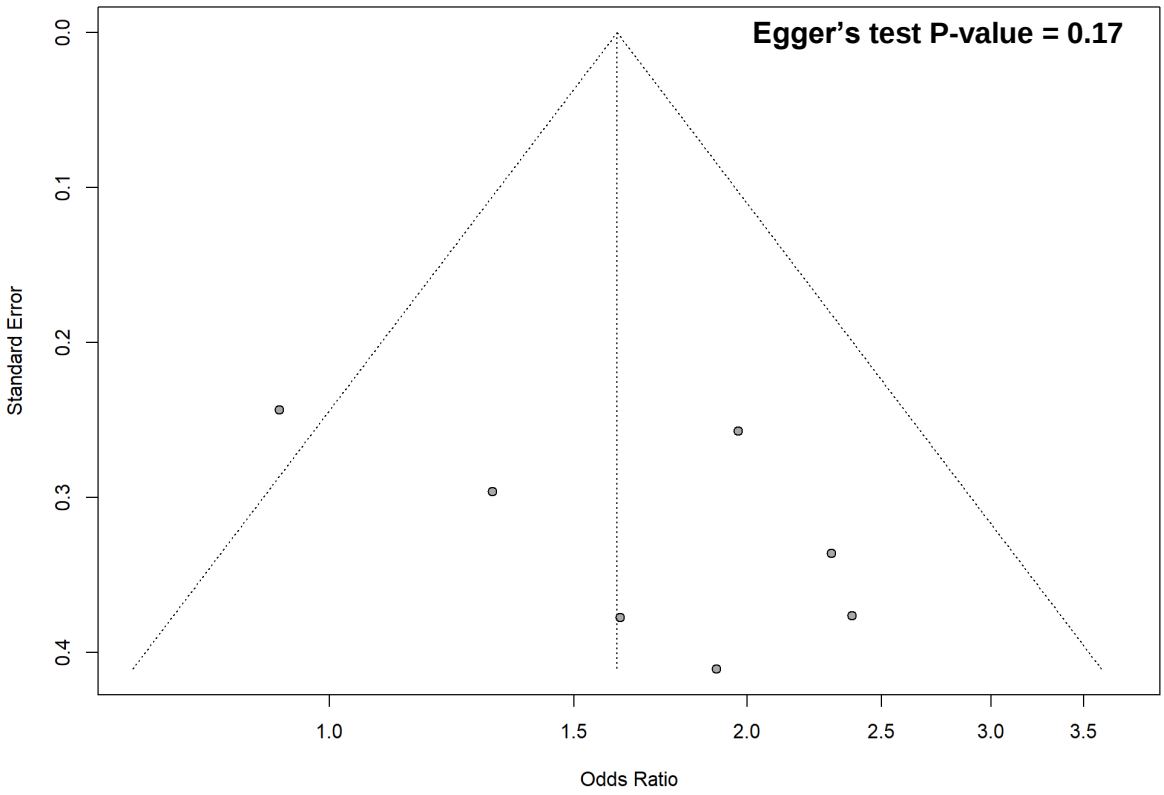


Figure 19. Adjusted OR (SE) of longitudinal association between high BMI at baseline and subsequent depression in young people.

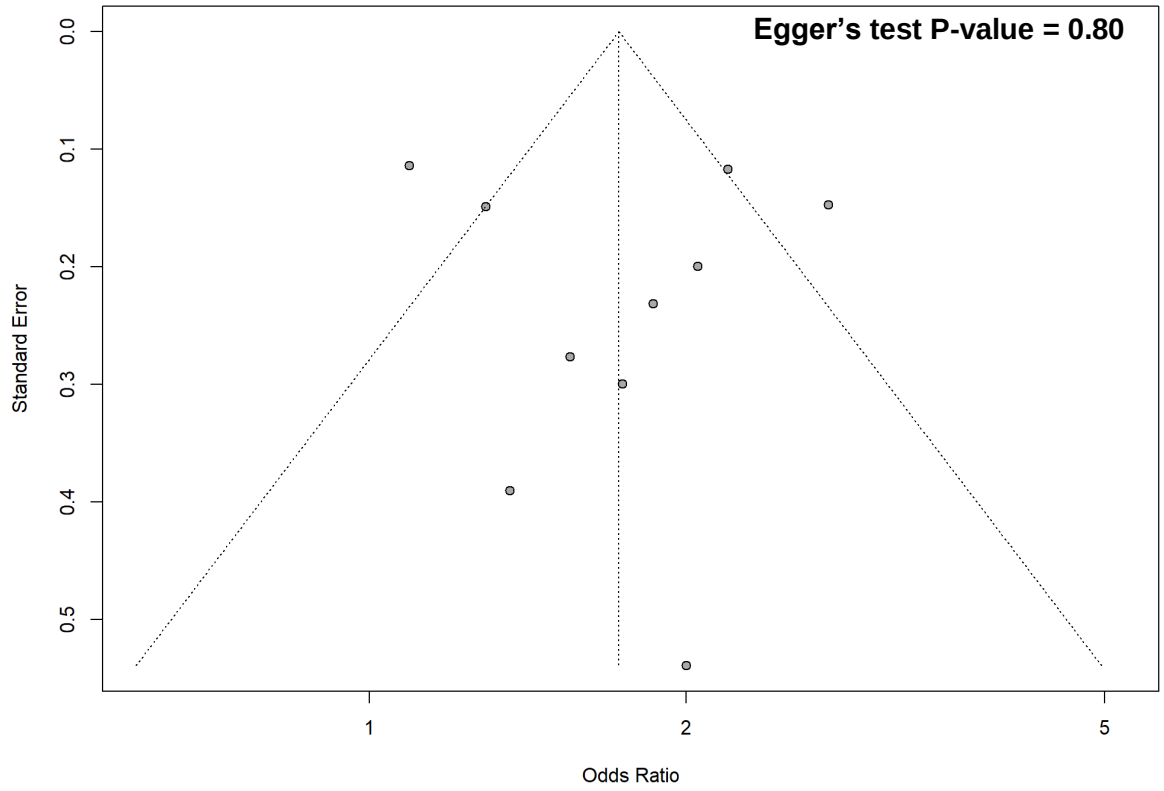


Figure 20. Adjusted OR (SE) of longitudinal association between smoking at baseline and subsequent depression in young people.

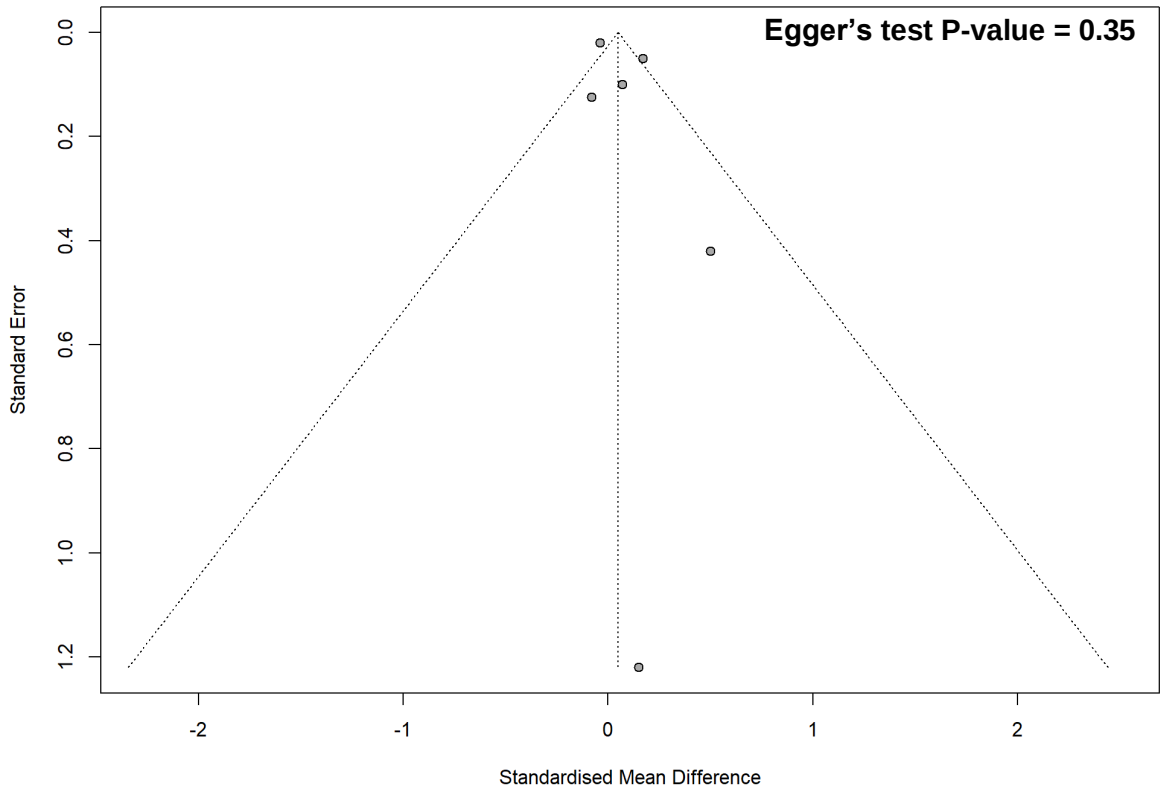


Figure 21. Adjusted SMD (SE) of longitudinal association between high BMI at baseline and subsequent depressive symptoms in young people.

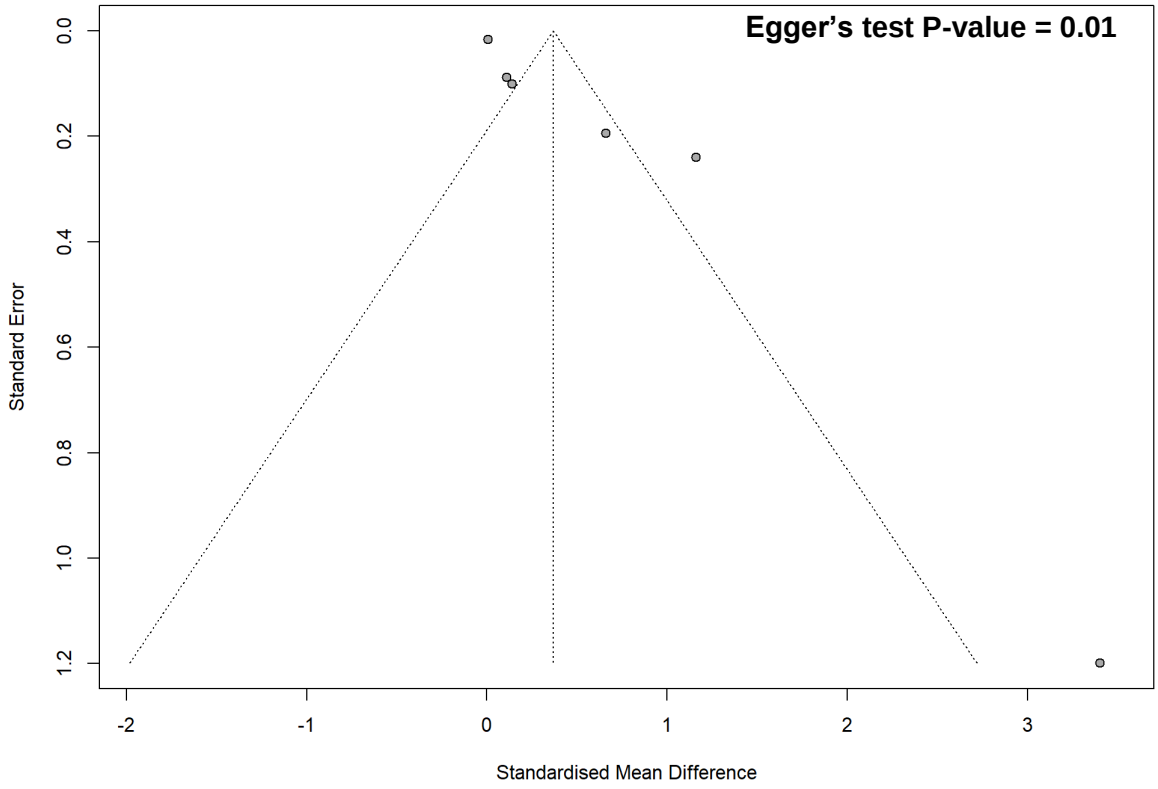


Figure 22. Adjusted SMD (SE) of longitudinal association between smoking at baseline and subsequent depressive symptoms in young people.

3.6 Discussion

Depression and CVD are associated with each other in mid- to late-adulthood. While depression is known to arise commonly in young people, the timing of the association with CVD risk is unclear and common risk factors for the two conditions raise the prospect of joint prevention. To the best of my knowledge, this is the first systematic review to consider the association between various CVD risk factors and subsequent depression in young people.

There are four key findings from this study: (i) BMI and smoking are the most well-studied risk factors for depression in this age group; (ii) both BMI and smoking at baseline are longitudinally associated with subsequent depression; (iii) smoking but not BMI is prospectively associated with depressive symptoms; and (iv) currently there is limited data on longitudinal associations of high SBP and cholesterol with subsequent depression in young people, which should be examined in future. These findings are consistent with hypotheses 1 and 2 (Section 3.3, Page 78) i.e. that high BMI and cigarette smoking are independently associated with depression in young people. There was insufficient data to test hypotheses 3 to 5 i.e. that high SBP, high total cholesterol, and low HDL are independently associated with depression in young people. Hypothesis 6, that CVD risk factors are similarly associated with depression and depressive symptoms, requires further assessment, since results for high BMI and smoking are difficult to compare in this context.

Our results suggest that obesity and smoking could be risk factors for depression in young people. The pooled OR of 1.61 for the association of high BMI and depression is remarkably similar to previous studies in adults. Previous meta-analyses have reported ORs of 1.51 and 1.70 for the prospective association between childhood high BMI and adult depression (94,334). Another meta-analysis reported that obese adolescents had a 40% increased risk of being depressed as adults (86). A recent Mendelian randomisation study using data from 812,000 adult participants also found that fat mass could be a causal factor for depression (335). I did not find an association between high BMI and depressive symptoms score,

indicating a possibly non-linear association between BMI and depression whereby association is restricted to only those with more severe symptoms.

Our findings also suggest smoking could be a risk factor for depression in young people. The pooled OR of 1.73 for the association between smoking and depression is consistent with a previous meta-analysis in adults, which reported an OR of 1.62 (336). Similarly, a meta-analysis of nine cross-sectional and longitudinal studies found that adolescents exposed to second-hand smoking had increased odds of depression (103). However, current evidence from observational cohort studies and genetic Mendelian randomisation studies reports mixed findings regarding the association between smoking and depression, with some reporting an association (337) and others no association (338,339). Therefore, residual confounding or reverse causality remain viable explanations for the observed association between smoking and depression. Further longitudinal studies and genetic Mendelian randomisation studies are required to investigate this issue.

A number of potential mechanisms may be involved in the association of high BMI and subsequent depression including low-grade systemic inflammation, HPA axis dysregulation, insulin resistance, and psychological distress. Inflammation is evident in around 25% of individuals with depression (171) and atypical depression is associated with inflammation and metabolic dysregulation (340,341). Adipose tissue also contains abundant inflammatory cytokines that are involved in fat metabolism (342). Similarly, the role of insulin in regulating adipocyte function contributes to the close link between insulin resistance and obesity (343). Furthermore, melancholic depression, higher levels of abdominal fat, HPA axis hyperactivity and cortisol dysregulation are inter-related (340,341,344). Adverse childhood experiences are also one of the most robust risk factors for depression (345), and are associated with increased risk of obesity and metabolic dysregulation (346). Low-grade systemic inflammation may be important to the association between smoking and depression (166). Studies are required to investigate the complex mechanisms that may underlie the association between high BMI and depression.

Low SBP, but not high SBP, appeared to be associated with risk of depression in young people. However, this meta-analysis was based on only two cohorts at high risk of depression and further work is required. Low SBP appears to be associated with depression in young people at high-risk of depression but not in the general population (322). Low SBP has also been associated with depression in cross-sectional and longitudinal studies of middle-aged and elderly adults (347,348). Conversely, higher SBP has been prospectively associated with fewer depressive symptoms in older adults with CVD risk factors (349). In adult populations, the relationship between SBP and depression may be independent of a range of lifestyle factors, age, and sex (347,348).

The reason why low SBP has a potentially causal role in depression remains unclear. Neurons controlling blood pressure could be implicated in the association between SBP and depression. Neuropeptide Y, for example, reduces blood pressure and is involved in stress responses that have been linked to increased risk of depression, such as the HPA axis (347,350). Further research is required to understand the relationship between SBP and depression in young people, including potential mechanisms.

There were no studies assessing the association of either total cholesterol or HDL with the risk of subsequent depression in young people. A meta-analysis of 30 cross-sectional studies reported that higher total cholesterol was associated with lower levels of depression in adults (351). Evidence from adults indicates both higher and lower HDL to be associated with increased risk of depression in adults. In a meta-analysis of 16 cross-sectional studies, high HDL was related to higher levels of depression, especially in women (351). Conversely, a meta-analysis of 11 case-control studies reported that lower HDL levels may be associated with first-episode MDD in adults (352). Given that abnormal HDL, LDL and triglyceride levels are increasingly common in adolescents (353), effort should be made to study potential effects on mental health as well as physical health.

3.6.1 Limitations

Strengths of this work include the systematic literature search which identified a large number of relevant studies comprising a total of 93,021 participants. I included studies considering the effect of various CVD risk factors on either binary or continuous measures of depression/depressive symptoms. The studies were assessed using the validated Newcastle-Ottawa Scale and sensitivity analyses were conducted to examine the robustness of our findings. However, this study is not without limitations.

First, the majority of studies came from North America and Europe, limiting the generalisability of the results to other parts of the world. The number of studies in each of the meta-analyses was also relatively small, which resulted in wide confidence intervals for the pooled effect estimates, and reduced the statistical power to detect publication bias. There was a considerable amount of heterogeneity between studies, particularly studies of depressive symptoms. Sensitivity analyses revealed that sex explained heterogeneity in some of the meta-analyses. However, stratifying by sex decreased the sample size, and consequently, statistical power to detect an association. In future, studies with larger samples are required. Finally, the possibility of residual confounding by unidentified factors remains high so any conclusion regarding causality should be interpreted with caution. Although studies included in this meta-analysis controlled for various potential confounding effects, other factors may also explain these associations. Further research is needed to examine whether observed associations are likely to be causal. Since randomised controlled trials are neither feasible nor ethical for some of the exposures under investigation (e.g. smoking, obesity), genetic approaches to dealing with residual confounding, such as Mendelian randomisation, would be particularly useful.

3.6.2 Conclusion

In summary, I present evidence for a longitudinal association between CVD risk factors, namely high BMI and smoking, in childhood/adolescence and subsequent depression in young people. These risk factors could be important targets for prevention of depression and CVD in young people and subsequently during the life course. Further work is needed to understand potential mechanisms for these associations as well as the relationship between other CVD risk factors, notably blood pressure and cholesterol and depression risk in young people.

SECTION C: ANALYSIS OF ALSPAC DATA

Chapter 4: Direction of Association between CVD Risk and Depressive Symptoms in Adolescence

4.1 Chapter Summary

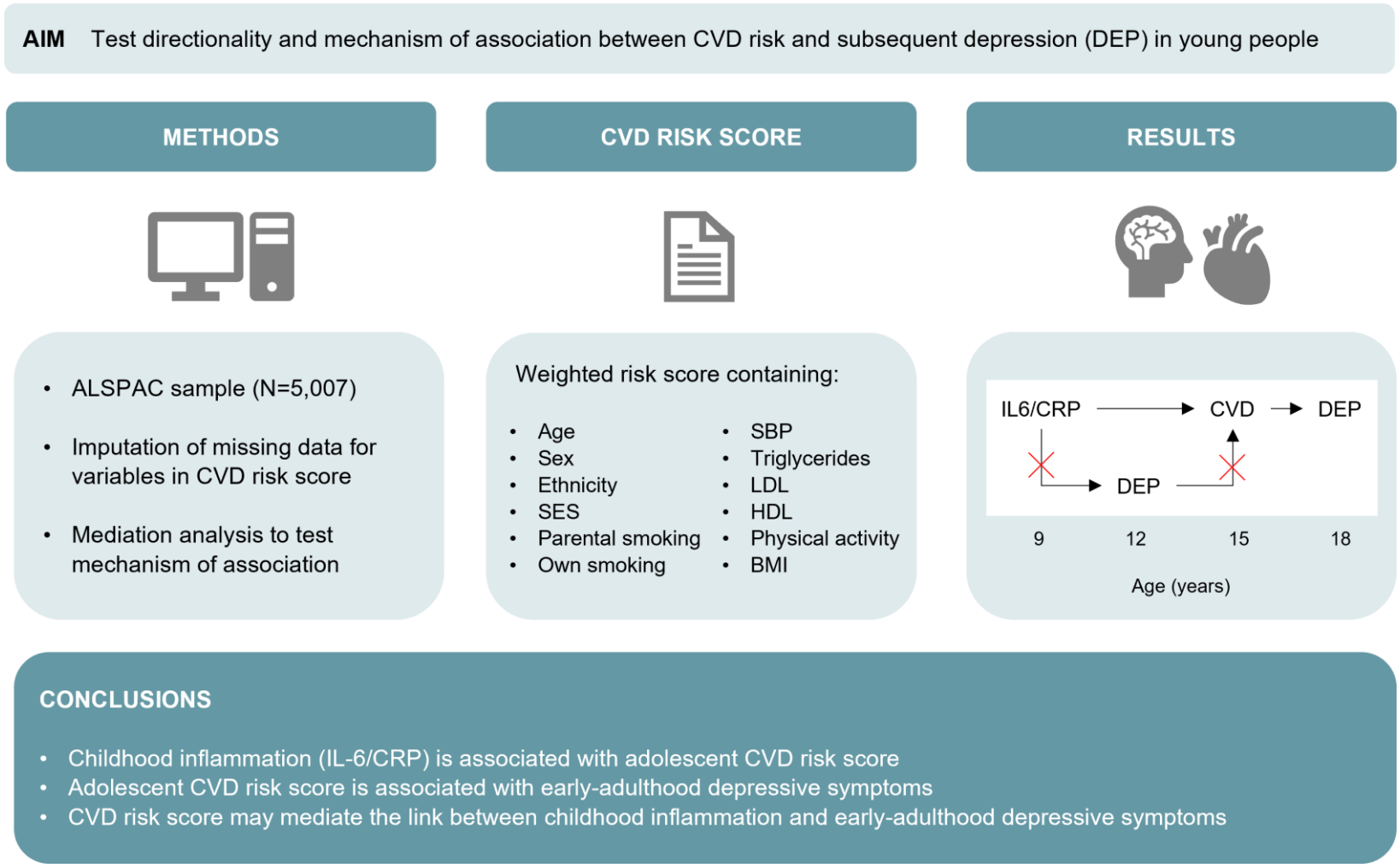


Figure 23. Visual summary of Chapter 4.

4.2 Introduction

Depression and CVD commonly co-occur and are bidirectionally associated in adults. Depression is associated with increased risk of CVD after adjusting for smoking and hypertension (295). Risk of depression is increased after acute myocardial infarction (354,355). It is also a marker of poor prognosis for myocardial infarction (296). Therefore, these conditions are likely to share risk factors and pathophysiologic mechanisms (293,294). Genome-wide association studies and epidemiological studies have reported relatively small genetic correlation between depression and CVD (294,300,356), suggesting that shared environmental risk factors are key to this comorbidity.

Despite a large number of studies testing the links CVD and depression in adults, the association between CVD risk factors and depression in young people remains poorly understood. Existing studies of CVD risk factors and depression in young people have often focused on individual risk factors. Current/past smoking has been linked with increased risk of depression in longitudinal studies of adolescents (307,317,357). Longitudinal studies have also reported an association between high BMI and subsequent depression in both girls and boys (318,320,324,332). One study reported association between SBP and depression only in children/adolescents with parental history of depression (322). No obvious link between total cholesterol and depression has been found in adolescents (358). However, studies of other CVD risk factors, such as HDL, low-density lipoprotein (LDL) and triglycerides, and depression in young people are lacking.

While the concept of a composite CVD risk score for adults is well established in clinical practice (359), to my knowledge, no study has considered a variety of CVD risk factors in adolescents to determine their combined effect on subsequent mental health outcomes in young people. Rarer still are studies testing the direction of association between CVD risk and depression in young people. This work is important as this may provide clues regarding the origin of the comorbidity between CVD and depression. Studies based on young people

are particularly advantageous as this age group is relatively less affected by confounders commonly present in older people, such as physical multi-morbidity.

Childhood determinants of adult CVD risk include a range of physical and social factors. The International Childhood Cardiovascular Cohort (i3C) Consortium was established to identify early-life risk factors associated with ideal cardiovascular health as defined by the AHA (360). A study of three i3C cohorts explored the association of the following factors with adult CVD risk: sex, age, ethnicity, family socioeconomic status, smoking, smoking, diet, BMI, SBP, HDL, LDL, and triglycerides (361). This study reported that family socioeconomic status and smoking in childhood were independently associated with adult cardiovascular health (361). Socioeconomic status and smoking are key indicators of social factors related to long term health outcomes, so called social determinants of health, which have been linked to depression in other studies (362).

In addition to social factors, which are important determinants of physical and mental health, biological processes could represent important shared mechanisms for CVD risk and depression. Inflammation could be one such mechanism, which is associated with both depression and CVD in adults. Using Mendelian randomisation analysis of data from the UK Biobank cohort, members of my lab group recently reported that inflammation and triglycerides could be shared risk factors for depression and IHD (294). Circulating markers of inflammation such as IL-6 and CRP are associated with depression and CVD in adults (63,168,363,364). Demonstrating an association between systemic inflammatory markers in childhood and subsequent CVD risk in young people would support the idea that childhood inflammation could be a shared mechanism for CVD and depression, but such studies are scarce.

Using prospective data from ALSPAC (272), I investigated the directionality and potential mechanism of association between a range of CVD risk factors and depression in young people (Figure 24). Regarding direction of association, I have tested: (i) association between CVD risk score at age 15 years and depressive symptoms at age 18 years; and (ii)

association between depressive symptoms at age 12 years and CVD risk score at age 15 years. I hypothesised that similar to adults there will be evidence for bidirectional association between CVD risk score and depression in young people. Regarding mechanism of association, I have tested associations of IL-6 and CRP levels at age 9 years with depressive symptoms at age 12 years and with CVD risk score at age 15 years. In addition, I tested the mediating effect of CVD risk score at age 15 years on the association between inflammatory markers at age 9 years and depressive symptoms at age 18 years. In line with the idea that inflammation could be a shared mechanism for depression and CVD, I hypothesised that childhood inflammatory markers would be associated with CVD risk score subsequently in mid-adolescence, and that childhood inflammatory markers increase depression risk in late-adolescence by influencing CVD risk score in mid-adolescence.

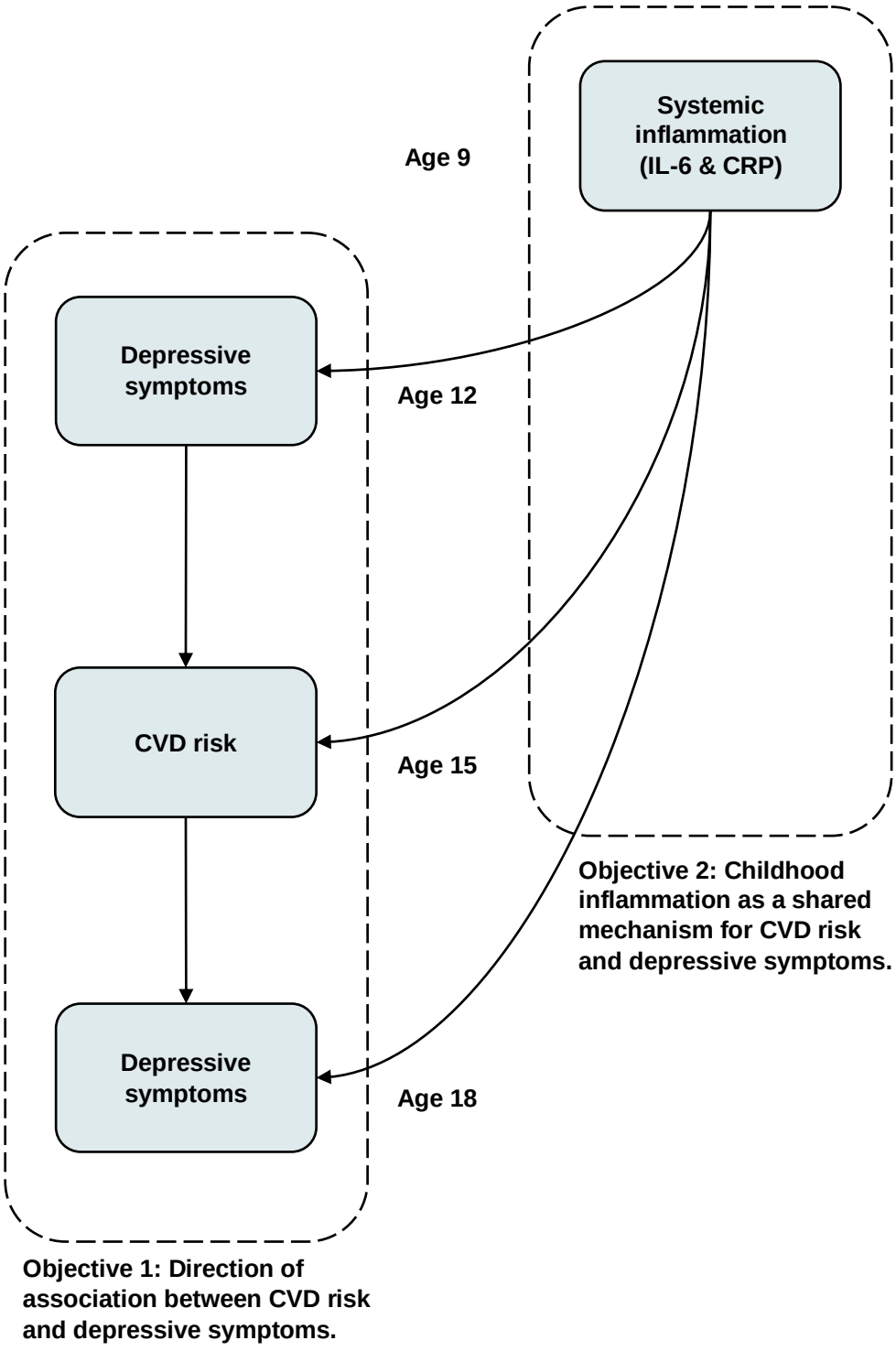


Figure 24. Conceptual model and objectives for analyses (age in years).

4.3 Hypotheses

1. Depressive symptoms at age 12 years are associated with CVD risk at age 15 years.
2. CVD risk at age 15 years is associated with depressive symptoms at age 18 years.
3. IL-6 at age 9 years is associated with depressive symptoms at age 12 and 18 years.
4. CRP at age 9 years is associated with depressive symptoms at age 12 and 18 years.
5. IL-6 at age 9 years is associated with CVD risk at age 15 years.
6. CRP at age 9 years is associated with CVD risk at age 15 years.
7. CVD risk at age 15 years mediates the association between IL-6 at age 9 years and depressive symptoms at age 18 years.
8. CVD risk at age 15 years mediates the association between CRP at age 9 years and depressive symptoms at age 18 years.

4.4 Methods

4.4.1 Description of sample

The primary risk set for this study comprised 5,007 unrelated individuals from the ALSPAC cohort with CVD risk scores computed after imputation of missing data for individual risk factors (Figure 25). Of the risk set 3,462 participants completed assessments at age 18 years for depressive symptoms. I repeated the analyses based on 1,810 participants with complete original data on all CVD risk factors.

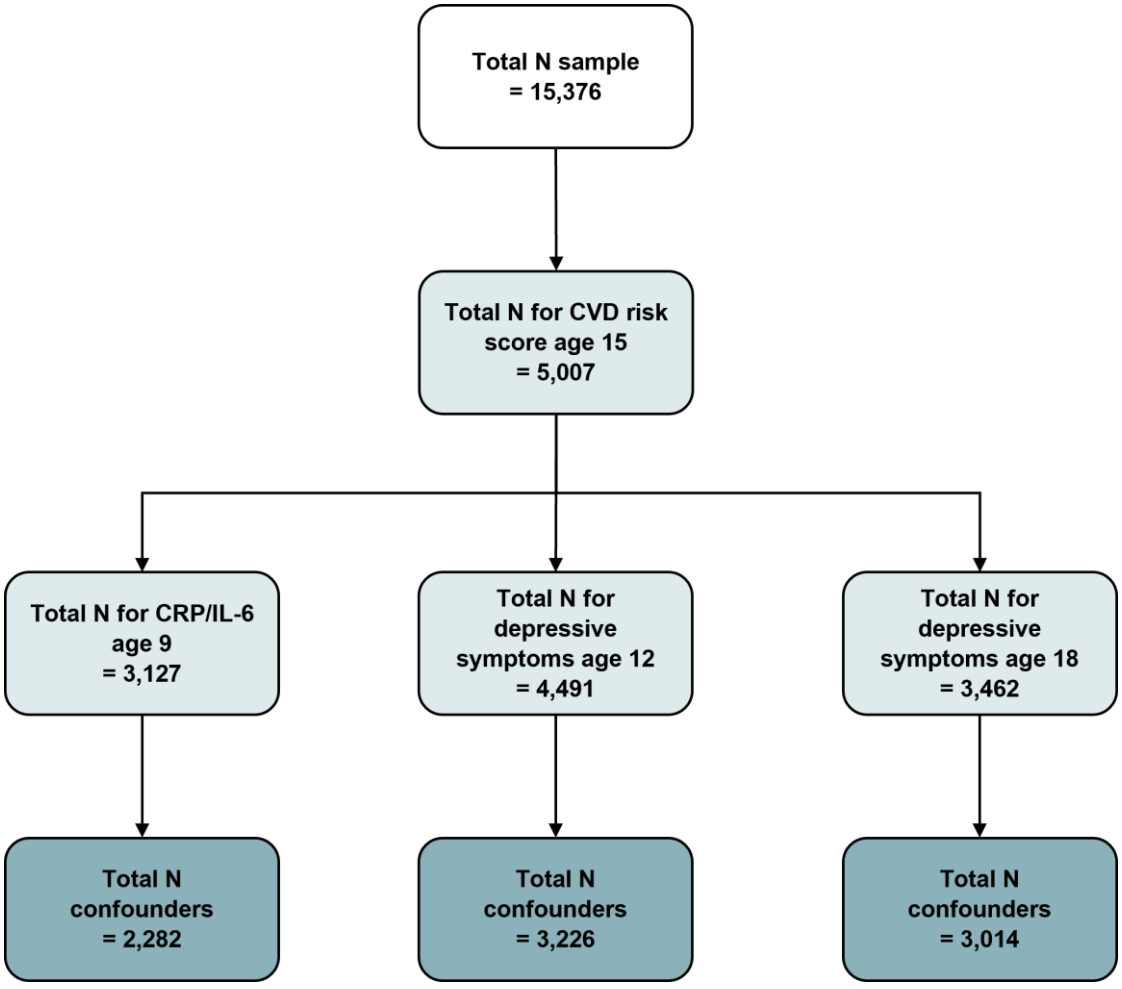


Figure 25. Flow chart showing inclusion of study participants after imputation.

4.4.2 Assessment of CVD risk factors at age 15 years

CVD risk factors were selected based on the AHA criteria for ideal cardiovascular health (29). The CVD risk score included: age, ethnicity, maternal SEP, maternal smoking, own smoking, physical activity, BMI, SBP, LDL, HDL, and triglycerides. All variables were measured at age 15 years, except ethnicity, maternal smoking, and maternal SEP which were assessed at birth.

Age (years) was used as a continuous variable. Self-reported ethnicity was originally coded as White, Black African, Black Caribbean, Black Other, Bangladeshi, Chinese, Indian, Pakistani, and Other. Ethnicity was recoded as a binary variable (0 = White; 1 = any other ethnicity) due to low counts for ethnicities other than White. Self-reported maternal SEP was documented using Office of National Statistics categories (365). Maternal SEP was recoded as a binary variable (0 = non-manual [I, II or IIIa]; 1 = manual [IIIb, IV or V]). Members of the armed forces (N = 4) were excluded because this category was so small.

Mothers self-reported frequency of smoking during the first three months of pregnancy and again during the last two months of pregnancy (no cigarettes per day; 1 to 4 cigarettes per day; 5 to 9 cigarettes per day; 10 to 14 cigarettes per day; 5 to 19 cigarettes per day; 20 to 24 cigarettes per day; 25 to 29 cigarettes per day; ≥30 cigarettes per day). Maternal smoking was used as a binary variable (0 = non-smoker at both time points; 1 = smoker at one or both time points). Own smoking was self-reported during the child-completed questionnaire and coded as an ordered categorical variable (no cigarettes/day; 1 to 5 cigarettes per day; 6 to 10 cigarettes per day; >10 cigarettes per day). Own smoking was also used as a binary variable (0 = non-smokers; 1 = smokers).

Participants self-reported frequency of physical activity during the past year (5 or more times per week; 1 to 4 times per week; 1 to 3 times per month; <1 time per month). A binary measure of weekly exercise was created for analysis (0 = exercise at least once per week; 1 = exercise less than weekly).

BMI, SBP, HDL, LDL, and triglycerides were all used as standardised continuous variables. To calculate BMI, weight was measured on Tania scales and height was measured using a Harpenden stadiometer. SBP was taken twice using a Dinamap 9301 Vital Signs Monitor (Morton Medical, London) and the mean of the two measurements was used in analysis. HDL, LDL and triglyceride concentrations were measured from fasting blood test as previously described (366).

4.4.3 Assessment of depressive symptoms at age 12 years

Depressive symptoms were self-reported using the Short Mood and Feelings Questionnaire (SMFQ) (367) at age 12 years. The SMFQ is an age-appropriate, widely used and validated tool. It comprises 13 items covering core symptoms of depression and anxiety experienced in the past two weeks. Each item is scored 0 (not true), 1 (sometimes true) or 2 (true) giving a total score of 0 to 26. Depressive symptoms score was used as a standardised continuous variable.

4.4.4 Assessment of depressive symptoms at age 18 years

Depressive symptoms were measured using a self-administered computerised version of the Clinical Interview Schedule Revised (CIS-R) (368,369). The CIS-R is a widely used, fully-structured assessment for measuring depression in large community samples (369). The CIS-R includes questions about a range of symptoms including depression, depressive thoughts, fatigue, concentration, and sleep problems. CIS-R sums these symptoms scores to provide a total depressive symptoms score (0 to 21), reflecting the severity of depressive symptoms in the past week. Depressive symptoms score was used as a standardised continuous variable.

CIS-R also provides diagnosis of depressive episode (mild, moderate, or severe) according to ICD-10 criteria. Depression diagnosis was used for presentation purposes in Table 8 only.

4.4.5 Assessment of inflammatory markers at age 9 years

IL-6 and CRP were assayed from the blood samples collected from non-fasting participants. The blood samples were spun and frozen at −80°C. After a median of 7.5 years in storage with no previous freeze-thaw cycles, IL-6 and CRP levels were measured by enzyme-linked immunosorbent assay (R&D Systems), and automated particle-enhanced immunoturbidimetric assay (Roche) respectively (168). IL-6 and CRP variables were log-transformed for analysis.

4.4.6 Assessment of potential confounders

Using the modified disjunctive cause criteria (370), I selected the following confounders for adjustment: sex, birthweight, maternal education, Strengths and Difficulties Questionnaire (SDQ) total difficulties score at age 7 years, and family history of CVD. Variables in the CVD risk score were not included as confounders to prevent over-adjustment.

Sex and birthweight were assessed at birth. Sex was coded as a binary variable. Birthweight (grams) was extracted from routine hospital birth records. Maternal education was self-reported at 32 weeks gestation as a categorical variable reflecting highest educational attainment (CSE/none; vocational; O-level; A-level; university degree). Mothers completed the parental version of the SDQ when their child was age 7 years. The SDQ is an age-appropriate, valid, and reliable tool for measuring psychological and behavioural problems in young children (371). It measures problems in four domains: emotional, conduct, hyperactivity, and social/peer group. Total difficulties score (0 to 40) was used as a standardised continuous variable. Family history of CVD (hypertension, diabetes, high cholesterol, or vascular disease) was self-reported by participants at the age 18 years clinic assessment as a binary variable.

4.4.7 Statistical analysis

All analyses were carried out using R version 3.6.1.

4.4.7.1 Imputation of CVD risk factors at age 15 years

At least one CVD risk factor was available for 5,007 participants but complete CVD risk scores were available for only 1,810 participants. Analyses were conducted after imputation of missing data for CVD risk variables (ethnicity, maternal SEP, maternal smoking, own smoking, physical activity, BMI, SBP, LDL, HDL, and triglycerides). Age had no missing data. The percentage of missing data across the CVD risk factors varied between 2% and 36% (Table 6).

Table 6. Missing data in the risk set before imputation (N = 5,007).

CVD risk factor [a]	Missing data (no. participants)	Missing data (%)
Age (years)	0	0
BMI (kg/m^2)	84	1.7
Ethnicity (White vs any other ethnicity)	152	3.0
SBP (mmHg)	176	3.5
Maternal smoking (no vs yes)	294	5.9
Maternal SEP (non-manual vs manual)	743	14.8
Own smoking (no vs yes)	1,540	30.8
Physical activity (weekly vs less than weekly)	1,588	31.7
LDL (mmol/L)	1,823	36.4
HDL (mmol/L)	1,823	36.4
Triglycerides (mmol/L)	1,823	36.4
Total missing data	-	20.1

[a] BMI: body mass index; CVD: cardiovascular disease; CI: confidence intervals; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure; SEP: socioeconomic position.

I used the fully conditional MCMC method for multiple imputation of the CVD risk variables. I included auxiliary variables that were indicators of missingness (financial difficulties, life events, family income, and housing/living conditions) as well as confounder and outcome variables.

I used the “mice” package version 3.0 to create and analyse the multiply imputed datasets (277). Missing data were present in 20% of participants, so I used 20 imputations as recommended (372). I used predictive mean matching with 10 donors and type one matching. I separately estimated the parameters of interest in each dataset before combining using Rubin’s rules.

4.4.7.2 Calculation of CVD risk score at age 15 years

CVD risk factors were weighted based on their reported association with AHA ideal cardiovascular health from three i3C cohorts (Table 7) (360,361). I summed the weighted CVD risk factors and applied z-transformation to create a standardised CVD risk score.

Seven i3C longitudinal cohort studies examine CVD risk factors in younger adults (360). The cohorts present beta estimates reflecting the association between CVD risk factors and AHA ideal cardiovascular health (29). One study combined three of these cohorts (Young Finns study, Childhood Determinants of Adult Health study, and the Princeton Follow-Up study) to give beta estimates for specific risk factors, adjusted for all other risk factors (361). Physical activity was adjusted for sex and age only. I used the relevant beta estimate(s) from this study as weights for our CVD risk factors (Table 7). I used fixed effects meta-analysis as appropriate to combine multiple beta estimates.

I used BMI instead of waist circumference to match i3C cohort measurements (Figure 26). Sex and family history of CVD were excluded from the CVD risk score because they independently produced distinct binomial distributions when they were included. Female sex is strongly associated with worse mental health outcomes while male sex is associated with increased CVD risk score. Fruit and vegetable consumption was also measured in the i3C Consortium but was not included in our CVD risk score due to the complexity of ALSPAC’s diet-related variables.

Table 7. Beta coefficients used as weights in the CVD risk score based on the association between risk factors from i3C Consortium cohorts and AHA ideal cardiovascular health.

CVD risk factor [a]	Beta (p-value)			Beta coefficient used as weight in CVD risk score [d]
	YFS (N = 1668)	CDAH (N = 1365)	PFS (N = 659)	
Age (years)	-0.04 (0.67)	0.06 (<0.01)	0.03 (0.09)	0.02
Sex (female vs male)	-1.06 (0.07)	-0.99 (0.06)	-0.83 (0.09)	-0.98
Ethnicity (White vs African American) [b]	-	-	-0.16 (0.18)	-0.16
SEP	0.21 (<0.01)	0.13 (<0.01)	0.12 (<0.01)	0.09 [e]
Parental smoking (no vs yes)	-0.26 (<0.01)	-0.10 (0.12)	-	-0.18
Own smoking (no vs yes)	-	-0.38 (0.12)	-	-0.38
BMI (kg/m^2)	-0.08 (0.42)	-0.10 (<0.01)	-0.07 (<0.01)	-0.08
SBP (per 10 mm/Hg)	-0.09 (<0.01)	-	-	-0.09
LDL (mmol/l)	-0.25 (<0.01)	-	-0.10 (0.09)	-0.19
HDL (mmol/l)	-	-	0.27 (0.09)	0.27
Triglycerides (mmol/l)	-0.17 (0.16)	-	-0.09 (0.45)	-0.13
Physical activity	0.01 (0.81) [c]	-0.01 (0.24) [c]	-	-0.01

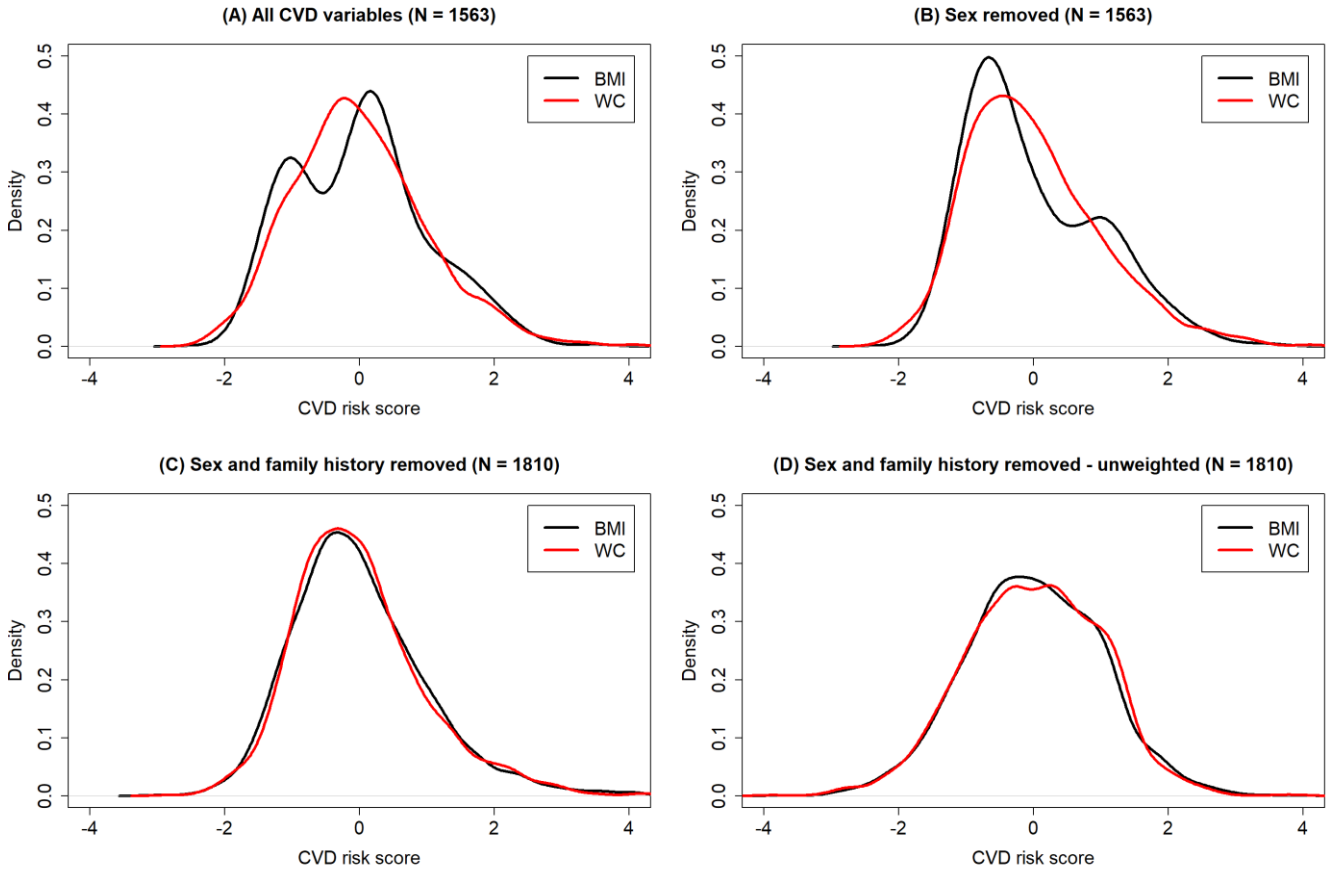
[a] BMI: body mass index; CDAH: Childhood Determinants of Adult Health study; CVD: cardiovascular disease; LDL: low-density lipoprotein; HDL: high-density lipoprotein; PFS: Princeton Follow-up Study; SBP: systolic blood pressure; SEP: socioeconomic position; YFS: Young Finns Study.

[b] Due to a lack of comparable published data from the UK, the i3C Consortium estimate for ethnicity (White vs African American) was interpreted as equivalent to White vs any other ethnicity.

[c] Estimates adjusted for age and sex only. YFS (N = 1810) measured the variable as physical activity index whereas CDAH (N = 1417) measured the variable as physical activity hours per week.

[d] Fixed effects meta-analysis used as appropriate to combine multiple estimates.

[e] Rescaled coefficient to reflect ALSPAC measure of maternal SEP since family income data is not available in ALSPAC.



All CVD variables refers to age, ethnicity, maternal socioeconomic position, maternal smoking, own smoking, physical activity, BMI/WC, systolic blood pressure, LDL, HDL, triglycerides, sex, and family history of CVD.

Figure 26. Distribution of CVD risk score including BMI or waist circumference (WC) under different conditions.

4.4.7.3 Direction of association between CVD risk and depressive symptoms

I used linear regression to assess the stability of depressive symptoms at age 12 and 18 years. Regression models were adjusted for sex, birthweight, maternal education, and SDQ total difficulties score at age 7 years.

I used linear regression to assess the association between depressive symptoms at age 12 years and CVD risk at age 15 years (Hypothesis 1, Page 116). Regression models were adjusted for sex, birthweight, maternal education, and family history of CVD.

I used linear regression to assess the association between CVD risk at age 15 years (composite risk score and individual risk factors) and depressive symptoms at age 18 years (Hypothesis 2). Regression models were adjusted for sex, birthweight, maternal education, and SDQ total difficulties score at age 7 years.

For continuous exposures, the beta estimates represent change in outcome (in SD) per one SD increase in exposure. For binary exposures, the beta estimates represent change in outcome (in SD) for presence of risk factor compared with its absence.

4.4.7.4 Association of inflammatory markers at age 9 years with depressive symptoms at age 12 or 18 years

Regression models were estimated before and after adjustment for sex, birthweight, maternal education, and total difficulties score at age 7 years. I used linear regression to assess the association between IL-6/CRP concentration at age 9 years and depressive symptoms at age 12 or 18 years (Hypothesis 3, 4). The beta estimates represent change in depressive symptoms (in SD) per unit increase in log-transformed IL-6/CRP values.

4.4.7.5 Association of inflammatory markers at age 9 years with CVD risk score at age 15 years

Regression models were estimated before and after adjustment for sex, birthweight, maternal education, and family history of CVD. I used linear regression to assess the

association between IL-6/CRP concentration at age 9 years and CVD risk score at age 15 years (Hypothesis 5, 6). The beta estimates represent change in CVD risk score (in SD) per unit increase in log-transformed IL-6/CRP values.

4.4.7.6 Mediation analysis testing mediating effects of CVD risk score at age 15 years on the association between inflammatory markers at age 9 years and depressive symptoms at age 18 years

I conducted mediation analysis to test whether CVD risk score at age 15 years mediates the relationship between IL-6/CRP at age 9 years and depressive symptoms at age 18 years (Hypothesis 7, 8). Mediation models were computed before and after adjustments for sex, birthweight, maternal education, and total difficulties score at age 7 years. I analysed mediation within a path analysis framework using the “lavaan” R package (283). Lavaan uses full information maximum likelihood procedures to handle missing data (283). Non-parametric bootstrapping, based on 1,000 bootstrap replicates, was used to calculate SE.

4.5 Results

4.5.1 Characteristics of the sample

Individuals meeting the ICD-10 criteria for depression at age 18 years, compared with those without depression, were more likely be female, be smokers, have mothers who smoked, have higher SDQ total difficulties score at age 7 years, and have higher BMI and lower SBP at age 18 years (Table 8).

4.5.2 CVD risk score at age 15 years

Females had slightly higher CVD risk scores than males (Figure 27). In the complete case set, the mean CVD risk score for females was 0.02 (SD = 1.04) and for males was –0.02 (SD = 0.95). After imputation (N = 5,007), the mean CVD risk score for females was 0.03 (SD = 1.04) and for males was –0.03 (SD = 0.95).

Table 8. Characteristics of the participants prior to imputation and using maximum available sample for each variable.

Characteristics [a]	All participants (N = 5,007) [c]	Without depression at age 18 (N = 3,208)	With depression at age 18 (N = 254) [d]	Difference between groups with and without depression at age 18 (T-test / X^2 p-value)
Potential confounders				
Sex – no. female (%)	2,639 (52.7)	1,725 (53.8)	189 (74.4)	<0.001
Birthweight (kg) – mean (SD)	3.4 (0.5)	3.4 (0.5)	3.4 (0.6)	0.66
Total difficulties score at age 7 (SQD) – mean (SD)	7.3 (4.7)	7.1 (4.5)	7.9 (5.1)	0.01
Maternal education – no. with less than O-level (%)	939 (19.3)	536 (17.1)	44 (17.7)	0.04
Family history of CVD – no. (%)	1,080 (29.9)	902 (29.3)	80 (32.4)	0.32
CVD risk factors [b]				
CVD risk score – mean (SD)	0.0 (1.0)	-0.03 (1.0)	-0.01 (1.0)	0.84
Age (years) – mean (SD)	15.5 (0.3)	15.5 (0.3)	15.5 (0.3)	0.39
BMI (kg/m^2) – mean (SD)	21.4 (3.5)	21.3 (3.4)	21.8 (3.7)	0.03
SBP (mmHg) – mean (SD)	122.9 (10.9)	123.1 (10.7)	121.2 (11.0)	0.01
LDL (mmol/L) – mean (SD)	2.1 (0.6)	2.1 (0.5)	2.1 (0.6)	0.11
HDL (mmol/L) – mean (SD)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	0.89
Triglycerides (mmol/L) – mean (SD)	0.8 (0.4)	0.8 (0.4)	0.8 (0.3)	0.82
Ethnicity – no. White (%)	4,763 (98.1)	3,062 (97.9)	243 (98.4)	0.59

Maternal SEP – no. manual (%)	642 (15.1)	404 (14.5)	33 (15.6)	0.67
Maternal smoking – no. smokers (%)	751 (15.9)	428 (14.0)	56 (23.7)	<0.01
Own smoking – no. smokers (%)	409 (11.8)	250 (9.8)	43 (22.3)	<0.001
Physical activity – no. less than weekly exercise (%)	792 (23.2)	551 (22.0)	50 (26.6)	0.17
Depressive symptoms				
SMFQ score at age 12 – mean (SD)	4.0 (3.8)	3.8 (3.7)	5.9 (4.9)	<0.001
CIS-R score at age 18 – mean (SD)	3.1 (3.9)	2.4 (2.9)	12.1 (3.3)	<0.001
Inflammatory markers				
IL-6 at age 9 (pg/mL) – mean (SD)	1.3 (1.6)	1.3 (1.5)	1.3 (1.4)	0.87
CRP at age 9 (mg/L) – mean (SD)	0.8 (2.7)	0.7 (1.9)	1.0 (4.3)	0.38
CRP at age 15 (mg/L) – mean (SD)	1.2 (3.8)	1.2 (3.6)	1.3 (3.7)	0.92

[a] BMI: body mass index; CIS-R: Clinical Interview Schedule-Revised; CRP: C-reactive protein; CVD: cardiovascular disease; DAWBA: Development and Wellbeing Assessment; HDL: high-density lipoprotein; IL-6: interleukin-6; LDL: low-density lipoprotein; SBP: systolic blood pressure; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire; SEP: socioeconomic position; SMFQ: Short Mood and Feelings Questionnaire.

[b] All CVD risk factors were assessed at age 15 years except ethnicity, maternal smoking, and maternal SEP which were assessed at birth.

[c] Not all participants have information about depression at age 18 years. The total number of participants (N = 5004) is therefore greater than the combined number of participants with and without depression (N = 3462).

[d] For the purposes of this table, depression is defined as ICD-10 mild/moderate/severe depression diagnosis at age 18 years.

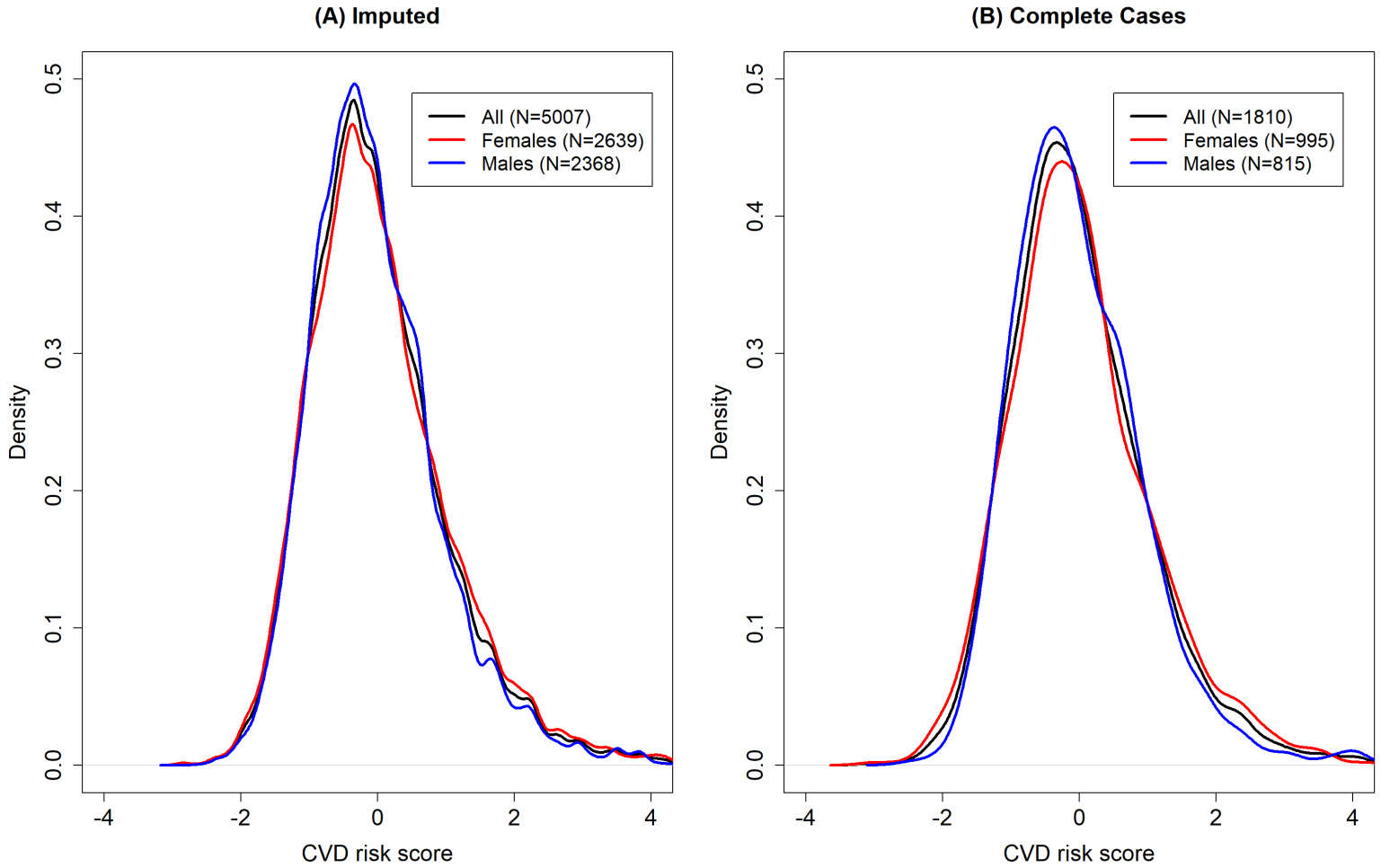


Figure 27. CVD risk score distribution at age 15 years (A) after imputation and (B) in complete cases.

4.5.3 Stability of depressive symptoms between ages 12 and 18 years

In the total sample (N = 2,844), depressive symptoms at age 12 years were associated with depressive symptoms at age 18 years (adjusted beta = 0.18; SE = 0.01; p <0.001) (Table 9). Depressive symptoms at age 12 years were also associated with depressive symptoms in sex-stratified analyses. Similarly, depressive symptoms at age 12 and 18 years were positively correlated (r = 0.28; 95% CI = 0.24, 0.31; p <0.001).

Table 9. Beta estimates (SE) for the association between depressive symptoms at age 12 and 18 years.

Participants	Sample (no.)	Unadjusted		Adjusted [a]	
		Beta (SE)	P-value	Beta (SE)	P-value
All	2,844	0.21 (0.01)	<0.001	0.18 (0.01)	<0.001
Female	1,549	0.20 (0.02)	<0.001	0.19 (0.02)	<0.001
Male	1,295	0.17 (0.02)	<0.001	0.17 (0.02)	<0.001

[a] Adjusted for sex (if applicable), birthweight, maternal education, and SDQ total difficulties score at age 7 years.

4.5.4 Direction of association between CVD risk and depressive symptoms

The analyses in this section are relevant to hypotheses 1 and 2 (Section 4.3, Page 116).

4.5.4.1 Association between depressive symptoms at age 12 years and CVD risk score at age 15 years

In the total sample (N = 3,226), depressive symptoms at age 12 years were not associated with CVD risk score at age 15 years (beta = 0.03; SE = 0.02; p = 0.09). Depressive symptoms at age 12 years were also not associated with CVD risk score in sex-stratified analyses (Table 10).

Table 10. Beta estimates (SE) for the association between depressive symptoms at age 12 years and CVD risk score at age 15 years.

Participants	Sample (no.)	Unadjusted		Adjusted [a]	
		Beta (SE)	P-value	Beta (SE)	P-value
All	3,226	0.03 (0.02)	0.09	0.03 (0.02)	0.11
Female	1,760	0.03 (0.02)	0.21	0.03 (0.02)	0.18
Male	1,466	0.03 (0.03)	0.35	0.03 (0.03)	0.34

[a] Adjusted for sex (if applicable), birthweight, maternal education, and family history of CVD.

4.5.4.2 Association between CVD risk score at age 15 years and depressive symptoms at age 18 years

In the total sample (N = 3,014), CVD risk score at age 15 years was associated with depressive symptoms score at age 18 years (beta = 0.07; SE = 0.02; p <0.001) (Table 11). Evidence for this association remained after adjusting for confounders (adjusted beta = 0.06; SE = 0.02; p <0.001).

In sex-stratified analysis, CVD risk score was associated with depressive symptoms at age 18 years in females (beta = 0.09; SE = 0.02; p <0.001) but not in males (beta = 0.03; SE = 0.02; p = 0.14). In females, evidence for association remained after adjusting for confounders (adjusted beta = 0.08; SE = 0.02; p <0.001).

Table 11. Beta estimates (SE) for the association between CVD risk score at age 15 years and depressive symptoms at age 18 years.

Participants	Sample (no.)	Unadjusted		Adjusted [a]	
		Beta (SE)	P-value	Beta (SE)	P-value
All	3,014	0.07 (0.02)	<0.001	0.06 (0.02)	<0.001
Female	1,647	0.09 (0.02)	<0.001	0.08 (0.02)	<0.001
Male	1,367	0.03 (0.02)	0.14	0.03 (0.02)	0.21

[a] Adjusted for sex (if applicable), birthweight, maternal education, and SDQ total difficulties score at age 7 years.

4.5.4.3 Association between individual CVD risk factors at age 15 years and depressive symptoms at age 18 years

In the total sample (N = 3,014), depressive symptoms at age 18 years were associated with the following CVD risk factors at age 15 years: own smoking (beta = 0.44; SE = 0.05; p <0.001); maternal smoking (beta = 0.20; SE = 0.04; p <0.001); physical activity (beta = 0.13; SE = 0.04; p <0.001); maternal SEP (beta = 0.11; SE = 0.05; p = 0.03); high LDL (beta = 0.06; SE = 0.02; p <0.001); and high BMI (beta = 0.05; SE = 0.01; p <0.01) (Table 12). After adjusting for confounders, evidence for association remained for own smoking (adjusted beta = 0.39; SE = 0.05; p <0.001) and maternal smoking only (adjusted beta = 0.17; SE = 0.04; p <0.001).

In sex-stratified analysis, own smoking, maternal smoking, high BMI, and low HDL were associated with depressive symptoms in females (Table 12). Evidence for association remained for own smoking, maternal smoking, and BMI after adjusting for confounders. In males, own smoking was associated with depressive symptoms. Evidence for association remained after adjusting for confounders.

Table 12. Beta (SE) for the association between CVD risk factors at age 15 years and depressive symptoms at age 18 years.

CVD risk factor [a, b]	All participants (N = 3,014)				Females (N = 1,647)				Males (N = 1,367)			
	Unadjusted		Adjusted [c]		Unadjusted		Adjusted [c]		Unadjusted		Adjusted [c]	
	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Own smoking (no vs yes)	0.44 (0.05)	<0.001	0.39 (0.05)	<0.001	0.47 (0.07)	<0.001	0.44 (0.07)	<0.001	0.30 (0.08)	<0.001	0.29 (0.08)	<0.001
Maternal smoking (no vs yes)	0.20 (0.04)	<0.001	0.17 (0.04)	<0.001	0.32 (0.06)	<0.001	0.26 (0.06)	<0.001	0.06 (0.06)	0.27	0.06 (0.06)	0.29
Physical activity (weekly vs less than weekly)	0.13 (0.04)	<0.001	0.06 (0.04)	0.16	0.07 (0.05)	0.19	0.04 (0.05)	0.41	0.09 (0.06)	0.15	0.08 (0.06)	0.19
Maternal SEP (non-manual vs manual)	0.11 (0.05)	0.03	0.06 (0.05)	0.23	0.08 (0.06)	0.24	0.03 (0.07)	0.68	0.10 (0.06)	0.11	0.10 (0.06)	0.12
Ethnicity (White vs any other ethnicity)	-0.08 (0.11)	0.45	-0.11 (0.11)	0.33	-0.15 (0.16)	0.35	-0.17 (0.16)	0.27	-0.01 (0.15)	0.92	-0.02 (0.15)	0.92
LDL (mmol/L)	0.06 (0.02)	<0.001	0.03 (0.02)	0.09	0.03 (0.03)	0.28	0.02 (0.03)	0.38	0.04 (0.02)	0.65	0.04 (0.02)	0.08
BMI (kg/m^2)	0.05 (0.02)	<0.01	0.03 (0.02)	0.08	0.06 (0.02)	<0.01	0.05 (0.02)	0.02	-0.01 (0.02)	0.68	-0.01 (0.02)	0.54
Triglycerides (mmol/L)	0.01 (0.02)	0.57	<0.01 (0.02)	0.90	0.01 (0.03)	0.81	<0.01 (0.03)	0.98	<0.01 (0.02)	0.99	-0.01 (0.02)	0.81
SBP (mmHg)	-0.03 (0.02)	0.03	<0.01 (0.02)	0.90	<0.01 (0.02)	0.93	-0.01 (0.02)	0.80	0.01 (0.02)	0.69	0.01 (0.02)	0.71
HDL (mmol/L)	-0.01 (0.02)	0.76	-0.05 (0.02)	0.03	-0.05 (0.03)	0.05	-0.05 (0.03)	0.08	-0.04 (0.03)	0.10	-0.04 (0.03)	0.12

Age (years)	-0.01 (0.02)	0.57	-0.02 (0.02)	0.21	<0.01 (0.03)	0.92	<0.01 (0.03)	0.88	-0.05 (0.03)	0.08	-0.05 (0.03)	0.05

[a] BMI: body mass index; CVD: cardiovascular disease; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure; SE: standard error; SEP: socioeconomic position.

[b] LDL, BMI, triglycerides, SBP, HDL, and age were used as standardised continuous variables (per SD increase in exposure). Own smoking, maternal smoking, physical activity, maternal SEP, and ethnicity were used as binary variables. The outcome for all analyses was standardised depressive symptoms score (per SD increase in outcome).

[c] Adjusted for sex (if applicable), birthweight, maternal education, and SDQ total difficulties score at age 7 years.

4.5.5 Mechanism of association between CVD risk and depressive symptoms

The analyses in this section are relevant to hypotheses 3 to 8 (Section 4.3, Page 116).

4.5.5.1 Associations between inflammatory markers at age 9 years and depressive symptoms at age 12 or 18 years

In the total sample (N = 2,574), IL-6 concentration at age 9 years was associated with depressive symptoms at age 12 years (beta = 0.13; SE = 0.05; p <0.01) (Table 13). Evidence for association did not remain after adjusting for confounders. In the total sample (N = 2,574), CRP concentration at age 9 years was not associated with depressive symptoms at age 12 years (beta = 0.06; SE = 0.04; p = 0.12) (Table 13).

In the total sample (N = 2,004), IL-6 concentration at age 9 years was associated with depressive symptoms at age 18 years (beta = 0.13; SE =0.05; p <0.01) (Table 13). Evidence for association did not remain after adjusting for confounders. In the total sample (N = 2,004), CRP concentration at age 9 years was not associated with depressive symptom at age 18 years (beta = 0.03; 0.03; p = 0.40) (Table 13).

Table 13. Beta estimate (SE) for the association between 1 unit increase in IL-6/CRP concentration at age 9 years and depressive symptoms at age 12 or 18 years.

Model [a]	Participants	Sample (no.)	Unadjusted		Adjusted [b]	
			Beta (SE)	P-value	Beta (SE)	P-value
IL-6 at age 9 → DEP at age 12	All	2,574	0.13 (0.05)	<0.01	0.08 (0.05)	0.11
	Female	1,303	0.17 (0.08)	0.03	0.15 (0.08)	0.06
	Male	1,271	0.03 (0.07)	0.62	0.02 (0.07)	0.76
IL-6 at age 9 → DEP at age 18	All	2,004	0.13 (0.05)	<0.01	0.06 (0.05)	0.19
	Female	1,068	0.14 (0.07)	0.05	0.11 (0.07)	0.14
	Male	936	0.02 (0.06)	0.66	0.02 (0.06)	0.73
CRP at age 9 → DEP at age 12	All	2,574	0.06 (0.04)	0.12	0.01 (0.04)	0.79
	Female	1,303	0.08 (0.06)	0.15	0.07 (0.06)	0.21
	Male	1,271	-0.04 (0.05)	0.44	-0.05 (0.05)	0.31
CRP at age 9 → DEP at age 18	All	2,004	0.03 (0.03)	0.40	-0.04 (0.03)	0.25
	Female	1,068	0.02 (0.03)	0.75	<0.01 (0.05)	0.96
	Male	936	-0.07 (0.04)	0.08	-0.08 (0.04)	0.07

[a] CRP: C-reactive protein; DEP: depressive symptoms; IL-6: interleukin-6.

[b] Adjusted for sex (if applicable), birthweight, maternal education, and SDQ total difficulties score at age 7 years.

4.5.5.2 Associations between inflammatory markers at age 9 years and CVD risk at age 15 years

In the total sample (N = 2,282), IL-6 concentration at age 9 years was associated with CVD risk score at age 15 years (beta = 0.32; SE = 0.05; p <0.001) (Table 14). In the total sample (N = 2,282), CRP concentration at age 9 years was also associated with CVD risk score at age 15 years (beta = 0.40; SE = 0.04; p <0.001) (Table 14). Evidence for these associations remained after adjusting for confounders.

Table 14. Beta estimate (SE) for the association between 1 unit increase in IL-6/CRP concentration at age 9 years and CVD risk score at age 15 years.

Exposure at age 9	Participants	Sample (no.)	Unadjusted		Adjusted [a]	
			Beta (SE)	P-value	Beta (SE)	P-value
IL-6	All	2,282	0.32 (0.05)	<0.001	0.30 (0.05)	<0.001
	Female	1,244	0.42 (0.08)	<0.001	0.40 (0.08)	<0.001
	Male	1,038	0.20 (0.08)	<0.01	0.21 (0.07)	<0.01
CRP	All	2,282	0.40 (0.04)	<0.001	0.39 (0.04)	<0.001
	Female	1,244	0.42 (0.06)	<0.001	0.41 (0.06)	<0.001
	Male	1,038	0.37 (0.06)	<0.001	0.36 (0.06)	<0.001

[a] Adjusted for sex (if applicable), birthweight, maternal education, and family history of CVD.

4.5.5.3 Mediating effect of CVD risk at age 15 years on the association between inflammatory markers at age 9 years and depressive symptoms at age 18 years

In the total sample (N = 2,004), there was evidence that CVD risk score at age 15 years mediated the association of depressive symptoms at age 18 years with both IL-6 (indirect effect: beta = 0.02; SE = 0.01; p = 0.01) and CRP concentration at age 9 years (indirect effect: beta = 0.02; SE = 0.01; p <0.01) (Table 15). Evidence for these associations remained after adjusting for potential confounders.

Table 15. Mediating effects of CVD risk score at age 15 years on the association between IL-6/CRP at age 9 years and depressive symptoms at age 18 years.

Model [a]	Sample (no.)	Type of effect	Unadjusted		Adjusted [b]	
			Beta (SE)	p-value	Beta (SE)	p-value
IL-6 → CVD → DEP	2,004	Direct	0.11 (0.05)	0.02	0.04 (0.05)	0.34
		Indirect	0.02 (0.01)	0.01	0.02 (0.01)	0.02
		Total	0.14 (0.05)	<0.01	0.06 (0.05)	0.19
CRP → CVD → DEP	2,004	Direct	<0.01 (0.04)	0.90	-0.06 (0.03)	0.07
		Indirect	0.02 (0.01)	<0.01	0.02 (0.01)	<0.01
		Total	0.03 (0.03)	0.40	-0.04 (0.03)	0.25

[a] CRP: C-reactive protein at age 9 years; CVD: cardiovascular disease risk score at age 15 years; DEP: depressive symptoms at age 18 years; IL-6: interleukin-6 at age 9 years.

[b] Adjusted for sex (if applicable), birthweight, maternal education, and SDQ total difficulties score at age 7 years.

4.5.6 Sensitivity analysis

I repeated analyses testing the direction of association between CVD risk and depressive symptoms based on the complete case-set (N = 1,810). The pattern of results was broadly similar to the main analyses, although effect sizes were smaller in the complete case-set (Table 16).

Table 16. Beta estimate (SE) for the association between CVD risk score at age 15 years and depressive symptoms at age 12 or 18 years in the complete case-set.

Model [a]	Sample (no.)	Participants	Unadjusted		Adjusted [b]	
			Beta (SE)	P-value	Beta (SE)	P-value
CVD → DEP	1,390	All	0.03 (0.02)	0.18	0.02 (0.02)	0.43
	757	Female	0.03 (0.03)	0.28	0.01 (0.03)	0.65
	633	Male	0.01 (0.03)	0.62	0.01 (0.03)	0.62
DEP → CVD	1,466	All	0.03 (0.03)	0.31	0.02 (0.03)	0.52
	804	Female	0.03 (0.03)	0.42	0.02 (0.03)	0.47
	662	Male	0.01 (0.04)	0.83	<0.01 (0.04)	0.98

[a] CVD: cardiovascular disease at age 15 years; DEP: depressive symptoms at age 12 or 18 years.

[b] Adjusted for sex (if applicable), birthweight, maternal education, and SDQ total difficulties score at age 7 years/family history of CVD as appropriate.

4.6 Discussion

This population-based longitudinal study in young people is one of the first to use a composite CVD risk score to investigate the associations between CVD risk and depressive symptoms in childhood and mid- to late-adolescence. In particular, I tested the direction of association between CVD risk and depressive symptoms and the potential role of childhood inflammation. I report that higher CVD risk score at age 15 years is associated with depressive symptoms subsequently at age 18 years. However, depressive symptoms at age 12 years were not associated with the CVD risk score at age 15 years. I also report that childhood IL-6 and CRP concentration at age 9 years are associated with CVD risk score at age 15 years. Furthermore, elevated IL-6/CRP levels at age 9 years appear to influence the risk of depressive symptoms at age 18 years via CVD risk score at age 15 years. Thus, the findings described above are consistent with hypotheses 2, 5, 6, 7, and 8 but do not support hypotheses 1, 3, and 4 (Section 4.3, Page 116).

The first objective of our analysis was to determine whether CVD risk and depressive symptoms are bidirectionally associated in young people. I report that higher CVD risk in mid-adolescence was associated with depressive symptoms in late-adolescence. Own smoking and maternal smoking were particularly strongly associated with depressive symptoms. The lack of association between depressive symptoms in childhood and subsequent CVD risk in mid-adolescence may suggest a unidirectional relationship in young people, where high CVD risk predicts subsequent depressive symptoms but not the other way around. Our findings are consistent with longitudinal studies reporting that high BMI and smoking are associated with depressive symptoms in young people (307,317,318,320). Other studies have reported an association between depressive symptoms in adolescence and subclinical measures of CVD that predict CVD in adulthood (373). Although I found no evidence of an association between childhood depressive symptoms at age 12 years and subsequent CVD risk in adolescence at age 15 years in this sample, it is possible that

childhood depressive symptoms may have a cumulative effect on CVD risk in young people which is not yet evident by mid-adolescence.

Social factors are important determinants of CVD risk and depression in young people. Mother's educational attainment and SEP have been shown to influence the relationship between CVD risk and depression in childhood (374,375). Consistent with this literature, I found some evidence for an association between low maternal SEP and depressive symptoms in early-adulthood. Low SEP is also associated with maternal smoking (374,375); I discovered that in the ALSPAC sample maternal smoking is associated with subsequent depressive symptoms in the offspring. The idea of programming by early-life factors is consistent with the DOHAD hypothesis of the developmental origins of adult disease (2). Socioeconomic gradients in adiposity and blood pressure exist in children at age 10 years, suggesting that inequalities in CVD risk factors will widen over time, along with depression cases (270). Withdrawal symptoms from smoking are also likely to exert psychological effects including regular mood fluctuations, which may increase risk of developing depression (166,310). In addition, a diet high in trans-fatty acids may contribute to the association between CVD risk and depression via increases in plasma LDL-cholesterol levels, proinflammatory cytokines, and endothelial dysfunction (376). Diverse psychosocial factors therefore influence the development of depression partly through CVD risk factors.

The second part of our analysis focused on childhood inflammation as a potential mechanism for the comorbidity between CVD risk and depression. I report that childhood IL-6 and CRP levels are associated with higher CVD risk score in mid-adolescence, and that adolescent CVD risk score mediates the association between childhood IL-6/CRP levels and depressive symptoms in late-adolescence. Infection and inflammation have been implicated in the pathogenesis of depression (145,168,377) and there is substantial evidence also linking inflammation with CVD risk (196,378,379). Childhood inflammation therefore could be a common risk factor for both depression and CVD. This idea is consistent with the idea that exposure to risk factors during a critical developmental window may alter certain physiologic

system(s) leading to increased risk of chronic illnesses subsequently in adulthood (380). Our findings suggest that inflammation could be one such common pathophysiologic mechanism because IL-6/CRP levels at age 9 years were associated with CVD risk score at age 15 years in this study. A previous study from the same cohort reported that childhood IL-6 levels were associated with depressive symptoms at age 18 years (168).

Inflammation may have different effects on different organs. In the brain, inflammation may lead to symptoms of depression, while inflammatory processes may contribute to changes in the cardiovascular system leading to increased risk of CVD. For instance, human and preclinical studies suggest that systemic inflammation may increase risk of depression by decreasing synaptic serotonin, and by increasing CNS levels of glutamate, excitotoxicity and oxidative stress (119,381). Similarly, inflammation has been reported to be associated with atherosclerosis (382) and endothelial dysfunction (383). Our findings are consistent with this literature suggesting that childhood inflammatory markers may increase the risk of subsequent depressive symptoms in late-adolescence by influencing CVD risk score.

Inflammation and CVD risk in young people may form a vicious cycle that perpetuates pathophysiologic changes and ultimately increase the risk of both CVD and depression in adults. For instance, inflammation is linked with insulin resistance (384). On the other hand, certain CVD risk factors, such as obesity, can also increase inflammation. Obesity has been reported to be associated with increased secretion of inflammatory mediators and low-grade inflammation due to progressive accumulation of adipocytes, macrophages and T lymphocytes in white adipose tissue, muscles and the liver (385). Overweight individuals also have increased gut permeability to bacteria and low bacterial diversity which further contribute to systemic inflammation (385).

4.6.1 Limitations

Our analysis is not without limitations. First, BMI was used in the CVD risk score as a measure of central adiposity. BMI is not necessarily the most appropriate measure to use, particularly in adolescents. However, using waist circumference instead of BMI made no difference to the CVD risk score distribution. In addition, although the AHA cardiovascular health guidelines have been shown to be applicable to CVD risk in younger adults, data on diet were not available to me and were not included in the CVD risk score. Relatively few participants had complete data, reducing statistical power. I attempted to address this issue by multiple imputation for missing data. The results appear to show a sex difference in the association between CVD risk and subsequent depressive symptoms, but this should be interpreted with caution in light of sample attrition and reduced statistical power. Finally, the cohort is primarily composed of White individuals, limiting generalisability.

4.6.2 Conclusion

The association between CVD risk and depressive symptoms in childhood/adolescence is unidirectional, with higher CVD risk increasing the risk of depressive symptoms. Childhood inflammation may increase risk of depression by influencing adolescent CVD risk. This model where inflammation is a shared, modifiable risk factor for adult CVD and depression requires replication in other samples, but may have important implications for the prevention of CVD and depression.

Chapter 5: Association between Common Early-Childhood Infection and Subsequent Depressive Symptoms and Psychotic Experiences in Adolescence

5.1 Chapter Summary

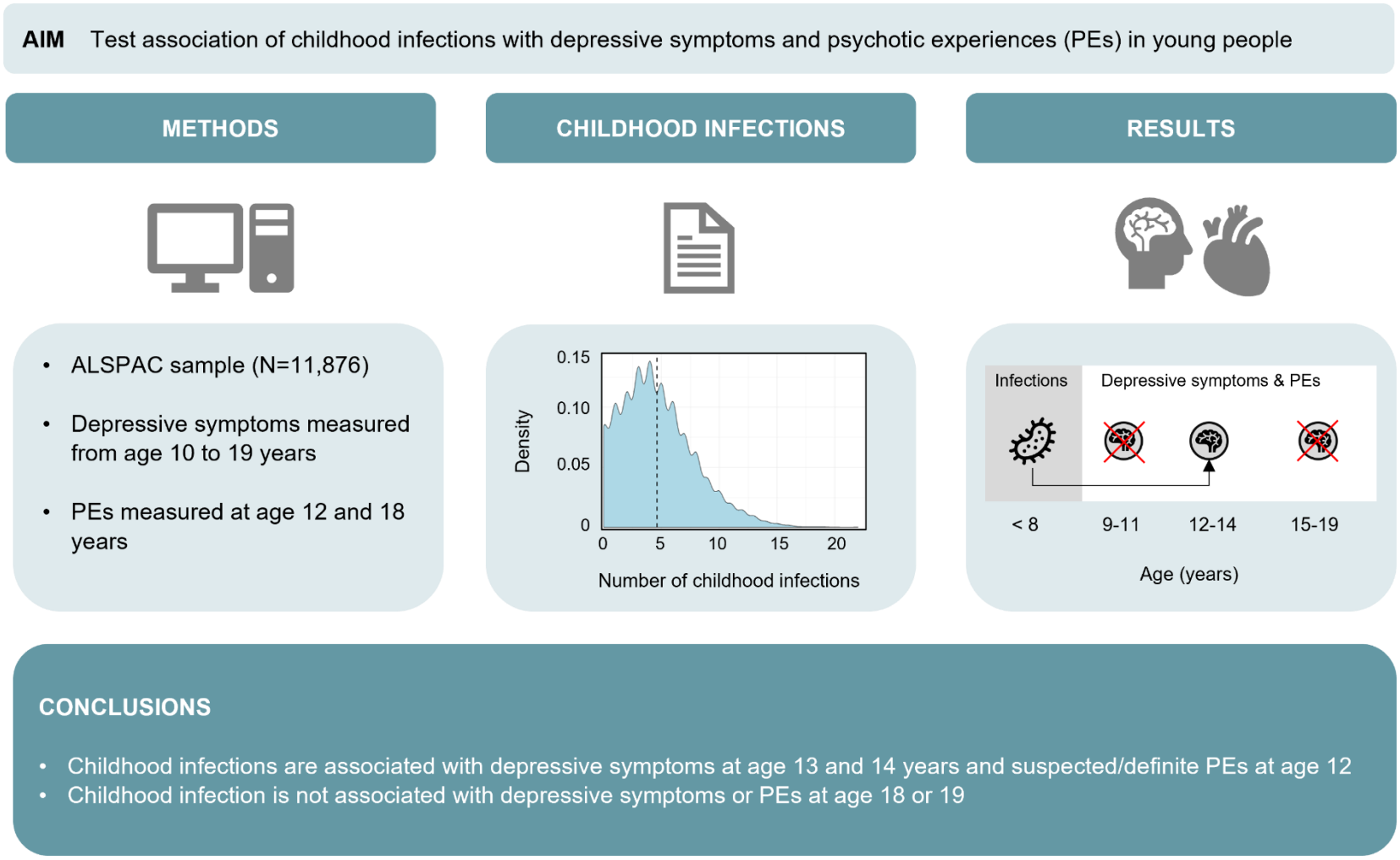


Figure 28. Visual summary of Chapter 5.

5.2 Introduction

Depressive symptoms and psychotic experiences (PEs) may be manifestations of a latent continuum of common mental distress, on which PEs measure severity (18). PEs in depression are associated with poor response to treatment, increased risk of self-harm, and worse outcomes (18). Individuals with PEs are also significantly less likely to reach remission of depressive symptoms than those without PEs (18). As such, PEs in depression are highly clinically relevant.

Early-life infections are associated with increased risk of serious mental health disorders in adulthood. There is an extensive literature linking prenatal maternal and childhood infections with schizophrenia and related psychotic disorders, which are associated with both central nervous system (CNS) and non-CNS infections (386–391). Early-life exposure to infection may result in activation of an acute inflammatory response potentially affecting neurodevelopment (392). Acute inflammation causes reductions in neuroplasticity, an important process for brain functioning, which may lead to neuropsychiatric outcomes later on (393). Compared with psychosis, longitudinal studies of early-life infection and depression are relatively rare, though inflammation is increasingly thought to play a role in pathogenesis of the illness (111,381,394). However, most of the existing longitudinal studies of early-life infection have focused on psychosis and depression in adults (386,395–399). Longitudinal studies of depressive and PEs during childhood/adolescence are scarce (155). Childhood/adolescent depressive symptoms are associated with adult depression (66–68,73). PEs during childhood/early-adolescence may be part of typical development and are transient for most individuals. However, population-based longitudinal studies suggest associations between early-life PEs with risk of psychotic disorders subsequently in adulthood (400,401), and with risk factors for schizophrenia including impaired neurodevelopment (402,403). They are also associated with adolescent psychiatric multi-morbidity (404), and with other psychiatric disorders in adulthood (405). Therefore studying

adolescent PEs and depressive symptoms may offer insights into development of adult psychotic and mood disorders.

Some previous longitudinal studies have considered the issue of timing, i.e., whether early-life infections are associated with psychotic outcomes closer to the time of exposure or subsequently after several years (386,406), but such studies of depression are scarce. Moreover, previous studies have typically examined effects of severe infections (145,386), but studies of common childhood infections and subsequent depressive/ psychotic outcomes, or studies of number of childhood infection and subsequent depression are scarce. Prospective cohort studies with repeated measures of depressive and psychotic experiences over a long period are required to address these issues, but such studies are relatively rare.

Infections are common during childhood, but some children are disproportionately prone to high infection burden possibly due to genetic and environmental factors. While childhood infection severity, duration, and related hospitalisation have been linked with depression and psychosis in adulthood (145,386,406), it is unclear whether the degree of childhood infection burden is associated with psychotic/depressive outcomes in childhood/adolescence. A high number of childhood infections may be a risk factor for psychiatric disorders, as a dose-response association between increasing number of childhood infection and adult mood or psychotic disorders has been reported (145,386). Early-life infections could also be a marker for shared genetic and environmental risk factors for infection and major psychiatric disorders (407). It is possible that inflammatory immune response during critical developmental window is detrimental for brain development/function (408). A high burden of common childhood infections may also reflect underlying familial factors predisposing to infection, such as SEP, living conditions, and genetic factors (407). Therefore, studies investing the effects of infection burden are required.

Using data from ALSPAC (272), I have investigated the longitudinal associations of childhood infections from age 1.5 to 7.5 years old with depressive symptoms measured six

times from age 10 to 19 years and with PEs at age 12 and 18 years. Comorbid depressive symptoms and PEs was not included as an outcome due to the small number of cases. I have examined not only the number of childhood infections as exposure, but also the effect of infection burden, grouped as low, medium, high or very high. I hypothesised that a higher overall number of infections and very high infection burden would be associated with higher risks for depressive symptoms and PEs subsequently up to late-adolescence.

5.3 Hypotheses

1. Childhood infections are associated with depressive symptoms from age 10 to 19 years.
2. Childhood infections are associated with PEs at age 12 and 18 years.
3. Childhood infection burden has a dose-response relationship with depressive symptoms from age 10 to 19 years.
4. Childhood infection burden has a dose-response relationship with PEs at age 12 and 18 years.

5.4 Methods

5.4.1 Description of sample

The risk set for this study comprised 11,786 unrelated individuals from the ALSPAC cohort with data on infections during childhood. Out of the risk set, the number of individuals with depressive symptoms data decreased from 6,685 at age 10 years to 3,101 at age 19 years (Figure 29). From the risk set, PE data were available for 6,176 individuals at age 12 years and for 4,253 individuals at age 18 years (Figure 30). These samples formed the basis for the analyses presented.

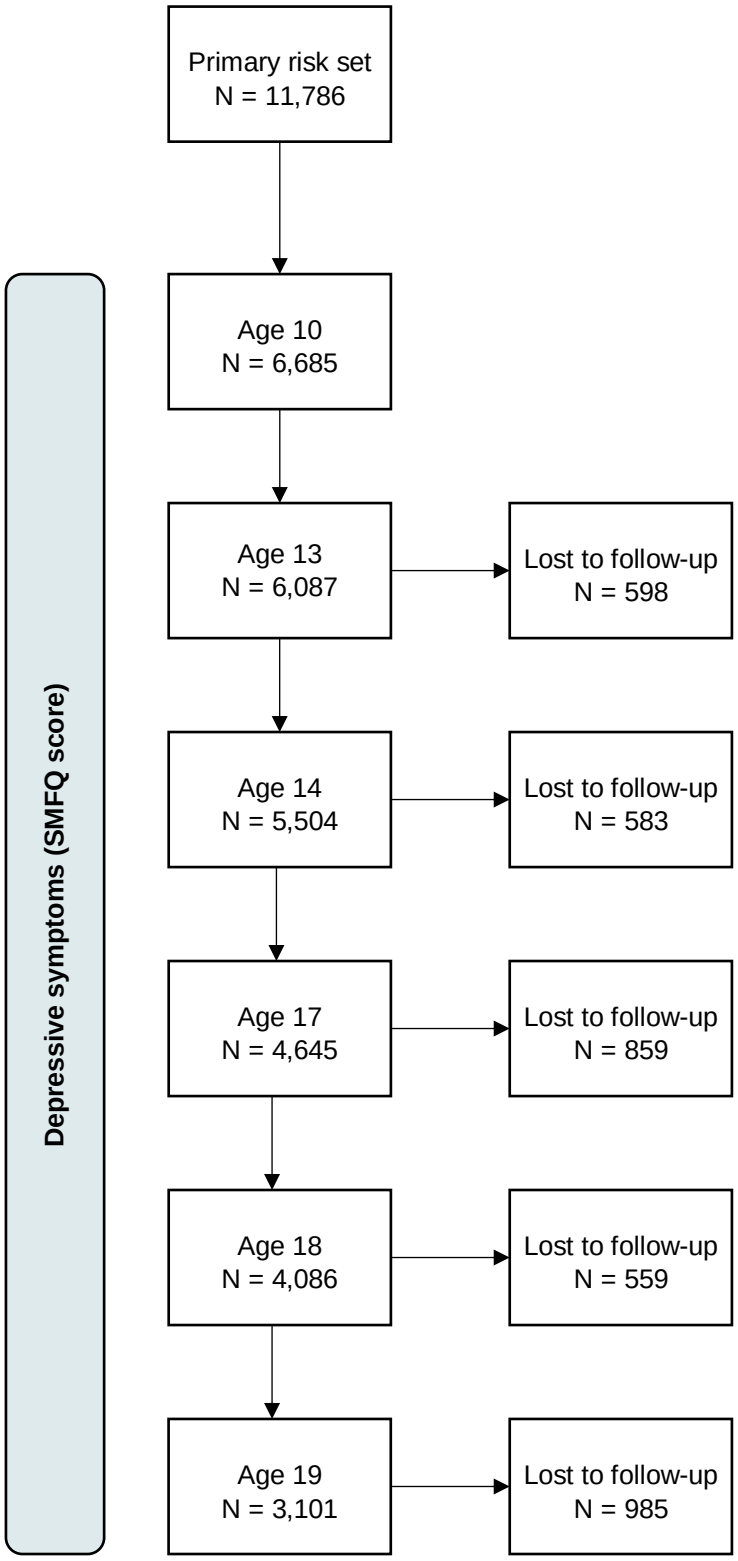


Figure 29. Maximum available sample from the risk set with data on depressive symptoms at each follow-up from age 10 to 19 years.

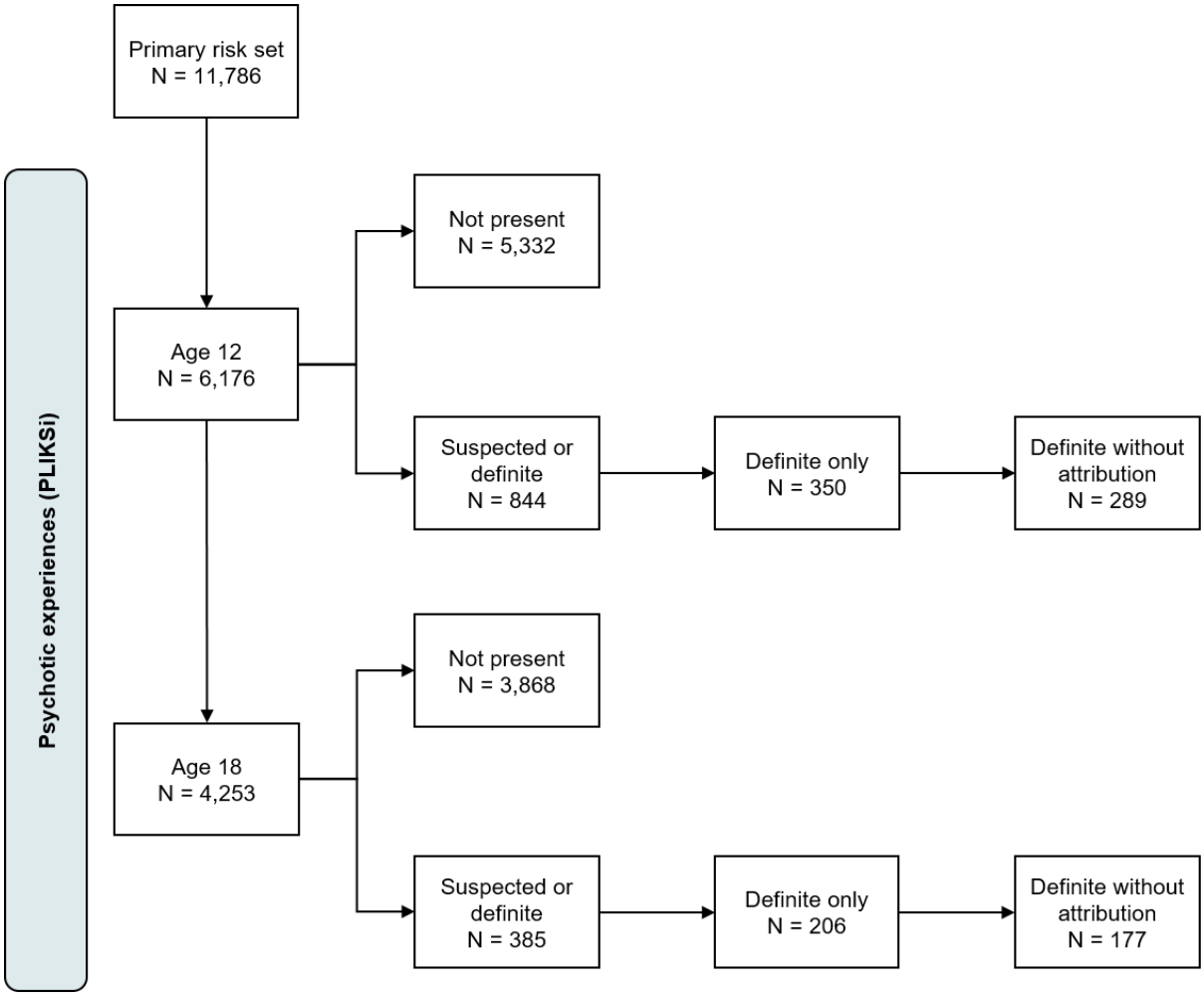


Figure 30. Maximum available sample from the risk set with data on psychotic experiences at age 12 and 18 years.

5.4.2 Assessment of childhood infections from age 1.5 to 7.5 years

Approximately once per year when the child was aged between age 1.5 and 7.5 years, caregivers completed seven postal questionnaires about common childhood infections experienced by their child. These included German measles, measles, chicken pox, mumps, meningitis, cold sores, whooping cough, urinary infections, eye infections, ear infections, chest infections, tonsillitis/laryngitis, scarlet fever, influenza, cold, and other.

Overall 11,786 children had fully/partly completed infection questionnaires from the seven time-points. In the questionnaire about childhood infections, caregivers could tick the “Yes” or “No” boxes for infections that their child has had. Some people simply ticked the “Yes” box to indicate that their child has had certain infections, but did not tick the “No” box for infections their child did not have. In those instances, the un-ticked boxes were coded as “No” that year rather than dropping the subject from analysis for missing data. However, if a parent had all boxes unticked they were coded as missing, as this lack of response gave no indication of whether their child had any infections that year.

Childhood infection count was used as a standardised continuous variable. Infection was also used as a categorical variable representing the degree of infection burden: low (50th percentile and below; 0 to 4 infections), medium (51-75th percentile; 5 to 6 infections), high (76-90th percentile; 7 to 9 infections), and very high burden (above 90th percentile; 10 to 22 infections). These categories were based on a prior study and were chosen to capture the positive skew of childhood infection distribution (409).

5.4.3 Assessment of depressive symptoms at age 10, 13, 14, 17, 18, and 19 years

Depressive symptoms were self-reported by the child/young person using the SMFQ (367). Depressive symptoms were measured at age 10 (mean = 10.6; SD = 0.3), 13 (mean = 12.8; SD = 0.2), 14 (mean = 13.8; SD = 0.2), 17 (mean = 16.7; SD = 0.2), 18 (mean = 17.8; SD = 0.4), and 19 years old (mean = 18.6; SD = 0.5). The SMFQ is a widely used, age-appropriate, and validated tool comprising 13 items that cover core symptoms of depression and anxiety experienced in the past two weeks. Each item is scored 0 (not true), 1 (sometimes true) or 2 (true) giving a total score of 0 to 26. Depressive symptoms was used as a standardised continuous variable.

5.4.4 Assessment of psychotic experiences at age 12 and 18 years

PEs were identified using the face-to-face, semi-structured Psychosis-Like Symptom Interview (PLIKSi) (401,410) conducted by trained psychology graduates in assessment clinics. PEs were coded according to the definitions and rating rules for the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), Version 2.0. (411). PLIKSi at age 12 years has “fair” inter-rater (kappa = 0.75) and test-retest (kappa = 0.48) reliability (410). PLIKSi at age 18 years has “good” inter-rater (kappa = 0.83) and test-retest (kappa = 0.76) reliability (401).

PLIKSi covered the three main domains of positive psychotic experiences: hallucinations (visual and auditory), delusions (spied on, persecuted, thoughts read, reference, control, grandiosity, and other), and thought interference (insertion, withdrawal, and broadcasting). After cross-questioning, interviewers rated PEs as “not present”, “suspected”, or “definitely present”. Uncertain responses were always “rated down”, and symptoms were rated as definite only if a clear example could be provided. For suspected or definite PEs, interviewers also recorded the frequency, affect, effects on social/educational/occupational function, help seeking, and attributions including fever, hypnopompic/hypnogogic state, or illicit drugs.

PEs measured at age 12 years refer to experiences from the previous six months while PEs measured at age 18 years refer to experiences since age 12 years. In line with previous papers originally describing PEs in the ALSPAC birth cohort, I used three increasingly strict definitions for this outcome, i.e. any PEs (suspected or definite PEs); definite PEs; and definite PEs without attribution. The number of participants meeting each of the outcome definitions are different (Figure 30) and the risk of each outcome was analysed separately. The comparison group for each outcome included all the individuals who did not meet that specific definition for the outcome (412).

5.4.5 Assessment of confounders

Based on previous studies, I included sex, ethnicity, birth weight, maternal SEP, and parental history of severe depression or schizophrenia as these are associated with exposure and/or outcome and so could be confounders (145,390,412,413).

Sex (binary) and birth weight (grams, continuous) were assessed at birth. Ethnicity was recorded as White, Black African, Black Caribbean, Black Other, Bangladeshi, Chinese, Indian, Pakistani, and Other. This variable was recoded as White and any other ethnic group due to low counts for non-White ethnic groups.

Maternal SEP was originally documented using Office of National Statistics categories (365) and re-coded as non-manual (I, II and IIIa) and manual (IIIb, IV and V). The armed forces was excluded as the sample size for this category was too small (N = 4).

Mothers and their partners completed separate questionnaires at 12 weeks gestation in which they self-reported having severe depression. The categories from the self-reported questionnaires were: “Yes, had it recently”, “Yes in past, not now”, “No never”, or “Don’t know”. A binary variable for severe depression was created for both the mother and their partner where 0 = “No never” and 1 = “Yes, had it recently” or “Yes in past, not now”. Individuals who answered “Don’t know” were excluded. Parental history of severe depression or schizophrenia were coded as a binary variable, with “yes” being recorded if at least one parent reported to having severe depression or schizophrenia.

5.4.6 Statistical analysis

All analyses were carried out using R version 3.6.1. Regression analyses were performed before and after adjusting for potential confounders. All main analyses were based on the dataset after imputation of missing values for confounders.

4.4.6.1 Imputation of Missing Confounder Variables

Regression analyses testing associations between exposure and outcomes were conducted after imputation of missing data for confounders (ethnicity, maternal SEP, birthweight, parental schizophrenia, and parental severe depression) to increase sample size. Sex had no missing data. The percentage of missing values across the relevant confounder variables varied between 1.5% and 35% (Table 17). I used the *TestMCARNormality* function to test whether data were missing completely at random (414). The missing completely at random hypothesis was to be rejected at 0.05 significance level. Using the *missing_compare* function, each variable returned significance ($p < 0.05$) with at least one other variable, suggesting that the data met the missing at random assumption.

I used multiple imputation using fully conditional MCMC method for the above confounder variables plus auxiliary variables that were indicators of missingness. Exposure and outcome variables were also included. The selected auxiliary variables included: housing/living conditions, parental education/employment status, financial difficulties, life events, and maternal characteristics (age, BMI, marital status, anxiety/post-natal depression, and smoking status).

I used the R package “mice” (version 3.0) to create and analyse the multiply imputed datasets (277). Since missing data were present in 20% of subjects, I used 20 imputations as recommended (372). The parameters of interest were estimated in each dataset separately, and combined using Rubin’s rules.

Table 17. Characteristics of the imputed confounders.

Confounder	Missing data (%)	Sample before imputation (no.) [a]	Value		Difference in values before and after imputation (t-test p-value)
			Before imputation	After imputation	
Birthweight (kg) – mean (SD)	1.5	11,613	3.4 (0.5)	3.4 (0.5)	0.90
Ethnicity – no. White (%)	6.0	11,080	10828 (97.7)	11511 (97.7)	0.70
Maternal SEP – no. manual (%)	22.1	9,183	1752 (19.1)	2621 (22.2)	<0.001
Parental history of severe depression – no. (%)	35.0	7,664	979 (12.8)	1677 (14.2)	<0.001
Parental history of schizophrenia – no. (%)	35.0	7,685	18 (0.2)	40 (0.3)	0.06
Total missing data	19.9	--	--	--	--

[a] The sample size after imputation was 11,786 participants.

4.4.6.2 Association of childhood infections with depressive symptoms and psychotic experiences

Linear regression was used to examine the association between the number of childhood infections/infection burden and depressive symptoms at age 10 to 19 years (Hypothesis 1, 3, Page 149). Low infection burden (0 to 4 infections) was used as the reference group where infection burden was used as the exposure. Regression models were adjusted for sex, birth weight, maternal SEP, ethnicity, and parental history of severe depression. Beta estimates and SEs from regression models are presented.

Logistic regression was used to calculate ORs and 95% confidence intervals (CI) for PEs at age 12 or 18 years associated with the number of childhood infections/infection burden (Hypothesis 2, 4). Low burden of infection (0 to 4 infections) was used as the reference group for the latter. Regression models were adjusted for sex, birth weight, maternal SEP, ethnicity, and parental history of schizophrenia.

For all analyses, I used the maximum available sample for each outcome measure to increase statistical power. Holm-Bonferroni P-value correction was performed to correct for multiple testing (Table 18, Table 19) (415).

4.4.6.3 Sensitivity analysis exploring impact of missing data

To explore the potential impact of missing data I repeated our main analyses based on complete case-set, defined as participants with no missing data for exposure, outcome or confounder measures. I then carried out a number of comparisons between different samples. First, I compared the risk set (i.e. participants with data on childhood infection) with the complete case-set for depressive symptoms (i.e., data on childhood infection, all confounders, and depressive symptoms at all follow-up time points are available). I did the same comparison for PEs. Second, I compared the analytic sample for depressive symptoms at age 19 years (i.e. data on both childhood infection and depressive symptoms at age 19 years available) with the missing sample (i.e. childhood infection data present but depressive symptoms data at age 19 years missing). I performed the same comparison for PEs at age 18 years separately.

Table 18. Corrected P-value for the association between childhood infections and depressive symptoms using the Holm-Bonferroni Method.

Age at depressive symptoms outcome (years)	Number of childhood infections		Medium infection burden		High infection burden		Very high infection burden	
	Original P-value [a]	Corrected P-value	Original P-value [a]	Corrected P-value	Original P-value [a]	Corrected P-value	Original P-value [a]	Corrected P-value
10	<0.01	0.02	0.05	0.62	0.47	1.00	0.02	0.24
13	<0.001	<0.001	0.86	1.00	0.14	1.00	<0.001	<0.001
14	<0.001	0.01	0.31	1.00	0.28	1.00	<0.01	0.02
17	0.04	0.48	0.85	1.00	0.53	1.00	0.01	0.12
18	0.19	1.00	0.95	1.00	0.34	1.00	0.24	1.00
19	0.31	1.00	0.97	1.00	0.22	1.00	0.25	1.00

[a] The P-values correspond to adjusted beta estimates for depressive symptoms. Beta estimates were adjusted for sex, birthweight, maternal SEP, ethnicity and parental history of severe depression.

Table 19. Corrected P-value for the association between childhood infections and psychotic experiences using the Holm-Bonferroni Method.

Outcome	Number of childhood infections		Medium infection burden		High infection burden		Very high infection burden	
	Original P-value [a]	Corrected P-value	Original P-value [a]	Corrected P-value	Original P-value [a]	Corrected P-value	Original P-value [a]	Corrected P-value
Suspected/definite PEs age 12	<0.001	<0.001	0.04	0.48	0.05	0.60	<0.001	<0.01
Definite PEs age 12	0.01	0.12	0.45	1.00	0.28	1.00	0.07	0.84
Definite PEs without attribution age 12	0.01	0.12	0.47	1.00	0.34	1.00	0.09	1.00
Suspected/definite PEs age 18	0.14	1.00	0.97	1.00	0.36	1.00	0.26	1.00
Definite PEs age 18	0.45	1.00	0.61	1.00	0.65	1.00	0.66	1.00
Definite PEs without attribution age 18	0.17	1.00	0.65	1.00	0.36	1.00	0.48	1.00

[a] The P-values correspond to adjusted odds ratios for psychotic experiences (PEs). Odds ratios were adjusted for sex, birthweight, maternal socioeconomic position, ethnicity and parental history of schizophrenia.

5.5 Results

5.5.1 Baseline characteristics of the sample

The risk set (N = 11,786) was predominantly of White ethnicity (98%) (Table 20). The average number of childhood infections in the total sample was 4.6 (SD = 3.2), and the median was 4 (inter-quartile range (IQR) = 2 to 6). The number of children with very high infection burden (≥90th percentile; 10 to 22 infections) was 947 (8%).

There was a general increase in depressive symptoms between age 10 and 19 years (Figure 29); mean SMFQ score at age 10 years was 4.0 (SD = 3.5), and was 6.8 (SD = 5.9) at age 19 years (Table 20). The percentage of participants with definite PEs was similar at age 12 years (6%) and at age 18 years (5%).

Table 20. Characteristics of participants in the risk set (using maximum available sample and after imputation of confounders).

Characteristics [a]	Total participants		Very high infection burden (≥10 infections)		Lower infection burden (<10 infections)		Difference between groups (X^2 / t-test p-value)
	Sample	Value	Sample	Value	Sample	Value	
Confounders							
Birthweight – mean (SD)	11,786	3.4 (0.5)	947	3.4 (0.5)	10,839	3.4 (0.5)	0.39
Sex – no. female (%)	11,786	5,710 (48.4)	947	483 (51.0)	10,839	5,227 (48.2)	0.10
Ethnicity – no. White (%)	11,786	11,511 (97.7)	947	922 (97.4)	10,839	10,588 (97.7)	0.63
Maternal SEP – no. manual (%)	11,786	2,621 (22.2)	947	184 (19.4)	10,839	2,437 (22.5)	0.04
Parental history of severe depression – no. (%)	11,786	1,677 (14.2)	947	158 (16.7)	10,839	1,519 (14.0)	0.07
Parental history of schizophrenia – no. (%)	11,786	40 (0.3)	947	3 (0.3)	10,839	37 (0.3)	0.91
Number of childhood infections							
Mean (SD)	11,786	4.6 (3.2)	947	11.6 (1.8)	10,839	4.0 (2.5)	-
Median (IQR)	11,786	4 (2-6)	947	11 (10-12)	10,839	4 (2-6)	-
Depressive symptoms – mean (SD)							
Age 10	6,685	4.0 (3.5)	697	4.4 (3.9)	5,988	4.0 (3.5)	<0.01
Age 13	6,087	3.9 (3.8)	661	4.6 (4.3)	5,426	3.9 (3.8)	<0.01
Age 14	5,504	4.9 (4.5)	604	5.5 (4.8)	4,900	4.8 (4.4)	<0.01
Age 17	4,645	5.9 (5.6)	506	6.6 (5.8)	4,139	5.8 (5.6)	<0.01
Age 18	4,086	6.6 (5.3)	448	6.9 (5.2)	3,638	6.5 (5.3)	0.17
Age 19	3,101	6.8 (5.9)	345	7.1 (6.1)	2,756	6.7 (5.8)	0.30
PEs – no. (%)							
Suspected/definite PEs at age 12	6,176	844 (13.7)	668	117 (17.5)	5,508	727 (13.2)	<0.01
Definite PEs at age 12	6,176	350 (5.7)	668	47 (7.0)	5,508	303 (5.5)	0.14
Definite PEs without attribution at age 12	6,176	289 (4.7)	668	39 (5.8)	5,508	250 (4.5)	0.17
Suspected/definite PEs at age 18	4,253	385 (9.1)	469	49 (10.4)	3,784	336 (8.9)	0.29

Definite PEs at age 18	4,253	206 (4.8)	469	22 (4.7)	3,784	184 (4.9)	0.87
Definite PEs without attribution at age 18	4,253	177 (4.2)	469	18 (3.8)	3,784	159 (4.2)	0.70

[a] IQR: interquartile range; PE: psychotic experiences; SD: standard deviation; SEP: socioeconomic position.

5.5.2 Association between number of childhood infections and depressive symptoms

The analyses in this section are relevant to hypothesis 1 (Section 5.3, Page 149).

Number of childhood infections from age 1.5 to 7.5 years was associated with subsequent depressive symptoms at age 10 (N = 6,685; beta = 0.14; SE = 0.04; p <0.01), 13 (N = 6,087; beta = 0.24; SE = 0.05; p <0.001), and 14 years old (N = 5504; beta = 0.23; SE = 0.06; p <0.001) (Table 21). Evidence for these associations remained after adjusting for potential confounders. Childhood infections were not associated with depressive symptoms at age 17, 18, or 19 years.

Table 21. Beta estimate (SE) for depressive symptoms from age 10 to 19 years per 1 SD increase in childhood infections.

Age at outcome (years)	Sample size (no.)	% with depression [a]	Unadjusted		Adjusted [b]	
			Beta (SE)	P-value	Beta (SE)	P-value
10	6,685	14.5	0.14 (0.04)	<0.01	0.14 (0.04)	<0.01
13	6,087	14.6	0.24 (0.05)	<0.001	0.22 (0.05)	<0.001
14	5,504	22.2	0.23 (0.06)	<0.001	0.21 (0.06)	<0.001
17	4,645	28.3	0.14 (0.09)	0.11	0.17 (0.08)	0.04
18	4,086	34.3	0.11 (0.09)	0.22	0.11 (0.08)	0.19
19	3,101	34.2	0.11 (0.11)	0.34	0.11 (0.11)	0.31

[a] For the purposes of this table, depression is defined as SMFQ score ≥8.

[b] Adjusted for sex, birthweight, maternal SEP, ethnicity and parental history of severe depression.

After correction for multiple testing, evidence remained for an association between number of childhood infections and depressive symptoms at age 10 (p = 0.02), 13 (p <0.001) and 14years (p <0.01) (Table 18).

5.5.3 Association between number of childhood infections and psychotic experiences

The analyses in this section are relevant to hypothesis 2 (Section 5.3, Page 149).

Number of childhood infections was associated with subsequent PEs at age 12 years (N = 6,176), including suspected/definite PEs (OR = 1.17; 95% CI = 1.09, 1.26), definite PEs (OR = 1.16; 95% CI = 1.04, 1.29), and definite PEs without attribution (OR = 1.17; 95% CI = 1.04, 1.31) (Table 22). Evidence for these associations remained after adjusting for potential confounders. The number of childhood infections was not associated with PEs at age 18 years.

Table 22. Odds ratio (95% CI) for the association between 1 SD increase in childhood infections and PEs at age 12 and 18 years.

Age at outcome (years)	Sample size (no.)	Psychotic experiences (PEs)	% with PEs	Odds ratio (95% CI)	
				Unadjusted	Adjusted [a]
12	6,176	Suspected/definite	13.7	1.17 (1.09, 1.26)	1.18 (1.09, 1.27)
		Definite only	5.7	1.16 (1.04, 1.29)	1.16 (1.05, 1.29)
		Definite without attribution	4.7	1.17 (1.04, 1.31)	1.18 (1.05, 1.32)
18	4,253	Suspected/definite	9.1	1.07 (0.97, 1.19)	1.08 (0.97, 1.20)
		Definite only	4.8	0.93 (0.81, 1.08)	0.94 (0.82, 1.10)
		Definite without attribution	4.2	0.88 (0.75, 1.03)	0.89 (0.76, 1.05)

[a] Adjusted for sex, birthweight, maternal SEP, ethnicity and parental history of schizophrenia.

After correction for multiple testing, evidence remained for an association between number of childhood infections and suspected/definite PEs at age 12 years ($p < 0.001$), but not with definite PEs ($p = 0.12$) or definite PEs without attribution at age 12 years ($p = 0.12$) (Table 19).

5.5.4 Association between childhood infection burden and depressive symptoms

The analyses in this section are relevant to hypothesis 3 (Section 5.3, Page 149).

Compared with low infection burden, very high infection burden was associated with depressive symptoms at age 10 (beta = 0.38; SE = 0.16; p = 0.01), 13 (beta = 0.76; SE = 0.17; p <0.001), 14 (beta = 0.66; SE = 0.21; p <0.01), and 17 years old (beta = 0.68; SE = 0.30; p = 0.02) (Table 23). Evidence for these associations remained after adjusting for potential confounders. Very high infection burden was not associated with depressive symptoms at age 18 years (beta = 0.33; SE = 0.29; p = 0.26) or age 19 years (beta = 0.41; SE = 0.38; p = 0.27).

After correction for multiple testing, evidence remained for association between very high infection burden and depressive symptoms at age 13 years (p <0.001) and age 14 years (p = 0.02) (Table 18).

5.5.5 Association between childhood infection burden and psychotic experiences

The analyses in this section are relevant to hypothesis 4 (Section 5.3, Page 149).

Compared with low infection burden, very high infection burden was associated with suspected/definite PEs at age 12 years (OR = 1.59; 95% CI = 1.24, 2.04). Evidence for this association remained after adjusting for potential confounders. Very high infection burden was not associated with PEs at age 18 years (Table 24).

After correction for multiple testing, evidence remained for an association between very high infection burden and suspected/definite PEs at age 12 years (p <0.01) (Table 19).

Table 23. Beta estimate (SE) for the association between childhood infection burden and depressive symptoms from age 10 to 19 years.

Infection burden between age 1.5 and 7.5 (no. of infections)	Age at outcome (years)	Sample size (no.)	% with depression [a]	Unadjusted		Adjusted [b]	
				Beta (SE)	P-value	Beta (SE)	P-value
Low (0 to 4)	10	2,869	14.6	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		1,703	12.3	-0.23 (0.11)	0.03	-0.20 (0.11)	0.05
High (7 to 9)		1,416	14.9	0.06 (0.12)	0.65	0.09 (0.12)	0.47
Very high (10 to 22)		697	18.1	0.38 (0.16)	0.01	0.36 (0.15)	0.02
Low (0 to 4)	13	2,572	13.5	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		1,538	13.8	-0.03 (0.12)	0.84	-0.02 (0.12)	0.86
High (7 to 9)		1,316	15.0	0.22 (0.14)	0.11	0.21 (0.14)	0.14
Very high (10 to 22)		661	20.0	0.76 (0.17)	<0.001	0.72 (0.17)	<0.001
Low (0 to 4)	14	2,328	21.4	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		1,383	21.0	-0.19 (0.15)	0.20	-0.15 (0.15)	0.31
High (7 to 9)		1,189	22.9	0.18 (0.17)	0.31	0.18 (0.17)	0.28
Very high (10 to 22)		604	26.8	0.66 (0.21)	<0.01	0.64 (0.21)	<0.01
Low (0 to 4)	17	1,917	27.6	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		1,184	28.8	-0.18 (0.21)	0.37	-0.04 (0.20)	0.85
High (7 to 9)		1,038	26.7	-0.30 (0.24)	0.20	-0.15 (0.23)	0.53
Very high (10 to 22)		506	33.0	0.68 (0.30)	0.02	0.79 (0.29)	0.01

Low (0 to 4)	18	1,708	33.8	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		1,053	33.6	-0.11 (0.20)	0.58	-0.01 (0.20)	0.95
High (7 to 9)		877	34.7	0.10 (0.24)	0.67	0.22 (0.23)	0.34
Very high (10 to 22)		448	37.5	0.33 (0.29)	0.26	0.34 (0.29)	0.24
Low (0 to 4)	19	1,236	34.2	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		829	32.6	-0.04 (0.26)	0.89	0.01 (0.26)	0.97
High (7 to 9)		691	35.3	0.26 (0.30)	0.39	0.36 (0.30)	0.22
Very high (10 to 22)		345	36.2	0.41 (0.38)	0.27	0.43 (0.37)	0.25

[a] For the purposes of this table, depression is defined as SMFQ score ≥8.

[b] Adjusted for sex, birthweight, maternal SEP, ethnicity and parental history of severe depression.

Table 24. Odds ratio (95% CI) for the association between childhood infection burden and PEs at age 12 and 18 years.

Infection burden between age 1.5 and 7.5 (no. of infections)	Sample size (no.)	Age at outcome (years)	Psychotic experiences (PEs)	% with PEs	Odds ratio (95% CI)	
					Unadjusted	Adjusted [a]
Low (0 to 4)	2,619	12	Suspected/definite	12.3	1.00 [ref]	1.00 [ref]
Medium (5 to 6)	1,561			14.0	1.20 (1.00, 1.44)	1.21 (1.01, 1.46)
High (7 to 9)	1,328			14.0	1.22 (0.99, 1.51)	1.24 (1.03, 1.54)
Very high (10 to 22)	668			17.5	1.59 (1.24, 2.04)	1.60 (1.25, 2.05)
Low (0 to 4)	2,619		Definite only	5.1	1.00 [ref]	1.00 [ref]
Medium (5 to 6)	1,561			5.9	1.08 (0.82, 1.42)	1.11 (0.84, 1.46)
High (7 to 9)	1,328			5.9	1.15 (0.84, 1.57)	1.19 (0.87, 1.63)
Very high (10 to 22)	668			7.0	1.39 (0.97, 2.01)	1.40 (0.97, 2.02)
Low (0 to 4)	2,619		Definite without attribution	4.0	1.00 [ref]	1.00 [ref]
Medium (5 to 6)	1,561			5.1	1.09 (0.81, 1.47)	1.12 (0.83, 1.51)
High (7 to 9)	1,328			4.8	1.14 (0.81, 1.61)	1.18 (0.84, 1.67)
Very high (10 to 22)	668			5.8	1.40 (0.94, 2.08)	1.41 (0.95, 2.10)
Low (0 to 4)	1,783	18	Suspected/definite	8.8	1.00 [ref]	1.00 [ref]
Medium (5 to 6)	1,089			8.4	0.97 (0.75, 1.26)	1.01 (0.77, 1.31)
High (7 to 9)	912			9.5	1.09 (0.81, 1.47)	1.15 (0.85, 1.55)
Very high (10 to 22)	469			10.4	1.21 (0.85, 1.73)	1.23 (0.86, 1.76)
Low (0 to 4)	1,783		Definite only	5.2	1.00 [ref]	1.00 [ref]

Medium (5 to 6)	1,089			4.5	0.87 (0.62, 1.23)	0.91 (0.65, 1.29)
High (7 to 9)	912			4.6	0.86 (0.58, 1.28)	0.91 (0.61, 1.36)
Very high (10 to 22)	469			4.7	0.88 (0.53, 1.44)	0.89 (0.54, 1.47)
Low (0 to 4)	1,783		Definite without attribution	4.6	1.00 [ref]	1.00 [ref]
Medium (5 to 6)	1,089			4.0	0.87 (0.61, 1.24)	0.92 (0.64, 1.32)
High (7 to 9)	912			3.6	0.75 (0.49, 1.17)	0.81 (0.52, 1.27)
Very high (10 to 22)	469			3.8	0.80 (0.47, 1.38)	0.82 (0.48, 1.42)

[a] Adjusted for sex, birthweight, maternal SEP, ethnicity and parental history of schizophrenia.

5.5.6 Results based on complete case-set analyses

Results from the complete case-sets for depressive symptoms (N = 1,133) and that for PEs (N = 2,495) were similar to the main results reported above.

In the complete case-set for depressive symptoms (N = 1,133), the number of childhood infections from age 1.5 to 7.5 years was associated with subsequent depressive symptoms at age 13 years (beta = 0.29; SE = 0.12; p = 0.01) and age 14 years (beta = 0.53; SE = 0.14; p <0.001) (Table 25). Evidence for these associations remained after adjusting for potential confounders. Childhood infections were not associated with depressive symptoms at age 10, 17, 18 or 19 years old.

In the complete case-set for PEs (N = 2,495), the number of childhood infections was associated with suspected/definite PEs at age 12 years (OR = 1.15; 95% CI = 1.02, 1.30) (Table 26). Evidence for this association remained after adjusting for potential confounders. Childhood infections were not associated with PEs at age 18 years.

Compared with low infection burden, very high infection burden in the complete case-set for depressive symptoms (N = 1,133) was associated with depressive symptoms at age 13 years (beta = 0.88; SE = 0.35; p = 0.01) and age 14 years (beta = 1.81; SE = 0.42; p <0.001) (Table 27). Evidence for these associations remained after adjusting for potential confounders. Very high infection burden was not associated with depressive symptoms at age 10, 17, 18 or 19 years old.

Compared with low infection burden, medium, high, and very high infection burden in the complete case-set for PEs (N = 2,495) were not associated with PEs at age 12 or 18 years (Table 28).

Table 25. Beta estimate (SE) for the association between 1 SD increase in childhood infections and depressive symptoms from age 10 to 19 years in the complete case-set (N = 1,133).

Age at outcome (years)	% with depression [a]	Unadjusted		Adjusted [b]	
		Beta (SE)	P-value	Beta (SE)	P-value
10	11.7	0.09 (0.10)	0.35	0.08 (0.10)	0.39
13	14.2	0.29 (0.12)	0.01	0.28 (0.11)	0.01
14	21.4	0.53 (0.14)	<0.001	0.51 (0.13)	<0.001
17	25.7	0.16 (0.16)	0.32	0.15 (0.16)	0.34
18	29.2	0.14 (0.15)	0.34	0.14 (0.15)	0.34
19	29.2	0.04 (0.17)	0.82	0.03 (0.17)	0.86

[a] For the purposes of this table, depression is defined as SMFQ score ≥8.

[b] Adjusted for sex, birthweight, maternal SEP, ethnicity and parental history of severe depression.

Table 26. Odds ratio (95% CI) for the association between 1 SD increase in childhood infections and PEs at age 12 and 18 years in the complete case set (N = 2,495).

Psychotic experiences (PEs)	% with PEs	Odds ratio (95% CI)	
		Unadjusted	Adjusted [a]
Suspected/definite at age 12	13.1	1.15 (1.02, 1.30)	1.15 (1.03, 1.30)
Definite only at age 12	5.1	1.13 (0.94, 1.36)	1.13 (0.95, 1.36)
Definite without attribution at age 12	4.4	1.15 (0.95, 1.39)	1.15 (0.95, 1.40)
Suspected/definite at age 18	8.1	1.13 (0.97, 1.31)	1.13 (0.98, 1.31)
Definite only at age 18	4.4	1.01 (0.82, 1.23)	1.01 (0.83, 1.24)
Definite without attribution at age 18	3.6	0.99 (0.80, 1.24)	1.00 (0.80, 1.25)

[a] Adjusted for sex, birthweight, maternal SEP, ethnicity and parental history of schizophrenia.

Table 27. Beta estimate (SE) for the association between childhood infection burden and depressive symptoms from age 10 to 19 years in the complete case-set (N = 1,133).

Infection burden between age 1.5 and 7.5 (no. of infections)	Age at outcome (years)	% with depression [a]	Unadjusted		Adjusted [b]	
			Beta (SE)	P-value	Beta (SE)	P-value
Low (0 to 4)	10	11.8	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		10.1	-0.10 (0.24)	0.68	-0.08 (0.24)	0.74
High (7 to 9)		11.5	0.02 (0.25)	0.93	0.04 (0.25)	0.86
Very high (10 to 22)		15.2	0.31 (0.30)	0.31	0.28 (0.31)	0.37
Low (0 to 4)	13	11.5	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		14.2	0.22 (0.27)	0.43	0.18 (0.27)	0.52
High (7 to 9)		15.1	0.52 (0.28)	0.07	0.55 (0.28)	0.05
Very high (10 to 22)		20.0	0.88 (0.35)	0.01	0.84 (0.35)	0.02
Low (0 to 4)	14	17.9	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		21.7	0.21 (0.32)	0.51	0.12 (0.32)	0.70
High (7 to 9)		20.8	0.21 (0.34)	0.53	0.27 (0.33)	0.41
Very high (10 to 22)		31.0	1.81 (0.42)	<0.001	1.68 (0.41)	<0.001
Low (0 to 4)	17	22.3	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		26.1	0.63 (0.38)	0.10	0.52 (0.37)	0.17
High (7 to 9)		27.6	0.34 (0.40)	0.40	0.49 (0.39)	0.21
Very high (10 to 22)		30.3	0.65 (0.49)	0.19	0.47 (0.48)	0.33
Low (0 to 4)	18	28.9	0.00 [ref]		0.00 [ref]	
Medium (5 to 6)		28.0	-0.01 (0.36)	0.98	-0.09 (0.36)	0.80
High (7 to 9)		27.6	-0.13 (0.37)	0.72	-0.06 (0.37)	0.88
Very high (10 to 22)		35.9	0.54 (0.46)	0.25	0.46 (0.46)	0.32
Low (0 to 4)	19	25.6	0.00 [ref]		0.00 [ref]	

Medium (5 to 6)		29.6	0.27 (0.41)	0.52	0.19 (0.41)	0.65
High (7 to 9)		33.3	0.54 (0.43)	0.21	0.61 (0.43)	0.15
Very high (10 to 22)		30.3	0.11 (0.53)	0.84	<0.01 (0.53)	1.00

[a] For the purposes of this table, depression is defined as SMFQ score ≥8.

[b] Adjusted for sex, birthweight, maternal SEP, ethnicity and parental history of severe depression.

Table 28. Odds ratio (95% CI) for the association between childhood infection burden and PEs at age 12 and 18 years (N = 2,495).

Infection burden between age 1.5 and 7.5 (no. of infections)	Psychotic experiences (PEs)	% with PEs	Odds ratio (95% CI)	
			Unadjusted	Adjusted [a]
Low (0 to 4)	Suspected/definite at age 12	11.8	1.00 [ref]	1.00 [ref]
Medium (5 to 6)		12.1	1.03 (0.76, 1.40)	1.04 (0.77, 1.42)
High (7 to 9)		15.1	1.33 (0.99, 1.63)	1.35 (1.00, 1.82)
Very high (10 to 22)		15.5	1.37 (0.94, 2.00)	1.37 (0.94, 1.99)
Low (0 to 4)	Definite only at age 12	5.0	1.00 [ref]	1.00 [ref]
Medium (5 to 6)		4.0	0.79 (0.48, 1.28)	0.79 (0.49, 1.29)
High (7 to 9)		6.4	1.30 (0.84, 2.02)	1.33 (0.86, 2.07)
Very high (10 to 22)		5.2	1.03 (0.57, 1.87)	1.02 (0.56, 1.85)
Low (0 to 4)	Definite without attribution at age 12	4.3	1.00 [ref]	1.00 [ref]
Medium (5 to 6)		3.5	0.82 (0.49, 1.38)	0.83 (0.49, 1.39)
High (7 to 9)		5.8	1.37 (0.86, 2.19)	1.39 (0.87, 2.23)
Very high (10 to 22)		4.5	1.05 (0.55, 1.99)	1.04 (0.55, 1.98)
Low (0 to 4)	Suspected/definite at age 18	7.3	1.00 [ref]	1.00 [ref]
Medium (5 to 6)		8.1	1.13 (0.78, 1.63)	1.13 (0.78, 1.65)
High (7 to 9)		8.8	1.23 (0.85, 1.80)	1.25 (0.86, 1.82)
Very high (10 to 22)		8.9	1.25 (0.78, 2.01)	1.26 (0.78, 2.02)
Low (0 to 4)	Definite only at age 18	4.5	1.00 [ref]	1.00 [ref]
Medium (5 to 6)		4.1	0.92 (0.56, 1.50)	0.93 (0.57, 1.52)
High (7 to 9)		4.6	1.02 (0.62, 1.67)	1.04 (0.63, 1.70)
Very high (10 to 22)		4.5	1.00 (0.53, 1.88)	1.01 (0.53, 1.91)
Low (0 to 4)	Definite without attribution at age 18	3.7	1.00 [ref]	1.00 [ref]
Medium (5 to 6)		3.5	0.95 (0.56, 1.61)	0.96 (0.56, 1.63)
High (7 to 9)		3.6	0.95 (0.55, 1.65)	0.97 (0.56, 1.68)

Very high (10 to 22)		3.8	1.01 (0.51, 2.02)	1.02 (0.51, 2.04)

[a] Adjusted for sex, birthweight, maternal SEP, ethnicity and parental history of schizophrenia.

5.5.7 Comparison between analytic and missing samples for depressive symptoms

Comparison between the risk set (N = 11,786) and the complete case-set (N = 1,133) showed that those in the complete case-set were more likely to be female ($p < 0.001$), White ($p = 0.02$), have a higher number of childhood infections ($p < 0.001$), and have lower depressive symptoms at age 10 ($p < 0.001$), 17 ($p = 0.03$), 18 ($p < 0.001$), and 19 years ($p < 0.01$) (Table 29). Individuals in the complete case-set were less likely to have a mother of manual SEP ($p < 0.001$) or have a parent with a history of severe depression ($p < 0.001$).

Similarly, comparison between the analytic sample for depressive symptoms (N = 3,101) and the missing sample (N = 8,685) showed that those included in analyses were more likely to be female ($p < 0.001$), White ($p = 0.05$), have a higher number of childhood infections ($p < 0.001$), and have lower depressive symptoms at age 10 and 18 years ($p < 0.001$) (Table 30). The analytic sample were less likely to have a mother of manual SEP ($p < 0.001$) or have a parent with a history of severe depression ($p < 0.001$).

Table 29. Missing data: Comparison of the risk set (data for childhood infections) and the complete case-set for depressive symptoms (data for childhood infections and depressive symptoms from age 10 to 19 years).

Characteristics	Risk set (N = 11,786)	Complete case-set for depressive symptoms (N = 1,133)	Difference between groups (X^2 / t-test p-value)
Confounders			
Sex – no. female (%)	5,710 (48.4)	706 (62.3)	<0.001
Ethnicity – no. White (%)	11,511 (97.7)	1,117 (98.6)	0.02
Maternal SEP – no. manual (%)	2,621 (22.2)	120 (10.6)	<0.001
Birthweight – mean (SD)	3.4 (0.5)	3.4 (0.5)	0.20
Parental history of severe depression – no. (%)	1,677 (14.2)	90 (7.9)	<0.001
Number of childhood infections			
Mean (SD)	4.6 (3.2)	6.0 (3.0)	<0.001
Median (IQR)	4 (2-6)	6 (4-8)	<0.001
Burden of infection – no. (%)			
Low (0 to 4 infections)	6,371 (54.1)	391 (34.5)	<0.001
Medium (5 to 6 infections)	2,480 (21.0)	318 (28.1)	<0.001
High (7 to 9 infections)	1,988 (16.9)	279 (24.6)	<0.001
Very high (10 to 22 infections)	947 (8.0)	145 (12.8)	<0.001
Depressive symptoms – mean (SD)			
Age 10	4.0 (3.5)	3.7 (3.1)	<0.001
Age 13	3.9 (3.8)	3.9 (3.6)	1.00
Age 14	4.9 (4.5)	4.8 (4.3)	0.40
Age 17	5.9 (5.6)	5.5 (5.1)	0.03
Age 18	6.6 (5.3)	6.0 (4.8)	<0.001
Age 19	6.8 (5.9)	6.2 (5.5)	<0.01

Table 30. Missing data: Comparison of the analytic sample for depressive symptoms (data for childhood infections and depressive symptoms at age 19 years) and the missing sample (data for childhood infections but not depressive symptoms at age 19 years).

Characteristics	Analytic sample for depressive symptoms (N = 3,101)	Missing sample for depressive symptoms (N = 8,685)	Difference between groups (X^2 / t-test p-value)
Confounders			
Sex – no. female (%)	1,983 (63.9)	3,727 (42.9)	<0.001
Ethnicity – no. White (%)	3,042 (98.1)	8,469 (97.5)	0.05
Maternal SEP – no. manual (%)	456 (14.7)	2,164 (24.9)	<0.001
Birthweight – mean (SD)	3.4 (0.5)	3.4 (0.5)	0.13
Parental history of severe depression – no. (%)	347 (11.2)	1,330 (15.3)	<0.001
Number of childhood infections			
Mean (SD)	5.6 (3.1)	4.3 (3.2)	<0.001
Median (interquartile range)	5 (3-7)	4 (2-6)	<0.001
Burden of infection – no. (%)			
Low (0 to 4 infections)	1,236 (40.0)	5,135 (59.1)	<0.001
Medium (5 to 6 infections)	829 (26.7)	1,651 (19.0)	<0.001
High (7 to 9 infections)	691 (22.3)	1,297 (14.9)	<0.001
Very high (10 to 22 infections)	345 (11.1)	602 (6.9)	<0.001
Depressive symptoms – mean (SD)			
Age 10	3.8 (3.4)	4.2 (3.6)	<0.001
Age 13	4.0 (3.8)	3.9 (3.8)	0.10
Age 14	5.0 (4.5)	4.8 (4.4)	0.20
Age 17	5.8 (5.4)	6.0 (5.8)	0.30
Age 18	6.2 (5.0)	7.0 (5.5)	<0.001
Age 19	6.8 (5.9)	--	--

5.5.8 Comparisons between analytic and missing samples for psychotic experiences

Comparison between the risk set (N = 11,786) and the complete case-set (N = 2,495) showed that those in the complete case-set were more likely to be female ($p < 0.001$), be of White ethnicity ($p < 0.01$), have high number of childhood infections ($p < 0.001$), and less likely to have mother of manual SEP ($p < 0.001$) (Table 31).

Similarly, comparison between the analytic sample for PEs (N = 4,253) compared with the missing sample (N = 7,533) showed that those included in analyses were more likely to be female ($p < 0.001$), have a higher number of childhood infections ($p < 0.001$), and less likely to have a mother of manual SEP ($p < 0.001$) (Table 32).

Table 31. Missing data: Comparison of the risk set (data for childhood infections) and the complete case-set for psychotic experiences (data for childhood infections and PEs at age 12 and 18 years).

Characteristics	Risk set (N = 11,786)	Complete case-set for PEs (N = 2,495)	Difference between groups (X^2 / t-test p-value)
Confounders			
Sex – no. female (%)	5710 (48.4)	1372 (55.0)	<0.001
Ethnicity – no. White (%)	11511 (97.7)	2457 (98.5)	<0.01
Maternal SEP – no. manual (%)	2621 (22.2)	327 (13.1)	<0.001
Birthweight – mean (SD)	3.4 (0.5)	3.4 (0.5)	0.08
Parental history of schizophrenia – no. (%)	40 (0.3)	9 (0.4)	0.90
Number of childhood infections			
Mean (SD)	4.6 (3.2)	5.8 (3.0)	<0.001
Median (IQR)	4 (2-6)	5 (4-8)	<0.001
Burden of infection – no. (%)			
Low (0 to 4 infections)	6371 (54.1)	936 (37.5)	<0.001
Medium (5 to 6 infections)	2480 (21.0)	677 (27.1)	<0.001
High (7 to 9 infections)	1988 (16.9)	591 (23.7)	<0.001
Very high (10 to 22 infections)	947 (8.0)	291 (11.7)	<0.001
Psychotic experiences (PEs) – no. (%)			
Suspected/definite PEs age 12	844 (13.7)	326 (13.1)	0.50
Definite PEs only age 12	350 (5.7)	127 (5.1)	0.30
Definite PEs without attribution age 12	289 (4.7)	111 (4.4)	0.60
Suspected/definite PEs age 18	385 (9.1)	201 (8.1)	0.20
Definite PEs only age 18	206 (4.8)	110 (4.4)	0.40
Definite PEs without attribution age 18	177 (4.2)	91 (3.6)	0.30

Table 32. Missing data: Comparison of the analytic sample for PEs (data for childhood infections and PEs at age 18 years) and the missing sample (data for childhood infections but not PEs at age 18 years).

Characteristics	Analytic sample for PEs (N = 4,253)	Missing sample for PEs (N = 7,533)	Difference between groups (X^2 / t-test p-value)
Confounders			
Sex – no. female (%)	2391 (56.2)	3319 (44.1)	<0.001
Ethnicity – no. White (%)	4164 (97.9)	7348 (97.5)	0.23
Maternal SEP – no. manual (%)	708 (16.6)	1913 (25.4)	<0.001
Birthweight – mean (SD)	3.4 (0.5)	3.4 (0.5)	0.10
Parental history of schizophrenia – no. (%)	17 (0.4)	24 (0.3)	0.51
Number of childhood infections			
Mean (SD)	5.5 (3.1)	4.1 (3.2)	<0.001
Median (IQR)	5 (3-7)	4 (2-6)	<0.001
Burden of infection – no. (%)			
Low (0 to 4 infections)	1783 (41.9)	4588 (60.9)	<0.001
Medium (5 to 6 infections)	1089 (25.6)	1391 (18.5)	<0.001
High (7 to 9 infections)	912 (21.4)	1076 (14.3)	<0.001
Very high (10 to 22 infections)	469 (11.0)	478 (6.4)	<0.001
Psychotic experiences (PEs) – no. (%)			
Suspected/definite PEs age 12	504 (13.4)	340 (14.0)	0.50
Definite PEs only age 12	203 (5.4)	147 (6.1)	0.30
Definite PEs without attribution age 12	174 (4.6)	115 (4.8)	0.80
Suspected/definite PEs age 18	385 (9.1)	--	--
Definite PEs only age 18	206 (4.8)	--	--
Definite PEs without attribution age 18	177 (4.2)	--	--

5.6 Discussion

Our findings suggest that common early-childhood infections, particularly a very high infection burden, are associated with: (i) the risk of depressive symptoms subsequently up to age 17 years, and (ii) the risk of suspected/definite PEs subsequently at age 12 years. The finding that very high infection burden has the strongest association with mental health outcomes is somewhat consistent with hypotheses 3 and 4 (Section 5.3, Page 149), which state that childhood infection burden has a dose-response relationship with both depressive symptoms and PEs. The associations of infection with depressive symptoms at age 13 and 14 years and with suspected/definite PEs at age 12 years were robust and persisted after correction for multiple testing. Childhood infections were not associated with risk of depressive symptoms or PEs at age 18 or 19 years. As such, hypotheses 1 and 2 were not supported since childhood infections were not associated with mental heath outcomes at all ages.

Strong links exist between child/adolescent and adult depression (66–68,73). Adolescents with recurrent depressive episodes are at particularly high risk of subsequent recurrent depression as adults (68). Longitudinal studies suggest that recurrence of depression may be similar in clinic and community samples (66). PEs in childhood or adolescence may also provide a valid method for studying the development of adult psychotic disorders (403,416). PEs in childhood may be transient but population-based studies suggest that PEs in the general population and those observed in psychotic disorders may exist on a continuum (417). Prospective birth cohort studies have reported that PEs in childhood are associated with increased risk of psychotic disorders in adulthood (401). Common underlying mechanisms for PEs in healthy individuals and in schizophrenia have also been reported (418). Early-life infections could increase psychosis risk by affecting neurodevelopment, consistent with the neurodevelopmental hypothesis of schizophrenia (419,420). In many cases, PEs in our sample are likely to be part of normal development while for other

participants these symptoms may be more pathological (421,422). Childhood PEs are also familial and heritable and associated with multiple risk factors for schizophrenia (423–426). PEs and depressive symptoms in children and adolescents appear to be markers of mental distress and represent useful indicators for subsequent mental health problems.

In our sample, associations observed between childhood infections and PEs/depressive symptoms in childhood and adolescence did not persist for these outcomes in late-adolescence. There could be a number of explanations for this, including that childhood infections do not have a lasting effect on the risk of adult mental health disorders. However, findings from other long-term follow-up studies argue against this. For instance, a meta-analysis of childhood infections reported that children exposed to viral infections of the central nervous system were at higher risk of adult psychosis (390). Longitudinal studies of childhood infection and subsequent non-affective psychosis found similar results (388,391). Furthermore, population-based longitudinal studies suggest that childhood infections and autoimmune disease increase risk of adult schizophrenia and mood disorders in a dose-response fashion (145,386). Benros and colleagues reported that a history of hospitalisation for infection increases the risk of mood disorders and schizophrenia by 62% and 60% respectively (145,386). One explanation for the null findings could be attrition. At age 19 years, 86% of the sample with data on childhood infections were missing from follow-up for depressive symptoms and at age 18 years, 68% of the sample were missing from follow-up for PEs. Another explanation could be choice of exposure and outcome used. For instance, previous studies used serious infections requiring hospitalisation as exposure (145,386), and diagnosis of schizophrenia or depression as outcome. I have used common childhood infections as exposure and depressive symptoms/PEs as outcomes. Nevertheless, I was still able to show that relatively common childhood infections are associated with risk of depressive symptoms and PEs in adolescence. Sample size for outcomes in late-adolescence was relatively small and there was attrition over time, a common issue for prospective studies. In future, studies with larger sample sizes for cases are required.

It is possible that childhood infections contribute indirectly (via inflammatory mechanisms) to the risk of mental health disorders. Inflammatory responses to infection, such as elevated cytokine levels and fever, may represent the mechanism through which risk of mental disorders is increased (427). Sickness behaviour is common in infection and is present in some cases of depression. Sickness behaviour is triggered by proinflammatory cytokines in response to infectious agents and includes symptoms such as fatigue, anhedonia, concentration difficulties, social withdrawal, and appetite changes (381,428). Along with sickness behaviour, proinflammatory cytokines may induce depression in physically ill individuals with no history of mental health disorders. Depression may be therefore a maladaptive form of cytokine-induced sickness in some individuals (381,428). In addition, infections in early-life have been associated with adult schizophrenia via inflammation (156,157,389,391,429–441). Infection-related inflammation may influence neurodevelopment resulting in heightened risk of schizophrenia (442). Inflammation represents a compelling link between infection and mental health disorders and requires further investigation.

The interaction of multiple genetic and environmental factors is likely to contribute to risk of psychosis or depression. Genetic susceptibility plays an important role in risk of mental health disorders, but there is evidence to suggest that a significant proportion of cases may be preventable through modification of the environment (443,444). I attempted to explore the effects of environmental factors by controlling for maternal SEP and birth weight. Evidence for the association between infection and PEs/depressive symptoms attenuated but did not disappear, suggesting that these environmental factors partly explain these associations. Some genetic and environmental risk factors for psychosis and depression may be shared (444). Childhood maltreatment, social disadvantage, and minority status are independently associated with both psychosis and depression (444). By recognising infection and other environmental factors that are associated with depression and psychosis, we may be able to identify at-risk individuals early and prevent the onset of symptoms.

5.6.1 Limitations

The strengths of this study include longitudinal design and repeated measures of depressive symptoms. A limitation is the method for collection of childhood infection data. The questionnaire containing questions on infections were completed by primary caregiver throughout childhood with a short period of recall (past 12 months), thus minimising, though not completely eliminating, the risk of erroneous recall. The questions on infections also require parents to have a good understanding of infectious diseases and may be vulnerable to misreporting. For example, 8.2% of parents reported that their children had no infections during childhood; a somewhat unlikely scenario. Another limitation is attrition; the number of completed mental health assessments decreases over time. This may be indicative of selective attrition of mental health cases since mental health problems have been associated with non-response and attrition (445). Attrition and subsequent smaller sample size could result in underestimation of the true effect of infection on mental health outcomes. Another possible explanation for the lack of association with PEs/depression in late-adolescence could be that the relative contribution of infection to mental health becomes negligible over time due to neuroplasticity and brain development. Finally, statistical power was an issue in some of the PE analyses, resulting in wide confidence intervals.

5.6.2 Conclusion

Childhood infections are inevitable, but the adverse outcomes of such physical health problems may go beyond physical health later in life. Here I present evidence that childhood infections, particularly a very high infection burden, can negatively impact mental health well into adolescence. Future work is needed (i) to replicate the observed associations between common childhood infections and mental health outcomes during adolescence; (ii) to examine whether common childhood infections have an effect on depressive symptoms and psychotic experiences in adulthood; and (iii) to elucidate potential mechanisms for these associations.

SECTION D: ANALYSIS OF UK BIOBANK DATA

Chapter 6: Systemic Inflammation and Comorbid Lifetime Depression and Ischaemic Heart Disease in Middle-Aged and Older Adults

6.1 Chapter Summary

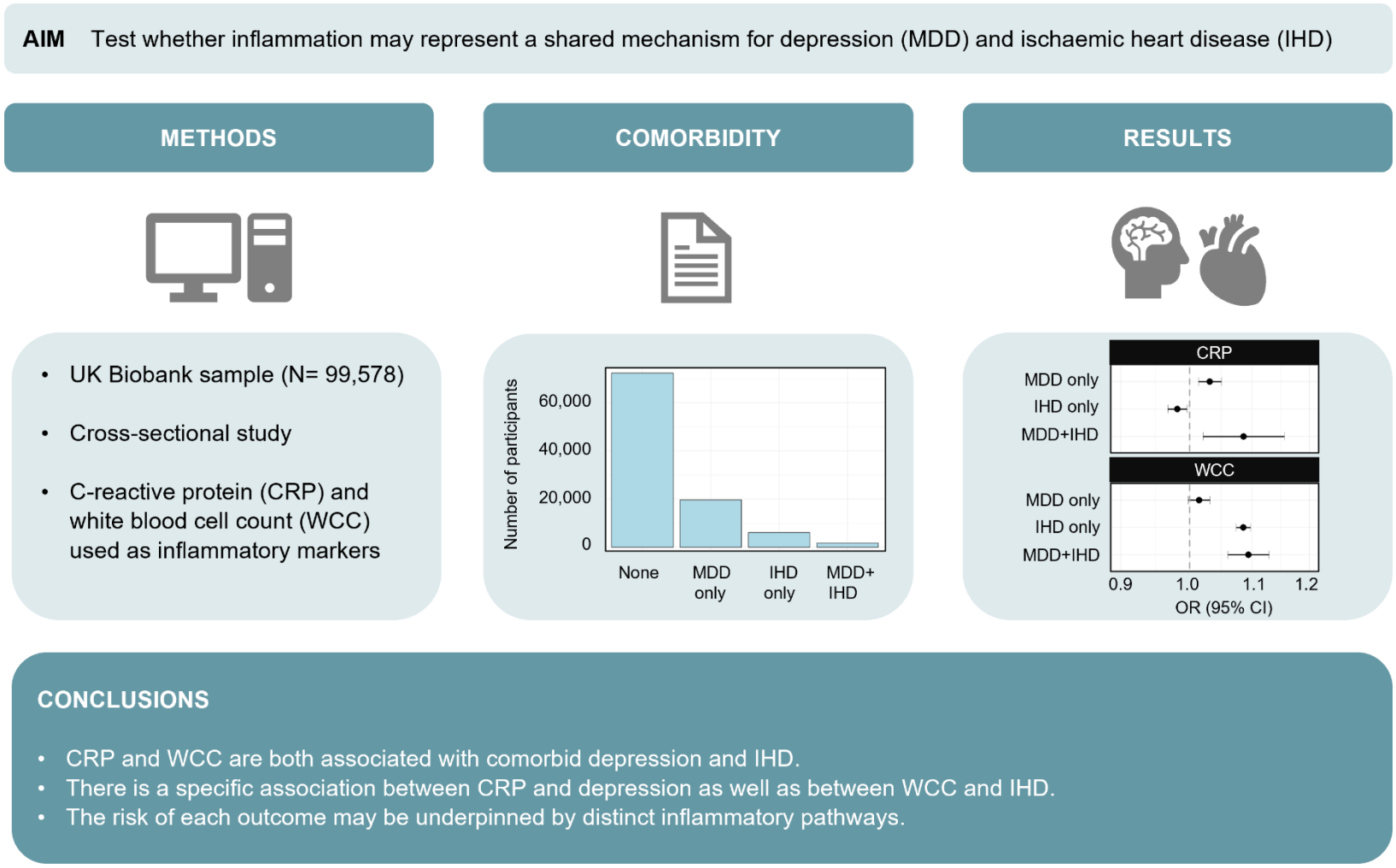


Figure 31. Visual summary of Chapter 6.

6.2 Introduction

Depression and IHD, both among leading causes of mortality worldwide (1), commonly co-occur in the population (34). Evidence for a bidirectional association between IHD and depression is now well established. For instance, pre-existing IHD is associated with an increased risk of subsequent depression (42,44) and *vice versa* (34). On average, one fifth of patients develop depression after IHD (36,37). Similarly, comorbid depression is associated with poor prognosis following MI (50,51). This bidirectional relationship points to shared risk factors and pathophysiologic mechanisms for depression and IHD, but these mechanisms are relatively poorly understood.

Emerging evidence implicates systemic inflammation in depression (446) and IHD (447). For both illnesses, most existing studies are based on assays of acute phase proteins like CRP or cytokines like IL-6 (446–448). Meta-analyses of these studies have reported elevated CRP levels (>3 mg/L) in a quarter of depressed patients (171). A linear dose-response association between CRP levels and severity of depressive symptoms has also been reported (449). Similarly, population-based prospective studies have reported an association between CRP and CVD (210). However, genetic approaches like Mendelian randomisation have suggested that this association may not be causal (294,450,451). WCC, another important inflammatory marker, has been reported to be a robust risk factor for fatal and non-fatal CVD (198). In contrast, WCC has been studied relatively less extensively in the context of depression (159).

To date, most studies have examined associations of systemic inflammatory markers with depression and IHD separately, while studies of comorbid depression and IHD are rare. Rarer still are studies of different types of inflammatory markers within the same population. Given that the innate immune response comprises protein and cellular components (452), studies of different types of inflammatory markers may provide important clues for shared/specific immune pathways involved in depression and IHD, but such studies are currently lacking.

Systemic inflammation is a complex trait, associated with various biologic and environmental factors such as obesity, socioeconomic deprivation, and physical activity; some of which are well established risk factors for depression and IHD. However, it is unclear to what extent confounding from socioeconomic and lifestyle factors contributes to previously reported associations of systemic inflammatory markers with depression and IHD. Furthermore, non-response and selection bias are common methodological issues in observational studies, yet most studies have not directly assessed the impact of these issues on observed associations.

In order to examine the potential role of inflammation in the comorbidity between depression and IHD, I have used data from the UK Biobank to test whether well-known protein and cellular measures of systemic inflammation (i.e., CRP and WCC) are associated with lifetime comorbid depression and IHD, and with depression and IHD separately. I have focused on IHD because it is one of the more severe CVD subtypes, with extensive evidence suggesting a link with depression (42,44,453–456), and with inflammation-related cardiovascular changes, namely atherosclerosis (457). I hypothesised that inflammatory markers would be more strongly associated with comorbid depression and IHD than either illness alone. In addition, to examine commonality verses specificity of association, I jointly modelled depression and IHD in relation to CRP and WCC, to test the similarity/difference of the effect estimates for the two outcomes. To examine potential confounding from socioeconomic and lifestyle factors, I have taken into account effects of age, sex, ethnicity, deprivation (proxy for SEP), BMI, smoking, alcohol, and physical activity. I also carried out sensitivity analysis to assess the effect of bias from selection of specific UK Biobank participants for respective analyses on observed associations.

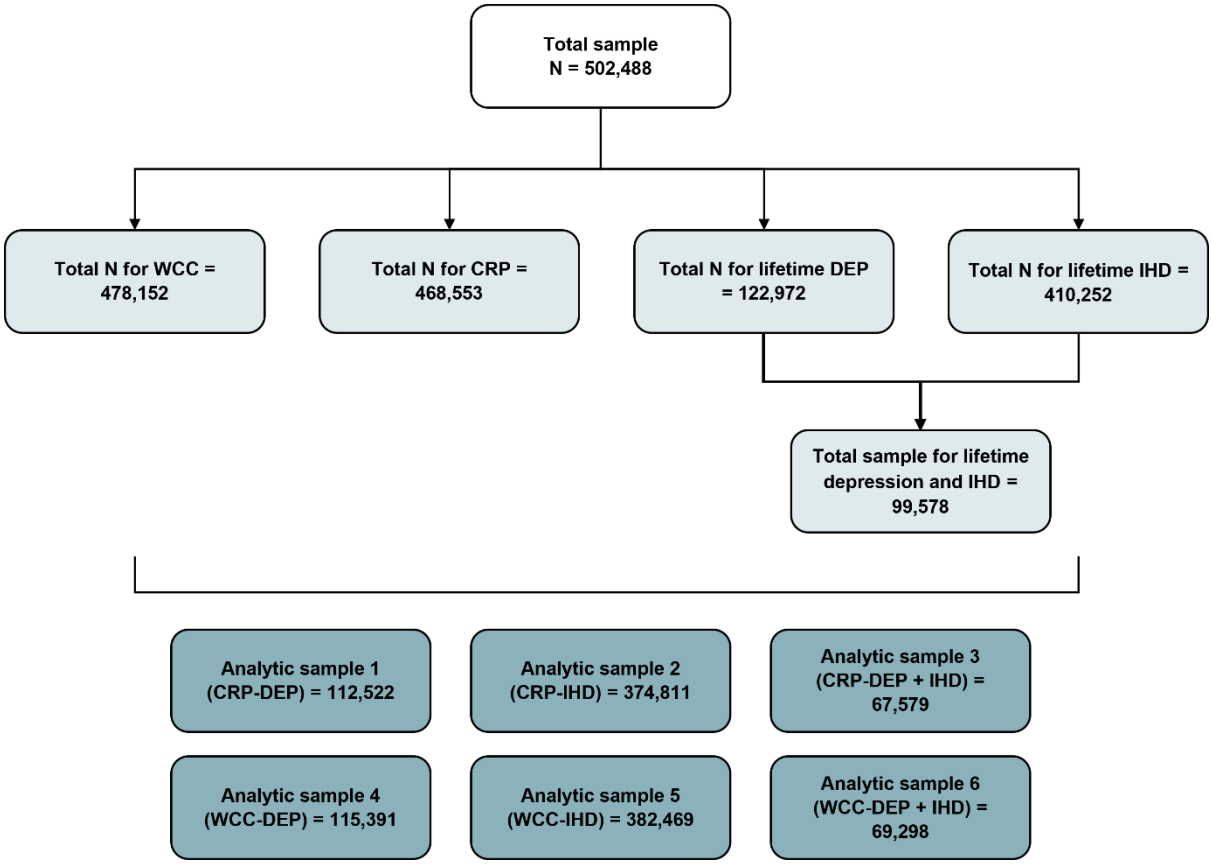
6.3 Hypotheses

1. CRP is associated with comorbid depression and IHD.
2. WCC is associated with comorbid depression and IHD.
3. CRP is more strongly associated with comorbidity than no illness/single illness.
4. WCC is more strongly associated with comorbidity than no illness/single illness.
5. CRP shows no specificity of association with either depression or IHD.
6. WCC shows no specificity of association with either depression or IHD.

6.4 Methods

6.4.1 Description of sample

The risk set for the analyses comprised 468,553 unrelated participants from the UK Biobank with data on CRP concentration at baseline (Figure 32). See Section 2.5 (Page 70) for details of the UK Biobank study. Of these individuals, 122,972 had data on lifetime depression and 410,252 had data on lifetime IHD. A total of 99,578 individuals had data on both lifetime depression and IHD.



CRP: C-reactive protein; DEP: depression; IHD: ischaemic heart disease; WCC: white blood cell count.

Figure 32. Flow diagram showing the number of participants with exposure and outcome measures.

6.4.2 Assessment of CRP concentration

During recruitment, blood samples (45 ml) were collected. The blood was collected in a silica clot accelerator collection tube and left to clot at room temperature for 30 minutes before the serum was separated by centrifugation at 4 ^{o}C. The serum was packed and later stored at the UK Biobank central facility in either –80 ^{o}C or in nitrogen-vapour (458). CRP concentration was measured by immunoturbidimetric high sensitivity analysis on a Beckman Coulter AU5800. CRP was used as a log-transformed standardised continuous measure in analyses.

6.4.3 Assessment of WCC

WCC assay was performed on blood samples obtained from UK Biobank assessment centre visits. The analyser operating range was 0 to $9x10^{11}$ cells/L. WCC was measured as 10^{9} cells/L. WCC was used as a standardised continuous measure.

6.4.4 Assessment of lifetime depression

A binary measure of lifetime probable moderate/severe major depression was derived from self-report data collected using a touchscreen questionnaire administered to UK Biobank participants at baseline (459). The questionnaire included information on past episodes of low mood, loss of interest, duration and number of episodes, help seeking from family physician or psychiatrist, which were systematically combined to derive categories of probable single episode or recurrent major depression (moderate or severe) (Table 33) (459). Probable lifetime depression was used as a binary variable (depression vs no depression).

Lifetime depression diagnosis was defined as ICD-10 code F32 to F33. Depression diagnosis was used as a binary variable (depression vs no depression). These data were collected from hospital inpatient records. ICD-10 diagnosis of depression was used in

sensitivity analysis only, as this is only available for hospital inpatients and are incomplete for mental health outcomes resulting in a very small and unrepresentative number of cases.

Table 33. Derivation of depression variables.

Criteria	Depression variable	Definition based on criteria
1. Ever felt depressed for a whole week 2. Ever disinterested or unenthusiastic for a whole week 3. Only one episode 4. ≥2 episodes 5. Episode lasted ≥2 weeks 6. Ever seen a GP for nerves, anxiety, tension or depression 7. Ever seen a psychiatrist for nerves, anxiety, tension or depression	Single episode of probable major depression	{(1) AND (3) AND (5) AND [(6) OR (7)]} **OR** {(2) AND (3) AND (5) AND [(6) OR (7)]}
	Probable recurrent major depression (moderate)	[(1) OR (2)] AND (4) AND (5) AND (6)
	Probable recurrent major depression (severe)	[(1) OR (2)] AND (4) AND (5) AND (7)

6.4.5 Assessment of lifetime IHD

Lifetime IHD diagnosis was defined as ICD-10 code I20 to I25. IHD was used as a binary variable (IHD vs no IHD). These data were collected from hospital inpatient records, which were more complete for physical health outcomes than mental health outcomes.

6.4.6 Assessment of comorbid lifetime depression and IHD

Comorbidity was defined as the presence of both lifetime depression and IHD.

6.4.7 Assessment of confounders

I adjusted for the following covariates: sex, ethnicity, age, TDI, BMI, smoking, alcohol, physical activity, mood disorders, metabolic disorders, chronic inflammatory conditions, and acute infections. All covariates were recorded at recruitment between 2006 and 2010.

Sex and ethnicity were used as binary variables. Sex (female or male) was acquired from NHS records. In some cases, recorded sex was updated by the participant. Ethnicity was recorded as White, Mixed, Asian/Asian British, Black/Black British, Chinese, and Other. The UK Biobank is relatively homogenous in terms of ethnicity, therefore ethnicity was recoded as White or any other ethnicity.

Age, TDI, and BMI were all used as continuous variables. Age (years) was based on self-reported date of birth and used as a continuous measure. TDI is a measure of material deprivation which was used as a proxy for socioeconomic status. TDI covers four components: (i) unemployment, (ii) non-car ownership, (iii) non-home ownership, and (iv) household overcrowding (460). These components are measured in a specific area, then combined and standardised to give an overall score for that area. A higher score represents a greater level of deprivation. BMI was calculated as body weight (kilograms) divided by height (meters squared).

Smoking status, alcohol intake, and physical activity were all used as categorical variables. Smoking status was categorised into three groups (never; previous; current). Alcohol intake was categorised into six groups (never; special occasions only; 1 to 3 times per month; 1 to 2 times per week; 3 to 4 times per week; daily or almost day). Physical activity in the last four weeks was categorised into six groups (none; walking for pleasure [not as a means of transport]; light DIY [e.g. pruning, watering the lawn]; heavy DIY [e.g. weeding, lawn mowing, carpentry, digging]; strenuous sports; other exercise [e.g. swimming, cycling, keep fit, bowling]). Participants could record doing more than one type of physical activity.

Mood disorders, metabolic disorders, chronic inflammatory conditions, and acute infections were all used as binary variables. Mood disorders were defined as diagnosis of bipolar disorder (ICD-10 code: F30 to F31), schizophrenia (F20 to F29) or anxiety disorder (F40 to F41). Metabolic disorders were defined as diagnosis of diabetes mellitus (E10 to E14) or obesity (E65 to E66). Chronic inflammatory conditions were defined as diagnosis of multiple sclerosis (G35), irritable bowel syndrome (K50 to K51), rheumatoid arthritis (M05 to M06), or

systemic lupus erythematosus (M32). Acute infections were defined as acute viral or bacterial infection (A00 to A49, A80, B00 to B19, J00 to J29). These data were collected from hospital inpatient records.

6.4.8 Statistical analysis

Analyses were carried out using R (version 3.6.1) unless otherwise specified. Regression models were estimated before adjustment for potential confounders and using sequential adjustment for: (i) age, sex, ethnicity, deprivation; (ii) additional adjustment for alcohol, smoking, physical activity; and (iii) additional adjustment for BMI.

6.4.9 Association of immune markers with lifetime depression and IHD

Logistic regression was used to calculate ORs with 95% CI for the three outcomes: (i) depression; (ii) IHD; and (iii) comorbid depression and IHD (Hypothesis 1 to 4, Page 191). Monomorbid depression and IHD outcomes were tested against their respective “no illness” control group (e.g. IHD vs no IHD). I used two different control groups for the comorbid depression and IHD outcome: (i) “single illness” i.e. either depression or IHD, but not both; and (ii) “no illness” i.e. no depression or IHD. I took the decision not to use just one control group (i.e. comorbidity vs no comorbidity) because the group with monomorbid depression or IHD is likely to be different from the group with neither of these conditions.

Where CRP concentration was the exposure, the ORs represent the odds of the outcome per one SD increase in log-transformed CRP concentration. Where WCC was the exposure, the ORs represent the odds of the outcome per one SD increase in WCC.

6.4.10 Specificity of association of CRP and WCC with lifetime depression and IHD

Bivariate probit regression was performed using Stata/IC 16.0. I jointly modelled depression and IHD outcomes with CRP/WCC to compare the effect estimates for the two outcomes

(Hypothesis 5, 6, Page 191). Specifically, to test equality of regression parameters for both outcomes, I compared a model that allowed exposure estimates to differ between outcomes with a model that constrained estimates to be equal for both outcomes using the likelihood ratio test (LRT). Probit estimates were converted to ORs by multiplying probit parameters by 1.6 (461).

6.4.11 Sensitivity analysis to explore potential influence of selection bias

I evaluated the influence of potential selection bias for participation in depression and IHD data collection using inverse probability weighted regression of the models of depression and IHD outcomes on either CRP or WCC (462). This method up-weights participants who were less likely to participate in outcome data collection and down-weights participants who were more likely to participate. In this way, weighted analyses estimate results as if the full UK Biobank dataset were used in analyses.

To obtain participant weights, I regressed participation in outcome data collection (0 = no participation; 1 = participation) on age, sex, ethnicity, BMI, and TDI as well as all possible variable interactions and quadratic and cubic effects for continuous variables. I then created stabilised inverse probability weights from the above regression model by dividing the mean proportion of outcome data collection participation by the fitted values from this regression (463).

I repeated logistic regression analyses of depression and IHD outcomes on CRP/WCC using the inverse probability weights as regression weightings.

6.4.12 Sensitivity analysis using depression diagnosis as the outcome

I assessed the robustness of the self-reported measure of lifetime depression by repeating logistic regression analyses of depression and IHD outcomes on CRP/WCC using ICD-10 depression diagnosis as the outcome measure.

6.4.13 Sensitivity analysis adjusting for additional potential confounders

I assessed the effect of mood disorders, metabolic disorders, chronic inflammatory conditions, and acute infections on associations from main analyses. I repeated logistic regression analyses of depression and IHD outcomes on CRP/WCC adjusting for these variables. BMI was excluded as a confounder in this sensitivity analysis since metabolic disorders includes diagnosis of obesity.

6.5 Results

6.5.1 Baseline characteristics of the sample

The UK Biobank sample (Figure 32) comprised mainly individuals of White ethnicity (94.6%) and low deprivation (TDI mean = –1.3; SD = 3.1) (Table 34). Over half of participants (54.4%) were women. The number of participants with lifetime depression, lifetime IHD, and comorbid depression and IHD were 24,642 (20%), 32,192 (8%) and 1,661 (2%), respectively.

Individuals with high CRP were more likely to be women ($p < 0.001$), be current smokers ($p<0.001$), have less frequent alcohol intake ($p < 0.001$), have higher BMI ($p < 0.001$), and have higher WCC ($p < 0.001$) (Table 34).

Table 34. Characteristics of the participants using maximum available sample size.

Characteristic [a]	All participants (N = 502,488)	Low CRP [b] (N = 362,255)	High CRP [b] (N = 106,298)	Difference between low and high CRP (X^2/T-test p-value)
Exposure				
WCC (10^9 cells/L) – mean (SD)	6.9 (2.1)	6.7 (2.1)	7.7 (2.2)	<0.001
Outcomes				
Depression (self-report) – no. (%)	24,642 (20.0)	17,194 (19.2)	5,724 (22.9)	<0.001
Depression (diagnosis) – no. (%)	1,515 (0.4)	995 (0.3)	520 (0.6)	<0.001
IHD (diagnosis) – no. (%)	32,192 (7.8)	21,535 (7.4)	8,372 (9.1)	<0.001
Comorbidity – no. (%)				
Depression (self-report) & IHD	1,661 (1.7)	1,053 (1.5)	491 (2.3)	<0.001
Depression (diagnosis) & IHD	156 (0.0)	97 (0.0)	59 (0.1)	<0.001
Confounders				
Age (years) – mean (SD)	56.5 (8.1)	56.3 (8.1)	57.4 (7.9)	<0.001
Deprivation (TDI) – mean (SD)	-1.3 (3.1)	-1.4 (3.0)	-0.9 (3.3)	<0.001
BMI (kg/m^2) – mean (SD)	27.4 (4.8)	26.6 (4.1)	30.3 (5.7)	<0.001
Sex – no. women (%)	273,375 (54.4)	191,387 (52.8)	62,783 (59.1)	<0.001
Ethnicity – no. White (%)	472,679 (94.6)	341,932 (94.8)	99,695 (94.3)	<0.001
Smoking status – no. (%)				
Never	273,513 (54.8)	203,578 (56.5)	51,589 (48.9)	<0.001
Previous	173,050 (34.6)	123,315 (34.2)	38,535 (36.5)	<0.001
Current	52,977 (10.6)	33,694 (9.3)	15,470 (14.7)	<0.001
Alcohol intake – no. (%)				
Never	40,639 (8.2)	26,432 (7.3)	11,174 (10.5)	<0.001
Special occasions only	58,006 (11.6)	37,881 (10.5)	15,927 (15.0)	<0.001
1 to 3 times per month	55,853 (11.1)	38,899 (10.8)	13,144 (12.4)	<0.001
1 or 2 times per week	129,288 (25.8)	93,888 (26.0)	26,809 (25.3)	<0.001
3 or 4 times per week	115,434 (23.0)	87,610 (24.2)	20,450 (19.3)	<0.001
Daily or almost daily	191,767 (20.3)	76,840 (21.3)	18,466 (17.4)	<0.001
Physical activity – no. (%)				
None	32,844 (6.6)	18,677 (5.2)	11,667 (11.1)	<0.001
Walking	350,932 (70.8)	263,322 (73.0)	67,253 (64.0)	<0.001
Light DIY	33,819 (6.8)	22,034 (6.1)	9,754 (9.3)	<0.001
Heavy DIY	12,707 (2.6)	8,810 (2.4)	3,191 (3.0)	<0.001
Strenuous sports	3,871 (0.8)	3,035 (0.8)	628 (0.6)	<0.001
Other	61,165 (12.3)	44,826 (12.4)	12,635 (12.0)	<0.001
Related conditions – no. (%)				
Mood disorders	1,973 (0.5)	1,331 (0.5)	642 (0.7)	<0.001
Metabolic disorders	3,056 (0.8)	1,743 (0.6)	1,313 (1.4)	<0.001

Chronic inflammatory conditions	5,723 (1.5)	3,442 (1.2)	2,281 (2.5)	<0.001
Acute infections	28,345 (7.4)	18,680 (6.4)	9,665 (10.5)	<0.001

[a] BMI: body mass index; IHD: ischemic heart disease; SD: standard deviation; TDI: Townsend deprivation index; WCC: white blood cell count.

[b] For the purposes of this table, low CRP defined as ≤3mg/L and high CRP defined as >3mg/L.

6.5.2 Associations of CRP with depression, IHD, and comorbid depression and IHD

The analyses in this section are relevant to hypotheses 1 and 3 (Section 6.3, Page 191).

There was consistent association of CRP with comorbid depression and IHD after fully adjusting for potential confounders, using the group with neither depression nor IHD as reference (adjusted OR = 1.07; 95% CI = 1.01, 1.13) or using the group with either depression or IHD alone as reference (adjusted OR = 1.07; 95% CI = 1.01, 1.14) (Table 35). CRP was also associated with depression (adjusted OR = 1.03; 95% CI = 1.01, 1.05) but not with IHD (adjusted OR = 0.98; 95% CI = 0.97, 1.00) after adjusting for potential confounders including BMI.

6.5.3 Associations of WCC with depression, IHD, and comorbid depression and IHD

The analyses in this section are relevant to hypotheses 2 and 4 (Section 6.3, Page 191).

There was consistent association of WCC with comorbid depression and IHD after adjusting for potential confounders, using the group with neither depression nor IHD as reference (adjusted OR = 1.10; 95% CI = 1.06, 1.13) or using the group with either depression or IHD alone as reference (adjusted OR = 1.11; 95% CI = 1.06, 1.17) (Table 35). WCC was also associated with IHD (adjusted OR = 1.09; 95% CI = 1.08, 1.10), but not with depression (adjusted OR = 1.02; 95% CI = 1.00, 1.03) after adjusting for potential confounders including BMI.

Table 35. Odds ratio (95% CI) for the association between 1 SD increase in CRP or WCC and depression/IHD outcomes.

Exposure [a]	Outcome	Sample size	No. with outcome (%)	Odds ratio (95% CI) for depression/IHD outcomes			
				Unadjusted	Adjusted 1 [b]	Adjusted 2 [c]	Adjusted 3 [d]
CRP	Depression	112,522	22,522 (20.0)	1.10 (1.09, 1.12)	1.11 (1.10, 1.13)	1.08 (1.07, 1.10)	1.03 (1.01, 1.05)
	IHD	374,811	29,023 (7.7)	1.16 (1.15, 1.18)	1.12 (1.10, 1.13)	1.07 (1.06, 1.08)	0.98 (0.97, 1.00)
	Comorbidity [ref: no illness]	67,579	1,491 (2.2)	1.34 (1.27, 1.41)	1.28 (1.22, 1.35)	1.20 (1.13, 1.26)	1.07 (1.01, 1.13)
	Comorbidity [ref: single illness]	24,896	1,491 (6.0)	1.21 (1.15, 1.27)	1.19 (1.13, 1.26)	1.15 (1.09, 1.21)	1.07 (1.01, 1.14)
WCC	Depression	115,391	23,085 (20.0)	1.09 (1.07, 1.10)	1.08 (1.06, 1.10)	1.04 (1.02, 1.05)	1.02 (1.00, 1.03)
	IHD	382,469	29,693 (7.8)	1.19 (1.18, 1.21)	1.15 (1.14, 1.16)	1.11 (1.10, 1.12)	1.09 (1.08, 1.10)
	Comorbidity [ref: no illness]	69,298	1,537 (2.2)	1.18 (1.13, 1.22)	1.15 (1.11, 1.20)	1.11 (1.08, 1.15)	1.10 (1.06, 1.13)
	Comorbidity [ref: single illness]	25,523	1,537 (6.0)	1.21 (1.15, 1.27)	1.18 (1.12, 1.24)	1.14 (1.08, 1.19)	1.11 (1.06, 1.17)

[a] CI: confidence interval; Comorbidity: presence of both lifetime depression and IHD; CRP: C-reactive protein; IHD: ischaemic heart disease; No illness: absence of both lifetime depression and IHD; Single illness: presence of either lifetime depression or IHD but not both; WCC: white blood cell count.

[b] Adjusted for age, sex, ethnicity, deprivation (TDI).

[c] Adjusted 1 + alcohol use, smoking, physical activity.

[d] Adjusted 2 + BMI.

6.5.4 Specificity of association of CRP and WCC with depression and IHD

The analyses in this section are relevant to hypotheses 5 and 6 (Section 6.3, Page 191).

In bivariate probit regression analysis, I demonstrated minimal evidence that adjusted ORs representing outcome-specific associations of CRP with depression and IHD differed from the adjusted OR representing a common effect of CRP on both outcomes (p-value for LRT <0.01 to 0.71), suggesting that CRP is not specifically associated with depression or IHD (Table 36).

Table 36. Odds ratio (95% CI) for association between 1 SD increase in CRP concentration and depression/IHD outcomes (N = 92,658).

Adjustment [a]	Odds ratio (95% CI) for depression/IHD outcomes			LRT comparing specific vs common effect (P-value)
	Specific effect on depression	Specific effect on IHD	Common effect on both outcomes	
Unadjusted	1.09 (1.08, 1.11)	1.12 (1.10, 1.28)	1.23 (1.16, 1.31)	0.04
Adjusted 1 [b]	1.10 (1.09, 1.12)	1.10 (1.08, 1.12)	1.10 (1.09, 1.12)	0.71
Adjusted 2 [c]	1.08 (1.06, 1.09)	1.06 (1.04, 1.08)	1.07 (1.06, 1.09)	0.22
Adjusted 3 [d]	1.03 (1.01, 1.05)	0.98 (0.96, 1.01)	1.02 (1.00, 1.03)	<0.01

[a] CI: confidence interval; CRP: C-reactive protein; IHD: ischaemic heart disease; LRT: likelihood ratio test.

[b] Adjusted for age, sex, ethnicity, deprivation (TDI).

[c] Adjusted 1 + alcohol use, smoking, physical activity.

[d] Adjusted 2 + BMI.

I also revealed evidence that adjusted ORs representing outcome-specific associations of WCC with depression and IHD differed from the adjusted OR representing a common effect of WCC on both outcomes (p-value for LRT <0.001), suggesting that WCC is specifically associated with IHD (Table 37).

Table 37. Odds ratio (95% CI) for association between 1 SD increase in WCC and depression/IHD outcomes (N = 93,795).

Adjustment [a]	Odds ratio (95% CI) for depression/IHD outcomes			LRT comparing specific vs common effect (P-value)
	Specific effect on depression	Specific effect on IHD	Common effect on both outcomes	
Unadjusted	1.08 (1.07, 1.10)	1.16 (1.14, 1.18)	1.11 (1.10, 1.12)	<0.001
Adjusted 1 [b]	1.08 (1.06, 1.09)	1.14 (1.12, 1.16)	1.10 (1.09, 1.11)	<0.001
Adjusted 2 [c]	1.04 (1.02, 1.05)	1.11 (1.09, 1.13)	1.07 (1.06, 1.08)	<0.001
Adjusted 3 [d]	1.02 (1.00, 1.03)	1.09 (1.07, 1.11)	1.05 (1.04, 1.06)	<0.001

[a] CI: confidence interval; IHD: ischaemic heart disease; LRT: likelihood ratio test; WCC: white blood cell count.

[b] Adjusted for age, sex, ethnicity, deprivation (TDI).

[c] Adjusted 1 + alcohol use, smoking, physical activity.

[d] Adjusted 2 + BMI.

6.5.4 Sensitivity analysis exploring potential influence of selection bias

Results mimicking main analyses in the full UK Biobank sample were largely unchanged for both CRP concentration and WCC (Table 38).

6.5.5 Sensitivity analysis using depression diagnosis as the outcome

The effect sizes were slightly larger for both CRP concentration and WCC when depression diagnosis was used as the outcome (Table 39).

6.5.6 Sensitivity analysis adjusting for additional potential confounders

Adjustment for mood disorders, metabolic disorders, chronic inflammatory conditions, and acute infections did not dramatically alter the results for either CRP concentration or WCC (Table 40).

Table 38. Sensitivity analysis exploring selection bias: Odds ratio (95% CI) for the association between 1 SD increase in CRP or WCC and depression/IHD outcomes.

Exposure [a]	Outcome	Sample size	No. with outcome (%)	Odds ratio (95% CI) for depression/IHD outcomes			
				Unadjusted	Adjusted 1 [b]	Adjusted 2 [c]	Adjusted 3 [d]
CRP	Depression	112,522	22,522 (20.0)	1.10 (1.09, 1.12)	1.11 (1.10, 1.13)	1.09 (1.07, 1.10)	1.03 (1.02, 1.05)
	IHD	374,811	29,023 (7.7)	1.17 (1.16, 1.18)	1.12 (1.11, 1.14)	1.07 (1.06, 1.09)	0.99 (0.97, 1.00)
	Comorbidity [ref: no illness]	67,579	1,491 (2.2)	1.35 (1.28, 1.42)	1.29 (1.22, 1.36)	1.20 (1.14, 1.27)	1.07 (1.01, 1.14)
	Comorbidity [ref: single illness]	24,896	1,491 (6.0)	1.22 (1.15, 1.28)	1.20 (1.13, 1.26)	1.15 (1.09, 1.21)	1.08 (1.01, 1.14)
WCC	Depression	115,391	23,085 (20.0)	1.09 (1.07, 1.11)	1.08 (1.07, 1.10)	1.04 (1.02, 1.05)	1.02 (1.00, 1.03)
	IHD	382,469	29,693 (7.8)	1.19 (1.18, 1.21)	1.15 (1.14, 1.16)	1.11 (1.10, 1.12)	1.09 (1.08, 1.10)
	Comorbidity [ref: no illness]	69,298	1,537 (2.2)	1.18 (1.14, 1.23)	1.16 (1.11, 1.20)	1.11 (1.08, 1.15)	1.10 (1.06, 1.13)
	Comorbidity [ref: single illness]	25,523	1,537 (6.0)	1.21 (1.15, 1.27)	1.18 (1.13, 1.24)	1.14 (1.09, 1.19)	1.11 (1.06, 1.17)

[a] CI: confidence interval; Comorbidity: presence of both lifetime depression and IHD; CRP: C-reactive protein; IHD: ischaemic heart disease; No illness: absence of both lifetime depression and IHD; Single illness: presence of either lifetime depression or IHD but not both; WCC: white blood cell count.

[b] Adjusted for age, sex, ethnicity, deprivation (TDI).

[c] Adjusted 1 + alcohol use, smoking, physical activity.

[d] Adjusted 2 + BMI.

Table 39. Sensitivity analysis using ICD-10 depression diagnosis: Odds ratio (95% CI) for the association between 1 SD increase in CRP or WCC and depression/IHD outcomes.

Exposure [a]	Outcome	Sample size	No. with outcome (%)	Odds ratio (95% CI) for depression/IHD outcomes			
				Unadjusted	Adjusted 1 [b]	Adjusted 2 [c]	Adjusted 3 [d]
CRP	Depression diagnosis	374,811	1,453 (0.4)	1.26 (1.20, 1.32)	1.24 (1.18, 1.30)	1.15 (1.10, 1.21)	1.12 (1.06, 1.19)
	IHD	374,811	29,023 (7.7)	1.35 (1.31, 1.38)	1.23 (1.20, 1.27)	1.15 (1.12, 1.19)	0.96 (0.93, 1.00)
	Comorbidity [ref: no illness]	344,633	149 (0.04)	1.48 (1.27, 1.72)	1.37 (1.18, 1.60)	1.26 (1.08, 1.48)	1.12 (0.94, 1.33)
	Comorbidity [ref: single illness]	30,327	149 (0.5)	1.29 (1.10, 1.51)	1.18 (1.01, 1.38)	1.14 (0.97, 1.34)	1.09 (0.92, 1.30)
WCC	Depression diagnosis	382,469	1,477 (0.4)	1.05 (1.03, 1.08)	1.04 (1.02, 1.07)	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
	IHD	382,469	29,693 (7.8)	1.18 (1.16, 1.19)	1.13 (1.12, 1.15)	1.11 (1.09, 1.12)	1.09 (1.07, 1.10)
	Comorbidity [ref: no illness]	351,603	152 (0.04)	1.04 (1.01, 1.06)	1.04 (1.01, 1.07)	1.03 (1.00, 1.07)	1.03 (0.99, 1.08)
	Comorbidity [ref: single illness]	31,018	152 (0.5)	1.09 (0.99, 1.19)	1.05 (0.92, 1.19)	1.00 (0.85, 1.18)	0.97 (0.82, 1.16)

[a] CI: confidence interval; Comorbidity: presence of both lifetime depression and IHD; CRP: C-reactive protein; IHD: ischaemic heart disease; No illness: absence of both lifetime depression and IHD; Single illness: presence of either lifetime depression or IHD but not both; WCC: white blood cell count.

[b] Adjusted for age, sex, ethnicity, deprivation (TDI).

[c] Adjusted 1 + alcohol use, smoking, physical activity.

[d] Adjusted 2 + BMI.

Table 40. Sensitivity analysis adjusting for additional potential confounders.

Exposure [a]	Outcome	Sample size	No. with outcome (%)	Odds ratio (95% CI) for depression/IHD outcomes			
				Unadjusted	Adjusted 1 [b]	Adjusted 2 [c]	Adjusted 3 [d]
CRP	Depression	90,984	19,385 (21.3)	1.10 (1.09, 1.12)	1.12 (1.10, 1.13)	1.08 (1.07, 1.10)	1.08 (1.06, 1.10)
	IHD	374,811	29,023 (7.7)	1.16 (1.15, 1.18)	1.12 (1.10, 1.13)	1.07 (1.06, 1.08)	1.06 (1.05, 1.07)
	Comorbidity [ref: no illness]	67,579	1,491 (2.2)	1.34 (1.27, 1.41)	1.28 (1.22, 1.35)	1.20 (1.13, 1.26)	1.17 (1.11, 1.23)
	Comorbidity [ref: single illness]	24,896	1,491 (0.6)	1.21 (1.15, 1.27)	1.19 (1.13, 1.26)	1.15 (1.09, 1.21)	1.13 (1.07, 1.19)
WCC	Depression	93,284	19,876 (21.3)	1.09 (1.07, 1.10)	1.08 (1.06, 1.10)	1.04 (1.02, 1.06)	1.03 (1.02, 1.05)
	IHD	382,469	29,693 (7.8)	1.19 (1.18, 1.21)	1.15 (1.14, 1.16)	1.11 (1.10, 1.12)	1.10 (1.09, 1.11)
	Comorbidity [ref: no illness]	69,298	1,537 (2.2)	1.18 (1.13, 1.22)	1.15 (1.11, 1.20)	1.11 (1.08, 1.15)	1.10 (1.07, 1.13)
	Comorbidity [ref: single illness]	25,523	1,537 (0.6)	1.21 (1.15, 1.27)	1.18 (1.12, 1.24)	1.14 (1.08, 1.19)	1.13 (1.07, 1.18)

[a] CI: confidence interval; Comorbidity: presence of both lifetime depression and IHD; CRP: C-reactive protein; IHD: ischaemic heart disease; Single illness: presence of either lifetime depression or IHD but not both; WCC: white blood cell count.

[b] Adjusted for age, sex, ethnicity, deprivation (TDI).

[c] Adjusted 1 + alcohol use, smoking, physical activity.

[d] Adjusted 2 + mood disorders, metabolic disorders, chronic inflammatory conditions, acute infections.

6.6 Discussion

In this large, population-based sample, I examined associations of protein and cellular measures of inflammation with comorbid depression and IHD, elucidating a number of key findings. First, both CRP and WCC are associated with comorbid depression and IHD, even after controlling for a number of potential confounders including BMI. These associations remain using either no illness or single illness as the reference category, which is consistent with hypotheses 1 to 4 (Section 6.3, Page 191). These associations also remain in sensitivity analyses, supporting the robustness of the findings. Second, concerning risk of single outcome, CRP is associated with depression while WCC is associated with IHD specifically. The specific association of WCC with IHD is replicated using bivariate probit regression. This suggests that while systemic inflammation is likely to be a shared mechanism for depression and IHD, the risk of individual outcomes could be underpinned by distinct inflammatory pathways. The findings regarding specificity of association support hypothesis 5 but contradict hypothesis 6 (Section 6.3, Page 191). Finally, these findings are not fully explained by selection bias or by adjustment for relevant mood, metabolic, and inflammatory conditions indicating that associations between inflammation, depression and IHD are likely to be robust within the UK Biobank sample.

The results are consistent with systemic inflammation increasing the risk of comorbid depression and IHD. Animal models and epidemiological studies support the idea that systemic inflammation plays a role in the link between depression and CVD (464,465). The increased risk of this comorbidity appears to be similar whether compared to individuals with neither outcome or with depression/IHD only and without comorbidity. In addition, the risk of comorbid depression and IHD seems to be similarly increased whether CRP or WCC is the exposure. There is some evidence to suggest that comorbidity between depression and CVD arises largely from shared environmental factors (294). For example, chronic exposure to social stress can lead to dysregulation of the immune system (466). Physical activity,

another environmental factor, can exert cardioprotective and antidepressant effects (466). Conversely, genetic factors may partly explain why women are disproportionately affected by this comorbidity (467,468). Despite these potential sex differences, systemic inflammation appears to contribute to depression and IHD via endothelial dysfunction, oxidative damage, and altered serotonin metabolism in both women and men (63,469). Therefore, the association between systemic inflammation and comorbid depression and CVD appears to be robust. Taken together, this suggests that inflammation could particularly predispose to comorbidity of these disorders, therefore constituting a crucial link. Further research is required to understand the role of other inflammatory markers on comorbid depression and IHD.

BMI may offer some explanation for how comorbidity can arise between depression and IHD. In my analysis adjusting for BMI attenuated, but did not fully explain, the associations of CRP/WCC with comorbid depression and IHD. It is possible that BMI acts as a (partial) mediator in the relationship between inflammation and subsequent comorbidity. For example, early-life factors such as childhood adversity, may programme immunometabolic pathways leading to inflammation and obesity which then contribute to risk of depression and IHD in adulthood. Previous studies report that childhood adversity is associated with increased circulating inflammatory markers (470) and BMI (471) as well as increased risk for adult depression (472) and cardiometabolic illness (473). Work from other members of my lab group who also used the ALSPAC birth cohort, suggests that increased BMI during puberty is associated with depression in early-adulthood, particularly in females (474). Childhood inflammation is also associated with adult psychiatric (168) and cardiometabolic risk (475,476). Studies are required to test whether inflammation mediates the effects of early-life factors operating during childhood and fetal development on the risk of adult psychiatric and cardiometabolic illness.

I showed that different markers of systemic inflammation show distinct associations with depression and IHD. Associations of CRP with depression and IHD were similar until

adjustment for BMI, with BMI explaining the former to some extent and fully explaining the latter. This is consistent with a meta-analysis reporting that adjustment for BMI did not fully explain the association between CRP and depression (446). This result is also supported by other observational studies reporting that CRP is more strongly associated with depression than IHD (477,478). However, bivariate probit analysis indicated that CRP is not specifically associated with depression, suggesting a common effect of CRP on both depression and IHD. Genetic evidence for a causal relationship between CRP and depression is mixed and may be due to upstream activity in proteins such as IL-6 (294,449,479–481). Similarly, Mendelian randomisation studies have suggested that IL-6 is a causal determinant of IHD (206,450), but that this is not the case for CRP (294,450,451). Thus, IL-6 may be a key driver in the comorbidity between depression and IHD (294).

Furthermore, I showed that associations of WCC with depression and IHD were also similar until adjustment for BMI. BMI fully explained the association between WCC and depression but only partly explained the association between WCC and IHD. Bivariate probit analysis indicated that WCC is specifically associated with IHD. WCC may contribute to IHD by playing a direct role in the destabilisation of atherosclerotic plaques (482,483). Relevant Mendelian randomisation studies of these factors are lacking. I did not find association between CRP and IHD, or WCC and depression. One possible explanation for this divergence is that BMI is strongly correlated with CRP. Mendelian randomisation provides evidence that BMI causally influences CRP but not the other way around (484). Adjusting for BMI may therefore represent overadjustment. However, BMI appears to attenuate the effect of CRP and WCC to a similar extent. BMI does not provide the full explanation for distinct association of CRP/WCC with depression and IHD. Therefore, it is possible that distinct inflammatory pathways underpin the risks for depression and IHD.

6.6.1 Limitations

There are a number of limitations to this study. A key limitation is the cross-sectional study design, though the results lay the foundation for longitudinal approaches that would establish the temporality of association between inflammatory markers and outcomes. Furthermore, the depression outcome used in main analysis was derived from various self-reported information on past low mood and help seeking, and not ICD-10 diagnosis of depression, since it only captures the most extreme cases of depression from hospital linkage data. However, sensitivity analysis using ICD-10 depression diagnosis as the outcome showed comparable results. Another limitation is that reverse causality and residual confounding may still explain the associations between systemic inflammation and depression/IHD. Moreover, medication use may influence these relationships but I did not include it as a confounder due to a lack of access to relevant measures. Finally, I explored the influence of selection bias and found that it had little impact on the results, but non-White groups are underrepresented in the UK Biobank (485), limiting generalisability of the findings to the larger UK population.

6.6.2 Conclusion

To conclude, systemic inflammation could be a shared mechanism for depression and IHD, but the mechanistic basis of each outcome is likely to be underpinned by distinct inflammatory pathways. Further research is required to test causality, potential for targeting inflammation for treatment and prevention of these illnesses, and to elucidate possible mechanisms of association.

SECTION E: CONCLUSION

Chapter 7: Discussion, Future Directions, and Conclusions

7.1 Main Findings

In this thesis, I have investigated the relationship between depression and CVD across the lifespan and the potential role of systemic inflammation in the pathogenesis of these conditions. The aims of this thesis were: (i) to determine the direction of association between CVD risk and depressive symptoms in young people; (ii) to test the convergence of evidence for systemic inflammation as a shared mechanism for depression and CVD across the lifespan; and (iii) to determine the influence that demographic factors have on associations between systemic inflammation, depression and CVD.

Given that CVD and depression are bidirectionally associated in adults, I hypothesised that the same relationship would be present in younger age groups. This was not supported; the evidence supported only a unidirectional relationship between CVD risk and subsequent depressive symptoms in young people (Chapter 4, Page 110). Mid-adolescent CVD risk was associated with depressive symptoms in late-adolescence but childhood depressive symptoms were not associated with mid-adolescent CVD risk. Both the meta-analysis of longitudinal studies and ALSPAC analysis suggested that obesity and cigarette smoking contribute to this association (Chapter 3, Page 74; Chapter 4, Page 110).

Regarding the second aim, I hypothesised that different markers of systemic inflammation would be similarly associated with depression and CVD across the lifespan. Results from ALSPAC and UK Biobank analysis indicated that different inflammatory markers may have distinct associations with these conditions. CRP was associated with outcomes in both adolescence and adulthood. Childhood IL-6 and CRP were both associated with adolescent CVD risk (Chapter 4, Page 110). CVD risk appeared to mediate the association between childhood IL-6/CRP and depressive symptoms in late-adolescence. Childhood infections were associated with depressive symptoms in late-adolescence but it was not possible to test association with CVD risk (Chapter 5, Page 144). In middle-aged and older adults, specific associations were present, particularly between WCC and IHD (Chapter 6, Page

187). Both CRP and WCC were associated with comorbid depression and IHD. BMI may play a role in these associations; see Section 7.3.2 (Page 225) for further discussion.

Finally, I demonstrated evidence of sex differences in the association between systemic inflammation and depression/CVD outcomes across the lifespan. Female ALSPAC participants were more likely to have high levels of depressive symptoms and CVD risk than male participants (Chapter 4, Page 110). Similarly, women participating in the UK Biobank had higher CRP concentration than men (Chapter 6, Page 187). Associations between inflammation, CVD risk, and subsequent depressive symptoms may be particularly relevant in child/adolescent females. In addition, sex, ethnicity, and SEP had the greatest attenuating influence on associations in older adults, suggesting complex, age-dependent interactions of multiple environmental and genetic factors.

A summary of the specific hypotheses tested in this thesis are presented in Table 41 below.

Table 41. Summary of hypotheses tested in the analytic chapters.

Chapter	Hypotheses	Supported by findings?
3	1. High BMI is associated with depression in young people.	Yes
	2. Cigarette smoking is associated with depression in young people.	Yes
	3. High SBP is associated with depression in young people.	--
	4. High total cholesterol is associated with depression in young people.	--
	5. Low HDL is associated with depression in young people.	--
	6. CVD risk factors are similarly associated with depression and depressive symptoms.	Somewhat
4	1. Depressive symptoms at age 12 years are associated with CVD risk at age 15 years.	No
	2. CVD risk at age 15 years is associated with depressive symptoms at age 18 years.	Yes
	3. IL-6 at age 9 years is associated with depressive symptoms at age 12 and 18 years.	No
	4. CRP at age 9 years is associated with depressive symptoms at age 12 and 18 years.	No
	5. IL-6 at age 9 years is associated with CVD risk at age 15 years.	Yes
	6. CRP at age 9 years is associated with CVD risk at age 15 years.	Yes
	7. CVD risk at age 15 years mediates the association between IL-6 at age 9 years and depressive symptoms at age 18 years.	Yes
	8. CVD risk at age 15 years mediates the association between CRP at age 9 years and depressive symptoms at age 18 years.	Yes
5	1. Childhood infections are associated with depressive symptoms from age 10 to 19 years.	No
	2. Childhood infections are associated with PEs at age 12 and 18 years.	No
	3. Childhood infection burden has a dose-response relationship with depressive symptoms from age 10 to 19 years.	Somewhat
	4. Childhood infection burden has a dose-response relationship with PEs at age 12 and 18 years.	Somewhat

6	1. CRP is associated with comorbid depression and IHD.	Yes
	2. WCC is associated with comorbid depression and IHD.	Yes
	3. CRP is more strongly associated with comorbidity than monomorbid depression or IHD.	Yes
	4. WCC is more strongly associated with comorbidity than monomorbid depression or IHD.	Yes
	5. CRP shows no specificity of association with either depression or IHD.	Yes
	6. WCC shows no specificity of association with either depression or IHD.	No

7.2 Methodological Limitations

The main findings should be considered in light of the limitations of the observational methodological approach. Key limitations include study design, selection bias, sample size, measurement bias, and residual confounding.

7.2.1 Study design

The results presented in this thesis are based on data from observational studies. I used both cohort and cross-sectional study designs depending on the availability of data. Both of these study designs have strengths and limitations which may affect the interpretation of the findings. The decision to use the ALSPAC and UK Biobank datasets also has an impact on the interpretation of the results.

The studies selected for inclusion in the systematic review and meta-analysis were all longitudinal cohort studies. The studies using data from the ALSPAC cohort were also longitudinal by design. Longitudinal cohort studies can be used to determine the temporality of association between an exposure and outcome; however, this type of study is vulnerable to a range of issues including attrition (see below) and acquisition of data at multiple time points. Repeated measures allow potential changes in the temporal association between an exposure and outcome to be scrutinised, contributing to more robust conclusions.

The UK Biobank study of systemic inflammation and comorbid depression and IHD is cross-sectional by design. Although the results lay the foundation for longitudinal approaches that would establish the temporality of association between inflammatory markers and outcomes, the possibility of reverse causality is a major limitation in cross-sectional studies.

In this thesis I aimed to cover associations between systemic inflammation, depression, and CVD across the lifespan. The study populations I used in analyses were young people in both the ALSPAC cohort and meta-analysis, and middle-aged and older adults in the UK Biobank study. I presented the definitions for these age groups in Section 2.3 (Page 63). The

decision to include these particular datasets led to two issues: (i) younger adults age 25 to 39 years were not included in any analyses; and (ii) relevant measures and data collection methods differed between the two datasets. These issues were the result of a trade-off between using datasets with longer follow-up times and using good quality studies containing the appropriate exposure, outcome, and confounder measures.

7.2.2 Selection bias

Selection bias occurs when the study participants are not representative of the target population. Criteria for selecting the risk set from the study population can lead to differences in key variables between the included and excluded participants. Incomplete responses to surveys and missing data due to attrition are further sources of bias. In addition, study participants may be different to the individuals who did not take enrol in the study.

The UK Biobank and ALSPAC cohort are primarily composed of White British individuals, which limits the generalisability of the results in this thesis to other parts of the population. Similarly, the majority of studies included in the systematic review and meta-analysis came from North America and Europe. Therefore, the results from these analyses may not be relevant to individuals from other ethnic groups or geographic locations. Moreover, the UK Biobank and ALSPAC slightly oversampled individuals from higher socioeconomic backgrounds, leading to further reduction in generalisability.

The results in this thesis suggest that there may be sex differences in the associations between systemic inflammation, depression and CVD (risk). Sensitivity analyses revealed that sex explained the heterogeneity in some of the meta-analyses. Similarly, the association between CVD risk and subsequent depressive symptoms appeared to be stronger in females than in males. These potential sex differences must be interpreted with caution given the role of selection bias, particularly attrition, may play in these stratified analyses. For example, female participants in the ALSPAC cohort were more likely to complete all assessments than male participants. Therefore, the relatively smaller male sample size may

not have sufficient power to detect associations raising the possibility of spurious sex differences.

Attrition was an issue in my longitudinal analyses, particularly where measures of exposure or outcome were required. For example, investigating associations of childhood infection with subsequent depressive symptoms and PEs across an 18 year period included measures of childhood infection at seven time points, depressive symptoms at six time points, and PEs at two time points. The individuals who completed all of these assessments were more likely to be female, of White ethnicity, and have a mother from the non-manual socioeconomic group, than those missed at least one assessment.

Furthermore, missing data due to attrition prevented any investigation into the association between childhood infections and subsequent CVD risk in young people. This analysis could not be performed because the exposure, outcome, and confounders would have had to be imputed to achieve a sufficiently large sample size.

7.2.3 Sample size

Both too small and very large samples have limitations that can alter the interpretation of findings. A small sample size may hinder statistical interpretation and prevent the results from being extrapolated, whereas a very large sample size may emphasise small statistical differences that are not biologically or clinically relevant (486). The number of required cases increases as the difference to be identified decreases. Larger sample sizes increase the statistical power to detect these differences and reduce the likelihood of type I and type II errors. However, too large samples may be problematic since statistical tests were developed to interpret difference in samples rather than within whole populations.

Several analyses were affected by small sample size. The number of studies in each of the meta-analyses in the systematic review was relatively small, restricting statistical precision. This was reflected by wide confidence intervals and reduced statistical power to exclude the

null hypothesis of no difference between groups (i.e. type II errors). There was also considerable heterogeneity between studies in the meta-analyses. In addition, relatively few participants had complete data to create the composite CVD risk score at age 15 years. Multiple imputation somewhat addressed the issue of missing data and helped to increase statistical power (Section 2.4.3, Page 68), but has its own problems. For example, multiple imputation is based on the assumption that data are missing at random and that the imputation model is appropriately specified (277). Moreover, small sample size and reduced statistical power was an issue in the analyses assessing relationship of infection and PE, resulting in wide confidence intervals. Attrition was an issue in analyses where depressive symptoms was an outcome. The number of completed mental health assessments decreased over time, leading to subsequently smaller sample size, which could result in underestimation of the true effect size.

7.2.4 Measurement bias

Measurement bias, also called misclassification or information bias, refers to the difference between the true and observed, measured value. This type of bias is potentially relevant to all of the analyses presented in this thesis.

Underreporting by participants on specific measures may have led to measurement bias. For example, parents involved in the ALSPAC study were asked to retrospectively report childhood infections over a number of years. Some parents reported that their children never had any infections during childhood. This unlikely scenario could be the result of underreporting of childhood infections by parents. Parents may underreport for many reasons including a lack of understanding of infectious disease terminology, recall issues, fear of potential scrutiny, etc.

Reliable and valid measurements are key to observational research and can influence the interpretation of results. Despite this, many of the measures used in analysis have not been

validated. Assessing the validity of measures for diagnosing conditions is not always possible or may have to be performed indirectly. The depression outcome I used in the UK Biobank analysis was derived from various self-reported information on past low mood and help seeking. Although this measure was not validated, I used this measure of depression rather than ICD-10 diagnosis, since the ICD-10 diagnosis measure only captures the most extreme cases of depression from clinical service linkage data. In contrast, the reliability of some ALSPAC measures has been performed. Within or between observer variation and random subject variation can limit the reliability of questionnaires and other measurements. For example, the semi-structured interview measuring PEs during childhood/adolescence in the ALSPAC cohort had good reliability at age 18 years but only fair reliability at age 12 years. The test-retest reliability at age 12 years was limited, suggesting that participants may give different answers over time. Issues with reliability and validity may lead to misclassification of cases and subsequent alteration to the effect sizes.

The way that variables are created can also introduce measurement bias. Dichotomisation of variables can lead to information losses and may also alter our understanding of how that particular variable affects other variables in analysis. For example, ethnicity was dichotomised in all ALSPAC and UK Biobank analyses due to low counts for groups other than White ethnicity. This decision meant it was not possible to investigate the role of ethnicity in associations beyond being a member of a minority ethnic group in the UK, which is not necessarily capturing the same information as an individual's specific ethnicity that may encompass a multiplicity of relevant factors. In addition, the way the composite CVD risk score was created using ALSPAC cohort data may have introduced bias. First, the variables included in the CVD risk score were imputed. Imputation requires selection of auxiliary variables to support the prediction of missing data. Auxiliary variables therefore influence the final CVD risk score values. Second, the CVD risk score was a combination of binary and continuous variables which were designed to reflect measures created in i3C consortium datasets. Ideally, the measures would all be continuous although this was not

possible given the data available. Certain measures such as diet were not available and other measures may not have been the most suitable for the target population. For example, waist circumference may be a better measure of central adiposity in young people than BMI, but I used BMI to reflect the i3C consortium datasets. Performing the same analysis without including i3C consortium-based weights in the CVD risk score may have produced different results.

Given the length of follow-up and volume of information collected from participants, human error during data collection in the ALSPAC and UK Biobank datasets is likely. Similarly, a number of steps in the systematic review and meta-analysis process were subject to human error, despite steps being taken to minimise this type of measurement bias. Study selection and data extraction is a long, manual process involving multiple individuals, meaning that errors in data collection are probable.

7.2.5 Residual confounding

Residual confounding refers to the bias by confounding that remains after controlling for potential confounders in analysis. While these factors can be balanced between comparison groups in randomised trials, they are endemic in research using observational designs. Residual confounding is difficult to measure or take into account in such studies so it is likely to affect all analyses presented in this thesis.

There may be additional confounders that were not considered in analysis due to the lack of data collected on these factors. For example, in the systematic review and meta-analysis, the possibility of residual confounding by unidentified factors remains high. This is partly because the studies included in the meta-analysis controlled for various confounders but these varied considerably between studies, meaning that other factors may also explain associations between CVD risk factors and subsequent depression/depressive symptoms.

Residual confounding could also occur due to a lack of precise data on the confounding variables. In the UK Biobank study of associations between systemic inflammation and depression/IHD, many confounders were categorical variables with somewhat arbitrary groups. For example, the alcohol measure was categorised based on frequency of alcohol consumption per day/month but did not account for volume of alcohol consumed during this time. As such, this measure may fail to capture precise enough information about alcohol use to fully control for this variable in analysis.

Finally, there may be measurement errors in the way that participants were classified with respect to potential confounders. Many of the variables used in ALSPAC and UK Biobank analyses were self-reported by participants. Participants may not give accurate answers for a number of reasons, but the result is the introduction of residual confounding. For example, in the ALSPAC study of association between childhood infections and subsequent depressive symptoms/PEs, many parents reported that their children experienced no childhood infections from age 1.5 to 7.5 years old. It is very unlikely that these children had no common infections during this time, however it is difficult to determine from this self-reported measure what the “true” values should be. Linkage with primary and secondary care electronic health record data may be useful to address residual confounding arising due to this type of measurement bias.

7.2.6 Personal time constraints

Time constraints meant that the systematic review and meta-analysis could only focus on associations between selected CVD risk factors and depression in one direction. I decided to investigate the association of CVD risk factors with subsequent depression/depressive symptoms in young people because some systematic reviews of the reverse relationship (e.g. depression as the exposure and obesity as the outcome) already existed. Unfortunately, this exclusion criterion left an analytical gap in this thesis.

7.3 Future Directions

The results presented in this thesis could lead to a variety of further research investigations. First, the findings require replication in other samples since the participants in the ALSPAC and UK Biobank samples are relatively homogenous. Second, there is some evidence that different inflammatory markers may exert their effect on mental and physical health conditions via distinct pathways. Further longitudinal studies and genetic analysis are needed to investigate potential mechanisms. Finally, a non-exhaustive list of specific research questions arising from the work in this thesis is given in the relevant subsection below.

7.3.1 Replication of findings in other samples

A number of results require replication in other samples with a different study design or larger sample size. For example, the results from the UK Biobank study require replication in a prospective sample. The study using UK Biobank data (Chapter 6) was cross-sectional by design and the extent to which systemic inflammation may predict comorbid depression and IHD (versus monomorbid illness) should be investigated in a longitudinal cohort and/or using genetic techniques such as Mendelian randomisation. A longitudinal study would allow direction of associations to be determined while reducing the risk of reverse causality. Moreover, the systematic review highlighted the lack of longitudinal studies investigating associations between CVD risk factors other than high BMI or smoking with subsequent depression in young people. Although I found no relationship between cholesterol, blood pressure, or triglycerides with depressive symptoms in the ALSPAC cohort, these results require replication in other larger samples to ensure the lack of association is not due to sample size issues. In addition, future work is required to replicate the observed associations between common childhood infections and depression outcomes in young people, given that this is another relatively understudied area of research.

Replication of findings is also required in more diverse study populations. Although the UK Biobank and ALSPAC contain relatively large study populations, there is little diversity in ethnic group or SEP measures in these datasets. As previously mentioned, selection bias means that the results presented in this thesis may not be generalisable to all ethnic groups (populations living in or outside the UK) or individuals of lower SEP. The reasons for low diversity in the UK Biobank and ALSPAC samples are likely to be multifaceted but continued effort is required to address such issues in future observational studies. Systemic inflammation, depression, and CVD may have distinct relationships depending on environmental factors related to ethnicity or SEP that cannot be adequately assessed in homogenous populations (487,488). As such, exploring the influence of related environmental factors may add a new layer of understanding (and complexity) to associations between systemic inflammation, depression, and CVD.

More generally, greater effort is required to understand how to increase participation of under-represented groups in observational studies containing measures of systemic inflammation, depression and CVD. Study recruitment, attrition, help-seeking behaviour, and disease diagnoses may differ according to characteristics such as age, sex, ethnicity, and SEP. Despite this, much of our clinical understanding is not based on findings from heterogenous datasets. Continued work is needed to increase representation of historically under-represented groups such as women, non-binary genders, diverse ethnic groups, low SEP groups etc in observational studies. This is important because findings based on homogenous datasets are likely to be biased and, if extrapolated to unrepresented groups, may lead to adverse outcomes. Translating non-generalisable results into clinical practice may result in misinterpretation or misdiagnosis of symptoms in different populations and prescription of inappropriate treatment options.

7.3.2 Investigating potential mechanisms and other inflammatory markers

In this thesis I have shown that various inflammatory markers (infections, WCC, IL-6, and CRP) are associated with depression and/or CVD across the lifespan, suggesting that systemic inflammation is a robust shared mechanism for these two conditions. There is some evidence that specific inflammatory markers have distinct associations with depression/CVD. Below, I discuss plausible mechanisms to explain the different effects of IL-6, CRP, and WCC in the pathogenesis of these two conditions. Further work, using longitudinal studies and genetic analysis, is required to confirm the existence of these distinct mechanisms and to better understand the pathophysiological mechanisms underlying these relationships.

The IL-6 trans-signalling pathway (Section 1.3.3, Page 41) has been directly implicated in the development of both depression (480) and CVD (206,207) (Figure 33). Much of the interaction between IL-6 and the brain occurs via trans-signalling (489). Increased trans-signalling (as indicated by increased sIL-6R) appears to have a causal effect on depression (480), perhaps via its role in neuroinflammation (490) and sickness behaviour (491). Subtypes of depression may be specifically associated with increased IL-6 trans-signalling (492). Moreover, the IL-6 trans-signalling pathway appears to be causally related to CVD (206,207). Trans-signalling contributes to the pathogenesis of atherosclerosis by initiating recruitment and infiltration of immune cells (493,494), which may increase the risk of future cardiovascular events (495). High levels of soluble glycoprotein-130 may protect against CVD by inhibiting IL-6 trans-signalling (495). Thus, IL-6 may have a causal role in the pathogenesis of depression and CVD via its trans-signalling pathway.

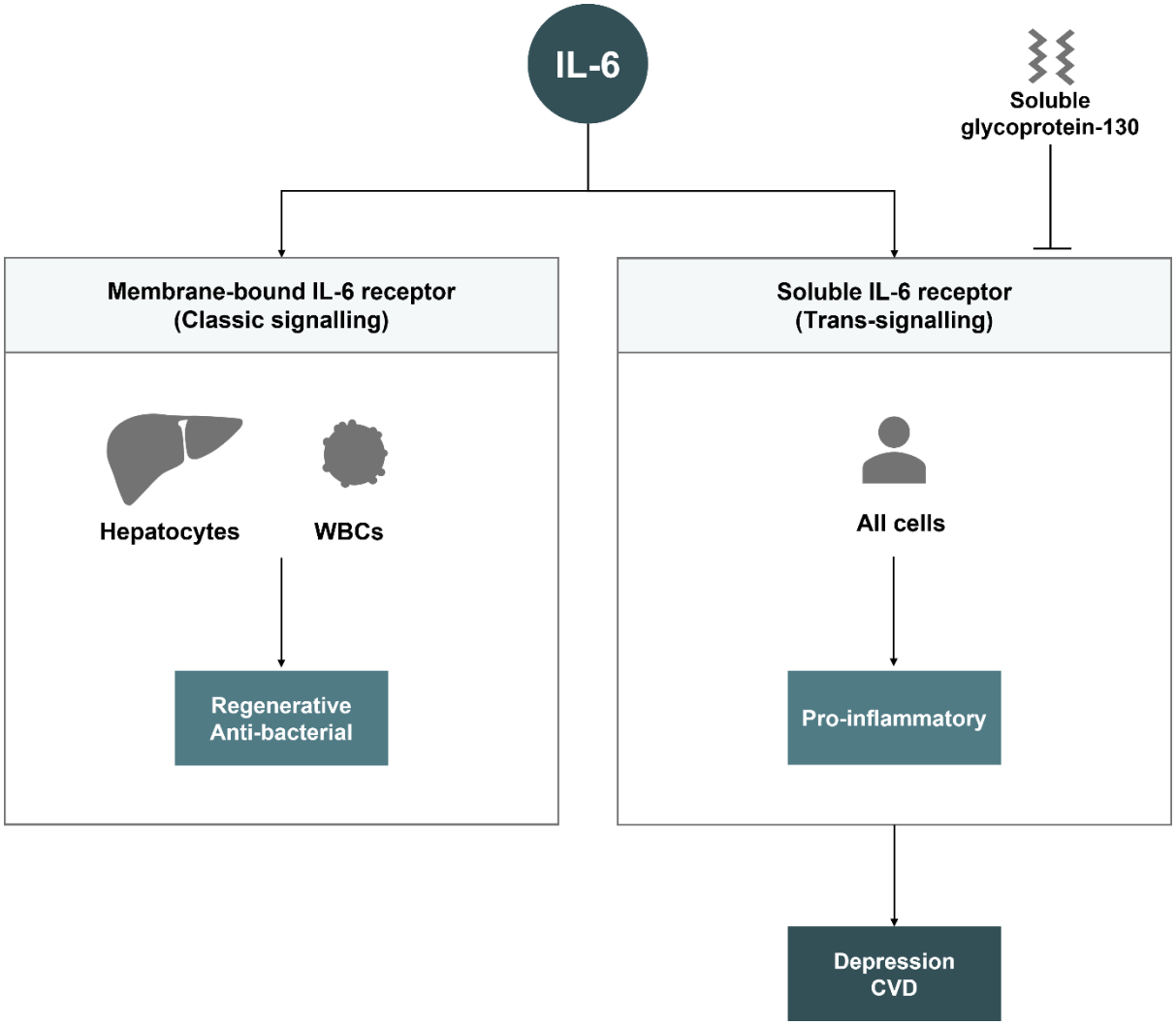


Figure 33. Summary of IL-6 signalling pathways and depression/CVD outcomes.

IL-6 activity may be key to understanding the distinct associations of CRP with depression and CVD. I have shown that CRP is specifically associated with elevated CVD risk in adolescents and depression in adults. CRP is unlikely to have a causal role in the pathogenesis of depression (294,449,480,481) or CVD (294,450,451) but the intrinsic link between IL-6 and CRP could explain the associations between CRP and CVD risk/depression. Although CRP is a marker of classic IL-6 signalling (480,495), it can promote shedding of sIL-6R by neutrophils, resulting in stimulation of resident tissue cells (139,496,497). Thus, is plausible that CRP amplifies IL-6 trans-signalling activity, thereby indirectly affecting the causal pathway between IL-6 and depression/CVD (Figure 34). The

precise role of CRP isoforms (Section 1.3.3, Page 41) in depression and CVD also remains unknown and requires investigation.

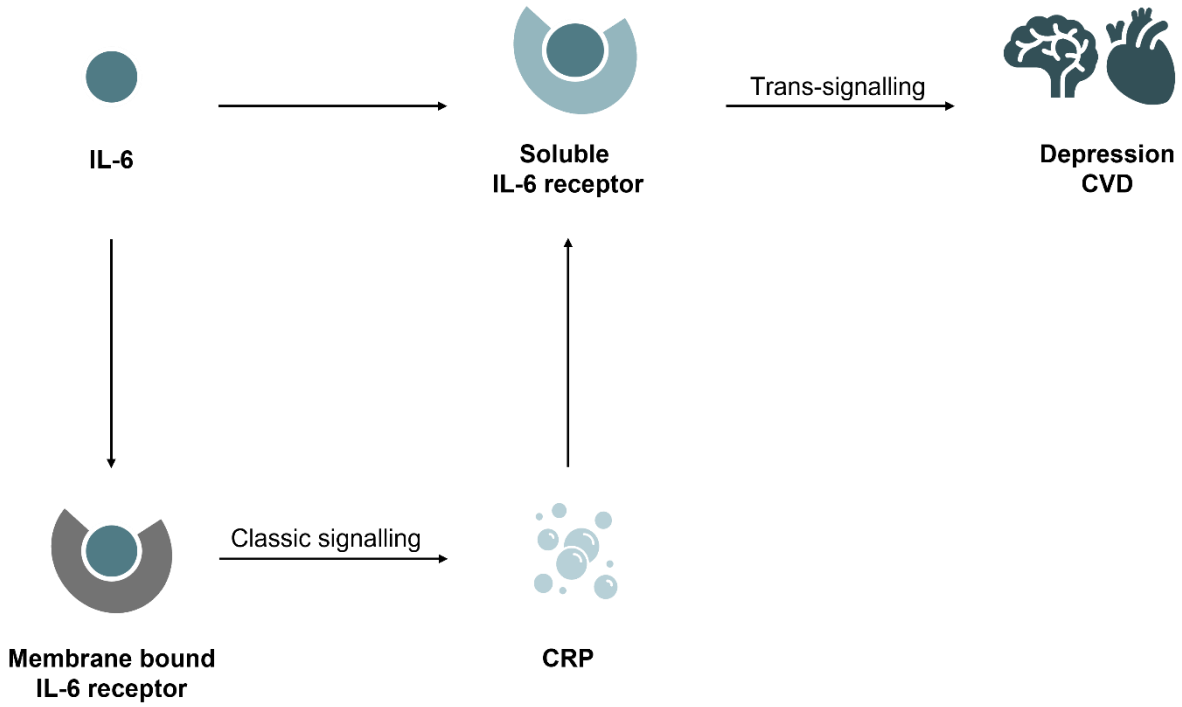


Figure 34. Possible links between CRP, IL-6 signalling, and depression/CVD outcomes.

Mechanisms regarding WCC and depression/CVD outcomes are less clear. I have demonstrated that WCC is specifically associated with IHD but not depression in adults. Elevated WCC may have a causal direct effect on CVD by contributing to atherosclerotic plaque development and destabilisation (482,483). Alternatively, WCC may be associated with but not causally related to CVD. As mentioned above, shedding of sIL-6R by neutrophils could play a role (139,496,497) since elevated IL-6 trans-signalling has been implicated in CVD (206,207). The lack of association between WCC and depression may simply indicate that total WCC as an inflammatory biomarker is too general. NLR (498) and platelet to lymphocyte ratio (499) may be more useful at predicting the inflammatory response in depression.

The associations described above are likely to be heavily influenced by a variety of factors across the lifespan (see Section 1.4, Page 50 for discussion of social and demographic factors). In particular, I discovered that BMI is a particularly important confounder. I found no association between CRP and CVD in adults after controlling for BMI, perhaps due to overadjustment since BMI has a causal effect on CRP concentration (484). WCC was also no longer associated with depression after controlling for BMI. Indeed, unhealthy lifestyle factors such as high BMI and smoking have a strong contributing role to systemic inflammation in individuals with depression (500). Furthermore, high BMI reflects external eating habits and internal metabolic dysregulations, which are both potentially involved in depression (501) and CVD (502).

Although I used a number of different inflammatory markers in this thesis, the role of other inflammatory markers in the development of depression and/or CVD also requires investigation. For example, GlycA is a relatively new nuclear magnetic resonance biomarker for systemic inflammation and CVD risk (503), and potentially also for depression (504). The GlycA test is a composite measure of changes in both the number and complexity of N-glycan side chains attached to acute phase proteins such as CRP (505,506). Compared with high-sensitivity CRP, GlycA is more stable with considerably lower biological variability (506,507) and has comparable predictive value for future CVD-related events (503). Understanding the mechanisms through which different inflammatory markers exert their effect on the body may contribute to a better understanding of the biological underpinnings of depression, in particular. It may also support the development of novel biotherapeutics that can target depression and/or CVD.

7.3.3 Specific questions arising from the work in this thesis

The findings presented in this thesis raise an array of additional questions, which could form the basis of future research projects. Below is a selection of such questions:

1. What can be done to increase the number of studies focusing on young people in relation to systemic inflammation, depression, and CVD risk?
2. Do e-cigarettes pose same risk as traditional cigarettes to development of subsequent depression and/or CVD?
3. Is high BMI a risk factor for depression in all settings, including in different ethnic and socioeconomic groups?
4. Is it possible to create clinically relevant CVD risk score for young people, which is comparable to the Framingham risk score in adults?
5. What are the underlying mechanisms for observed sex differences in associations between systemic inflammation, depression and CVD?
6. Why does the relationship between CVD risk and depression differ in young people and adults?
7. Is CVD risk linearly associated with depression severity across the lifespan?
8. How are CVD risk and depression trajectories related across the lifespan?
9. What are the mechanisms underlying the distinct associations of specific markers of systemic inflammation with depression, CVD, and comorbidity?
10. To what extent does IL-6 explain the distinct associations between CRP and WCC and depression/CVD outcomes?

7.4 Conclusion

To conclude, I showed that there is evidence of an inflammatory component to both depression and CVD. This is evident in both young people and adults, suggesting that associations between systemic inflammation, depression, and CVD (risk) are robust across the lifespan.

The prospective relationship between CVD risk and subsequent depression in young people differs to the bidirectional relationship present in adults. The bidirectional relationship between depression and CVD found in adults appears to take time to develop and may be influenced by other environmental and/or social factors. As such, finding from adult studies should not be extrapolated to young people.

Systemic inflammation appears to play a role in the development of depression and CVD, and comorbidity between these conditions. However, specific inflammatory markers may increase risk of these outcomes through distinct mechanisms in adults and young people. Female sex, high BMI and smoking appear to play important roles in the associations between systemic inflammation, depression, and CVD across the lifespan. It may be important to target these higher risk groups for early-intervention or prevention strategies for depression and CVD in young people and subsequently across the lifespan. Moreover, greater understanding of the relationship between systemic inflammation, depression, and CVD is required in clinical and pharmaceutical context, as well as knowledge of key demographic influences.

Taken together, these findings suggest new avenues for research and the prospect of new holistic approaches to the prevention and treatment of mental and physical health conditions.

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