Associations of physical activity, sedentary behaviour, and physical fitness with common mental health symptoms in the population

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PhD thesis

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Declaration: I, Aaron Kandola, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. Signed 26 June 2021.

Abstract

Objectives

1) Develop a framework of the biological and psychosocial pathways through which physical activity may influence depressive symptoms.

2) Examine the association of device-measured physical activity and sedentary behaviour with common mental health disorder (CMD; depression and anxiety) symptoms across the lifespan.

3) Investigate the associations of cardiorespiratory and muscular fitness with CMDs in the population.

Methods

Objective 1: A narrative review on potential biological and psychosocial mechanisms underpinning the association between physical activity and depressive symptoms.

Objective 2: Three prospective cohort studies of associations between accelerometer-based sedentary behaviour and physical activity with CMD symptoms in adolescents and adults.

Objective 3: A systematic review and meta-analysis of prospective studies of associations between cardiorespiratory fitness and CMD symptoms and a prospective cohort study on associations of cardiorespiratory and muscular fitness with CMD symptom scales.

Results

Objective 1: The conceptual framework included neuroplasticity, oxidative stress, inflammation, endocrine responses, self-esteem, and social support as possible mediators underlying the association between physical activity and depressive symptoms.

Objective 2: Sedentary behaviour was positively associated with CMD symptoms. An hour of light activity was associated with 8-16% lower CMD scores in adolescents but 1% lower depressive scores and 4% higher anxiety in adults. An hour of moderate-vigorous activity was associated with 6-12% lower CMD scores in adults but there was no association in adolescents.

Objective 3: The meta-analysis showed that low cardiorespiratory fitness was associated with 47% higher risk of CMD incidence than high cardiorespiratory fitness. The prospective cohort study showed that low cardiorespiratory and muscular fitness were associated with 1.48 and 1.38 higher odds of CMD incidence, respectively compared to high fitness.

Conclusions

High sedentary behaviour and low cardiorespiratory or muscular fitness are CMD risk factors, but the optimal intensity for replacing sedentary behaviour was unclear and could vary by age.

Impact statement

CMDs are a major source of global disability that is becoming increasingly prevalent. Practical, population-level approaches for reducing and preventing CMD symptoms are essential in reducing their adverse effects on daily functioning and long-term physical health risks. My PhD work highlights high sedentary behaviour and low physical fitness as modifiable risk factors for CMD symptoms in adolescents and adults. I used various epidemiological methods to demonstrate a positive association between sedentary behaviour and physical fitness with CMD symptoms and have published these findings in high-impact journals that include *The Lancet Psychiatry, Psychological Medicine, Journal of Affective Disorders, Neuroscience and Biobehavioural Reviews, and BMC Medicine*. My PhD work has been impactful inside and outside of academia. For example, my *Lancet Psychiatry* paper received an Altmetrics score of 922 (<5% of publications). It was the first paper using device-based activity measures to prospectively show that high sedentary behaviour is a CMD risk factor, and even light-intensity physical activity could reduce this risk in adolescents. Light intensity activity interventions could be a highly accessible and practical method to promote mental health in adults and adolescents. I also developed a novel biological and psychosocial framework to explain how physical activity might influence depressive symptoms in 2019, which is already cited 110 times and has an Altmetric score of 610 (<5% of publications). I have also contributed robust evidence highlighting links between physical and mental health. For example, my 2020 *BMC Medicine* paper identified new associations of physical fitness with CMDs in the population, with an Altmetric score of 542 (<5% of publications). My findings highlight the potential for low physical fitness as a population-level marker of CMD risk and the importance of public health interventions to prevent low fitness in the population.

I have discussed my findings through different academic mediums, such as a Turing Data Science for Mental Health seminar, European Psychiatric Association 2021 conference, and *The Lancet Psychiatry* podcast. The high Altmetric scores of my published papers also encapsulate the substantial media attention on my work, a crude index of public interest. Global media outlets have covered my research and invited me to discuss my findings, including The New York Times, BBC, The Telegraph, The Times, CNN, Le Monde, Times of India, ITV News, BBC Radio 4, and NPR. My findings also have public health implications for reducing sedentary behaviour and preventing low physical fitness in the population. For example, I led a commission funded by the Wellcome Trust on reducing excessive sitting to improve employee mental health at work, with recommendations such as providing sit-stand workstations and promoting a physically active working culture. I presented these findings to global business and HR leaders at an event hosted by the World Economic Forum. Some businesses are revising their HR policies based on my recommendations to reduce workplace sitting, including the World Economic Forum. Similar approaches for reducing sedentary behaviour could be implemented in schools and colleges to reduce CMD risks in adolescents.

Contents

Thesis summary

This thesis's primary objectives were to develop a conceptual framework of the biological and psychosocial mechanisms underlying the association between physical activity and depressive symptoms and examine the association of device-measured physical activity, sedentary behaviour, and physical fitness with common mental health symptoms across the lifespan. I addressed these objectives through a narrative review, a systematic review with meta-analysis, and five prospective cohort studies. These studies collectively present evidence on population-level associations of physical activity, sedentary behaviour, and physical fitness with common mental health symptoms and a model of several potential mechanisms that may underlie these associations. I triangulate my findings with other studies in the field and discuss their potential public health relevance and implications. I also highlight some directions for future research and discuss the strengths and limitations of my thesis.

1. Chapter 1: Introduction

1.1. Summary

This chapter provides the background and rationale for my thesis. I review the scale and burden of depression and anxiety disorders (common mental health disorders) and symptoms in the population. I highlight the need for preventative approaches for common mental health symptoms and physical activity as a new, promising candidate. I also discuss the rise in low-energy sedentary behaviours as a new risk factor for common mental health symptoms in the population. Physical activity is a major influence on physical fitness, another related but distinct population-level marker of common mental health symptoms risk. The final sections describe some key evidence gaps in the existing literature that I aim to address in my thesis. For example, I highlight the insufficient understanding of possible mechanisms underlying the association between physical activity and depressive symptoms, a lack of device-based activity measures and 24-hour approaches, and paucity of high-quality research in adolescents and physical fitness as an exposure.

1.2. Common mental health symptoms and disorders

1.2.1. The scale of the problem

Depression is the most common mental health disorder (CMD) worldwide, with a substantial individual and societal burden (1). Depression is characterised by persistent low mood, dysphoria, impaired motivation, anhedonia, hopelessness, low energy, appetite changes, and several psychomotor, affective, and cognitive symptoms (2). The global prevalence of depression is around 4.4%, according to the World Health Organization, which suggests that around 322 million people currently have depression (1). These data are based on a 2015 iteration of the Global Burden of Diseases, Injuries, and Risk factors study that collates health and mortality data covering 204 countries and territories since 1990 (3). The number of incident (new) cases of depression has risen from 172 million cases in 1990 to 258 million in 2017, an increase of 49.9% when including data from 2017 (4). These data suggest that depression is widespread and growing each year worldwide.

Anxiety disorders are another CMD with a global prevalence of around 3.6%, affecting around 264 million people, according to the World Health Organization (1). Anxiety disorders are characterised by symptoms of excess worry, fear, and hyperarousal that can be debilitating and interfere with normal daily functioning (5). Depression and anxiety disorders commonly co-occur but have distinct symptomologies and risk factors (Kessler et al., 2008). Public health bodies, such as the World Health Organization, and researchers commonly describe the burden of depression and anxiety disorders collectively as CMDs (1). I will use CMD to refer to both symptomologies or diagnoses throughout this thesis but specify depression or anxiety where relevant.

Global estimates of CMDs may underestimate the true scale of the problem as many people who meet the criteria for these disorders do not receive a clinical diagnosis or formal treatment from a doctor (7). The Adult Psychiatric and Morbidity Survey is a large, nationally representative survey of households in the United Kingdom covering psychiatric problems in people aged 16 to 64 with and without a clinical diagnosis (7). The most recent 2016 survey estimates that the prevalence of CMDs in the UK is around 17% and is higher in women (20.7%) than men (13.2%) (7). This estimated CMD prevalence has increased from 6.9% in the first 1993 survey. However, the survey does not include some high-risk groups, such as those without a registered address or hospital inpatients. The survey also highlighted an emerging treatment gap, with 39% of people who met the criteria for a CMD not receiving treatment. This treatment gap reflects a global trend and is perpetuated by major barriers that include limited access to treatment, stigma, and a preference for self-management (8).

1.2.2. CMDs over the life course

CMDs can have a substantial burden on an individuals' quality of life, social and occupational functioning, and risk of psychiatric and physical comorbidity (1). CMDs cause a wide range of symptoms (see Box 1) that can be debilitating and typically have an early onset during adolescence and young adulthood (9,10). Adolescence and young adulthood are characterised by potentially stressful life events, such as moving away from home or making study or career decisions (11). Stressful life events are a common trigger of CMD symptoms (12). Early CMD symptoms can cause substantial social, educational, and family problems (13). These disruptions at an important developmental and transitional period of life can have long-term consequences (9). For example, adolescent anxiety symptoms are associated with poor family relationships, difficulty adjusting to work, fewer coping skills, and chronic stress during adulthood (14). Adolescent CMD symptoms are associated with an increased risk of future CMDs and other mental or behavioural problems, such as substance misuse and domestic violence (15–17).

Box 1. Overview of depression and anxiety disorders

What is depression?

Depression is an umbrella term referring to depressive symptoms on a continuum or as a clinical diagnosis. Depression causes symptoms that include changes in mood, interest, pleasure, cognition, and energy or fatigue. The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) describes subtypes of depressive disorders separately from bipolar disorders that include major depressive disorder, persistent depressive disorder (previously dysthymia), disruptive mood dysregulation disorder, seasonal affect disorder, peripartum depression, premenstrual dysphoric disorder, and atypical depression. Major depressive disorder is where five or more symptoms must present for at least two weeks for a clinical diagnosis. There is considerable heterogeneity in the nature, severity, timing, and development of depressive symptoms, which create many different phenotypes that may have different aetiologies (597).

What are anxiety disorders?

Anxiety disorders are a group of common mental disorders with core features that include excessive fear, anxiety, and hyperarousal. Fear is a state of immediate threat and anxiety is the anticipation of future threats (598). People with anxiety symptoms experience these responses to internal or external triggers out of proportion to the actual danger posed, such as social situations. Some anxiety disorders also include panic attacks, which induce sudden bouts of fear with strong physiological responses, such as difficulty breathing.

Anxiety disorders share similar diagnostic criteria in the DSM-5 and ICD-10, but can also be conceptualised in dimensions of severity from mild to severe (599). Anxiety disorders include separation anxiety disorders, panic disorders, specific phobias, selective mutism, social anxiety disorders, generalised anxiety disorders, and agoraphobia. Post-traumatic stress disorder and obsessive-compulsive disorder are no longer categorised as anxiety disorders in the most recent DSM-5, but still share some features.

CMDs during adulthood are associated with long-term physical health risks, including an increased risk of cardiovascular and metabolic diseases (18–20) and all-cause mortality (21,22). Shared genetic causes may partially account for the increased risk of chronic illness in people with CMDs (23). Lifestyle factors may also play a role. For example, physical inactivity, inadequate diet, and smoking

are associated with an increased risk of CMDs and chronic physical illnesses, including cardiovascular and metabolic diseases (24). Beyond potentially shortening the lifespan, co-morbid physical health problems can elicit additional symptoms that affect daily living and require additional treatments.

Their early-onset, potentially debilitating symptoms, and increased physical health risks underlie the substantial disability burden attributable to CMDs. The World Health Organization now recognise depression as the first and anxiety as the sixth-largest contributor to the global disability burden (1). Recent findings from the 2019 Global Burden of Diseases, Injuries, and Risk factors study indicate that the contribution of depression to the global years lived with a disability is increasing (3). Understanding CMDs in terms of years lived with a disability is an important step beyond prevalence or incidence to estimate their lifelong impact on an individual. A similar conceptualisation of these data is that CMDs shorten the healthspan and lifespan. Healthspan is a term derived from aging research and typically refers to the period of 'healthy' life without developing chronic illnesses that become more common with aging (25). But the substantial burden of CMDs and their symptoms on daily living and risk of co-morbidity warrants a repurposing of the term.

At the population level, the individual burden of CMDs compounds to have major societal and economic implications. CMDs cost the global economy an estimated $1.15 trillion per year through loss in productivity and labour force participation (26). The loss in productivity is primarily due to CMD symptoms causing people to take time off work (absenteeism) and or work at a reduced capacity (presenteeism). These costs do not account for the physical co-morbidities associated with CMDs and likely underestimate their true economic impact.

National and international efforts to improve the treatment of CMDs and prevent their onset in the population are greatly needed but are still lacking (3,4,7). Mental health research continues to receive funding that is disproportional to its vast global burden and economic costs, accounting for just 4% of global health research spending (27). A similar disparity exists within healthcare services for mental health treatment. For example, the UK government launched a mental health strategy in 2011 to balance mental and physical health services more evenly, which included funding reforms (28). However, the National Health Service currently only spends around 14% of the total budget (£14 billion) on mental health services (29), despite the fact that the disease burden attributable to mental health in high-income countries is around 23% (3). These figures do not account for the large proportion of people with CMD symptoms not seeking treatment in the UK (7).

1.2.3. Limitations of treatment and the potential for prevention

Several treatments are available for CMDs. First-line treatments include pharmacotherapy and psychotherapy, which are moderately effective for depression (30,31) and anxiety (32,33) symptoms in people with CMDs. However, many trials in this area have a moderate or high risk of bias, lack adequate statistical power, and use incomparable outcome measures (34). Beyond methodological limitations, relapse rates are high in people with CMDs, and some people do not respond to treatment at all (33,34). Even assuming complete coverage and adherence with treatments, one study estimated that such treatments would only reduce the burden of mental health disorders in the population by around a third (35). While this study used data from 2004, there have been minimal improvements in the efficacy of pharmacotherapy or psychotherapy for CMD symptoms (36) or in our understanding of their underlying mechanisms (37). These data are inherently based on treatment-seeking individuals, which only account for around 60% of people with CMD symptoms in the UK (7) and potentially fewer in other nations (8).

Current treatment approaches will continue to improve the quality of life for many people with CMDs and help them reach remission. The widespread use of these treatments is also testament to

their scalability at a population-level and accessibility in the UK, to an extent (38). However, pharmacotherapy is also associated with several side effects that could outweigh their benefits in less efficacious cases, such as headaches, nausea, sleep disturbances, or weight gain (39). There are also growing concerns over an insufficient clinical recognition of antidepressant withdrawal effects (40). Neither pharmacotherapy nor psychotherapy can address the long-term physical health complications that occur in people with chronic CMDs. There is also considerable room for improving efficacy in many cases and insufficient progress to address this. Despite the increased provision of pharmacotherapy and psychotherapy for treating CMDs (41), global and national data suggest a growing prevalence of CMD symptoms in the population (3,4,7), highlighting a pressing need for new approaches to tackling the problem.

Primary prevention refers to intervening before the onset of symptoms across the entire population (universal prevention), in people at an elevated risk of CMD (selective prevention), or those with subthreshold CMD symptoms or early signs of a CMD (indicated prevention) (42). Prevention typically involves identifying modifiable factors that are associated with the risk of CMD symptoms and intervening to influence these factors at an individual, community, or population-level. Prevention has traditionally received less empirical and clinical attention than treatment in mental health (43) but has been successful elsewhere.

For example, many Western countries have recorded substantial declines in deaths from cardiovascular disease since their peak in the 1960s and 1970s (44). These declines were largely attributable to identifying and screening risk factors (e.g., high blood pressure) to facilitate preventative approaches rather than major advances in treatment (45). The example forms the basis for Geoffrey Rose's high-risk and population strategies for prevention (46). The high-risk strategy describes a form of indicated prevention, where interventions focus on preventing a disease (e.g., cardiovascular disease) in specific groups with conditions that substantially increase the risk of incidence (e.g., high blood pressure). A population strategy is a form of universal or secondary prevention that aims to shift the distribution of a disease in the entire population by intervening on a widespread risk factor. The population strategy can theoretically produce greater reductions in incidence by reaching more people at the expense of smaller changes at an individual level.

However, applying this theory or seeking to replicate successful preventative strategies in cardiovascular disease to mental health is challenging. Kenneth Rothman conceptualised the causes of disease as a set of components that are collectively sufficient to produce disease (47). There are a modest number of clearly defined, measurable components of cardiovascular disease risk (e.g., high blood pressure) that are universal and responsive to specific behaviours (e.g., diet or exercise). However, many possible components of CMD risk, which each have relatively small effects, are sometimes difficult to define or measure, vary from person to person, and are not necessary or sufficient to cause a disorder alone (43). The diversity of component risk factors is paralleled by the heterogenous manifestation of CMD symptoms. For example, the heterogeneity of depression is exemplified by the fact that two people can share the same diagnosis without a single symptom in common (48). Such heterogenous symptomologies require more individualised approaches to prevention. There are also components of cardiovascular disease risk that are necessary for onset. For example, a build-up of plaque in an artery is necessary to cause a heart attack. However, there are currently no necessary components of CMD risk to cause the onset of symptoms.

Prevention of CMDs and their symptoms in the population is a complex but potentially surmountable problem. For example, a 2014 systematic review found that psychological interventions could reduce the incidence of major depressive disorder by 21% (incident rate ratio = 0.79, 95% confidence intervals (CI) 0.69 to 0.91) compared to a control group (49). A 2016 trial found that a web-based self-help intervention reduced the incidence of major depressive disorder in people experiencing subthreshold depressive symptoms at a 12 month follow-up (hazard ratio = 0.59, 95% CI = 0.42 to 0.82), highlighting the possibility of indicated prevention (50). Systematic

reviews in young people (5 to 18 years) have found universal, selective, and indicated preventative interventions as having small effect sizes (Hedges g = 0.2) for reducing CMD symptoms (51) or reducing CMD incidence by 49% to 53% (52).

Early signs suggest that CMD symptoms can be preventable, but the varying effect sizes indicate room for improvement. The effect of current preventative interventions also decreases over time (52) and may lack sustainability. Most preventative interventions aim to build individual-level cognitive skills to cope with adversity in at-risk groups (secondary and indicated prevention). These approaches are difficult to implement on a larger scale or as a universal prevention strategy due to their resource intensiveness, varied strategies and delivery platforms, and personalised or context-specific activities (43).

Findings from individual-level cognitive strategies for preventing CMDs symptoms are promising. However, the prevalence of CMD symptoms and heterogeneity of their component causes require additional preventative solutions to maximise their population-level impact. Universal approaches that are practical to implement on a large scale could provide important foundations for preventing CMD symptoms that complement more targeted, individual-level cognitive interventions in high-risk groups. Universal approaches that have dual benefits for preventing CMD symptoms and physical health complications are a priority given the long-term health risks associated with CMDs (18–20).

Interventions that target modifiable lifestyle factors are increasingly recognised as promising methods of treating and preventing mental health symptoms with well-established physical health benefits (53). The following section will focus on physical activity and sedentary behaviour as modifiable lifestyle factors that could be potential targets for universal CMD prevention programmes.

1.3. Physical activity, sedentary behaviour, and common mental health symptoms

1.3.1. Physical activity as a health risk factor in epidemiology

Physical activity refers to any bodily movement produced by the skeletal muscles resulting in energy expenditure (54). There are many ways to conceptualise physical activity for understanding its relationship to health, including by its modality, duration, or volume. A common paradigm involves breaking physical activities down into different intensities, such as light, moderate, or vigorous. Determining the intensity of physical activity can be through assessing someone's subjective exertion during the activity or objectively measure their energy expenditure. Each intensity category encapsulates different types of physical activities, which have different relationships with health outcomes. For example, moderate-to-vigorous intensity activities include running or swimming. Exercise is a subset of physical activity for training physical fitness and describes many moderate-to-vigorous activities.

Around 4% of waking time is attributable to moderate-to-physical activities in working-aged adults (55). Most of daily physical activity is attributable to light-intensity activities, including walking around the house or washing dishes. Many forms of light-intensity physical activity are incidental and dispersed throughout the day without a consistent structure (56). These properties make light-intensity physical activity harder to detect using traditional measures, such as self-report questionnaires (56). Activity monitoring devices (described in Section 1.6.2. Measurement bias in assessing physical activity and sedentary behaviour in epidemiology studies, and Section 2.3.3. Overview of exposure variables) can continuously record daily movement and are potentially better equipped to measure light-intensity physical activity. The falling cost of activity monitoring devices has increased their availability to researchers (57), facilitating growth in our understanding of the positive relationship between light-intensity physical activity and health outcomes (58).

In epidemiological research, the relationship between physical activity and disease is well-established. In 1953, Morris *et al.* demonstrated that those in physically inactive professions, such as bus drivers and telephonists, had a higher incidence of coronary heart disease than those with physically active jobs, such as postmen (59). Since these landmark findings, a series of prospective cohort studies have found a consistent relationship between moderate-to-vigorous physical activity and the incidence of cardiovascular disease, diabetes, cancer, and related risk factors, such as blood pressure and obesity (60–64). Physical activity is modifiable at a population-level through informational, social, and behavioural approaches in people of different demographics, countries, and communities (65).

The importance of physical activity to disease prevention in the population is reflected in the widespread adoption of global physical activity guidelines (66,67). Moderate-to-vigorous intensity activities are strongly associated with improved health outcomes and have traditionally formed the basis of most national and international physical activity guidelines recommendations (66,67). However, the increased recognition of incidental physical activity in research is reflected in the recent expansion of guidelines to promote all forms of daily movement alongside moderate-to-vigorous intensity activity (68). Despite the widespread recognition of physical activity for health, around 42% of adults and 81% of young people in Western nations are physically inactive, in that they fail to meet physical activity guidelines (69,70). Sustained global efforts to increase physical activity have been largely ineffective in adults and young people (69,70). One estimate suggests that reducing physical inactivity by just 25% would prevent around 1.3 million deaths each year (71). Another study in 2021 suggested that 7.2% of global deaths are attributable to physical inactivity, with high-income countries bearing the highest relative burden (72).

1.3.2. The relationship between physical activity and common mental health symptoms

1.3.2.1. Physical activity as a mental health treatment

Physical activity is gaining traction to treat mental health symptoms, including for CMDs (73). A single bout of physical light, moderate, or vigorous cycling for 20 minutes can reduce symptoms 10 and 30 minutes later in people with depression (74). Repeated physical activity bouts in a structured format can accumulate to have lasting benefits for people with CMD symptoms. Results from several systematic reviews of randomised controlled trials have found that structured physical activity interventions effectively reduce CMD symptoms with small to large effect sizes in people with and without a CMD diagnosis or chronic physical illness (75–86). The vast majority of randomised controlled trials include primary outcomes for depression rather than anxiety symptoms and rarely target concurrent CMD symptoms (87). Structured physical activity interventions typically last for around 12 weeks and 2 to 3 aerobic exercise sessions per week, such as with a stationary bike. Exercise or other professionals commonly supervise each session. Virtually all randomised controlled trials focusing on moderate-to-vigorous intensity activity. However, one of the largest randomised controlled trials to date found that all physical activity intensities effectively reduce symptoms in people with depression compared with treatment as usual after 12 weeks (88). The study also showed that light-intensity physical activity was most effective at a 12-month follow up (89). Some interventions focus on resistance training, which can involve weightlifting to improve muscular fitness (81,84). A 2018 systematic review of randomised controlled trials in adolescents and young adults found that physical activity can treat depressive symptoms in this age group, but substantial trial design and publication biases exist (90).

Some have concerns over the quality of evidence underlying the effectiveness of physical activity-based interventions, with one review finding no effect on depressive symptoms when restricting their analysis to randomised controlled trials rated as low risk of bias (91). However, some of these

studies included active control groups where participants performed light-intensity physical activity exercises that may improve symptoms and skew comparisons with the treatment group (92). This review's findings that physical activity had no effect on depressive symptoms are also based on restricting the analysis to only four studies (all with active controls and two led by the review's lead author) and has attracted criticism for these methods (93) . Other reviews that restrict to randomised controlled trials with a low risk of bias have still found an effect of physical activity on depressive symptoms, including after adjusting for possible publication biases (75). Dropout rates are another area of concern for physical activity interventions (91). Dropout rate in physical activity-based interventions is around 18% for depression and 22% for anxiety disorders (94,95). However, these rates are similar to the typical dropout rates for physical activity interventions in people with diabetes (26%) and obesity (18% to 35%) (96,97) or pharmacotherapy (26% to 28%) and psychotherapy (17% to 20%) in people with CMDs (98,99). Improving adherence and acceptability remains an important step towards a better implementation of physical activity-based treatments in mental health (100). However, it is not a specific limitation to treatments in people with CMDs or physical activity-based interventions.

The use of physical activity interventions is also growing in other areas of mental health treatment. I conducted a narrative review on the use of physical activity intervention in severe mental illness, focusing on people with diagnoses of non-affective psychosis, bipolar disorder, and major depressive disorder (101). The review highlights evidence for physical activity improving treatment outcomes in these groups, including for psychiatric symptoms (102–104), and wider benefits for depression and anxiety symptoms, improving cognitive functioning, sleep, quality of life, and social adjustment (73,103–107). The dual physical and mental health benefits of physical activity are of particular importance in people with severe mental illness, given the high risk of physical health complications in these groups (24). The British Association of Psychopharmacology and European Psychiatric Association recommend lifestyle approaches to manage physical health risks in severe mental illness, including physical activity (108,109). However, there are several barriers to their implementation in routine care, such as adherence to interventions, awareness amongst healthcare staff, cost, and limited service integration (110–112).

1.3.2.2. Evidence for physical activity as a preventive mental health approach

These randomised controlled trials collectively provide good evidence that physical activity has a causal relationship with CMD symptoms and other aspects of mental health, but the mechanisms underlying this relationship do not necessarily apply to preventive approaches or groups without prior CMD diagnoses. Meta-analyses suggest that structured physical activity interventions can reduce depressive symptoms in people with subthreshold symptoms (77,78). While this is promising evidence for the potential of physical activity as a selective prevention approach, both studies highlight a lack of high-quality work with insufficient follow-up periods and sample sizes. For example, one study rated just two of 14 randomised controlled trials included in the meta-analysis as having a low risk of bias, and only three had a follow-up period of longer than six months (77). Randomised controlled trials are a strong form of evidence. However, robustly demonstrating the impact of a preventive intervention on the incidence of mental health symptoms will have substantial practical and financial limitations, including large sample sizes and long follow-up periods (113). The underlying issue is that even in high-risk groups, mental health symptoms and disorders are relatively uncommon within a one or two-year timeframe, which necessitates a large sample for selective prevention approaches and even larger for universal prevention (114).

Preventive trials in mental health will remain an invaluable resource for causal evidence but epidemiological studies can provide a complementary stream of evidence whereby large sample

sizes and long follow-up periods are more feasible, particularly for examining universal prevention. Epidemiological work on physical activity as a modifiable CMD risk factor in the last couple of decades provides another source of evidence that complement trial data to highlight physical activity as a promising preventative approach in mental health. These studies utilise observational data to make causal assumptions about the relationship between physical activity and CMD symptoms, typically in population-based datasets. Observational studies are generally more limited than randomised controlled trials in their capacity to assess causal effects, for reasons I discuss in Chapter 2.3. Observational studies use several study designs with different degrees and types of systematic biases that limit causal inferences. For example, several cross-sectional studies have found an inverse association between physical activity engagement and CMD symptoms in population-based surveys (115–118). However, most cross-sectional study designs cannot determine the direction of a proposed relationship and are unable to assess reverse causality. Reverse causation is a form of bias due to the proposed outcome influencing the proposed exposure to confound their association. These issues limit how effectively I can isolate potential causal effects from cross-sectional studies. Assessing reverse causality is particularly important in this relationship as people with CMD symptoms typically engage in less physical activity than the general population. A cross-sectional study cannot investigate the direction or temporality of a proposed exposure-outcome association, such as whether physical activity engagement potentially causes fewer CMD symptoms or vice versa.

Prospective cohort studies are better suited to overcoming the potential risks of reverse causality as they can examine whether the exposure temporality precedes the outcome and allows for the statistical adjustment of baseline factors (e.g., CMD symptoms) that could confound the exposure-outcome association. Prospective studies can reduce the risk of reverse causation by including models with final estimates that are statistically adjusted for baseline CMD symptoms (confounding variable) in assessing the association between physical activity (exposure) and a CMD at follow-up (outcome). Several possible systematic biases prevent this method from eliminating confounding due to reverse causation, such as assuming no effect modification inherent to this method or measurement error in the baseline or outcome variables. Prospective study designs also have other properties that enhance our capacity to isolate causal effects in observational data. For example, they can assess whether an outcome precedes an exposure through longitudinal measures. This refers to the temporal relationship between exposures and outcomes that is fundamental to assigning causality.

A 2018 meta-analysis of 49 prospective cohort studies, including 1,837,794 person-years of follow-up found that people with high physical activity levels at baseline had 17% lower odds of depression (odds ratio = 0.83, 95% CI = 0.79 to 0.88) than people with low physical activity (119). These associations were consistent across age groups and geographical location, with studies typically of a moderate-to-high quality (Newcastle-Ottawa Scale = 6.3). A 2019 meta-analysis of 13 prospective cohort studies with 357,424 person-years of follow-up found that high physical activity was associated with 26% lower odds of an anxiety disorder (odds ratio = 0.74, 95% CI = 0.62 to 0.88) compared with low physical activity (120). The largest effect sizes in this analysis were associated with the agoraphobia (odds ratio = 0.42, 95% CI = 0.18 to 0.98) and post-traumatic stress disorder (odds ratio = 0.57, 95% CI = 0.39 to 0.85). Both studies used the author's definition of high or low physical activity group, based on the frequency, intensity, volume, or energy expenditure. Most included studies of both analyses focus on moderate-to-vigorous intensity leisure-time activity, largely in adult populations. There is a notable lack of information on the association of light-intensity activity with CMD outcomes, despite accounting for the vast majority of daily activity for most people (55).

The findings of these recent reviews coincide with those of other meta-analyses (121,122) that broadly suggest an inverse relationship between physical activity engagement and the risk of CMD symptoms in the population, mostly in adults. However, virtually all epidemiological studies have

used self-report measures of physical activity that are subject to cognitive biases (e.g., recall bias, see Section 1.6.2.) and cannot continuously assess 24-hour movement patterns or the interrelationship between physical activity intensities throughout the day (see Section 1.6.2. Measurement bias in assessing physical activity and sedentary behaviour). These studies also typically use dichotomised outcome measures indicating the presence or absence of clinically significant symptoms, such as meeting a validated threshold on a self-report symptom scale. Such outcomes have several advantages, including providing a clear clinical interpretation of the results. However, quasi-continuous outcomes (e.g., symptom presence and severity scores) more closely reflect the reality of symptoms occurring on a continuum and can improve statistical power (123) (see Section 2.3.4. Overview of outcome variables). Some studies using clinical diagnoses may also overlook the substantial number of people with CMD symptoms who do not seek treatment (7). Examining continuous outcomes is particularly important for understanding associations between exposures and subthreshold symptoms to inform preventive approaches. Dichotomous and continuous outcomes each convey useful information, but many studies presenting dichotomous outcomes alone provides an imbalanced picture of the associations between physical activity and CMD symptoms.

Evidence from randomised controlled trials presents a strong case for a causal relationship between physical activity and CMD symptoms that may extend to prevention. Epidemiological studies can assess the association between physical activity and CMD symptoms within the context of prevention with several fewer practical limitations than randomised controlled trials. Emerging epidemiological evidence suggests that there is an inverse association between physical activity and CMD symptoms in adults. However, more robust epidemiological work is first necessary to address methodological limitations and evidence gaps in the literature, which I expand on in Section 1.6. (1.6. Evidence gaps in understanding the associations of physical activity, sedentary behaivour and fitness with common mental health symptoms) In particular, there is a clear absence of high-quality research on physical activity and mental health in adolescents (119,120), despite the importance of this period for preventing the first onset of CMD symptoms (9,10) (see Section 1.6.4. Physical activity, sedentary behaviour, and mental health in adolescents).

There are several benefits of physical activity-based approaches to reducing CMD risks in the population that highlight the importance of strengthening the evidence base in this area. For example, the relationship between increased physical activity and a lower incidence of chronic physical illnesses is well-established (60–64). Promoting physical activity in people at risk or with CMD symptoms could mitigate some of the cardio-metabolic and premature mortality risks associated with CMD disorders should they develop (18–22). In people with existing CMD diagnoses, physical activity-based interventions can reduce cardio-metabolic health risk factors (124–126). It can also have supplementary benefits for other aspects of daily functioning and wellbeing, including improving sleep quality in people with CMD symptoms (107).

Physical activity is relatively low risk and highly accessible to different population groups, including people with CMDs or serious mental illness (94,127). While global physical activity levels have been relatively stable over the last decade (70), physical activity is modifiable at a population-level at a relatively low cost through scalable, community-based approaches. For example, the rapid growth in popularity of ‘parkrun’ is a practical example of how community-based physical activity programmes can achieve global success. Parkrun is a free, weekly run in parks across 20 countries worldwide that has attracted an estimated 3 million unique participants (128) with some direct evidence of mental health benefits (129).

1.4. The evidence for sedentary behaviour as an emerging mental health risk factor

Sedentary behaviour is any waking activity with low energy expenditure (≥1.5 metabolic equivalents, standardised energy expenditure units) in a sitting, lying, or reclining posture (130). This conventional definition of sedentary behaviour places it on the energy expenditure below light-intensity physical activity. Sedentary behaviour covers a wide range of activities that are becoming increasingly pervasive in modern life, such as watching television or browsing the internet. Overall physical activity levels decrease by around 7% each year between the ages of 10 and 19 (131). This may be influenced by increasing sedentary behaviour and decreasing light-intensity physical activity throughout adolescence (132–136). The majority of leisure-time sedentary behaviour during adolescence is due to screen-based device use, such as television watching or using social media (137). Desk-based occupations are also a growing contributor to total daily sedentary behaviour in adults. Employed adults spend around 9.4 hours sedentary per day, according to when measured using activity monitoring devices, with office workers accumulating 72.5% of this time at work (55). Its growing integration with work and leisure-time activities means that much of the day for many people is attributable to sedentary behaviour.

Spending large proportions of the day sedentary is associated with a higher risk of several chronic diseases and premature mortality (138). These chronic health risks associated with high sedentary behaviour typically persist after studies make statistical adjustments for the time in moderate-to-vigorous physical activity. Sedentary behaviour is inherently related to physical activity through its place on the energy expenditure spectrum. However, these studies suggest that its potential risks could be partially independent of low moderate-to-vigorous physical activity. For example, a 2016 meta-analysis of data from 1,005,791 adults found that meeting national physical activity guidelines of 150 minutes per week of moderate-to-vigorous physical activity was insufficient to mitigate the elevated risk of early death associated with spending over 8 hours sedentary per day (139). A more recent meta-analysis in 44,370 adults using device-based measures of daily sedentary time found that at least 30 to 40 minutes of moderate-to-vigorous physical activity per day was necessary for there to be no association between sedentary behaviour and premature mortality (140). These findings suggest that the risks of high sedentary behaviour are only partially accounted for by insufficient moderate-to-vigorous physical activity. Recently updated physical activity guidelines from the World Health Organisation and Canadian Government now recommend limiting sedentary behaviour in addition to increasing moderate-to-vigorous physical activity, reflecting its emergence as an independent risk factor of disease (67,141).

The recognition of sedentary behaviour as a risk factor for adverse health is now extending to mental health. For example, a 2020 meta-analysis of 12 prospective studies found that high sedentary behaviour was associated with a 10% increased risk of depression (risk ratio = 1.10, 95% CI = 1.03 to 1.19) (142). A 2019 meta-analysis of 13 studies with mixed designs found that high sedentary behaviour was associated with 1.48 times higher odds of an anxiety disorder (odds ratio = 1.48, 95% CI = 1.25 to 1.75) (143). These findings broadly corroborate with several other population-based studies that show higher levels of self-reported sedentary behaviour and lower levels of physical activity are associated with an increased risk of CMD symptoms and disorders in adults and young people (119,120,122,142–148). Another systematic review found that lower sedentary behaviour levels were associated with higher physical health-related quality of life (estimated average effect *r* = -.140, 95%CI, -.191 to -.088) (149).

However, there have been several conflicting findings on the association between sedentary behaviour and CMD symptoms (142–147,150,151). These studies typically use a wide range of definitions for high sedentary behaviour that are difficult to directly compare, including either ≥2 or ≥8 hours per day of sedentary behaviour or screen-based device use, which is a common proxy measure of sedentariness. These studies also use similar self-report measures with inherent cognitive biases to the physical activity studies in Section 1.3 (also see Section 1.6.2. Measurement bias in assessing physical activity and sedentary behaviour). Using device-based measures that can continuously track physical activity and sedentary behaviour over 24 hours (see Section 2.3.3.

Overview of exposure variables) could reduce measurement error and facilitate the use of more sophisticated statistical analysis methods, such as compositional analysis (see Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms). Prospective studies have typically assessed the association of daily time in sedentary behaviour with CMDs using standard regression models in real space without sufficiently adjusting for time in other activities during the day, such as light or moderate physical activity. For example, the association between sedentary behaviour and CMD symptoms could depend on the extent of daily moderate-vigorous activity, and replacing time in sedentary behaviour for light, moderate, or vigorous activity could differentially affect CMD symptoms. Continuously recorded physical activity and sedentary behaviour data over 24-hours with compositional analysis methods are well suited to assessing these issues (152) but have been absent from previous prospective studies. I return to these issues in Section 1.6.3. (Section 1.6.3. Understanding physical activity and sedentary behaviour in a 24-hour context) and Chapter 6 (Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms).

The evidence for high sedentary behaviour as a health risk factor is growing, and recent epidemiological work shows that there may also be some mental health risks. However, there is less evidence on the association between sedentary behaviour and CMD symptoms than physical activity (Section 1.3. Physical activity, sedentary behaviour, and common mental health symptoms), but studies share similar limitations in their exposure and outcome measures, and analytical methods. The widespread and growing global prevalence of high sedentary behaviour necessitates high-quality epidemiological work to appropriately assess the potential mental health risks of this trend. There may also be an association between sedentary behaviour and other domains related to mental health that further highlight the need for more work in this area, such as cognitive performance. For example, a 2017 systematic review found that high sedentary behaviour was associated with poorer cognitive performance in 6 of 8 studies, including memory, executive functioning, and global cognitive functioning (153). However, the review highlighted a low quality of evidence prohibiting any firm conclusions. Another 2019 review of 25 studies with mixed designs found some evidence of an association between high sedentary behaviour and poorer memory performance, but findings were generally inconsistent (154). Improving our understanding of high sedentary behaviour as a mental health risk factor can have transdiagnostic value across several domains related to mental health.

1.5. The relationship between physical fitness and physical and mental health

Physical fitness refers to the capacity to perform any physical activity and is an important predictor of overall health and mortality across all ages (155–157). Two primary constituents of health-related physical fitness are cardiorespiratory fitness and muscular fitness. Cardiorespiratory fitness refers to the capacity of the cardiovascular and respiratory systems to supply oxygen to muscles and other bodily tissues during exertion (158). Exercise tests are a standard method of measuring cardiorespiratory fitness, such as using a stationary bike with increasing resistance to exhaustion or a pre-specified time limit (159). These tests aim to measure maximum or peak oxygen consumption (VO_{2max} or VO_{2peak}) directly or indirectly in the blood, reflecting the efficiency of the cardiovascular and respiratory systems during exertion as a marker of cardiorespiratory fitness (I return to these measures in Chapter 2.3.2). Some evidence suggests that a substantial proportion of variability in cardiorespiratory fitness is attributable to genetic variance, with one twin study estimating its heritability at around 40 to 50% (160). However, regular engagement in aerobic physical activities has a major impact on cardiorespiratory fitness levels, such as running or cycling (161).

Maintaining a medium or high cardiorespiratory fitness is associated with several health benefits, including a lower risk of cardiovascular disease and all-cause mortality (156,158,162–164). As physical activity is a major influence on cardiorespiratory fitness, it could represent a useful surrogate marker of physical activity in the population (161). However, the relationship between cardiorespiratory fitness and health likely extends beyond physical activity alone. For example, cardiorespiratory fitness also captures the complex interplay between a range of other relevant factors to health, such as smoking and obesity (162). The value of this is increasingly being recognised in physical health, with several studies finding cardiorespiratory fitness to be a stronger predictor of cardiovascular disease than physical activity levels in population-based studies (164,165).

There is some preliminary evidence of an association between cardiorespiratory fitness and mental health indicators and CMD incidence in the population. Several population-based studies have found cross-sectional associations between low cardiorespiratory fitness and an increased risk of psychological distress (166), stress (167), and common mental health disorders (168–171). A 2016 meta-analysis of prospective studies found that people with low cardiorespiratory fitness had a 76% increase in the rate of incident depression (hazard ratio = 1.76, 95% CI = 1.61 to 1.91) and people with medium cardiorespiratory fitness had a 23% increase (hazard ratio = 1.23, 95% CI = 1.20 to 1.38) compared to those with high cardiorespiratory fitness (172). However, the meta-analysis only included two studies, which limits the strength of evidence I can draw from these findings. There have also been no attempts to synthesise associations of cardiorespiratory fitness and anxiety at a population level.

Changes in cardiorespiratory fitness could also influence CMD symptoms in people with a diagnosis. For example, Rahman *et al*. found in a 12-week exercise trial that increased cardiorespiratory fitness predicted greater symptom reductions in people with depression, independently of exercise intensity, age and body mass (173). They also found that improvements in cardiorespiratory fitness increased the odds of positive treatment responses at follow-up (odds ratio = 3.73, 95% CI = 1.22 to 11.43). A systematic review in people with and without depression found a modest correlation between cardiorespiratory fitness and the severity of depressive symptoms (correlation coefficient = -0.16, 95% CI = -0.21 to -0.10) in 16 randomised controlled trials and population-based studies (174). However, most studies included people with depression diagnoses and the findings may be inapplicable to people without depression. Included studies that included only healthy participants had relatively small sample sizes (n = 9 to 141, mean = 47).

Muscular fitness broadly refers to the capacity to perform physical activity against resistance and is commonly built through resistance training or weightlifting (157). It is associated with a reduced risk of several chronic health conditions, and its importance is reflected by its inclusion in recent physical activity guidelines (66,175). Measuring handgrip strength is a quick and practical test that correlates moderately-to-strongly with overall muscular strength across all age groups (176,177). Muscular fitness has received comparatively less attention than cardiorespiratory fitness, but some cross-sectional and longitudinal studies have found grip strength is negatively associated with CMD symptoms (178–184). A recent systematic review found that sarcopenia, a syndrome characterised by the loss of muscle mass and strength, is also associated with increased odds of depressive symptoms (odds ratio = 1.821, 95% CI = 1.16 to 2.86). However, there has been a general lack of robust, prospective evidence on the association between physical fitness and CMDs in the population and studies have focused on each type of fitness as an independent rather than combined exposure (see Section 1.6.5. Lack of research on associations between physical fitness and common mental health disorders).

1.6. Evidence gaps in understanding the associations of physical activity, sedentary behaviour, and fitness with common mental health symptoms in this thesis

There is some epidemiological evidence of associations between physical activity, sedentary behaviour, fitness, and CMD symptoms or disorder incidence in the population, but more robust studies are necessary. Data from randomised controlled trials indicate a causal relationship between moderate-to-vigorous physical activity and CMD symptoms in people with mental health diagnoses. However, it remains unclear whether this extends to groups without existing CMD diagnoses or the associations with light-intensity physical activity. There have also been some conflicting findings as to whether sedentary behaviour is a risk factor for CMD symptoms or disorders in the population (142–147,150,151). Few studies investigate physical fitness as an exposure (172). In the following section, I highlight several evidence gaps in this section that are either issues in previous studies that restrict their capacity to draw causal inferences or research questions that previous studies are yet to address sufficiently.

1.6.1. Underlying mechanisms of the association between physical activity and CMD symptoms

Despite mounting causal evidence of a protective relationship between moderate-to-vigorous physical activity and depressive symptoms, I know little about possible psychosocial or biological mechanisms underlying this relationship. For example, one narrative review examined evidence on psychosocial and biological mechanisms of physical activity in children's cognitive and mental health (185). However, it did not assess the relationship in adults or focus on depression. A 2016 systematic review examined the neurobiological effects of physical activity in people with major depressive disorder (186). However, the study overlooked any psychosocial mechanisms, and its systematic review format limited its scope to only consider biomarkers recorded in trials of people with major depressive disorder.

Establishing these psychosocial and biological pathways is important for observational and interventional studies in this area. In observational studies, the absence of a counterfactual outcome for individual cases prohibits making true causal inferences from the data under the potential outcomes framework (187). A counterfactual outcome is an outcome that would have occurred if a participant with an exposure of interest was unexposed or vice versa. For example, I may have data on a participant who meets national physical activity guidelines (observed exposure) not receiving a diagnosis of depression (observed outcome), but I cannot estimate whether the same participant would have depression (unobserved outcome) if they did not meet activity guidelines (unobserved exposure). It is necessary to have information on both contrasting scenarios to determine whether the exposure caused the outcome. However, it is possible to estimate causal effects from observational data under certain assumptions according to the potential outcomes framework that I will return to in Section 2.3.1 (Section 2.3.1. Rationale for observational study designs and approach to causal inferences in this thesis) (187).

Sir Austin Bradford Hill developed a set of criteria to determine the strength of evidence supporting findings from an observational study reflecting a causal effect (188). The nine criteria include strength of association, consistency, specificity, temporality, biological gradient (dose-response), plausibility, coherence, experimental evidence, and analogy. Meeting these criteria does not prove causality, but it does strengthen the case for it. Plausibility and coherence refer to the exposure being a logical cause of an outcome and coinciding with what I know about the disease or disorder. Identifying clear mechanisms of action that explain why physical activity might influence depressive symptoms can demonstrate plausibility and coherence to strengthen the evidence that their association in observational studies is causal.

Randomised controlled trials are more suited to establishing causal effects than observational studies, but understanding these mechanisms is still important in randomised controlled trials. In a perfectly designed and implemented randomised controlled trial, participants are randomly selected and assigned to a treatment or exposure. The difference between the group-level outcomes should represent a causal effect. The randomisation procedure theoretically ensures that there are no systematic differences between participant characteristics at baseline, such that participants are 'exchangeable' between groups. In theory, the difference in depressive symptoms at the end of a randomised controlled trial is attributable to the physical activity intervention itself. However, establishing possible mechanisms of action extends beyond supporting causality in randomised controlled trials. It can advance understanding of the underpinnings of depressive symptoms and inform other methods of prevention and treatment. For example, physical activity could reduce depressive symptoms by promoting vasculature changes that improve glucose delivery to key brain regions, such as the hippocampus. This finding could suggest that some depressive symptoms partially reflect energy dysregulation in the brain and pharmacological agents that target these systems could be a novel form of treatment.

1.6.2. Measurement bias in assessing physical activity and sedentary behaviour in epidemiological studies

I evaluated methods to measure physical activity in large epidemiological studies to inform upcoming data collection sweeps in cohorts with Economic and Social Research Council funding (189). I have incorporated some arguments from that report into this sub-section. Most prospective studies on the associations of physical activity, sedentary behaviour, and CMD symptoms in the population use self-reported exposure measures rather than activity monitoring devices, such as accelerometers (119,120,142). For example, the International Physical Activity Questionnaire (IPAQ) is a common measure in these studies (190) that contains 31 questions (9 in the short-form version) on time spent sitting, in light-intensity physical activity (e.g., walking), moderate activity (e.g., leisure cycling), and vigorous activity (e.g., running) in a week. These measures have several important properties underlying their widespread use. The self-report measures provide contextual information about activities, such as the type or domain of an activity and its perceived intensity. I will return to the importance of this contextual information in Section 9.4.1. (Section 9.4.1. Moving beyond energy expenditure to examine behaviour types and domains). They can also group patterns of movement under a single activity that involve rapid fluctuations in intensity or bouts of inactivity, such as gardening. The measures are generally cheap to administer and have a low participant burden.

However, self-report activity measures also introduce substantial measurement errors when quantifying physical activity and sedentary behaviour. Activity monitoring devices are wearable mechanisms that continuously record motion that is interpretable as bodily movement. For example, accelerometers estimate bodily acceleration in one to three directions (I discuss these devices in more detail in Section 2.3.3. Overview of exposure variables). Self-reported measures of past or typical activity patterns are inherently subject to several sources of cognitive bias that device-based measures are not, such as recall and social desirability biases. Systematic reviews of studies comparing estimates of total physical activity volume from IPAQ and device-based measures commonly report weak correlations (e.g., r = 0.09 to 0.39) (191). These findings coincide with other systematic reviews highlighting low to moderate correlations between self-report and device-based measures in estimating physical activity volumes in adults or children and adolescents (192,193) or estimating sedentary behaviour (194).

In most cases, participants tend to overestimate their moderate-to-vigorous physical activity compared to device-based measures (e.g., 49 minutes compared to 23 minutes per day) (195) and underestimate their sedentary behaviour (e.g., by around 1.74 hours per day) (194). These discrepancies vary by domain and activity type. For example, self-report questionnaires commonly focus on leisure-time moderate-to-vigorous physical activity and insufficiently account for light-intensity physical activity (196,197). Light intensity physical activity has the lowest test-retest reliability from self-report measures of all intensities, possibly due to its unstructured nature and dispersion throughout the day (56).

The use of self-report activity measures for mental health outcomes may be subject to further confounding due to the presence of affective, motivational, and cognitive symptoms that could bias how people estimate their recent or typical activity levels (198–201). For example, people with major depressive disorders can experience memory deficits (202) that may influence their capacity to recall recent physical activity trends accurately. They could also experience negative cognitions that cause an underestimation of their past physical activity trends. There are consistent differences between estimates of physical activity time and intensity from self-report measures and devices in people with various mental health diagnoses (198,203–205). To date, just one physical activity questionnaire is validated against devices for use in people with mental health symptoms (206). These biases increase the risk of reverse causation measurement error in some studies, as the outcome (i.e., mental health symptoms) can influence the measurement of the exposure (i.e., physical activity).

Device-based measures have different some different limitations to self-report questions, such as their inability to directly measure the context or domain of activity. However, self-report and device-based measures have complementary benefits that mean an overreliance on either method will produce limited representations of the complex relationships of physical activity, sedentary behaviour, and CMD symptoms. Most prior studies use self-report measures to quantify participants' total physical activity volume or time in different intensities or sedentary behaviour to estimate their association with CMD symptoms. This approach likely introduces substantial measurement error due to the inherent cognitive biases of self-report measures and may be more suitable for device-based measurement (57). For example, underestimating time in sedentary behaviour reduces a study's statistical power to detect its potential association with CMD symptoms, which may contribute to some of the inconsistent findings (144,150). Studies that assess the association of total physical activity volume from self-report measures may insufficiently measure light-intensity physical activity, which accounts for most of daily movement. These studies may underestimate the magnitude of the association between physical activity and CMD symptoms or overestimate the relative contribution of moderate-to-vigorous physical activity (119,120). The presence of such measurement error in these studies misrepresents the underlying structure of the relationships between physical activity, sedentary behaviour, and CMD symptoms, and limits our capacity to assess the likelihood of causality.

1.6.3. Understanding physical activity and sedentary behaviour within a 24-hour context

There is a growing shift to investigating physical activity, sedentary behaviour, and sleep in a 24-hour context (152). Physical activity, sedentary behaviour, and sleep are physiologically related (e.g., through energy expenditure) but have distinct biological, psychological, or social influences that may differentially effect CMD symptoms. These behaviours account for discrete but dependent periods of the day. For example, an intervention that increases time in moderate-to-vigorous physical activity will require reductions in light-intensity physical activity, sedentary behaviour, or sleep within the day. To estimate how increasing moderate-to-vigorous physical activity might influence CMD

symptoms, it may also be necessary to appropriately account for this reduction of time in other co-dependent behaviours. For example, increasing moderate-to-vigorous physical activity may exert a greater protective effect on CMD symptoms when replacing sedentary behaviour than light-intensity physical activity or sleep, which could have their own mental health benefits.

Accounting for this co-dependence of time throughout the day is challenging with widespread forms of statistical analysis that assume a single exposure (i.e., time in moderate-to-vigorous physical activity) that is independent of a set of confounding variables (e.g., time in sedentary behaviour). Recent studies have aimed to address this problem by applying iso-temporal substitution modelling and compositional data analysis methods to physical activity data (207,208). I will expand on these methods in Chapters 5, 6, and 7. Another important element in shifting towards a 24-hour approach is using measures that continuously estimate physical activity, sedentary behaviour, and sleep over 24-hours. Data on all behaviours are necessary to appropriately estimate the influence of one on CMD symptoms while accounting for the others. Extracting this data from self-report measures is possible but the level of detail necessary to capture these complex interrelationships between different behaviours in the day is more feasible with device-based measures (152).

National physical activity guidelines are also beginning to recognise the importance of considering these behaviours in a 24-hour context. Canada became the first country to develop 24-hour movement guidelines that focus on promoting combinations of optimal movement and sleep behaviours (209), rather than individual behaviours in isolation. Despite contention over whether these guidelines are sufficiently evidence-based (210), the move sends a clear message for researchers to consider a 24-hour framework for investigating physical activity, sedentary behaviour, and sleep echoed in recent World Health Organization guidelines (67).

1.6.4. Physical activity, sedentary behaviour, and mental health in adolescents

CMD symptoms commonly first occur during adolescence (9,10), which are associated with an increased risk of CMD diagnoses and other behavioural, functional, and social problems at the time and during adulthood (9,13–17). Early interventions that target modifiable risk factors in adolescents could be an effective method of preventing CMD symptoms. However, most prospective studies of the associations between physical activity, sedentary behaviour, and CMD symptoms only include adults (119,120). For example, from four recent systematic reviews (120,143–145), only three prospective studies focus on sedentary behaviour (211,212) or physical activity (213) and anxiety symptoms in adolescents. A 2020 systematic review of prospective studies for sedentary behaviour and depressive symptoms (142) included only one study in adolescents (214), which used self-reported screen-time as the exposure in a relatively small sample (n = 435). From studies using mostly cross-sectional study designs in adolescents, findings have been inconsistent on the associations between physical activity, sedentary behaviour, and CMD symptoms (144,215–222). A 2019 meta-review findings on the relationships of physical activity and mental health in adolescents suggested that protective associations between physical activity and depressive symptoms were null or small, and there was only limited evidence of benefits for anxiety symptoms (223). The review found some evidence to suggest associations with depression could be causal according to the Bradford Hill criteria but insufficient evidence from studies of anxiety for causal assessments, despite improvements in research quality for both outcomes since an earlier iteration of the review in 2011.

1.6.5. Lack of research on associations between physical fitness and common mental health disorders

Cardiorespiratory and muscular fitness are an increasingly important marker of health and chronic disease status (155–157), but research into its role in mental health has been lacking. The only systematic review of prospective studies on cardiorespiratory fitness and depressive symptoms identified just three studies and included two in the meta-analysis with substantial heterogeneity (I^2 = 85.1%) (172). There have been no systematic reviews of prospective studies on cardiorespiratory fitness and anxiety, with some cross-sectional evidence of an association (169). Fewer studies have focused on the role of overall muscular strength. Some small cross-sectional (224,225) and longitudinal (181–183) studies suggest that low muscular strength is associated with a higher incidence of depression and one with anxiety (226) in specific populations, such as obese adults. There is limited data to conclude the association between physical fitness and CMD symptoms in the population, with much of the data coming from cross-sectional studies. The risk of reverse causation with physical fitness as the exposure is similar to physical activity as physical fitness and physical activity is typically lower in people with mental health diagnoses than in the general population (124,200,227). Existing research also focused on assessing the risks of cardiorespiratory and muscular fitness with mental health as independent exposures. In reality, these types of fitness co-exist and studies should examine how different combinations of cardiorespiratory and muscular fitness are associated with CMDs.

1.6.6. Addressing evidence gaps in this thesis

I conducted a comprehensive narrative review to outline a framework of biological and psychosocial mechanisms that may underpin the possible influence of physical activity on depressive symptoms in Chapter 3. There is a paucity of direct evidence from randomised controlled trials in people with depression that limited previous attempts to identify possible mechanisms of action (186). However, there is a growing number of relevant studies in other areas that examine the biological influence of physical activity on the brain, such as in treatments for dementia or cognitive decline (228). I used a narrative review to incorporate evidence from a wide range of fields and outline a conceptual model of how physical activity could influence depressive symptoms by eliciting neuroplasticity changes, inflammation, oxidative stress, the endocrine system, self-esteem, social support, and self-efficacy. I also discussed how modifying and confounding variables may influence these mechanisms to affect the relationship between physical activity and depressive symptoms.

In Chapters 4, 5, and 6, I aimed to address problems with measurement error as well as the risk of reverse causality by prospectively examining associations between device-measured physical activity and sedentary behaviour with CMD symptoms. I used data from accelerometers, which are moderate-to-strongly correlated with direct measures of physical activity-based energy expenditure, such as doubly labelled water or indirect calorimetry (229). I examined these associations in adolescents and adults to address the paucity of prospective studies using device-based measures in both population groups. I then build on this work by adopting a 24-hour approach to physical activity and sedentary behaviour in Chapters 5 and 6 using increasingly advanced statistical methodologies using iso-temporal substitution modelling (Chapter 5) and compositional data analysis (Chapter 6). These approaches allowed me to account for other time-use variables in the day and estimate substitution effects. For example, I estimated how theoretically replacing 60 minutes of sedentary behaviour with light-intensity physical activity might influence CMD symptoms. I hypothesised that high sedentary behaviour would be associated with increased CMD symptoms across all studies and increased light or moderate-to-vigorous intensity physical activity would be associated with fewer CMD symptoms.

In Chapters 7 and 8, I contributed to the prospective research on the association between physical fitness markers and CMD symptoms in the population. I first conducted a systematic review (Chapter

7) to update findings from a previous review from 2016 on the prospective association between cardiorespiratory fitness and depression incidence in the population that only included 3 studies. I also included studies with outcomes relating to the incidence of anxiety disorders. I hypothesised that low cardiorespiratory fitness would be associated with higher CMD incidence. While I identified additional studies in my review since the 2016 paper, there was still a paucity of research in the area, particularly in relation to anxiety outcomes. In Chapter 8, I conducted a new prospective study on the associations between cardiorespiratory and muscular fitness with CMD symptoms in the population. I hypothesised that low cardiorespiratory or muscular fitness would be associated with a greater CMD risk, and the combination of low cardiorespiratory or muscular fitness would have the highest degree of risk.

1.6.7. Objectives of this thesis

My thesis aims to examine the relationship of physical activity, sedentary behaviour, and physical fitness with CMD symptoms in adolescents and adults in the population. This will involve addressing three objectives:

1. Develop a framework to describe the biological and psychosocial pathways through which physical activity may influence depressive symptoms (Chapter 3)

2. Examine the prospective association of device-measured physical activity and sedentary behaviour with CMD symptoms across the lifespan (Chapters 4, 5, and 6)

3. Investigate the prospective associations of cardiorespiratory and muscular fitness with CMD symptoms and incidence in the population (Chapters 7 and 8)

2. Chapter 2: Methodology overview

2.1. Summary

This chapter provides an overview of the methods I use in this thesis. I provide an overarching description of the study designs, data sources, and key exposure and outcome measures. I split the chapter into three sections according to the objective that each chapter and methodology is addressing. I first describe why I chose to conduct a narrative review in Chapter 3 based on the available literature to provide a comprehensive psychosocial and biological framework, as per Objective 1. I then provide the rationale for using observational study designs to address Objective 2 in Chapters 4 to 6. I discuss the challenge of isolating causal effects in observational research, which is a major issue when interpreting observational studies. I also describe the data sources and exposure and outcome variables used for my prospective cohort studies in Chapters 4 to 6. Finally, I outline my use of a systematic review with a meta-analysis and prospective cohort study to address Objective 3 in Chapters 7 and 8. I focus on describing the exposure variables for Chapter 8 in this section as the study design, data source, and outcome variables overlap with the analysis in Chapter 6 described in the previous section. This section provides an overview of methodologies, but more comprehensive and specific methods sections are available in Chapters 3 to 8. I also provide further discussion on the methods' strengths and limitations throughout the thesis in Chapter 9.

2.2. Objective 1 methodology: Develop a framework to describe the biological and psychosocial pathways through which physical activity may influence depressive symptoms

I addressed Objective 1 through a narrative review in Chapter 3 (Chapter 3. Physical activity and depression: Understanding the possible mechanisms of action underlying the relationship of physical activity and depressive symptoms). In the following section, I provide the rationale for following a narrative review format to address Objective 1.

2.2.1. Rationale for narrative review format

I chose to conduct a narrative rather than systematic review to address Objective 1 in Chapter 3. Systematic reviews are a robust method of synthesising evidence with clearly defined interventions or exposures, outcomes, and population groups. However, I decided that a systematic review format is too restrictive to develop a comprehensive framework of biological and psychosocial mechanisms underlying the association between physical activity and depressive symptoms from existing evidence. As discussed in Section 1.6.6. (Section 1.6.6. Addressing evidence gaps in this thesis), there is a paucity of research examining biological or psychosocial mechanisms underlying the association between physical activity and depressive symptoms. For example, a 2016 systematic review on the neurobiological effects of exercise in people with major depressive disorder identified 20 studies, but most of these only measured peripheral biomarkers that correlate poorly with changes in the brain (186). The review was also reliant on two large trials with poor adherence and showed no antidepressant effects (230,231). There are a growing number of physical activity-based trials in mental health. However, the field is still relatively new and typically lacks the resources for robust mechanistic work that has been fundamental in outlining the mechanisms of antidepressant pharmacotherapy, including neuroimaging-based methods (232).

The narrative review format allowed me to incorporate evidence from related areas to inform my framework, such as dementia or cognitive decline (228). Physical activity also has a broad impact on biological processes throughout the body that could be relevant to depressive symptoms. Whereas pharmacological agents typically target specific mechanisms of action, such as serotonin neuroavailability. Physical activity also has a variety of psychosocial impacts that are relevant to depression, such as promoting self-esteem (233). A narrative review format allowed me to incorporate evidence from a broad range of areas and make inferences about how each mechanism or combination of mechanisms could produce antidepressant effects following physical activity. In this chapter, I also chose to focus specifically on exercise and depressive symptoms as this relationship is where most of the prior research focuses. An overarching aim of Chapter 3 was to develop a comprehensive framework to identify promising mechanisms and stimulate more targeted research to explore their role in preventing or treating CMD symptoms.

2.3. Objective 2 methodologies: Examine the prospective association of device-measured physical activity and sedentary behaviour with CMD symptoms across the lifespan

I conducted three prospective cohort studies using two population-based data sources from adolescents (Chapter 4: Device-measured physical activity and sedentary behaviour and depressive symptoms throughout adolescence, and Chapter 5: Device-measured sedentary behaviour and anxiety symptoms during adolescence) and adults (Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms) to address Objective 2. In the

following section, I discuss the rationale for using observational study designs and provide a description of the approach I take to making causal inferences in this thesis. I also provide an overview of the data sources and exposure and outcome variables used in Chapter 4 to 6.

2.3.1. Rationale for observational study designs and approach to causal inferences in this thesis

I conducted the analyses in Chapters 4 to 6 using observational data. Observational study designs have several advantages over experimental research that are well suited to the types of research questions I investigate in this thesis. For example, they provide a framework for assessing whether a naturally occurring behaviour (e.g., high sedentary behaviour) may increase the risk of CMD symptoms over time. There have been examples of studies experimentally inducing sedentary behaviour and monitoring mood and stress changes in small groups of participants (n = 43) (234). These studies can provide unique insights into the acute effects of increasing sedentary behaviour. However, observational studies explore these relationships in a natural setting and identify whether sedentary behaviour influences the development of CMD symptoms in large groups of participants over several years. The large sample sizes and long follow-up periods of cohort studies can provide sufficient statistical power to assess associations and explore how they differ across population groups (e.g., effect modification) or identify possible underlying mechanisms (e.g., mediators). Gathering this information in experimental research can be resource-intensive and time-consuming.

However, well-conducted randomised controlled trials can provide robust evidence of causal effects that are more challenging in observational studies. Randomisation theoretically ensures that participants are 'exchangeable' between treatment and control groups by randomly distributing predictors of the outcome (i.e., potential confounding variables). As participants are exchangeable between a treatment and control group, any difference in their outcomes should be attributable to their treatment or exposure group assignment. Group differences represent causal effects of the treatment or exposure in randomised controlled trials. However, confounding variables are not randomly distributed in observational studies. Systematic differences between participants at baseline can partially explain differences in their outcomes that are not directly attributable to an exposure or treatment of interest. For example, people with high physical activity may have lower depression scores because they are wealthier, which may reduce psychosocial stress from material or area-level deprivation and increase access to gyms or education on health behaviours.

The lack of exchangeability in observational research is a major limitation in assessing causal associations. However, there is a range of analytical procedures that can reduce confounding and other sources of bias in observational studies to improve the capacity for causal inferences. In some cases, observational studies can approximate a randomised study. According to the potential outcome framework, an observational study must have consistency (well-defined and uniform exposure or intervention), positivity (the probability of receiving every level of the treatment or exposure is greater than 0), and exchangeability to meet the criteria of a conditionally randomised controlled study (187).

A growing number of analytical methods have been developed to assess causal associations in observational data using the potential outcomes framework principals. For example, marginal structural models are a method of estimating causal effects with a time-dependent exposure (e.g., physical activity patterns) in the presence of time-varying confounding (e.g., baseline depressive symptoms). I had initially intended to use marginal structural models to assess the time-varying association of physical activity and sedentary behaviour with anxiety symptoms in Chapter 5. However, I chose against using this method after attending the Causal Inference in Epidemiology course at the University of Bristol and discussing the idea with potential collaborators. Marginal structural models can address some methodological issues with longitudinal, observational data

within a potential outcomes framework, such as reducing time-varying confounding. However, the method is still relatively new and makes strict assumptions that are primarily applicable to a limited range of research questions and study designs, such as target trial designs with electronic health records data. For example, the method is still reliant upon a dichotomised exposure variable with a clear contrast (e.g., exposure to a medication or surgery) to satisfy the consistency assumption. The lack of dose-response information on the association of physical activity or sedentary behaviour with CMD symptoms would have required selecting an arbitrary threshold to dichotomise these variables into high-low groups for the analysis.

Meeting the assumptions to estimate causal effects from observational data within a potential outcomes framework is challenging, particularly outside of controlled settings. For example, the consistency assumption requires that exposures or treatments be uniform across exposed or treated participants. A one-hour increase in physical activity per day could include a range of different behaviours and experiences across participants. If the exposure differs across individuals, it is unclear what is affecting the outcome and what the counterfactual outcome would have been.

While meeting the assumptions to isolate causal effects in observational data is challenging, it is possible to strengthen the evidence of causal associations by reducing random and systematic biases (e.g., reducing confounding) as much as possible and triangulating findings with other studies. Triangulating findings provide stronger evidence for causality when studies do not share the same biases. For example, the evidence of a causal relationship between physical activity and depression is strengthened when findings from an observational study and randomised controlled trial corroborate. Observational data can also guide experimental work. For example, a robust observational study could highlight high sedentary behaviour as a potential risk factor for CMD symptoms that an interventional study may target to produce a reduction in CMD symptom risk.

In this thesis, I aim to strengthen the evidence of causal associations between sedentary behaviour, physical activity, physical fitness, and CMD symptoms in the population using various analytical and epidemiological methods. For example, I address the exchangeability assumption by statistically adjusting my analysis for variables that confound my exposure-outcome associations. To do this, I identify possible confounding variables from existing literature and my own knowledge and develop a directed acyclic graph (DAGs). These graphs allow the mapping of proposed causal effects of the exposure, outcome, and confounding variables. DAGs have a mathematical basis in graph theory and are useful for explicitly outlining the proposed causal and statistical model and identifying different types of bias to causal effects. After using a DAG to identify a set of confounding variables for my exposure-outcome association, I can include variables that directly or indirectly (proxy variables) measure these confounding influences in my models. There are a variety of methods to adjust model estimates to account for each confounding variable. I use stratification-based adjustment methods, which can pool the total estimated influence of multiple confounding variables into a final effect estimate.

Adjusting final models for the influence of confounding variables does not ensure exchangeability between participants, but it does reduce bias to estimate potential causal effects more closely in the data. I also take a variety of additional measures to test the robustness of my findings to confounding. For example, I estimate e-values in Chapters 5 and 6. These values estimate the minimum strength that an unmeasured confounding variable would have to have to invalidate the observed exposure-outcome association while considering all other measured confounding variables (235). Calculating e-values does not overcome the problem of unmeasured confounding, but it can help to estimate its potential bias on the final effect estimates. This is one example of how I aim to address biases to causal inferences with observational data in my thesis. I discuss my methods for dealing with various biases to causal inference through Chapters 4 to 8 in more detail.

2.3.2. Outline of data sources for observational studies

2.3.2.1. ALSPAC

In Chapters 4 and 5, I use data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study. ALSPAC is a longitudinal cohort study that is ongoing today. Pregnant women living in the Avon area (South-West England) with an expected delivery date between April 1, 1991 and December 31, 1991 were invited to join the ALSPAC study (236,237). The target was a dynamic sample that made prohibited convenience sampling methods. There were 20,248 pregnancies eligible for recruitment into ALSPAC, and 14,541 (71.8% of total eligible sample) were enrolled in the first instance. There were another two systematic recruitment phases when the offspring were around 7 and 8 years old. Phase 2 and 3 recruited an additional 453 (2.2% of eligible sample) and 254 (1.2% of eligible sample) participants, respectively. The total sample from all recruitment phases was 15,454 pregnancies (75.3% of eligible) and 14,901 children alive at 12 months of age.

The ALSPAC study includes frequent follow-up assessments that largely focus on the offspring (237). These include a battery of self-report questionnaires on demographics, health, psychological and social, developmental, and educational factors. There were also 10 clinical assessments that measured a variety of physiological, cognitive, genetic, psychological, and social factors. ALSPAC data is also linked to health and administrative records, such as primary care and school records. The ALSPAC cohort has provided a rich source of epidemiological data, producing over 2000 academic papers since 1990. Its sample size, broad and diverse array of data collection methods, the availability of repeated measures, and rich clinical, genetic, and biobank data are key strengths of the cohort (237).

However, ALSPAC also has several limitations. The regional recruitment approach of ALSPAC had logistic advantages but limits representativeness with the UK population at large. For example, the catchment area for ALSPAC recruitment is more affluent and largely white-British, compared to other parts of the UK (237). The systematic recruitment of only 75.3% of eligible births may have also introduced selection biases in those agreeing to participate, exaggerating these representation issues. There has also been substantial attrition in the ALSPAC sample over time, which has led to an overrepresentation of affluent groups and underrepresentation of non-white minority ethnic groups (237). Several health-related factors also predict attrition from ALSPAC, such as BMI and smoking (238).

Representativeness is a major issue for estimating prevalence, where incidence may differ across population groups that are over or underrepresented, biasing population-level estimates. Assessing prevalence is not a primary aim of my thesis, which examines exposure-outcome associations that may be unaffected by unrepresentative prevalence estimates. However, there are still situations where representativeness can bias exposure-outcome associations. For example, participant selection and adjustments can induce collider bias. This is where the exposure and outcome variables can independently cause a third collider variable, such as participation in the study. Assessing associations between an exposure (e.g., smoking) and outcome (e.g., BMI) that predict recruitment or retainment in a cohort (e.g., ALSPAC) can induce spurious correlations between the two variables as it requires conditioning on the collider variable, which is selection into the cohort (238). I discuss how these representation issues might influence my findings and some methods to assess the risk of selection bias in Chapters 4 and 5.

2.3.2.2. UK Biobank

In Chapters 6 and 8, I use data from the UK Biobank study. The UK Biobank is a large, multisite cohort study of 502,682 participants aged 40 to 69 years recruited from the general population of England, Scotland, and Wales, between April 2006 and December 2010 (239). Anyone aged 40 to 69 registered with the National Health Service and living within 25 miles of a study assessment centre was invited to join the UK Biobank. There were 22 assessment centres across England, Scotland, and Wales, which yielded 9.2 million invitations. The final sample of 502,682 participants represents a 5.5% response rate. The study aims to examine genetic and non-genetic causes of disease in middle and older-aged adults. The large sample size was based on statistical power calculations showing that at least 5,000 to 10,000 cases of any condition would be necessary to reliably detect exposure-outcome associations with 1.3 to 1.5 odds ratios and around 20,000 for associations with at least 2.0 odds ratios (240).

At baseline, participants completed various questionnaires, physical measures, imaging, genetic, and biological assessments (241). The baseline assessments in the UK Biobank were comprehensive as data linkages are the principal means of follow-up for Biobank participants, including primary care and hospital records. However, the difficulty of measuring some lifestyle factors using questionnaires at baseline means there are also a variety of bespoke data sweeps, such as collecting 24-hour dietary data and accelerometer-based physical activity. There is also a range of supplementary follow up measures, such as for mental health, blood-based biomarkers, and medical imaging. The sample size, a broad range of high-quality measures, and data linkages are key strengths of the UK Biobank. However, selection bias is a major limitation of the cohort. The UK Biobank has attracted criticism for recruiting participants who are unrepresentative in some sociodemographic factors (e.g., area-level deprivation) and healthier in some behaviours (e.g., less physical inactivity) and disease incidence (e.g., lower cancer incidence) than the general population (242–244). I return to these issues of selection bias in Chapters 6 and 8.

2.3.3. Overview of exposure variables

The exposure variables in Chapters 4, 5, and 6 were measured using accelerometers. Accelerometers are electromechanical devices that measure bodily movements through changes in acceleration on one or multiple planes over time. Participants wear the device on a part of the body most likely to capture movement from its centre of gravity, usually the wrist or hip. The data is captured at a high sampling rate of more than once a second, typically between 40 and 100 hertz (57). The data is typically processed at a lower resolution. For example, in Chapters 4 and 5, the acceleration data is from hip-worn Actigraph 7164 or 71256 devices and summarised as units of ‘counts’ over one-minute epochs to create a ‘counts per minute’ variable. The ALSPAC cohort ran a calibration study in 246 participants to determine what count per minute thresholds are suitable for determining sedentary behaviour, light-intensity, and moderate-to-vigorous intensity physical activity through comparison with a portable metabolic unit that directly measures energy expenditure (245). In Chapter 6, I use data from a wrist-worn Axivity AX3 triaxial accelerometer. Triaxial accelerometers measure acceleration in three directional planes to capture a greater range of mobility than the uniaxial devices in Chapters 4 and 5. The output units are gravitational units (milli-gravities), and intensity thresholds are based on different calibration studies in adults (246–248). The correct method of processing and interpreting accelerometer data remain a subject of substantial debate (57,249).

Accelerometers have useful properties that make them suitable for my exposure measures here. They can continuously record movement throughout the day without recall or other cognitive biases. The data can provide information on frequency, duration, patterns, and intensity of activity. My exposure variables focus on estimating average daily time in sedentary behaviour, light-intensity,

and moderate-to-vigorous intensity physical activity per day. However, they have several limitations that I discuss in Chapters 4, 5, and 6. For example, they cannot reliably record cycling or weightlifting (57), which may represent substantial proportions of daily moderate-to-vigorous physical activity for some people.

2.3.4. Overview of outcome variables

The outcomes in my thesis are CMD symptoms. In Chapters 4, 5, and 6, I use validated self-report scales of depressive or anxiety symptoms, which include the Patient Health Questionnaire-9 (PHQ-9), Computerized Clinical Interview Schedule-Revised (CIS-R), and Generalized Anxiety Disorder-7 (GAD-7) scale. Both ALSPAC and the UK Biobank have linked primary care and hospital records that provide diagnostic CMD data. However, as discussed in Chapter 1.2.1., almost half of the people with CMD symptoms do not seek treatment in the UK (7). Primary care and hospital data can provide robust and standardised data on psychiatric diagnoses but may only capture cases of people with severer symptoms or more willingness to seek help. Self-report scales are a useful alternative measure for capturing community-level CMD symptoms. The scales typically involve a set of questions on the presence and severity of CMD symptoms on a 3-point scale. The sum of responses to each item produces a combined symptom severity score. I primarily use the score as a continuous measure to maximise statistical power and represent symptoms on a continuum that more closely approximates how they manifest than a binary diagnosis.

However, it is also possible to derive a dichotomised outcome using standardised cut-off scores that indicate severe enough symptoms for a possible clinical CMD diagnosis (250). While dichotomising a quasi-continuous variable reduces statistical power (123), it can aid interpretability. For example, I can quantify the risk of high sedentary behaviour as a percentage change in the risk of depression instead of as a unit change in the depression scale score. I initially used only continuous outcomes in my PhD work, which is evidence in Chapters 4 and 5. However, continuous and dichotomised outcomes have complementary advantages, and I chose to include both types of outcomes in my PhD, as in Chapters 6, 7 and 8.

2.4. Objective 3 methodologies: Investigate the prospective associations of cardiorespiratory and muscular fitness with CMD symptoms and incidence in the population

I conducted a systematic review with a meta-analysis (Chapter 7: The association between cardiorespiratory fitness and the incidence of CMDs) and a prospective cohort study (Chapter 8: Individual and combined associations between cardiorespiratory fitness and grip strength with CMDs) to address Objective 3 in this thesis. Both chapters use observational study designs following the same principles as described above (Section 2.3.1. Rational for observational study designs and approach to causal inferences in this thesis). The data source (UK Biobank) and outcome variables (CMD symptoms from validated self-report symptom scales) in Chapter 8 are also described above in Section 2.3.2.2. (Section 2.3.2.2. UK Biobank) and 2.3.4. (Section 2.3.4. Overview of outcome variables), respectively. I present continuous and dichotomised outcomes in Chapter 8, as in Chapters 5 and 6. In the following section, I provide the rationale for conducting a systematic review and meta-analysis (Chapter 7) and describe the exposure variables for Chapters 7 and 8.

2.4.1. Rationale for a systematic review and meta-analysis

In Chapter 7, I conducted a systematic review and meta-analysis to examine associations between cardiorespiratory fitness and CMDs in the population. I aimed to build on a 2016 systematic review on the association of cardiorespiratory fitness and depression incidence that only included two studies in its final meta-analysis (172). The review did not include outcomes for anxiety, and there have been other prospective studies with outcomes for depression published since 2016. I chose to focus on cardiorespiratory fitness as my preliminary searches were unable to identify any prospective studies of other health-related forms of physical fitness with CMDs in the population. Focusing on cardiorespiratory fitness also more closely aligns with most randomised controlled trials that utilise aerobic exercise for treating CMD symptoms (75–86). However, other forms of fitness could be associated with CMDs in the population, and I aimed to partially address this knowledge gap in Chapter 8.

2.4.2. Overview of exposure(s) variables

The exposures in Chapters 7 and 8 were cardiorespiratory and muscular fitness. Chapter 7 is a systematic review that includes a variety of measures for cardiorespiratory fitness. The gold standard measure of cardiorespiratory fitness is a maximal exercise test with gas analysis (159). These tests typically involve participants using a cycle ergometer or treadmill with an increasing (graded) intensity to exhaustion (maximal), while wearing a face mask to measure respiration directly. The face mask captures the total volume and gas concentration of inspired and expired air. Analysing this respiratory data can determine a participant's maximal oxygen consumption (VO_{2max}), a measure of oxygen in the blood at exhaustion. Higher VO_{2max} values are interpretable as higher cardiorespiratory fitness levels as they indicate the body's capacity to circulate oxygen as an energy source to muscles around the body during intensity activity.

Gold standard measures of cardiorespiratory fitness are rare in large, population-based studies as they are resource-intensive, require specialist equipment, and have a high participant burden due to discomfort. I only identified one study meeting my inclusion criteria in Chapter 7 using maximal exercise testing with gas analysis (251). However, there is a range of cost and time-effective exercise tests with outputs comparable with gold-standard testing that I discuss in Section 9.3.2. (Section 9.3.2. The importance of physical fitness and its mental health risks), such as walk or run tests (252). In Chapter 8, I use data from a submaximal cycle test in the UK Biobank and extrapolate the outputs to estimate cardiorespiratory fitness levels. I also use data from a handgrip strength test to estimate muscular fitness.

3. Chapter 3: Physical activity and depression: Understanding the possible mechanisms of action underlying the relationship of physical activity and depressive symptoms

3.1. Summary

In this chapter, I conducted a narrative review to examine the possible mechanisms underlying the relationship between physical activity and depressive symptoms. While there is strong evidence that physical activity interventions can reduce CMD symptoms (see Section 1.3.2.1. Physical activity as a mental health treatment), there has been an insufficient focus on understand how physical activity could influence mental health, particularly within epidemiology (see Section 1.6.1. Evidence gaps in understanding the associations of physical activity, sedentary behaviour, and fitness with common mental health symptoms in this thesis). Identifying possible mechanisms of action can strength the causal arguments for an association between physical activity and CMD symptoms at a population level. In this chapter, I integrate literature from a range of different fields to identify several psychosocial and biological pathways and develop a conceptual model of how physical activity could influence depressive symptoms (Objective 1). Much of the evidence uses data from exercise (as a subset of physical activity) interventions and trials to treat depressive symptoms. While these data are particularly relevant for understanding physical activity as a mental health treatment, the mechanisms that I identify should be reasonably applicable to prevention. For example, enabling and maintaining neuroplasticity or physical self-esteem may reduce or maintain a low risk of depressive symptoms in people with or without a mental health diagnosis.

I chose to focus on depressive symptoms as there was little empirical work on the mechanisms of physical activity on anxiety symptoms. Physical activity has a broad physiological and psychological impact. This approach also helped to provide a focussed and consistent narrative from the broad pool of evidence and to make specific links between mechanisms and individual symptoms. I aimed to select mechanisms that were most relevant to the pathophysiology of depressive symptoms, including the capacity for exercise to elicit changes in neuroplasticity, inflammation, oxidative stress, the endocrine system, self-esteem and social support. I also discussed how improving our understanding of these mechanisms can inform how I design and implement exercise-based interventions to maximise their antidepressant effects on an individual basis. I focus on I also discuss how a better understanding of these mechanisms I conclude by presenting a conceptual framework of the key biological and psychosocial mechanisms underlying the relationship between physical activity and depressive symptoms, and the moderators and confounders that may influence it.

There are some mechanisms relevant to the physical activity-depression relationship that is increasingly gaining traction but were not included in this review. For example, physical activity could influence depressive symptoms through interactions with the endocannabinoid system or influencing the composition of gut microbiota. An important takeaway from this narrative review is that physical activity could influence mental health through a variety of mechanisms, some of which have complex interrelationships that I lack data on. More robust evidence is necessary to determine which influences are strongest and most relevant to depressive symptoms. My original aim with this review was to strengthen causal evidence by highlighting potential pathways through which physical activity can influence depressive symptoms. After completing the review, I believe it also highlights critical gaps in our understanding that are important for developing physical activity-based approaches in mental health and understanding the pathophysiology of depression.

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3.2. Introduction

As highlighted in Chapter 1, depression affects around 300 million people and is the leading cause of disability worldwide (1). Depression is associated with serious physical health comorbidities including cardiovascular disease (19,20), metabolic risk factors, such as adiposity (253), premature mortality (19,22), and a high financial cost to society (26). The heterogeneity of depressive symptoms (48) poses considerable challenges for widespread treatments, including pharmacotherapy, psychotherapy, or a combination of both. These therapies have demonstrable scalability, accessibility, and efficacy for reducing depressive symptoms (38,254,255). However, the cost-benefit balance of these treatments is not always convincing when considering the high risk of relapse, potential pharmacological side-effects, small-to-moderate treatments effects, and limited impact on the long-term physical health risks of depression (see Section 1.2.3. Limitations of treatment and the potential for prevention). There is room for improving treatment and a strong argument for developing approaches to prevent depressive symptoms.

As discussed in Section 1.3.2.1. (Section 1.3.2.1. Physical activity as a mental health treatment), increased physical activity is associated with a lower incidence of depression in the population (119). Systematic reviews of randomised controlled trials indicate that physical activity-based interventions can reduce depressive symptoms in people with and without a depression diagnosis (76,79,80,90,94,256). Most of these trials focus on exercise, a structured subset of physical activity for improving physical fitness or performance, such as running or cycling. However, there has been insufficient research on understanding how physical activity might influence depressive symptoms in people with or without a diagnosis. As discussed in Chapter 1.6.1. (Chapter 1.6.1. Underlying mechanisms of the association between physical activity and CMD symptoms), previous reviews have assessed possible the psychosocial and biological mechanisms of physical activity influencing cognitive and mental health in young people (185) and biological mechanisms in adults with major depressive disorder (186). However, a comprehensive narrative review and conceptual framework of possible biological and psychosocial mechanisms of exercise on depressive symptoms in adults are lacking.

This narrative review provides a comprehensive summary of the key biological and psychosocial mechanisms through which physical activity produces an antidepressant effect. I conducted non-systematic literature searches to identify possible mechanisms that exercise influences and may play a role in the pathophysiology of depression. I primarily included mechanisms based on the strength of the evidence on their relationship with exercise and depression. However, there is a paucity of direct, high-quality evidence in this area, particularly psychosocial mechanisms. To avoid omitting potentially important but understudied mechanisms, I also considered other factors such as their conceptual plausibility or role in other forms of depression treatment. I will also detail how furthering our understanding of these mechanisms can help to identify other factors that moderate or confound the relationship between physical activity and depression. For simplicity, I will assume a fundamental overlap in the mechanisms through which physical activity and exercise influence mental health.

3.3. Biological mechanisms of exercise and depressive symptoms

Physical activity elicits a wide range of biological changes in the brain, with most studies focusing on exercise specifically (257). The breadth and diversity of these changes suggest that exercise may act through multiple pathways. This section will outline several pathways of potential relevance to depression. I focus on pathways that respond to repeated exercise bouts or training rather than the acute effects of exercise in adults.

The exercise protocols vary across studies in this review, which may have produced some differences in their results. However, most studies used moderate-to-vigorous intensity aerobic exercise at around 50% to 80% of participants' heartrate reserve or maximal heartrate. Exercise sessions were typically between 30 and 60 minutes, between one and three times per week over one to 12 months. The type of activity also varied, such as individual or group-based exercise and supervised or unsupervised exercise. Some studies incorporate resistance training that could elicit a different physiological response and impact depressive symptoms (258). However, it is beyond this review's scope to comprehensively document the differential impact of these other forms of exercise.

It is also important to note that due to technological and ethical issues, studies on molecular or cellular mechanisms tend to use animal models. However, research has increasingly replicated these findings directly or indirectly in humans (257). I prioritise findings from human interventional or observational studies where possible but use animal models to fill in knowledge gaps and provide supplementary detail.

3.3.1. The relationship of neuroplasticity to depression and exercise

Disruptions in neuroplasticity pathways may contribute to the pathophysiology of depression (259) 2008) and targeting these mechanisms of neuroplasticity could be a promising, novel treatment approach (260,261). Several meta-analyses have found associations between depression and structural abnormalities in the brain, including reductions in hippocampal, prefrontal, orbitofrontal, and anterior cingulate cortex volumes (262–269) and white-matter integrity (270). These findings appear to be independent of key confounders such as medication use, age, and comorbid psychiatric conditions (263,269,271). Depression is also associated with differences in cerebral blood flow across multiple brain regions (272).

The most consistently affected region in people with depression is the hippocampus (268), an area implicated in processes relevant to depression, such as emotional processing (273) and stress regulation (274). Several key cellular and molecular mechanisms of neuroplasticity are also disrupted in depression (259). For example, meta-analyses indicate that peripheral brain derived neurotrophic factor (BDNF) levels are lower in people with depression (275,276) and this may contribute to the pathophysiology of depression and antidepressant treatment (259,277). Animal models suggest that depression can impair several cellular processes, including hippocampal neurogenesis, which directly influences stress regulation, depression, and anxiety symptoms (278–280).

Several recent systematic reviews have found that exercise can increase the volume of both the left and right portions of the hippocampus and several cortical regions in healthy participants (273,281,282). Several randomised controlled trials have also found that exercise interventions can produce increases in prefrontal and anterior cingulate cortex volumes (283,284). Several cross-sectional and longitudinal studies in healthy participants have also found that exercise and higher cardiorespiratory fitness levels are associated with larger volumes in the hippocampus (285–291) and cortical regions (285,292–300). There is also some evidence that exercise and cardiorespiratory fitness improvements can promote white matter integrity (301,302). However, not all studies have found an influence of exercise on brain morphology (e.g., (303)).

Exercise stimulates several cellular and molecular processes in the brain that support its functioning. Exercise and cardiorespiratory fitness improvements are associated with adaptive improvements in cerebral blood flow (304–306) and animal models suggest this is driven by angiogenesis (307,308). By creating a more efficient vascular delivery system for neurotrophic factors and oxygen, these vascular changes could be crucial to exercise-induced neuroplasticity (309). It also supports other cellular mechanisms, such as neurogenesis (310). While a direct study *in vivo* is not currently

possible, there is indirect evidence that exercise increases the rate of neurogenesis in humans (306,311). This is supported by consistent evidence in animals that exercise independently stimulates hippocampal neurogenesis (312–314), including in models of stress and depression (315).

Exercise is associated with increases the circulation of several neurotrophic factors. Most notably, it is associated with increased concentrations of BDNF in serum or plasma samples from humans (316,317). Animal models suggest that the exercise-induced increase in BDNF occurs in the brain (312–314). Exercise has also been found to increase BDNF in animal models of stress and depression (318–320). Animal studies also show that exercise increases the circulation of vascular endothelial growth factor (VEGF) (308), an essential growth factor for angiogenesis that also mediates neurogenesis and synaptic plasticity (321).

Exercise also induces several other cellular and molecular changes that contribute towards neuroplasticity, such as synaptic plasticity or the release of insulin growth factor 1 (IGF-1) and fibroblast growth factors (FGF) (322). Through the release of neurotrophic factors, exercise stimulates a cascade of cellular mechanisms that produce changes in the structure and function of several brain regions, including the hippocampus (323–325). However, it is beyond this review's scope to cover all these changes in detail, or the complex interactions between them.

Evidence from human and animal studies suggests that depression is associated with structural abnormalities and dysregulation of some neuroplastic mechanisms. Exercise stimulates many of the same neuroplastic mechanisms. It is associated with growth in several brain regions adversely affected in people with depression, such as the hippocampus, prefrontal and anterior cingulate cortices (326). It also stimulates cerebral blood flow (305,306), which appears to affect people with depression (272). It stands to reason that exercise could counteract some of the impairments seen in people with depression, but there is a lack of research investigating this.

Schuch *et al.* (186) conducted a systematic review of exercise's biological effects in people with depression, which found exercise produces changes in cortical activity, endocrine response, and oxidative stress. However, the authors note the lack of research in this area and methodological limitations make it difficult to draw any definitive conclusions. The difficulty of accurately measuring cellular and molecular changes in human brains has made it difficult to replicate animal findings in humans. For example, the meta-analyses results have been mixed as to whether exercise increases serum or plasma BDNF levels in people with depression (327–330). However, animal models consistently show exercise can produce elevations of BDNF in the brain (257).

Longitudinal data suggest that improvements in cardiorespiratory fitness are associated with improvements in depressive symptoms and brain morphological changes (291), but interventional studies are lacking. Only one randomised controlled trial by Krogh *et al.* has investigated the impact of exercise on brain structure in people with depression. In this study, 79 people with depression were randomised to an exercise group with three 45-minute supervised cycling sessions per week at 80% of their maximal heart rate or to a control condition. They found no change in hippocampal volume or serum samples of BDNF, VEGF, or IGF-1 in either group after the trial. However, this trial also found no significant changes in depressive symptoms (303,331), making it difficult to infer anything about the antidepressant mechanisms of exercise. Poor adherence to the exercise intervention may have contributed to these findings, with participants in this study attending an average of just one session per week. A recent pilot of a 12-week exercise programme in 11 younger and older people with depression had a mean adherence of 91% to exercise sessions (296). This study found improvements in cardiorespiratory fitness, which correlated with increases in anterior cingulate cortical volume.

3.3.2. The relationship of inflammation to depression and exercise

There are several lines of evidence to suggest that chronic, low-grade inflammation may play a role in the pathophysiology of depression (332–334). Several meta-analyses have found that people with depression have elevated levels of a range of pro-inflammatory markers, including interleukin (IL)-6, IL-1, tumour necrosis factor alpha (TNF-α), C-reactive proteins (CRP) and several other IL receptors and receptor antagonists (335–338). Prospective cohort studies have also found people with depression have elevated IL-6 and CRP levels (250), including using Mendelian randomisation study designs (339). People with depression are also more likely to have a greater proportion of adipose tissue and metabolic dysregulations that can promote the circulation of pro-inflammatory adipokines (253). Inflammatory medication can also produce depressive symptoms (340). Finally, people with depression are also at a greater risk of conditions that indicate a dysfunctional or weakened immune system (341). Inflammation can disrupt multiple pathways involved in depression, such as dysregulating BDNF (342) or neurotransmitter systems through kynurenine pathways (343,344). A 2014 systematic review of 14 trials also found that anti-inflammatory medications can reduce depressive symptoms (345).

Several meta-analyses have found exercise interventions can reduce several circulating inflammatory factors, including IL-6, IL-18, CRP, leptin, fibrinogen, and angiotensin II (346,347). Physical activity and exercise act through several pathways to create an anti-inflammatory environment (348,349). While I am focussing on long-term effects, it is useful first to understand the acute effects of exercise on inflammation. Muscles are secretory organs that release myokines when contracting during exercise (350). The most responsive is IL-6 (351). According to one meta-analysis, 30 to 60 minutes of moderate-to-high intensity exercise elicits around a 145% increase in IL-6 (352). IL-6 is typically preceded by the release of TNF-α, triggering inflammation (350). However, with acute exercise, IL-6 does not cause inflammation as it is associated with the release of anti-inflammatory IL-10 and IL-1 receptor antagonists (IL-1ra) that inhibit the production of inflammatory markers by monocytes and macrophages, such as IL-1β, IL-1α, and TNF-α (353–355). IL-1ra continues to increase for several hours post-exercise (355), extending the post-exercise period of anti-inflammation. During this process, the adrenal gland and medulla also secrete adrenaline and cortisol, which help to promote IL-10 and reduce TNF-α even further (355,356).

Repeating these acute bouts of exercise causes a homeostatic adjustment to lower basal levels of inflammation. In addition to the actions of myokines, exercise also reduces inflammation by modulating the circulation of adipokines. The accumulation of adipose tissue increases the circulation of adipokines that can include elevations in IL-6, TNF-α, and leptin (357). Exercise can reduce this inflammation by counteracting the accumulation of adipose tissue (358). Animal models suggest exercise can also modulate the immune cell profile of adipose tissue to contain a greater proportion of anti-inflammatory M2 to pro-inflammatory M1 macrophage cells (359,360). There is also some evidence to suggest that exercise can influence the morphology of monocyte cells to have a reduced expression of toll-like receptor (TLR) subtypes that modulate inflammatory responses, such as TLR4 (361,362), which regulates TNF-α (363).

There is converging evidence that exercise has anti-inflammatory effects and that inflammation plays a role in the pathophysiology and treatment of depression (364,365). However, there is a lack of direct research into the anti-inflammatory properties of exercise in people with depression. Of the limited data available, findings are mixed. In their meta-analyses, Schuch *et al.* identified three studies (331,366,367) measuring long-term changes in inflammatory markers and found exercise did not produce any significant changes in people with depression. However, in a more recent 2017 randomised controlled trial by Euteneuer *et al.* in 98 participants with major depression were assigned to cognitive behavioural therapy treatment with or without an exercise component or a waiting list for 16 weeks (368). The exercise protocols included four individualised 40-minute,

unsupervised exercise sessions per week of at least moderate intensity. They found an increase in the anti-inflammatory marker IL-10 in the plasma of those in the exercise group relative to the other two groups. They also found no significant difference in symptom reduction between the cognitive behavioural therapy groups, so it is unclear whether the inflammatory changes relate to symptom improvements. Another recent 12-week trial found that exercise was associated with reductions in serum samples of pro-inflammatory IL-6 and symptoms in people with depression (369).

In a 10-week exercise trial in elderly participants without a diagnosis of depression by Kohut *et al.*, serum CRP, IL-6, and IL-8 decreased compared to a control (370). There was also a decline in depressive symptoms. However, a decline in depressive symptoms was also found in the control group, suggesting it may not be related to exercise's anti-inflammatory effects. Another study in people without depression found that a six-week moderate-intensity exercise programme led to reductions in depressive symptoms and TNF-α (371). However, the study also found that high-intensity interval training increased TNF-α and IL-6 levels, despite decreased depressive symptoms. This suggests that the decreases in depressive symptoms were not the result of inflammation. One population-based study found that CRP levels explained less than 5% of the association between physical activity and depression risk (372). Findings in animal models have been more consistent (364,365). Several animal studies have found that exercise can reduce depression-like behaviours, and this is associated with inflammatory changes, such as increases in IL-10 and decreases in pro-inflammatory myokines in the hippocampus (373,374).

While there is a lack of research in people with depression, some preliminary findings from recent trials show an association between exercise, inflammation, and depressive symptoms. Exercise may reduce depressive symptoms through modulating inflammation, predominantly in people with elevated levels of inflammatory markers, such as TNF-α. For example, Rethorst *et al.* found that higher baseline TNF-α levels were associated with larger reductions in depressive symptoms following an exercise intervention (367). More work is necessary to determine whether exercise can reduce inflammation in people with depression, whether these inflammatory changes influence depressive symptoms and if this is influenced by baseline inflammation.

3.3.3. The relationship of oxidative stress to depression and exercise

Oxidative and nitrosative stress occurs when excess reactive oxygen species (ROS) and reactive nitrogen species are produced as a by-product of metabolic processing and have harmful effects on the body. When ROS and reactive nitrogen species begin to outweigh antioxidants, they can cause damage to lipids, proteins, DNA, and even cell death (375). For simplicity, I will refer to this as oxidative stress. Organs such as the brain are particularly vulnerable to this damage because it has a high metabolic rate and lower antioxidant levels (375). As a result, oxidative stress pathways may contribute to the pathophysiology of psychiatric disorders, such as depression. A recent systematic review by Black *et al.* collected data from 18 studies on two markers of oxidative stress, 8-hydroxy-2'-deoxyguanosine and F2-isoprostanes (376). They found evidence of DNA and lipid damage in people with depression. An earlier review of 23 observational studies found that depression was associated with greater oxidative stress and lower antioxidant levels (377).

Oxidative stress may affect depression through multiple pathways. For example, it can degrade antioxidant defences, and stimulate the production of pro-inflammatory (375). Over time, the resulting damage may counteract neuroplasticity and contribute to some structural abnormalities in people with depression. Methods for promoting antioxidant defences to counteract oxidative stress could be a novel treatment strategy for psychiatric conditions such as depression (378).

Exercise causes acute spikes in oxidative stress, but long-term exercise is protective against oxidative stress (379). A meta-analysis by de Sousa *et al.* of 19 trials found that exercise was associated with a reduction in indicators of oxidative stress and an increase in antioxidants (380). The association remained after adjusting for intensity, volume, type of exercise, or population group. Regular exercise produces an adaptive response to ROS by increasing antioxidant enzymes and enzymes that repair ROS damage (381). This may be partially achieved through the upregulation of antioxidant genes (382). This leads to a reduction in ROS damage and greater resilience to ROS damage in the future. Animal models suggest that exercise may reduce oxidative stress in specific brain regions, such as the hippocampus (383).

Oxidative stress may contribute to the pathophysiology of depression, and exercise could be a useful tool for counterbalancing this. However, studies on people with depression are lacking. Schuch *et al.* conducted a 12-week exercise intervention in 26 people with severe depression (384). The exercise sessions consisted of three supervised sessions per week using either a treadmill, stationary bike, or a stepper at an intensity chosen by the participant. They found that exercise was associated with a reduced level of serum thiobarbituric acid-reactive substances, a marker of oxidative stress. More research is necessary to understand how exercise influences oxidative stress in people with depression.

3.3.4. The neuroendocrine system in depression and exercise

The neuroendocrine system maintains homeostasis by regulating the body's internal environment and influencing mood and behaviour. In healthy people, the hypothalamic-pituitary-adrenal (HPA) axis effectively mediates physiological responses to stress. However, several psychiatric conditions are associated with dysregulation of the HPA axis, including depression (385). In humans, prolonged cortisol exposure may cause similar neurotoxicity, and contribute towards structural brain changes (271,386) and cognitive deficits (387) associated with depression. Animal models of HPA dysfunction have shown that persistent increases in glucocorticoid circulation (cortisol in humans) exert a range of neurotoxic effects across prefrontal and hippocampal regions, including desensitisation of associated cell receptors, microglial activation, cell death, and reduction of neurogenesis and BDNF circulation (388). Interventions that normalise HPA axis tone may minimise the corresponding neural harms and support the treatment of depression.

Exercise causes initial elevations in cortisol circulation to elevate blood glucose for energy production, but regular engagement produces an adaptive, protective response (389,390). Habitual exercise leads to a blunting of the cortisol response that may reflect increased HPA resilience (391). Endurance runners show a normalising of awakening cortisol levels following a rest day (392), compared to chronic psychological stress where cortisol levels remain elevated (393). A 10-week exercise intervention combined with meta-chlorophenylpiperazine to exert neuroendocrine stress resulted in a blunted cortisol response following the training period, compared to placebo (394). While limited, available evidence suggests that exercise may be a positive stressor for select neuroendocrine pathways, with regular engagement dampening HPA activity and cortisol sensitivity.

Several lines of evidence point to the direct influence of exercise on the neuroendocrine system and HPA activity (391). HPA hyperactivity and prolonged elevation of cortisol levels may contribute to the pathophysiology of depression, and exercise may help to negate these effects. However, there is a lack of research into the effects of exercise on the neuroendocrine system in people with depression, and results are mixed. A 2008 pilot study conducted by Foley *et al.* on 23 people with depression found that a 3-month exercise intervention reduced depressive symptoms and decreased cortisol awakening response (395). However, a subsequent larger-scale 16-week trial failed to replicate these effects (231). In Krogh *et al*.'s 12-week exercise intervention in individuals with

depression who maintained high participation rates showed reductions in copeptin levels, a surrogate measure of vasopressin and corticotrophin secretion (396).

3.4. Psychosocial mechanisms of exercise and depressive symptoms

Physical activity has several psychosocial benefits that may influence depressive symptoms. Studies in this area are more balanced about their investigation of physical activity or exercise, but aerobic exercise is still most common. Some studies also focus on engagement in sport. For simplicity, I will consider sport as a proxy measure of exercise engagement. It is important to note that psychosocial research in this section includes fewer randomised controlled trials and relies on observational and cross-sectional research. In this section, I will explore the associations between exercise and self-esteem, and social support with depression.

3.4.1. The relationship of self-esteem to depression and exercise

Self-esteem is a global evaluation of self-worth and self-image, encompassing cognitive, behavioural, and affective processes. People with depression have lower self-esteem levels, which may contribute to symptoms such as a sense of worthlessness (397–399). The relationship between self-esteem and depression may be cyclical; poor self-esteem can increase depressive symptoms, further exacerbating self-esteem deficits. Physical self-perception is a sub-domain of self-esteem that refers to how a person perceives their physical self-concept and body image (400). Physical self-perception may be an important component of the relationship between self-esteem and depression (401).

There is an inverse association between perceived weight status and mental health (402). Those with body image dissatisfaction or who perceive themselves as unattractive have an elevated risk of depression (403). People with depression also have lower scores on physical self-perceptions than controls, and this relationship explains some of the variances in affect between people with and without depression (399). While it is impossible to rule out reverse causality here, preliminary evidence suggests poor physical self-perceptions are potentially associated with increased depressive symptoms, which could underlie the relationship between self-esteem and depression. Exercise could remediate this by promoting self-esteem, potentially through improving physical self-perception, such as and body image. However, research on people with depression is lacking.

Aerobic and resistance exercise interventions, of intensities ranging from light to vigorous, can promote physical self-perception (404,405) and improve body image (406,407). The improvements in physical self-perception may underlie improvements in self-esteem. Cross-sectional studies have found that physical activity is associated with higher self-esteem scores, quality of life, and positive affect, and this relationship is mediated by physical self-perception (405). Improvements in body composition underlie the improvements in physical self-perception, such as reductions in body fat and increases in muscle mass. However, Anderson *et al*. found improvements in self-perceptions regardless of actual changes to body composition (404). A systematic review by Campbell *et al.* also found that exercise improved body image, independent fitness level, or actual changes in body composition (407). Overall, this suggests that exercise could positively impact self-esteem, potentially even in the absence of body composition changes.

Studies using structural equation modelling have found that self-esteem, or physical self-concept, mediates the association between physical activity and depression (408,409). Knapen *et al.* conducted A 16-week psychomotor therapy intervention with an exercise component in psychiatric inpatients (32% with depression) and found decreases in anxiety and depression levels post-

intervention, which were correlated with improvements in physical self-concept (401). Legrand *et al.* found in women with elevated depressive symptoms that a seven-week exercise intervention led to increases in self-esteem, physical self-perception, and decreases in depressive symptoms compared to a wait-list control group (410). These initial findings suggest that through improving self-esteem and physical self-perception, exercise could influence depressive symptoms.

3.4.2. The relationship of social support to depression and exercise

Social support refers to the assistance that social relationships and transactions provide. It encompasses both supportive actions and perceptions of those actions. People with depression sometimes report a perceived lack of social support (411,412), while feelings of sufficient social support are inversely associated with depression (413). Social support may play a role in the pathophysiology of depression by restricting the number of opportunities for interaction and emotional disclosure. Improving social support could act as a buffer against stressful events and prevent depressive symptoms from worsening (414).

Physical activity could help to improve social support networks, providing opportunities for interaction and socialisation. These benefits may be particularly pronounced in cooperative forms of exercise, such as team sports. A systematic review of 20 prospective studies by Scarapicchia *et al.* found support from friends and family was associated with physical activity engagement in the future (415). In a prospective cohort study of 5,395 adults, Kouvonen *et al.* found that those meeting recommended physical activity guidelines with high levels of emotional support at baseline were more likely to maintain this activity level at follow-up (416). I also conducted an analysis using data from the Millennium Cohort Study to show that potentially replacing 60 minutes of social media or television time with team sports was prospectively associated with lower emotional distress scores in adolescents, but there was no association with individual exercise (e.g., jogging). I describe this study in more detail in Section 9.4.1. In a randomised controlled trial of 946 people with depression by Hallgren *et al.*, a 12-week exercise intervention led to greater reductions in symptom severity in those with greater access to supportive social relationships compared to those with less access (417). There was also a better treatment response in those with high compared to low availability of social relationships (odds ratio = 2.17, 95% CI = 1.40 to 3.36).

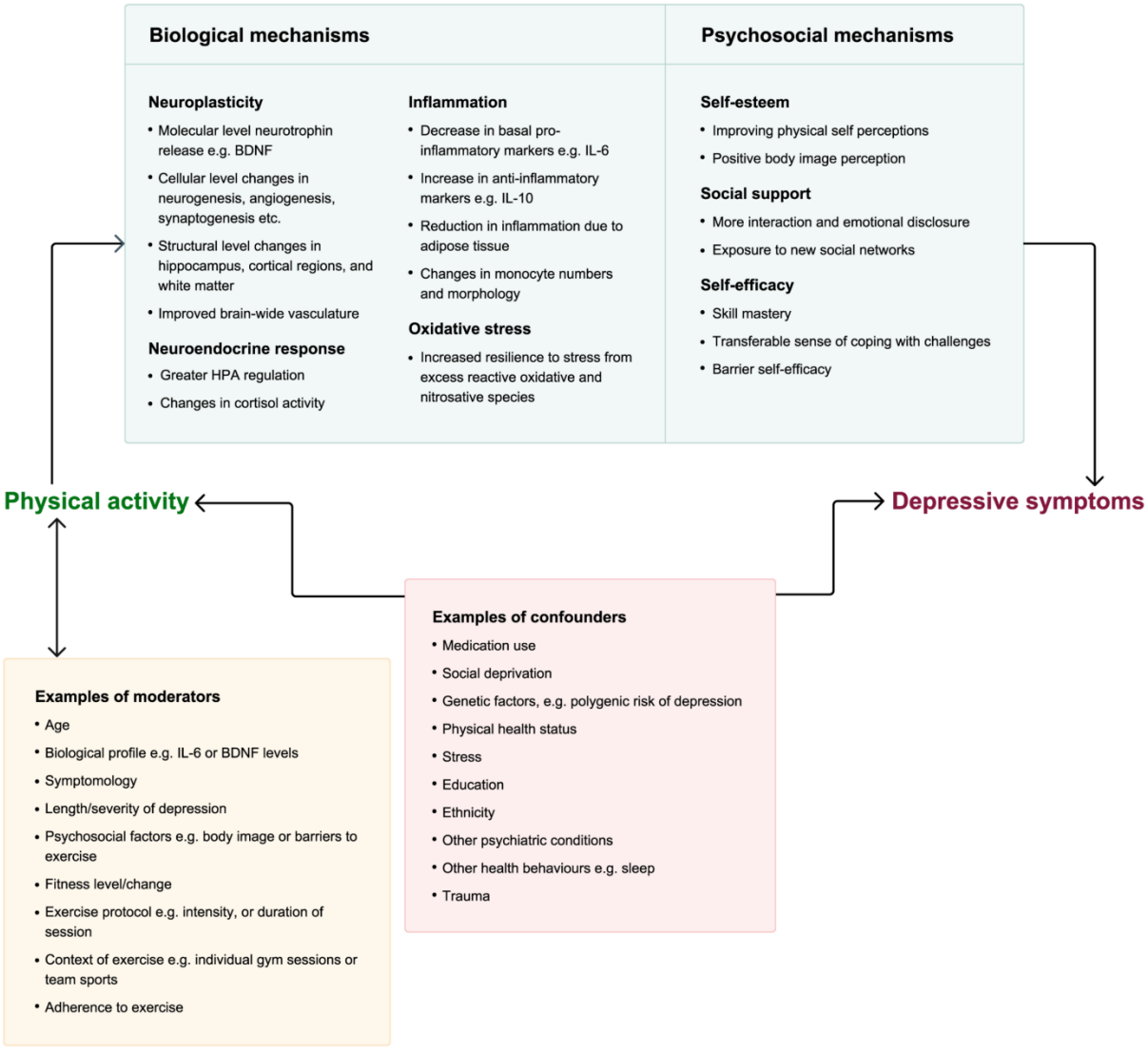
3.5. Conclusion

Exercise could influence depressive symptoms through multiple biological and psychosocial pathways. I summarised these pathways in Figure 1, which is from the published version of this paper (418). The figure also highlights self-efficacy as a possible pathway and several confounding and modifying influences on these pathways that I discuss in the published version of this review but not included in this chapter. As shown in Figure 1, a variety of interdependent changes can take place in the brain to produce an environment that is protective against depression. For example, neurotrophins (e.g., VEGF) stimulate downstream cellular processes (e.g., angiogenesis) that cause lasting changes in brain structure (e.g., improved vasculature) that improve brain functioning in areas implicated in depression (e.g., hippocampus) and related processes (e.g., stress regulation). While our understanding of how exercise affects the brain is growing, little is known about the complex interplay between these pathways and how they may relate to depression. For example, there is evidence that the IL-6 gene directly influences hippocampal morphology (419) and may represent a shared mechanism through which exercise influences depressive symptoms.

There may be some overlap in the mechanisms between the possible influences of exercise and antidepressant medications. For example, animal models suggest that antidepressants and exercise both impact neurogenesis through similar pathways, and their combination could have a complementary effect on reducing depression-like symptoms (420). A better understanding of these mechanistic overlaps between exercise and other forms of depression treatment will be beneficial for maximising their treatment potential.

Several psychosocial factors may accompany and potentially interact with these biological changes to influence depression. While there is less research into the psychosocial effects of exercise on depression, they are likely to be of parallel importance. Even less attention has been attributed to identifying factors that moderate or confound the relationship between exercise and depression. Research continues to quantify a growing number of social, psychological, and environmental factors that influence mental health and may confound the effects of exercise. It will be essential to incorporate this into any attempts to understand exercise as an antidepressant.

Figure 1. Potential pathways underlying the relationship between physical activity and depressive symptoms from (418)



There are a wide range and diversity of adaptive biological mechanisms that exercise stimulates, complicating any attempt to provide a comprehensive summary. I chose to focus on the mechanisms with the strongest evidence base in human research. Determining which mechanisms have the strongest evidence base will inherently involve a degree of subjectivity given the lack of research focusing on depression prohibiting a more systematic approach. There are other biological mechanisms not covered here that may also play an important role in the antidepressant effects of physical activity and exercise, such as endocannabinoid signalling (e.g., (421)) or mitochondrial functioning (e.g., (422)).

4. Chapter 4: Device-measured physical activity and sedentary behaviour and depressive symptoms throughout adolescence

4.1. Summary

In this chapter, I conducted my first prospective cohort study to address Objective 2: examine the prospective association of device-measured physical activity and sedentary behaviour with CMD symptoms across the lifespan. The aim was to address several limitations of previous studies, including measurement bias in self-report activity questionnaires (Section 1.6.2. Measurement bias in assessing physical activity and sedentary behaviour in epidemiological studies) and the lack of research in adolescents (Section 1.6.4. Physical activity, sedentary behaviour, and mental health in adolescents). To do this, I examined associations of physical activity, sedentary behaviour, and depressive symptoms in 4,257 population-based adolescents from the ALSPAC cohort. The cohort included accelerometer-based measures of physical activity and sedentary behaviour accelerometers at ages 12, 14, and 16, with depressive symptoms at age 18 measured using the computerised Clinical Interview Schedule-Revised. At the time, it was the first prospective study of the association between accelerometer-measured physical activity and sedentary behaviour with depressive symptoms in adolescents. The repeated measures of activity were another major advantage over previous studies using exposures measured at a single time point. I analysed associations with negative binomial regression and group-based trajectory modelling to utilise the repeated measures over time.

My findings highlighted a trend of total physical activity decreasing from age 12 to 16, driven by falling light-intensity physical activity and rising sedentary behaviour. My analysis showed that an additional 60-minute increase in sedentary behaviour per day at ages 12, 14, and 16 were associated with an increased depression score at age 18 of 11.1% (95% CI, 5.1, 17.6), 8% (95% CI, 1.2, 15.2), and 10.5% (95% CI, 1.5, 20.8), respectively. Those with consistently high or average sedentary behaviour at all ages had a 28.2% (95% CI, 6.1, 54.8) and 24.9% (95% CI, 7.8, 44.6) higher depression score than those with consistently low sedentary behaviour. Depression scores at age 18 were 9.6% (95% CI, 3.9, 15), 7.8% (95% CI, 0.8, 14.3), and 11.1% (95% CI, 2.6, 19.1) lower per additional 60-minutes of light-intensity physical activity time per day at ages 12, 14, and 16. Consistently high light-intensity physical activity was associated with a 20% (95% CI = 1, 34.8) decrease in subsequent depression scores. Moderate-to-vigorous physical activity only at age 12 and total physical activity at ages 12 and 14, were negatively associated with depressive symptoms.

I concluded that sedentary behaviour increases throughout adolescence and is consistently associated with a greater risk of depressive symptoms at age 18. The use of accelerometer-based measures here provided robust evidence to build on findings from previous self-report studies that highlight high sedentary behaviour as a mental health risk factor. Light activity was negatively associated with depressive symptoms but decreased throughout adolescence. These findings were particularly important as self-report activity measures are poor at detecting light activity (see Section 1.6.2. Measurement bias in assessing physical activity and sedentary behaviour in epidemiological studies) and its association with mental health was largely unknown in any age group. The repeated measures study design highlighted the displacement of light-intensity physical activity with sedentary behaviour during adolescence and its potential implications for adolescent depression.

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4.2. Introduction

Depression has an estimated prevalence in adolescents of 11% to 14%, which appears to have increased since 2005 (423,424). As the first onset of depression tends to be during adolescence, this represents an important window for identifying modifiable risk factors and intervening to prevent depression in later life (9,425). A growing body of evidence highlighted in Chapter 1 suggests that physical activity can reduce symptoms in people with depression in clinical and non-clinical populations (76,79,80,90,94,256). Most prior studies focus on moderate-to-vigorous intensity physical activity, such as brisk walking or cycling, which may act through several biological and psychosocial pathways to reduce depressive symptoms from Chapter 3. There is increasing evidence that time spent in sedentary behaviour is also associated with the risk of depression in adults (146,147).

Findings in adolescents have been limited and inconsistent regarding associations between overall physical activity, moderate-to-vigorous physical activity (215–220), or sedentary behaviour (144,221,222) and depressive symptoms. Nearly all previous studies in adolescents use self-report physical activity measures, subject to mood, attention, recall, and social desirability biases that limit their reliability (192). As highlighted Sections 1.6.2. (Section 1.6.2. Measurement bias in assessing physical activity and sedentary behaviour in epidemiological studies) and 2.3.2 (Section 2.3.3. Overview of exposure variables), obtaining reliable estimates of daily time in physical activity using these self-report measures is challenging in adults and adolescents (192,193). They typically produce underestimates of sedentary behaviour and insufficiently account for light-intensity physical activities (196,197), which have the lowest test-retest reliability from self-report measures of all physical activity intensities (56). Subsequently, light-intensity physical activity has been relatively understudied. Both light-intensity physical activity and sedentary behaviour make up the vast majority of waking daily activity, and better methods are necessary to estimate their impact.

Device-based measures, such as accelerometers, are uncommon in psychiatric epidemiological research but are a suitable method of estimating total physical activity levels and time spent in sedentary behaviour, light-intensity physical activity, and moderate-to-vigorous physical activity (426). To the best of my knowledge, only one prospective study had examined associations between physical activity and depressive symptoms in adolescents using device-based measures with a heartrate and movement sensory at the time of this study (220). There was no evidence of longitudinal associations between total physical activity or moderate-to-vigorous physical activity at age 15 and depression at age 17.5. By focussing on moderate-to-vigorous physical activity, this study potentially overlooked associations between depressive symptoms and sedentary behaviour or light-intensity physical activity. The study also only measured physical activity at baseline and was unable to examine associations between changes in physical activity levels over time and depressive symptoms.

Total physical activity levels decrease by around 7% each year between 10 and 19 (131). Accelerometer data suggest that this may be driven by increasing sedentary behaviour and decreasing light-intensity physical activity throughout adolescence (132–134), but the impact of this activity shift on mental health is unclear. There are growing concerns over rising sedentary behaviours in young people, such as screen-time (221). However, I still lack high-quality evidence to suggest that this increases the risk of adverse physical health (427,428) or mental health outcomes, including depression (144,221,222). In adults, cross-sectional accelerometer data suggest sedentary behaviour and light-intensity physical activity are positively and negatively associated with depressive symptoms, respectively (429–431). The same may also be true in adolescence. A 2020 prospective study using device-based measures found an inverse association between light-intensity physical activity in girls aged 7 and depressive symptoms 7 years later (432). The study found no association between sedentary behaviour and depressive symptoms or in boys.

To address these key gaps in the literature, I examined associations between total physical activity and time in sedentary behaviour, light-intensity physical activity, and moderate-to-vigorous physical activity, measured using accelerometers at three points during adolescence and depressive symptoms at age 18. My repeated measures design also allowed me to examine how changes in physical activity and sedentary behaviour over time were associated with subsequent depressive symptoms. I hypothesised that total physical activity and time in light-intensity physical activity and moderate-to-vigorous physical activity would be negatively associated with depressive symptoms, while time in sedentary behaviour would be positively associated with depressive symptoms.

4.3. Methods

4.3.1. Sample

Data for this study were from the ALSPAC cohort study described in Section 2.3.2.1. (Section 2.3.2.1. ALSPAC). The study website contains details of all ALSPAC cohort data that is available through an online data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). Ethical approval for this study was obtained from the ALSPAC Law and Ethics committee and the local research ethics committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. My sample includes participants with at least one accelerometer recording and a Clinical Interview Schedule-Revised (CIS-R) depression score at age 17.8 (n = 4,257), or age 18 for simplicity. A flowchart of ALSPAC participants for this study can be found in Supplementary Materials Figure 1.

4.3.1.1. Measures

4.3.1.1.1. Outcome: Depressive symptoms

My primary outcome was depressive symptoms measured using the computerised CIS-R depression score completed by participants at assessment clinics around the age of 18. The CIS-R is commonly used for assessing depression and anxiety according to criteria from the *International Statistical Classification of Diseases, 10th Revision* (433). It gives a score for the presence and severity of depressive symptoms in the past week, ranging from 0 to 21.

I used the Short Moods and Feelings Questionnaire (MFQ) to assess baseline depression at age 12. It is also measured at ages 14 and 16. This is a self-report measure of symptoms over the past two weeks, with scores ranging from 0 to 26. It is validated for assessing depressive symptoms in adolescents in population-based research (434). I use discrete-continuous depression scores as the primary outcome in the main analyses. Otherwise, I defined possible cases of depression as scores of at least 10 on the MFQ (435) and 7 on the CIS-R (250).

4.3.1.2. Exposure(s): Physical activity and sedentary behaviour

Physical activity and sedentary behaviour were measured at ages 11.8, 13.9 and 15.5 (reported as 12, 14, and 16) using accelerometers, the details of which are described elsewhere (245,436). physical activity data was collected with MTI Actigraph 7164 or 71256 accelerometers (Actigraph LLC, Fort Walton Beach, FL, USA) worn on the right hip for seven days. Both are of the same

generation of uniaxial accelerometers, and there are no significant differences between their outputs in comparison studies (437). Actigraph accelerometers have been validated for use in young people against indirect calorimetry (426).

Participants wore accelerometers during waking hours, except when washing or doing water sports. Data were recorded in raw accelerometer counts and averaged over 60-second epochs to create a count per minute (CPM) variable. I only include data from participants who recorded over 10 hours of wear time for at least three days, as previously shown to provide good statistical power and reliability (245).

I calculated total physical activity as the average CPM per day, from the full recording period. This measure accounts for the amount and intensity of physical activity undertaken and its use is validated against doubly labelled water (438). Time spent at different physical activity intensities was calculated as average minutes spent in predefined intensity thresholds from a calibration study in a subsample of 246 ALSPAC children (245). A value of $\geq$ 3600 CPM was defined as the threshold for moderate-to-vigorous physical activity (moderate-to-vigorous physical activity) (e.g., brisk walking or jogging), 200 to 3,599 CPM was light-intensity physical activity (e.g. slow walking) and $\leq$ 199 CPM was sedentary behaviour (e.g., lying or sitting still). I also calculated the time spent in each activity intensity as a percentage of total wear time to account for differences in wear time.

4.3.1.3. Confounding variables

I included several confounding variables in our models based on existing literature in the field and the use of a DAG (Figure 2 of the Supplementary Materials). The covariates in my main analyses include sex (male or female), ethnicity (white or non-white), maternal social class (manual or non-manual, measured at 32 weeks), baseline depression (MFQ), IQ (measured at age 8), parental psychiatric history (prior diagnoses of depression or schizophrenia), highest parental education (secondary level or degree/higher-level education, measured at 32 weeks), and baseline total accelerometer wear time. I derived maternal social class from the 1991 British Office of Population and Census Statistics that uses the most recent occupation from I (professional) to V (unskilled manual workers). These variables were measured at baseline unless specified otherwise. As smoking and alcohol use were measured after baseline at ages 16 and 15, they were only included as covariates in sensitivity analyses. My DAG indicated body mass index (BMI) as an intermediate variable on the causal pathway between physical activity and sedentary behaviour and depression. To avoid over adjustment (439), I only included BMI as a confounding variable in a sensitivity analysis.

4.3.2. Analysis

4.3.2.1. Descriptive statistics

I calculated means and standard deviations for normally distributed, continuous variables and medians and interquartile ranges for non-normal distribution.

4.3.2.2. Main analysis

I first assessed cross-sectional associations between physical activity, sedentary behaviour, and depressive symptoms (MFQ) at baseline (age 12). I included total physical activity (mean CPM) and

sedentary behaviour, light-intensity physical activity, and moderate-to-vigorous physical activity time as exposure variables in separate negative binomial regression models. I chose this model as the MFQ, and CIS-R outcome variables were highly positively skewed due to over-dispersion (see Figure 3 of the Appendix). In line with previous studies, I used units of 15 minutes for moderate-to-vigorous physical activity, 60 minutes for light-intensity physical activity and sedentary behaviour, and 100 CPMs for total activity. This was to avoid large numbers of minutes and counts, producing very small model coefficients that are hard to interpret. I first ran univariate models before fully-adjusted models. In models with total activity as the exposure variable, I did not adjust for total wear time as total CPM already accounts for time.

I then investigated the longitudinal associations between physical activity and sedentary behaviour at ages 12, 14, and 16 with depressive symptoms at age 18, measured using CIS-R. I used the same approach as in the cross-sectional models, but my outcome variable was CIS-R depression score. I ran separate models for each time point to avoid collinearity from including multiple time points in the same model.

4.3.2.3. Group-based trajectory modelling

I also investigated the associations between different physical activity and sedentary behaviour trajectories over time and depressive symptoms. This allowed me to better account for the time-varying nature of physical activity, sedentary behaviour, and depressive symptoms. I used group-based trajectory modelling (440) to identify unobserved (latent) subgroups of participants with statistically similar trajectories of total physical activity, sedentary behaviour, light-intensity physical activity, and moderate-to-vigorous physical activity time through ages 12, 14, and 16.

Group-based trajectory modelling is a form of finite mixture modelling that can identify latent subgroups of people with statistically similar physical activity trajectories (441). The method uses a finite set of polynomial functions of age or time to describe the trajectory for each group, based on maximum likelihood estimation. After estimating groups and their trajectories, each participant is assigned a probability of group membership and allocated to the group they have the highest probability. Group-based trajectory modelling using the *traj* command in STATA. I specified the final number of groups and their polynomial functions based on their Bayesian Information Criterion (BIC), an adequate sample size in each group, an average posterior probability (APP) value of >= 0.7, and the interpretability of the model for explaining the data (440). The model imputes missing values using maximum likelihood estimates (442).

I evaluated the associations between physical activity trajectory groups and depressive symptoms at age 18 using negative binomial regression with the same adjustments as in the main analysis. The sample includes the same participants as in the longitudinal models from age 12 with complete exposure, confounder, and outcome data. I used group-based trajectory modelling to generate trajectories of depressive symptoms through ages 12, 14, and 16 using MFQ scores. I then entered this as a categorical covariate into the regression models, instead of baseline depression. This allowed me to adjust for varying depressive symptoms throughout adolescence.

4.3.2.4. Sensitivity analysis and missing data

I conducted several sensitivity analyses determined a priori. I reran our main analyses: 1) excluding participants with elevated depressive symptoms at baseline (MFQ score of 10 or more), to minimise the risk of reverse causation with depressive symptoms explaining physical activity and sedentary

behaviour levels, 2) with BMI as a confounder, 3) with smoking and alcohol use as confounders, 4) with sex as an effect modifier as there were sex differences in physical activity levels, 5) with depression as a binary outcome using logistic regression models.

To reduce the risk of bias from missing data, I conducted multiple imputations using chained equations for all participants with a CIS-R score (n = 4,257). I conducted multiple imputations with chained equations to create "complete" 30 datasets (443). Missing values are imputed based on observed values for a given individual. The imputed dataset contains complete data from 4,257 participants, which is the total number of participants with a complete CIS-R depression score at age 18. Results from each of the 30 imputed datasets were pooled into a single multiple-imputation result. Multiple imputations yield accurate standard errors and takes account of the uncertainty of the predictions because multiple predictions are made for each missing value.

My multiple imputation model contained all exposure, outcome, and confounding variables: CIS-R depression score at 18, total CPM, sedentary, light, MVPA time at ages 12, 14, and 16, maternal social class, ethnicity, mental health diagnoses at age 13, BMI at ages 11, 13 and 17, MFQ at ages 12, 14, and 16, gender, parental mental health, parental education, and IQ at age 8. I included three further variables to improve the prediction of missingness in the ALSPAC cohort: maternal smoking during pregnancy, alcohol use at age 13, and psychosis (at least one reported episode of psychosis) at age 16. For non-normally distributed variables, I use predictive mean matching. I reran the main analysis in this imputed sample and compared the results with the non-imputed sample.

4.4. Results

4.4.1. Study sample

From my sample of 4,257 participants with a CIS-R depression score at age 18, the complete case cross-sectional analysis included 3,352 participants. The longitudinal analyses included 2,486, 1,938, and 1,220 participants at ages 12, 14, and 16, respectively. Total follow-up time was 6 years.

Table 1 shows the baseline characteristics of participants included in my analysis (n = 4,257). A comparison of baseline characteristics with those not included (n = 10,664) can be found in Table 1 of the Supplementary Materials.

Table 1. Baseline characteristics of included participants (n = 4,257)

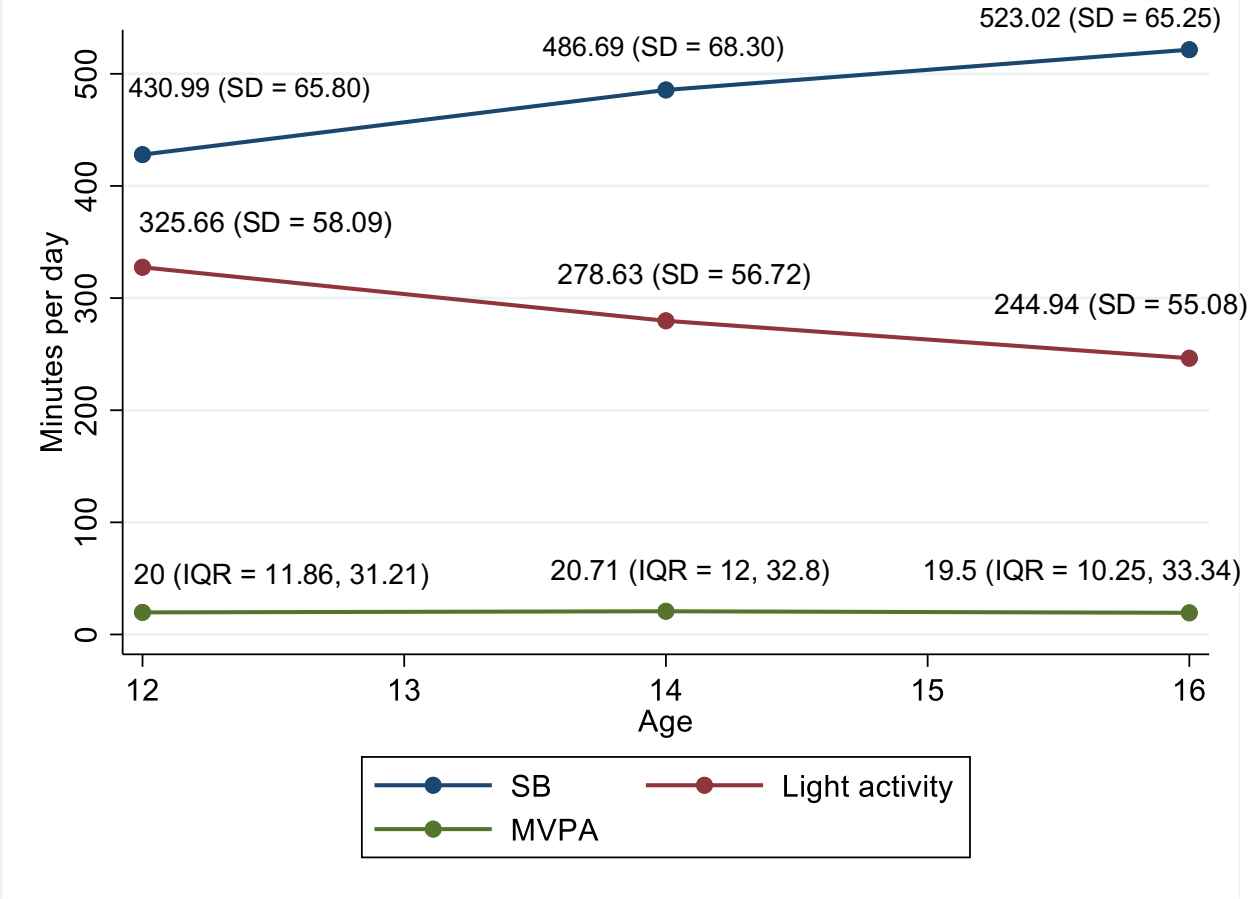
Characteristic (n with complete data)		**n (%)**
Sex (4,257)	Male	1,867 (43.86)
	Female	2,390 (56.14)
Ethnicity (4062)	White	3,889 (95.74)
	Non-white	173 (4.26)
Parental education (4,257)	Degree or higher	1,207 (28.35)
	Secondary	3,050 (71.65)
Maternal social class (3626)	Manual	553 (15.25)
	Non-manual	3,073 (84.75)
Parental psychiatric diagnosis (4257)	Severe depression or schizophrenia	422 (9.91)
	No diagnosis	3,835 (90.09)
BMI (3671)	Overweight or obese	270 (7.35)
	Normal or under	3,401 (92.65)

Baseline depression (3,683)	MFQ > = 10	344 (9.34)
	MFQ < 10	3,339 (90.66)

4.4.2. Physical activity and sedentary behaviour trends

Total physical activity levels are higher in males than females at all ages, but the trends across time remain the same. A full table of physical activity levels by sex and time in each intensity as a percentage of total wear time can be found in Table 2 of the Supplementary Materials. Mean total daily physical activity decreased from 603.32 CPM (SD = 177.62) at age 12 to 474.83 CPM (SD = 158.68) at age 16 (p <0.001). Mean sedentary behaviour increased from 430.99 minutes (SD = 65.80) per day at age 12 to 523.02 minutes (SD = 65.25) at age 16 (p <0.001). Light activity time decreased from 325.66 (SD = 58.09) minutes per day at age 12 to 244.94 (SD = 55.08) minutes per day at age 16 (p <0.001). Time spent in moderate-to-vigorous physical activity remained stable.

Figure 1. Physical activity levels at different ages



SD = standard deviation; moderate-to-vigorous physical activity = moderate to vigorous physical activity; IQR = interquartile range; sedentary behaviour = sedentary behaviour.

4.4.3. Main analysis

From my sample (n = 4,357) the median CIS-R depression scores at age 18 was 2 (IQR = 0, 5) and there were 747 (17.55%) possible cases of depression. My primary outcome for all longitudinal models is CIS-R depression score at age 18.

The fully adjusted cross-sectional models indicated that higher total physical activity, sedentary behaviour, and light-intensity physical activity time were associated with baseline depression, but not moderate-to-vigorous physical activity. In the longitudinal analysis, higher total physical activity at ages 12 (IRR = 0.941 (95% CI, 0.910, 0.972), $p < 0.001$) and 14 (IRR = 0.965 (95% CI, 0.932, 0.999), $p = 0.044$), but not age 16, were associated with a lower depression score at age 18. A 60-minute increase in sedentary behaviour was associated with an 11.1% (IRR = 1.111 (95% CI, 1.051, 1.176), $p <0.001$), 8% (IRR = 1.080 (95% CI, 1.012, 1.152), $p = 0.020$), and 10.7% (IRR = 1.107 (95% CI, 1.015, 1.208), $p = 0.021$) higher depression score at ages 12, 14, and 16 respectively. Per 60 minutes of light-intensity physical activity time, I found depression scores at 18 were 9.6% (IRR = 0.904 (95% CI, 0.850, 0.961), $p = 0.036$), 7.8% (IRR = 0.922 (95% CI, 0.857, 0.992), $p = 0.030$), and 11.1% (IRR = 0.889 (95% CI, 0.809, 0.974), $p = 0.013$) lower at ages 12, 14, and 16 respectively. For every 15 minutes of moderate-to-vigorous physical activity at age 12, I also found depression scores to be 9% lower at age 18 (IRR = 0.910 (95% CI 0.857, 0.966), $p = 0.002$), but no association at ages 14 and 16.

Table 2. Cross-sectional and longitudinal associations between physical activity, sedentary behaviour, and depression scores

	Age	Model (n)	CPM (per 100)			Time spent at different intensities							
						Sedentary (per 60 mins)			Light (per 60 mins)			Moderate-to-vigorous physical activity (per 15 mins)	
			IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*
Cross-sectional	12	Unadjusted (3,352)	0.963	0.947, 0.980	<0.001	1.049	1.020, 1.080	0.001	0.930	0.904, 0.965	<0.001	0.955	0.927, 0.984	0.003
		Fully adjusted (3,352)	0.981	0.963, 0.100	0.045	1.047	1.014, 1.081	0.005	0.949	0.916, 0.983	0.004	0.991	0.959, 1.023	0.586
Longitudinal	12	Unadjusted (2,486)	0.910	0.882, 0.939	<0.001	1.108	1.054, 1.165	<0.001	0.883	0.834, 0.933	<0.001	0.848	0.863, 0.965	<0.001
		Fully adjusted (2,486)	0.941	0.910, 0.972	<0.001	1.111	1.051, 1.176	<0.001	0.904	0.850, 0.961	0.001	0.910	0.857, 0.966	0.002
	14	Unadjusted (1,938)	0.933	0.902, 0.965	<0.001	1.114	1.057, 1.175	<0.001	0.908	0.851, 0.970	0.004	0.913	0.863, 0.965	0.001
		Fully adjusted (1,938)	0.965	0.932, 0.999	0.044	1.080	1.012, 1.152	0.020	0.922	0.857, 0.992	0.030	0.960	0.905, 1.018	0.169
	16	Unadjusted (1,220)	0.939	0.896 0.983	0.007	1.101	1.026, 1.180	0.007	0.882	0.810, 0.961	0.004	0.938	0.883, 0.997	0.041
		Fully adjusted (1,220)	0.984	0.937, 1.033	0.509	1.107	1.015, 1.208	0.021	0.889	0.809, 0.974	0.013	1.001	0.936, 1.071	0.966

CPM = counts per minute; moderate-to-vigorous physical activity = moderate-to-vigorous activity; IRR = incident rate ratio; CI = confidence interval. Fully adjusted models control for sex, maternal social class, paternal psychiatric history, paternal education, ethnicity, baseline depression, and total accelerometer wear time at each time point.

4.4.4. Group-based trajectory modelling

I identified two latent subgroups of people with similar trajectories for total physical activity and three subgroups for each physical activity intensity as seen in Table 3. I used persistently low as the reference group. There was no association between the trajectories of total physical activity and depressive symptoms. People with persistently average or high sedentary behaviour had 24.9% (IRR = 1.249 (95% CI 1.078, 1.446), p = 0.003) and 28.2% (IRR = 1.282 (95% CI 1.078, 1.446), p = 0.003) higher depression scores than those with low sedentary behaviour. Those with persistently high light and moderate-to-vigorous physical activity time had a 19.96% (IRR = 0.804 (95% CI 0.652, 0.990), p = 0.041) and 31.1% (IRR = 0.699 (95% CI 0.515, 0.950), p = 0.022) lower depression score at age 18, respectively. I found no association persistently average light or moderate-to-vigorous physical activity groups and depression scores at age 18. Graphical representations of each trajectory model in my analyses can be found in Figures 4 to 8 of the Supplementary Materials and Table 3 contains the model fit indices from all models that I considered.

Table 3. Physical activity and sedentary behaviour trajectories with depression scores

Physical activity variable	**Group (%) N = 2,486**	**Reference group**	**Parameter estimates**		
			IRR	95% CI	*P*
Total physical activity (CPM)	Persistently high (21)	Persistently low (79)	0.934	0.823, 1.060	0.291
Sedentary	Persistently average (59.2)	Persistently low (19.3)	1.249	1.078, 1.446	0.003
	Persistently high (21.5)		1.282	1.061, 1.548	0.010
Light	Persistently average (44.8)	Persistently low (46)	0.936	0.843, 1.040	0.225
	Persistently high (9.2)		0.804	0.652, 0.990	0.041
Moderate-to-vigorous physical activity	Persistently above average (22.7)	Persistently low (73.9)	1.006	0.884, 1.145	0.928
	Persistently high (3.4)		0.699	0.515, 0.950	0.022

CPM = counts per minute; moderate-to-vigorous physical activity = moderate-to-vigorous activity; IRR = incident rate ratio; CI = confidence interval.

4.4.5. Sensitivity analyses

My multiple imputation models included complete data from 4,257 participants who had a CIS-R score at age 18. I observed similar patterns in the imputed models as in the complete cases analysis, without any substantial differences (Table 4 of the Appendix page 12). The results of all sensitivity analyses can be found in Tables 4 to 8 of the Supplementary Materials. There was no interaction between physical activity or sedentary behaviour and sex, and there were no substantive differences between the findings of the main analyses and any sensitivity analysis.

4.5. Discussion

4.5.1. Main findings

To the best of my knowledge, this was the first prospective study using repeated device-based measures to examine associations between physical activity, sedentary behaviour, and depressive symptoms in adolescents. I found that sedentary behaviour increased, and light-intensity physical activity decreased throughout adolescence and was consistently associated with depressive symptoms at age 18. An additional hour of sedentary behaviour per day was associated with an 8 to 11% increase in depression score at age 18. Participants with persistently high or average sedentary behaviour levels between ages 12 and 16 had a 25% and 28% increased depression score at age 18 than those with persistently low sedentary behaviour. An additional hour of light-intensity physical activity per day was associated with an 8 to 11% decrease in depression score. Maintaining persistently high light-intensity physical activity was associated with a 20% reduction in depression score. Moderate-to-vigorous physical activity only at age 12 and total physical activity only at ages 12 and 14, were negatively associated with depressive symptoms. However, those with persistently high moderate-to-vigorous physical activity had a 32% lower depression score than those with persistently low moderate-to-vigorous physical activity. These findings were robust to a series of sensitivity analyses, including models with imputed missing data.

My data suggest that overall physical activity levels decline and support recent evidence from other accelerometer studies that sedentary behaviour proportionally displaces light-intensity physical activity throughout adolescence (132–134). There is a paucity of high-quality, longitudinal research using device-based measures to assess the possible harms of rising sedentary behaviour in young people (144,221,222,427,428). I have shown using repeated, device-based measures that this rise could increase the risk of adolescent depression, which partially aligns with some cross-sectional accelerometer data in older adults (429,431). Data on light-intensity physical activity is also scarce due to the difficulty of recording it without device-based measures (56). My results showed that light-intensity physical activity was consistently associated with reducing depressive symptoms in adolescents, supporting cross-sectional accelerometer findings in adults (430,431) and prospective findings in young girls (432).

Despite being the focus of most prior research, total and moderate-to-vigorous physical activity were not consistently associated with depressive symptoms here. This contrasts with some previous self-report data in adolescents (215,217–219), but coincides findings from the only other prior prospective accelerometer study in adolescents (220). This could be related to the fact that activity levels decline throughout the study.

Physical activity may influence depressive symptoms through various psychosocial and biological mechanisms, such as stimulating neuroplasticity in brain regions implicated in depression, reducing inflammation, or promoting self-esteem as highlighted in Chapter 3. Most studies have demonstrated these effects with moderate-to-vigorous physical activity, but light-intensity physical activity may act through similar pathways. Long periods of sedentary behaviour may forgo these protective benefits, potentially increasing the risk of depressive symptoms. The type of activity that young people engage in during sedentary periods may also influence its association with depressive symptoms. For example, young people with high social media usage during sedentary periods could have a higher risk of depressive symptoms that those high video game usage (444). Some pathways highlighted in Chapter 3 (Chapter 3: Physical activity and depression: Understanding the possible mechanisms of action underlying the relationship of physical activity and depressive symptoms) may be less applicable here. For example, I might expect ceiling effects for some biological changes in neurodevelopmentally healthy adolescents, such as angiogenesis or hippocampal growth. Much of

the literature examining these changes in response to physical activity were from studies in middle-to-older aged adults. Adolescents may be more responsive to the social aspects of physical activity. For example, light activity (e.g., walking) could increase the opportunities for social interactions, strengthening social support networks.

4.5.2. Strengths and limitations

Some strengths of this analysis include its prospective design over 6 years, large population-based sample, repeated accelerometer measurement, and rich data on covariates for model adjustments and sensitivity analyses. However, I must also consider potential limitations. Selection bias due to attrition over time or missing data could have influenced the results of my complete case analysis. The number of participants with valid accelerometer data dropped at each time point from 5,252 at age 12 to 1,922 at age 16. While my results did not differ in my fully imputed samples, I only imputed missing data from my subsample with complete exposure data (n = 4,257). The initial ALSPAC sample of children who were alive at 12 months (n = 14,901) may differ from my subsample in ways that affected my results. For example, participants in the full ALSPAC sample were more likely to have higher BMI and be from a non-white ethnic group and less likely to have parents with higher education or social class. This could limit the generalisability of the findings in my analytic sample to the full ALSPAC sample and potentially to the general population. There may also have been residual or unmeasured confounding factors that I have not accounted for, such as season or day of accelerometer recording, screen-based device use, physical health, or living environment.

I may have lacked the statistical power to detect consistent associations between moderate-to-vigorous physical activity and depressive symptoms. At baseline, just 1.5% of participants (*n* = 63) were meeting the UK national guidelines of 60 minutes of moderate-to-vigorous physical activity per day for young people (66). However, the 3% of participants identified by my models as having relatively high moderate-to-vigorous physical activity through ages 12 to 16 had 32% lower depression scores than the 74% of participants with persistently low moderate-to-vigorous physical activity. Statistical power was also affected by the sample size decreasing throughout the study, which may partially explain why the p values in my adjusted models were smaller at age 12 than age 16 for all exposure variables. Associations are statistically weaker at ages 14 and 16 and it is also possible some of these p values are a result of chance due to multiple testing.

Group-based trajectory modelling is useful for identifying distinct developmental trajectories but relies on polynomial curves that lack flexibility. This limits their ability to capture real world, individual variability. As group assignment is based on the highest probability, some participants with low probabilities for all groups may have been assigned a group that does not fit their individual trajectory well. However, the impact of this is likely to be small as the average probability values for all groups were ≥0.7 and in some groups ≥0.9. It is important to note that these are approximations of a continuous reality, I cannot estimate whether latent groups actually exist in the data (440).

I also used negative binomial regression to fit best my data, which is commonly applied to count variables. My outcome variable (CIS-R score) has a similar structure to count data (i.e., discrete, independent, and without negative values) and have been used in this way before (445). However, CIS-R scores have a severity weighting that are inconsistent with a true count variable. I do not expect this to have had a substantial impact on my results, as findings from the sensitivity analyses using logistic regression were consistent with my main analysis.

Finally, some limitations of using accelerometers include their difficulty accurately recording certain activities as discussed in Section 2.3.3. (Section 2.3.3. Overview of exposure variables), such as cycling or weightlifting. They are also unable to record posture, which requires an inclinometer.

Despite robust validation studies (426), it is possible that wearing the accelerometer may have influenced normal physical activity behaviour during this observation period.

4.5.3. Implications and future research

Novel approaches are needed to address the global burden of depression. Adolescence represents an important window for intervention given the early onset of depression (9,425). My findings suggest that the displacement of light-intensity physical activity with sedentary behaviour during adolescence could be an important target for public health interventions to reduce the risk of depression. Physical activity guidelines and strategies to promote activity should more directly focus on the mental health benefits of activity, develop specific targets for reducing sedentary behaviour in young people, and promote light-intensity physical activity interventions.

By emphasising its mental health benefits, public health bodies could motivate improvements in adherence to physical activity guidelines by young people, which is currently low (446). Current physical activity guidelines in the UK and US focus on the long-term physical health and developmental benefits of activity for young people, such as improving coordination skills, strengthening bones, or improving cardiovascular fitness (66,175). Given the early onset and increasing prevalence of depression in adolescents (9,423–425), promoting activity for its mental health benefits could be a more relatable message for young people to increase their activity.

Physical activity guidelines lack sufficient high-quality evidence regarding dose-response to recommend specific targets for reducing sedentary behaviour (66). Developing these recommendations using data from self-report studies alone could be misleading given the extent to which they underestimate daily sedentary behaviour time (447). My data suggested that a 2-hour reduction in daily sedentary behaviour between ages 12 to 16 was associated with a 16 to 22% reduction in depression scores by age 18. For young people with subclinical symptoms, a reduction of this magnitude can have a substantial impact. Specific targets would set measurable and achievable goals that send a stronger public health message for addressing high sedentary behaviour in young people.

Light activity interventions could be a practical method of reducing sedentary behaviour and the risk of depression in young people. Current physical activity guidelines in the UK and US primarily discuss light-intensity physical activity as a means of promoting activity in older adults or those with low fitness (66,175). This is likely due to the paucity of studies using device-based measures to investigate light-intensity physical activity. Public health bodies could promote individual-, school-, or community-level changes to incorporate extended bouts of light-intensity physical activity into young people's daily routines, such as standing lessons, increasing active travel time between classes, or promoting lightly active hobbies like playing an instrument and painting.

I only investigated depressive symptoms in this study. Future research should use repeated, device-based measure assessments to examine associations between physical activity and sedentary behaviour with the risk of other mental health conditions. In the subsequent chapter, I apply similar methods to examine associations between physical activity and sedentary behaviour with anxiety symptoms. Future research should also focus on the possible impact of other activity changes in young people would also be beneficial. For example, the extent to which breaks in sedentary behaviour or meeting national moderate-to-vigorous physical activity guidelines influence the association between sedentary behaviour and depressive symptoms.

Studies using device-based measures of physical activity and sedentary behaviour to examine their association with CMD symptoms are rare in any age group, relative to the number of studies using self-report measured activity. Chapters 4 and 5 in this thesis apply these methods to adolescents and

Chapter 6 to adults. The findings of these analyses provide important insights on the structure of the relationship of physical activity, sedentary behaviour, and mental health across the lifespan. However, they are not replacements for studies using self-report activity questionnaires, which can provide important contextual information about the type of activity. Recent findings suggest that mentally-active sedentary behaviours, such as working at a desk, are associated with a lower risk of depressive symptoms than mentally-passive sedentary behaviours, such as watching television (448). I have also conducted two studies in adolescents from the Millennium Cohort Study that show how different types of sedentary behaviour (e.g., watching television versus playing video games) and physical activity (e.g., individual versus team sports) have different associations with mental health outcomes (see section 9.4.1. and (444)). Self-report and device-measured activity measures have complementary benefits and their concurrent use could be a novel method of examining these nuances in future research (449). I return to this point in Section 9.4.1. (Section 9.4.1. Moving beyond energy expenditure to examine behaviour types and domains).

4.6. Conclusion

Using device-based measures, I found that declining light-intensity physical activity and increasing sedentary behaviour between the ages of 12 to 16 were associated with greater depressive symptoms at age 18. Most of the mechanisms identified in Chapter 3 relate to exercise, rather than light activity. However, some of these mechanisms could be relevant to light activity, such as reducing inflammatory markers. Displacing sedentary behaviour with light-intensity physical activity in young people warrants more direct and specific consideration in physical activity guidelines and public health interventions to reduce the prevalence of depression.

5. Chapter 5: Device-measured sedentary behaviour and anxiety symptoms during adolescence

5.1. Summary

In this chapter, I conducted my second prospective cohort study to address Objective 2: examine the prospective association of device-measured physical activity and sedentary behaviour with CMD symptoms across the lifespan. Similarly to in Chapter 4 (Chapter 4: Device-measured physical activity and sedentary behaviour and depressive symptoms throughout adolescence), I addressed some of the limitations of previous studies, including measurement bias in self-report activity questionnaires (Section 1.6.2. Measurement bias in assessing physical activity and sedentary behaviour in epidemiological studies) and the lack of research in adolescents (Section 1.6.4. Physical activity, sedentary behaviour, and mental health in adolescents). I originally aimed to assess the associations of physical activity, sedentary behaviour, and anxiety symptoms by using marginal structural models to estimate causal effects within a potential outcomes framework (see Section 2.3.1. Rationale for observational study designs and approach to causal inference in this thesis). However, as discussed in Section 2.3.2., this approach was not appropriate for exposures and research questions of this complexity. I instead focused on addressing the issue of including multiple co-dependent and reciprocal time-use variables (i.e., time in different activity states) in a 24-hour context (see Section 1.6.3. Understanding physical activity in a 24-hour context). I used accelerometer-measured sedentary behaviour and physical activity data from 4,257 ALSPAC participants at ages 12, 14, and 16 to assess their association with anxiety symptom scores at age 18 from a CIS-R. I used iso-temporal substitution modelling to examine these associations. This method allows for the mutual adjustment of all time-use variables in the same model (e.g., time in sedentary behaviour is adjusted for time in light and moderate-to-vigorous activity) and the estimation of replacement effects on the outcome (e.g., replacing 60 minutes of sedentary behaviour for light activity on anxiety symptom scores).

I found a positive association between sedentary behaviour at ages 12, 14, and 16, with anxiety symptoms at age 18. Using iso-temporal modelling, I found that theoretically replacing an hour of daily sedentary behaviour for light-intensity physical activity at ages 12, 14, and 16, was associated with lower anxiety symptoms by age 18 by 15.9% (95% CI = 8.7% to 22.4%), 12.1% (95% CI 3.4% to 20.1%), and 14.7% (95% CI 4% to 24.2%) respectively. Whereas, theoretically replacing an hour of sedentary behaviour with moderate-to-vigorous physical activity was not associated with differences in anxiety symptoms. These findings highlight high sedentary behaviour as a risk factor for adolescent anxiety and light activity as a promising replacement to break up and reduce sedentary behaviour throughout the day. This chapter extends the findings of Chapter 4 to anxiety symptoms, which I show is an independent association from depressive symptoms in the sensitivity analysis using multivariate models. It also builds on Chapter 4's findings by addressing the co-dependence of these time-use exposure variables within a 24-hour context and estimating replacement effects that more closely approximate how changes in activity might occur following an intervention. Chapters 4 and 5 provide robust demonstrations of how sedentary behaviour displaces light activity during adolescence, and this activity shift is associated with increases in CMD symptoms.

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5.2. Introduction

As discussed in Chapter 1 (Chapter 1: Introduction), anxiety is a common mental health problem, characterised by excess worry, fear, and hyperarousal that can be debilitating and interfere with normal daily functioning (5). Anxiety disorders have a widespread global prevalence of around 7.3% in adults (450) and 6.5% in children and adolescents (451). While anxiety disorders frequently co-occur with depression (Kessler et al., 2008), the diagnoses have different symptomologies (452). Collectively, anxiety disorders represent the sixth leading cause of disability worldwide (World Health Organisation, 2017) and are associated with long-term physical health complications, including cardiovascular disease (18) and premature mortality (22). Most anxiety symptoms first occur during adolescence (Kessler, Chiu, Demler, Merikangas, & Walters, 2005) and cause substantial disruptions to the social, education, and family lives of young people (13) and their functioning in later life (14). Identifying risk factors for anxiety symptoms that are modifiable during adolescence is essential to reducing the prevalence and burden of anxiety disorders. Interventions that simultaneously address the long-term physical and mental health outcomes could be particularly important for reducing the mortality gap between people with anxiety disorders and the general population (Firth et al., 2019; Kandola et al., 2018).

Some population-based studies have found that higher levels of self-reported sedentary behaviour and lower physical activity levels are associated with an increased risk of anxiety symptoms and disorders (120,122,143–145). Sedentary behaviour is directly modifiable through increasing physical activity in the day. Several randomised controlled trials have demonstrated that structured physical activity interventions can reduce anxiety symptoms in adults with and without anxiety disorders (81,456–458).

However, there has been little research on adolescents. Most studies in this area are cross-sectional and unable to account for reverse causality (120,143–145). From four recent systematic reviews (120,143–145), only three prospective studies focus on sedentary behaviour (211,212) or physical activity (213) and anxiety symptoms in adolescents. These studies used self-reported measures, which have limitations I have discussed in Chapter 2 and 4. I showed in Chapter 4 that the activity shift from light-intensity physical activity to sedentary behaviour during adolescence was associated with an increased risk of depressive symptoms by age 18 in ALSPAC. However, I lack evidence regarding the impact on anxiety symptoms. Most prospective studies of sedentary behaviour or physical activity interventions focus on depressive symptoms (87,119,120)**,** creating a knowledge gap regarding their relationship with anxiety symptoms. Anxiety symptoms are associated with a substantial global health burden and likely have different underlying mechanisms from depressive symptoms that warrant further investigation in their own right.

High sedentary behaviour may forgo some of the possible benefits of physical activity I discussed in Chapter 3 and cause additional problems that increase mental health risks, such as social isolation or sleep problems (459,460). While increasing activity will be essential to reducing sedentary behaviour, associations between sedentary behaviour and anxiety symptoms may be independent of total physical activity volume. This independence would suggest that the risks of sedentary behaviour are more than simply a product of low energy expenditure. For example, unengaging sedentary behaviours may induce prolonged bouts of minimal cognitive stimulation that could pose mental health risks, such as watching television (449,461).

Advances on traditional regression-based methods are also necessary to account for the reality that reducing sedentary behaviour requires increasing other forms of activity to displace it. Traditional methods only estimate the impact of increasing time in one activity. For example, I estimated in Chapter 4 that a one hour increase in daily sedentary behaviour was associated with around a 10% increase in depressive symptoms. However, this estimation does not account for whether the

increase in daily sedentary behaviour comes at the expense of light-intensity physical activity or moderate to vigorous activity, both of which may impact anxiety symptoms differently. Isotemporal substitution models are a novel method for estimating how substituting time in one activity (e.g., sedentary behaviour) for time in another (e.g., light-intensity physical activity) might affect an outcome (e.g., anxiety symptoms) (Mekary, Willett, Hu, & Ding, 2009; Mekary et al., 2013).

I prospectively investigated associations between sedentary behaviour, light-intensity physical activity, and moderate-to-vigorous physical activity measured using accelerometers during adolescence with anxiety symptoms at age 18 with isotemporal substitution models. I specifically assessed whether associations between sedentary behaviour and anxiety symptoms were independent of total physical activity volume.

My hypotheses were:

1. Higher sedentary behaviour at ages 12, 14, and 16 is associated with increased anxiety symptoms at age 18
2. Associations between sedentary behaviour and anxiety symptoms are independent of total physical activity volume
3. Substituting periods of daily sedentary behaviour for light-intensity physical activity or moderate-to-vigorous physical activity during adolescence is associated with reductions in anxiety symptoms at age 18

5.3. Methods

5.3.1. Study participants

This is a prospective study with repeated measures using data from the ALSPAC cohort, which I describe in Section 2.3.2.1. (Section 2.3.2.1. ALSPAC). I defined my sample as any participant with a complete Clinical Interview Schedule-Revised (CIS-R) anxiety symptoms score at age 18 (n = 4,257), following the flowchart in Figure 1 of the Supplementary Materials.

5.3.2. Measures

5.3.2.1. Outcome: Anxiety symptoms

The primary outcome in this analysis was anxiety symptoms, measured using a computerised version of the CIS-R anxiety score at age 18. The CIS-R is a common tool for assessing depression and anxiety symptoms in community-based samples, using criteria from the *International Statistical Classification of Diseases, 10th Revision* (ICD-10) (433). It performs similarly to diagnosis by a trained psychiatrist and shows good reliability (r = .90) (433). The anxiety score ranges from 0 to 16 and indicates the number and severity of recent anxiety symptoms, including feelings of anxiety, nervousness, tenseness, or physical symptoms, such as changes in heartrate. I used a discrete-continuous score for our primary outcome.

To measure baseline anxiety, I used data from the Development and Well-being Assessment (DAWBA) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000), completed by the mother around age 11 (10.8 years) and 14 (14.2 years). The DAWBA consist of questions about mental health

symptoms up to the last 6-months following diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (464) and ICD-10. A computer algorithm creates ordered categorical measures to indicate the probability of an anxiety disorder (Goodman, Heiervang, Collishaw, & Goodman, 2011).

5.3.2.2. Exposure(s): Sedentary behaviour and physical activity

Activity data were collected at ages 12, 14, and 16 using MTI Actigraph 7164 or 71256 accelerometers (Actigraph LLC, Fort Walton Beach, FL, USA) worn during waking hours on the right hip for seven days. I used the same protocols and quality controls as described in Chapter 4.2.3.1. to estimate total activity volume, time in sedentary behaviour, light-intensity physical activity and moderate-to-vigorous physical activity.

5.3.2.3. Confounding variables

I based my confounding variable selection on existing knowledge and a DAG to represent my understanding of the proposed causal associations between sedentary behaviour, physical activity, and anxiety symptoms (Supplementary Materials, Figure 9). According to this DAG, the necessary adjustments for estimating the total effect of sedentary behaviour on anxiety symptoms include: Sex, ethnicity, social class (maternal manual or non-manual occupation), IQ (measured at age 8), parental psychiatric history (prior diagnosis of depression or schizophrenia), parental education (secondary or degree/higher level education), total physical activity volume (mean daily CPM), baseline anxiety symptoms (DAWBA at age 11 and 14), and total accelerometer wear time. Models at age 16 used the DAWBA at age 14 as the closest baseline measure of anxiety. Total physical activity volume is measured in counts rather than minutes to reduce the risk of collinearity with sedentary behaviour.

My sensitivity analyses (detailed below) included the covariates: Alcohol use and smoking (age 16), baseline depressive symptoms (Short Moods and Feelings Questionnaire at ages 12, 14, and 16), body mass index (BMI) (ages 12, 13, and 16) and physical health status (presence of a severe physical illness before age 17).

5.3.3. Analysis

For normally distributed, continuous variables, I calculated means and standard deviations. For non-normally distributed variables, I used medians and interquartile ranges.

For the main analysis, I used negative binomial regression models as the distribution of anxiety scores had a high positive skew and were over-dispersed (Supplementary Materials Figure 10). My main analysis consists of two sets of models. The first set (models 1 to 9) use single-exposure models (described below) to assess associations between sedentary behaviour, light-intensity physical activity, moderate-to-vigorous physical activity, and anxiety symptoms (hypothesis 1) and the possible independence of sedentary behaviour from total physical activity volume (hypothesis 2). The second set (models 10 to 13) use isotemporal substitution models to examine substitution effects (hypothesis 3). I present the results of our models as percentage changes in anxiety scores.

5.3.3.1. Single-exposure models

Single-exposure models estimate the 'total' association between each activity category (sedentary behaviour, light, and moderate-to-vigorous physical activity) at ages 12, 14, and 16 and anxiety symptoms at age 18. I used three separate models for each time point of sedentary behaviour measurement. The single-exposure models assess total associations because they do not mutually adjust for other activity categories but do adjust for all other covariates. In addition to crude and adjusted models, I ran additional analyses for sedentary behaviour that also adjusted for total physical activity volume (mean daily CPM). These models assessed whether any association between sedentary behaviour and anxiety symptoms was independent of total physical activity volume (aim 2).

5.3.3.2. Iso-temporal substitution models

The single models assume time is infinite and only estimate the impact of increasing time in one activity on anxiety. These models do not account for the reality that increasing time in one activity must displace time in another activity as time is finite throughout the day.

isotemporal substitution models estimate the percentage change in anxiety symptoms from substituting a unit of sedentary behaviour time for an equivalent unit of light-intensity physical activity or moderate-to-vigorous physical activity time. isotemporal substitution models use the same set of linear parameters and operate as any generalised linear model. They include all three exposure variables and a total time variable, which is the summation of the three exposure variables. A simple illustration of these parameters using a linear set of parameters would look like this:

$$\text{Log(anxiety score)} = \beta_0 + \beta_1 * \text{sedentary behaviour} + \beta_2 * \text{light-intensity physical activity} + \beta_3 * \text{moderate-to-vigorous physical activity} + \beta_4 * \text{total measurement time} + \beta_5 * \text{covariates}$$

isotemporal substitution models assume that time in one activity displaces an equal amount of time in another, while holding total measurement time (β_4) and other covariates (β_5) constant. As all three exposure variables (β_1, β_2, and β_3) are from the same measure and in the same units of time (e.g., 60-minute blocks), I then drop sedentary behaviour (β_1) from the model. The resulting exposure coefficients (β_2 and β_3) now represent their association with anxiety, absent sedentary behaviour, while total measurement time is still held constant (β_4). I then interpret these coefficients as the consequence of substituting a unit of sedentary behaviour time for a unit of light-intensity physical activity or moderate-to-vigorous physical activity time per day on anxiety scores.

I entered activities into these isotemporal substitution models in units of 60-minutes. As there are no specific guidelines for reducing daily sedentary behaviour, I based this on national recommendations for adolescents to achieve at least 60 minutes of moderate-to-vigorous physical activity per day (66).

5.3.3.3. Sensitivity analyses and missing data

I conducted a series of sensitivity analyses to explore other possible explanations for my results and test the robustness of our main findings from the isotemporal substitution models. Some analyses include possible covariates that were measured after the exposure and could represent mediators or colliders, such as physical illness, smoking, and alcohol use. Sensitivity models included: 1) baseline depressive symptoms as a covariate (ages 12, 14, and 16), 2) smoking and alcohol use (age 16 only) as covariates, 3) serious physical illness before age 17, 4) excluding anyone with a possible anxiety disorder at baseline, 5) linear, instead of negative binomial, regression models, 6) sex as an interaction term, 7) baseline BMI as a covariate (ages 12, 13, and 16).

To examine the extent to which any attrition bias from the missing data affected my results, I repeated the main analyses in a full cohort with imputed data. The missing data were estimated by multiple imputation models by chained equations. I generated 30 datasets containing fully imputed data from all 4,257 participants in my sample using multiple imputations with chained equations (443). The chained equation method uses a separate condition distribution per imputed variable. Results from all 30 datasets were pooled into a single multiply imputed data set. The data set contained adjusted standard errors and account for the uncertainty of each prediction as multiple predictions are made for each value. The multiple imputation model contained the same variables as in Chapter 4. I also included additional variables for measures of anxiety from the CIS-R and DAWBA and physical illness. I used predictive mean matching for non-normally distributed variables.

I calculated the e-value to examine the risk of unmeasured confounding (44). The e-value estimates the minimum strength that an unmeasured confounding variable would have to have to nullify the observed association between exposure and outcome while considering all other measured covariates (235). The e-value helps to assess the plausibility of unmeasured confounding and contributes towards the evidence for causality (466).

5.3.4. Results

5.3.4.1. Sample

My sample included 4,257 participants with a complete CIS-R anxiety score at age 18. Over the 6-year follow-up period, the complete case analyses at ages 12, 14, and 16, included 2,292, 18,66, and 1,128 participants, respectively. Table 9 of the Supplementary Materials compares baseline characteristics between included and excluded participants from the full ALSPAC sample. Table 4 contains participant characteristics and physical activity levels.

Table 4. Participant characteristics and activity changes of included participants (n = 4,257)

Characteristic (n with complete data)		**n (%)**
Sex (4,257)	Male	1,867 (43.86)
	Female	2,390 (56.14)
Ethnicity (4,062)	Caucasian	3,889 (95.74)
	Other	173 (4.26)
Parental education (4,257)	Degree or higher	1,207 (28.35)
	Secondary	3,050 (71.65)
Maternal social class (3,626)	Manual	553 (15.25)
	Non-manual	3,073 (84.75)
Parental psychiatric diagnosis (4,257)	Depression or schizophrenia	422 (9.91)
	No diagnosis	3,835 (90.09)
BMI (3,671)	Overweight or obese	270 (7.35)
	Normal or underweight	3,401 (92.65)
Self-reported serious physical illness before 17 (4,130)	Yes	218 (5.27)
	No	3,877 (94.73)
Alcohol use in last 30 days at age 16 (2,922)	1 to 3 times	2,041 (69.85)
	4 to 6 times	848 (30.05%)
	7 or 8 times	33 (1.13)
Smoking status at age 16 (3,087)	Never	1,694 (54.88)
	Have tried/former smoker	823 (26.66)
	Current smoker	570 (18.46)
Baseline anxiety symptoms (3,584)	Possible anxiety (algorithm derived)	65 (1.81)
	No anxiety	3,519 (98.19)
Baseline depression (3,683)	Possible depression (MFQ > = 10)	344 (9.34)
	No depression (MFQ < 10)	3,339 (90.66)
Physical activity and sedentary behaviour		

	Overall physical activity in daily mean CPM (SD)	Sedentary behaviour in hours (SD)	Light activity in hours (SD)	moderate-to-vigorous physical activity in minutes (SD)
12 (3832)	602.33 (177.62)	7.18 (1.10)	5.43 (0.97)	23.279 (15.37)
14 (2749)	539.12 (181.43)	8.11 (1.14)	4.64 (0.95)	24.273 (16.91)
16 (1504)	474.83 (158.68)	8.72 (1.09)	4.08 (0.92)	23.523 (17.58)

5.3.4.2. Single-exposure models

Table 5 shows results from the single-exposure models. The adjusted models without total activity volume (models 2, 5, and 8) suggest that an additional 60-minutes of sedentary behaviour at ages 12, 14, and 16, was associated with an 18.22% (95% CI 10.10%, 26.87%), 10.19% (95% CI 1.37%, 19.79%), and 15.75% (95% CI 3.71%, 29.12%) higher anxiety score at age 18. An additional 60-minutes of light-intensity physical activity at 12, 14, and 16, was associated with a -16.82% (95% CI -22.99%, -10.16%), -11.57% (95% CI -19.30%, -2.98%), and -14.81% (95% CI -24.29%, -4.14%) decrease in anxiety score. The model estimates suggest no association between moderate-to-vigorous physical activity and anxiety scores in this sample.

When adjusting for total activity (models 3, 6, and 9), sedentary behaviour at ages 12, 14, and 16 was associated with a 21.12% (95% CI 8.36%, 35.65%), 16.19% (95% CI 2.47%, 31.74%), and a 17.43% (95% CI 0.67%, 36.99%) higher anxiety scores at age 18.

Table 5. Associations between sedentary behaviour, light-intensity physical activity, and moderate-to-vigorous physical activity and anxiety symptoms in single negative binomial model

Age	Model #	Model (n)	CIS-R anxiety symptoms score								
			Per 60 minutes of daily sedentary behaviour			Per 60 minutes of daily light-intensity physical activity			Per 60 minutes of daily moderate-to-vigorous physical activity		
			% change	*P*	95% CI	%Δ	*P*	95% CI	%Δ	*P*	95% CI
12	1	Unadjusted (2,292)	20	<0.001	13.09, 27.88	-18.2	<0.001	-23.5, -12.46	-46.6	<0.001	-59.40, -29.79
	2	Adjusted without total activity (2,292)	18.22	<0.001	10.10, 26.87	-16.82	<0.001	-22.99, -10.16	-22.11	0.109	-42.5, 5.67
	3	Adjusted with total activity (2,292)	21.12	0.001	8.36, 35.56	-	-	-	-	-	-
14	4	Unadjusted (1866)	13.20	<0.001	6.02, 20.87	-14.31	<0.001	-20.94, -7.12	16.82	0.187	-36.64, 9.21
	5	Adjusted without total activity (1866)	10.19	0.023	1.37, 19.79	-11.57	0.010	-19.30, -2.98	2.26	0.881	-23.7, 36.88
	6	Adjusted with total activity	16.19	0.019	2.47, 31.74	-	-	-	-	-	-
16	7	Unadjusted (1,128)	15.99	0.001	6.34, 26.51	-16.06	0.001	-24.20, -6.92	-16.63	0.224	-37.71, 11.66
	8	Adjusted without total activity (1,128)	15.75	0.009	3.71, 29.12	-14.81	0.008	-24.29, -4.14	-7.62	0.646	-33.83, 29.05

9	Adjusted with total activity	17.43	0.041	0.67, 36.99	-	-	-	-	-	-

% change: Percentage change in anxiety score based on incident rate ratios; 95% CI: 95% confidence intervals; moderate-to-vigorous physical activity: moderate-to-vigorous physical activity

Adjusted without total activity (models 2, 5, and 8): Conditioned on sex, ethnicity, maternal social class, baseline anxiety, parental psychiatric history, parental education, IQ, and total wear time

Adjusted with total activity (models 3, 6, and 9): Conditioned on same as models 2, 5, and 8, with total activity volume (average daily CPM)

5.3.4.3. Iso-temporal substitution models

Table 6 displays results from the iso-temporal substitution models. These models suggest that substituting 60 minutes of sedentary behaviour for 60 minutes of light-intensity physical activity at ages 12, 14, and 16, was associated with a 16.4% (95% CI 9.4%, 22.7%), 12.1% (95% CI 3.4%, 20.1%), and 14.7% (95% CI 4%, 24.2%) reduction in anxiety scores at 18. I found no associations between moderate-to-vigorous physical activity and anxiety.

Table 6. Iso-temporal substitution models for replacing sedentary behaviour with light-intensity physical activity and moderate-to-vigorous physical activity

Age	Model #	Substitute 60 minutes of ↓	with 60 minutes of →	Activity category			
		Activity category		Light activity		moderate-to-vigorous physical activity	
				% change	95% CI	% change	95% CI
12	10	**Sedentary**		-16.41	-22.79, -9.49	-7.62	-32.42, 26.38
14	11			-12.17	-20.11, -3.46	-10.99	-17.71, 49.53
16	12			-14.74	-24.24, -4.05	-5.91	-32.52, 31.47

% change: Percentage change in anxiety score based on incident rate ratios 95% CI: 95% confidence intervals; moderate-to-vigorous physical activity: moderate-to-vigorous physical activity

Adjustment for all models: light-intensity physical activity, moderate-to-vigorous physical activity, total measurement time (sedentary behaviour + light-intensity physical activity + moderate-to-vigorous physical activity), sex, ethnicity, maternal social class, anxiety disorder (ages 10 and 14), parental psychiatric history, parental education, and IQ

5.3.4.4. Sensitivity analyses

I reran the main analyses in a cohort of participants with complete exposure data (n = 4,257) and imputed missing data (Supplementary Materials Methods 3) and the results did not substantially differ from our main findings (Supplementary Materials Table 9). There were also no substantial differences in the results of all other sensitivity analyses and my main findings, and I found no evidence of an interaction with sex. Sensitivity analyses results are presented in Supplementary Materials Table 9 to 14.

The e-values (rate ratios) for the point estimate and lower confidence bound were 1.68 and 1.44 at age 12, 1.53 and 1.23 at age 14, and 1.62 and 1.25 at age 16, respectively. To nullify the observed

association, an unmeasured confounding variable must be associated with both the exposure and outcome by a risk ratio of at least the e-value of each time point, having conditioned on the other confounding variables. For example, an unmeasured confounding variable would need to be associated with sedentary behaviour and anxiety score by a risk ratio of at least 1.68 at age 12, independent of the other confounding variables in the model. Most risk ratios for included covariates range between 1 and 1.3 at age 12, except for sex (IRR = 1.59, 95% CI 1.37, 1.84).

5.3.5. Discussion

5.3.5.1. Main findings

This population-based study prospectively examines associations between device-measured sedentary behaviour and anxiety symptoms in adolescents. I found that higher sedentary behaviour at ages 12, 14, and 16 were consistently associated with higher anxiety symptoms at age 18. Higher light-intensity physical activity during the same period was associated with a decrease in anxiety symptoms. After adjusting for physical activity, an hour of daily sedentary behaviour during adolescence was independently associated with 16% to 21% higher anxiety symptoms at age 18. The isotemporal substitution models demonstrated that theoretically substituting an hour of daily sedentary behaviour for light-intensity physical activity during adolescence was associated with a 12% to 16% reduction in anxiety symptoms at age 18. I found no associations between moderate-to-vigorous physical activity and anxiety. There were no substantial changes to these results following a series of sensitivity analyses or in the cohort following multiple imputations for missing data.

These results support previous cross-sectional and prospective findings that self-reported high sedentary behaviour is associated with a greater risk of anxiety symptoms in adolescents (120,143–145). Sedentary behaviour is an established risk factor for physical health (467), and my findings suggest it may also be a risk factor for anxiety symptoms independently of physical activity. Activity will be essential for reducing sedentary behaviour, but these findings suggest that other factors than energy expenditure are relevant to its association with anxiety symptoms. I previously found that sedentary behaviour is a possible risk factor for depressive symptoms in adolescents in Chapter 4, where I did not assess sedentary behaviour as independent from physical activity. Here I showed that the associations between sedentary behaviour and anxiety symptoms are independent of baseline depressive symptoms.

For example, substituting mentally-passive (e.g., watching television) for mentally-active (e.g., reading) sedentary behaviours is associated with a reduced risk of depression in adults (448). Engaging activities could help to distract young people from pathological thought patterns leading to states of anxiety. Stimulating activities could also approximate a form of cognitive training that elicits some resilience to attentional biases associated with developing anxiety symptoms in young people, such as threat detection (468,469).

The timing and bouts of activity may also be relevant. For example, long bouts of sitting could increase the duration within which pathological thought patterns might occur and develop into anxiety. Recent studies have found that breaking up prolonged bouts of sitting using light-intensity physical activity in adults benefits the brain and mental health, such as reducing fatigue and promoting brain plasticity and cognitive performance (470–472). These benefits may accumulate to reduce the risk of anxiety symptoms developing. Young people who frequently break up bouts of sitting with activity could reduce this risk while still having a similar overall activity level. It may also interrupt other behaviours that occur with long bouts of sitting, increasing the risk of anxiety symptoms. For example, watching television is associated with a less healthy diet, including higher consumption of energy-dense snacks and sugar-sweetened drinks (473), which may increase the risk of anxiety symptoms in adolescents (474).

While the results are not directly comparable due to the different analytical procedures, the effect sizes also appear larger in this chapter compared to Chapter 4 (Chapter 4: Device-measured physical activity and sedentary behaviour and depressive symptoms throughout adolescence). For example, an hour of light activity was associated with 8 to 11% lower depression scores in Chapter 4 but replacing an hour of sedentary behaviour with light activity was associated with 12 to 16% lower anxiety scores here. The difference could be due to the different analytical procedures or baseline adjustments, or different pathways underlying the association with anxiety versus depression.

In Chapter 3 (Chapter 3: Physical activity and depression: Understanding the possible mechanisms of action underlying the relationship of physical activity and depressive symptoms), I identified several mechanisms that could explain the relationship between physical activity and depressive symptoms. While the biological mechanisms underlying associations between sedentary behaviour and anxiety symptoms will overlap with physical activity, there may also be some unique pathways. For example, avoiding long bouts of sedentary behaviour could maintain constant mitochondrial activity throughout the day, reducing the risk of mitochondrial dysfunction in the brain leading to anxiety symptoms (475). It is worth noting that research to identify possible biological mechanisms that differentiate the influence of sedentary behaviour from physical activity on health is an emerging area (476). Much of the research underlying the mechanisms in Chapter 3 are also based on moderate-to-vigorous activity but could also apply to light activity.

5.3.5.2. Strengths and limitations

There are several strengths to this study, including the use of accelerometers, a prospective, repeated measures study design with a 6-year follow-up, and a large sample size. Strengths in the analysis methods include using isotemporal substitution models to account for the reciprocal relationship between changes in time-use variables. These methods produce a more realistic estimation of how interventions to reduce sedentary behaviour using different intensities of activity might affect anxiety symptoms. I also included adjustments for baseline anxiety symptoms to lower the risk of reverse causation and adequate adjustment of total physical activity volume. I used several sensitivity analyses, including calculating e-values to assess the strength of unmeasured confounding necessary to nullify my results, baseline depressive symptoms to examine anxiety symptoms independently, and multiple imputation models to account for potential selection bias due to attrition. The use of DAGs determined *a priori* also improves my ability to assess causal associations in the data.

A limitation of my study is the lack of 24-hour activity, which means that the isotemporal substitution models only account for the waking portion of the day. Participants did not wear accelerometers while sleeping, so I was unable to examine how substituting sedentary behaviour for sleep might affect the risk of anxiety symptoms. There could also be gaps in the data if participants did not wear their devices for all waking behaviours. There is a further risk that our results are confounded by other unmeasured factors, such as social support, self-esteem, or physical health at baseline. Baseline adjustment was for the possible incidence of an anxiety disorder, which overlooks participants with sub-threshold anxiety symptoms. Baseline assessments of anxiety were also completed by the mother, rather than the participant. There was no assessment of anxiety symptoms at age 16, so in the age 16 models, I used anxiety symptom scores from age 14, which is a further limitation.

To assess anxiety symptoms independently of depressive symptoms, I adjusted for baseline depressive symptoms in our sensitivity analyses. However, there may still have been an overlap in the outcome of depressive and anxiety symptoms. The magnitude of the e-value relative to included confounding variables suggests that an unmeasured confounding variable is unlikely to nullify the

observed association between sedentary behaviour and anxiety symptoms. However, multiple unmeasured confounding variables may accumulate to impact my findings.

There was also substantial attrition within my sample during the study period that could have caused selection bias. Results did not differ in my multiple imputation models, which does not indicate a high risk of attrition bias in our sample. However, I only imputed missing data from the subsample with completed CIS-R anxiety scores at age 18 (n = 4,257), not the entire ALSPAC sample (n = 14,901). Differences between my sample and the larger ALSPAC sample could have influenced our results. Participants also had low moderate-to-vigorous physical activity levels, with the average being around 40 minutes lower than the nationally recommended guidelines of 60 minutes of daily moderate-to-vigorous physical activity for adolescents in the UK. This may have contributed to the lack of an association between replacing sedentary behaviour with moderate-to-vigorous physical activity and changes in anxiety symptoms, as in Chapter 4 with depressive symptoms.

Accelerometers provide reliable estimates of activity, but they cannot record posture and differentiate between sitting and standing. Standing behaviours may be misclassified as sedentary behaviour in our study. Thigh-worn devices are preferable for recording sedentary behaviour, such as ActivPAL (ActivPAL Technologies Ltd., Glasgow, UK). However, misclassifying light-intensity physical activity (standing) would increase sedentary behaviour, and its true association with anxiety symptoms could be even larger.

A broader issue with most devices is their inability to record the type and context of activities. This limitation prevented me from investigating how different types of sedentary behaviour are associated with anxiety, such as mentally-active vs. mentally-passive behaviours (449), which I will return to in Chapter 9. However, accelerometers still provide novel insights that were absent in previous studies that over-rely on self-report measures for quantifying aspects of activity, such as time in sedentary behaviour (477).

5.3.5.3. Future directions and implications

Most research focuses only on depression, despite anxiety being a major cause of global disability (World Health Organisation, 2017). Sedentary behaviour may be a risk factor for both depressive and anxiety symptoms. Future research focusing on both paradigms together as common mental disorders may highlight common pathways. However, my results suggest that there may be independent pathways linking sedentary behaviour to anxiety symptoms, and the paucity of direct research into anxiety symptoms warrants further investigation.

Adolescence is an important window for preventing CMD symptoms (9,10) and a period in which sedentary behaviour increases and total physical activity volumes decline (132–134). There is a need to evaluate public health strategies and interventions to reduce anxiety symptoms in adolescents using light-intensity physical activity to replace sedentary behaviour. While just 29% of adolescents achieve national moderate-to-vigorous physical activity guidelines in developed nations (136), efforts to increase light-intensity physical activity could be more successful. Compared with moderate-to-vigorous physical activity, light-intensity physical activity is less effortful and more pleasurable for most people, likely to stimulate higher motivation (478). Light activity is also sustainable over extended periods and does not require designated time during the day. Simple changes to incorporate more light-intensity physical activity at school could include standing desks or active breaks during classes. Approaches at home could include standing up during commercial breaks or doing house chores while watching television, more frequent trips to pick up groceries, or walking during phone calls.

Both findings in this and the previous chapter highlight the need for strong public health messaging on the importance of light-intensity physical activity, which should be made in tandem with the moderate-to-vigorous physical activity guidelines that have essential physical health and developmental implications. Simply increasing movement will likely benefit more young people. It should be possible to increase light-intensity physical activity beyond the current target of one hour for moderate-to-vigorous physical activity, which may substantially impact anxiety. For example, my models suggest that substituting two hours of sedentary behaviour for light-intensity physical activity per day during adolescence could lead to a 24% to 32% reduction in anxiety symptoms by age 18.

I also found that associations between sedentary behaviour and anxiety symptoms were independent of total physical activity. Some sedentary behaviours may be particularly detrimental and represent specific targets for intervention, such as watching television. As highlighted in Section 5.5.3. (Section 5.5.3. Analysis) and 9.4.1. (Section 9.4.1. Moving beyond energy expenditure to examine behaviour types and domains), self-report activity measures will be important in deciphering whether specific forms of sedentary behaviour are more or less detrimental to mental health. For example, time in sedentary behaviour during adolescence is largely due to the use of screen-based devices (137). Different uses of screen-based devices provide distinct user experiences that may affect mental health differently, such as watching television versus video gaming (444). My analyses in Chapters 4 and 5 provide clear and robust data on the relationship between sedentary behaviour, physical activity, and CMD symptoms in adolescents. I focused on providing data on the quantitative aspects of sedentary behaviour and physical activity, such as the time at different intensity thresholds. Future research can build on these foundations by investigating nuances that could modify the impact of physical activity-based interventions for preventing CMD symptoms in adolescents, such as the targeting specific domains (e.g., non-leisure time) or types (e.g., social media use) of sedentary behaviour that may be associated with higher mental health risks. I return to this point in Section 9.4.1. (Section 9.4.1. Moving beyond energy expenditure to examine behaviour types and domains)

Future research should also focus on identifying mediators of the association between light activity and CMD symptoms. Chapter 4 and 5 show a proactive association between light activity and CMD symptoms, but there is limited data on the mechanisms that might underlie this association. Chapter 3 highlighted several mechanisms that could explain the association between physical activity and depressive symptoms, but the evidence primarily focuses on exercise and in people with existing symptoms. Advancing our understanding of how light activity could influence CMD symptoms can strengthen arguments for causation and inform the development of light activity interventions. It can also provide information on the biological and psychosocial factors that underpin CMD symptoms.

5.3.5.4. Conclusions

My findings suggest that sedentary behaviour could be a risk factor for anxiety symptoms in adolescents that is modifiable through light-intensity physical activity. These findings produce new insights to relate specifically to the development of anxiety disorders. Instead of focusing on moderate-to-vigorous activity, replacing daily sedentary behaviour with light-intensity physical activity during adolescence could be a suitable method of reducing future anxiety symptoms. These findings coincide with Chapter 4, where I showed an association between light but not moderate-to-vigorous activity and depressive symptoms. Collectively, these chapters suggest that light activity can have cross-diagnostic benefits for reducing CMD risks. The mechanisms identified in Chapter 3

mostly relate to moderate-to-vigorous activity (e.g., exercise), but could extend to partially explain the associations in Chapters 4 and 5.

6. Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms

6.1. Summary

In this Chapter I conducted the final study to assess Objective 2: examine the prospective association of device-measured physical activity and sedentary behaviour with CMD symptoms across the lifespan. The previous two chapters focused on assessing these associations in adolescents, both providing consistent evidence for high sedentary behaviour as a CMD risk factor. There was also evidence that light activity was inversely associated with CMD symptoms but no evidence of an association with moderate-to-vigorous activity. In this chapter, I examine these associations in adults using data from the UK Biobank. This study addresses limitations of the previous literature that include measurement bias in self-report activity questionnaires (Section 1.6.2. Measurement bias in assessing physical activity and sedentary behaviour in epidemiological studies). I also assess these associations within a 24-hour context (see Section 1.6.3. Understanding physical activity in a 24-hour context) using similar principles but a more sophisticated statistical method than in Chapter 5 (Chapter 5: Device-measured physical activity and anxiety symptoms during adolescents). A key difference between these methods is that the iso-temporal substitution method in Chapter 4 assume time in each variable are independent and so are unconstrained to a total of 24-hours or to each other. Compositional data analysis methods assume data (e.g., time in sedentary behaviour, physical activity, and sleep) make up a finite whole (e.g., 24-hours) and are co-dependent, such that increasing sedentary behaviour time decreases physical activity and/or sleep within the constraints of 24-hours. I discuss this method in detail in Section 6.3. (Section 6.3. Methods).

I examine associations of accelerometer-measured sedentary behaviour, physical activity, and self-reported sleep with CMD symptoms in 60,235 UK Biobank participants using negative binomial regression models within a compositional data analysis framework. Sedentary behaviour was positively associated with CMD symptoms in adults, as in the previous two chapters. Replacing 60 minutes of sedentary behaviour with light-intensity physical activity, moderate-to-vigorous activity, and sleep was associated with lower depression symptom scores by 1.3% (95%CI, 0.4%-2.1%), 12.5% (95%CI, 11.4%-13.5%), and 7.6% (95%CI, 6.9%-8.4%), and lower odds of depression by 0.95 (95%CI, 0.94-0.96), 0.75 (95%CI, 0.74-0.76), and 0.90 (95%CI, 0.90-0.91) at follow-up. Replacing 60 minutes of sedentary behaviour with moderate-to-vigorous activity and sleep was associated with lower anxiety symptom scores by 6.6% (95%CI, 5.5%-7.6%) and 4.5% (95%CI, 3.7%-5.2%), and lower odds of meeting the threshold for an anxiety disorder by 0.90 (95%CI, 0.89-0.90) and 0.97 (95%CI, 0.96-0.97) at follow-up. However, replacing 60 minutes of sedentary behaviour with light-intensity physical activity was associated with higher anxiety symptom scores by 4.5% (95%CI, 3.7%-5.3%) and higher odds of an anxiety disorder by 1.07 (95%CI, 1.06-1.08).

These findings were broadly consistent with my findings in adolescents from the previous two chapters, suggesting that high sedentary behaviour is a CMD risk factor in adults. However, there were some differences. For example, there was an association with moderate-to-vigorous physical activity in this chapter that was not present in adolescents, which could be due to differences in statistical power as the Biobank sample had higher moderate-to-vigorous activity levels than ASLPAC. Light activity was associated with lower depressive symptoms, as in Chapter 4 (Chapter 4: Device-measured physical activity and sedentary behaviour and depressive symptoms throughout adolescence). However, light activity was also associated with higher anxiety symptoms in this chapter, which diverges from my findings in Chapter 5 (Chapter 5: Device-measured physical activity and anxiety symptoms during adolescents) as discussed in Section 6.5. (Section 6.5. Discussion).

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6.2. Introduction

Physical activity and sedentary behaviour appear to be associated with the risk of depression and anxiety disorders in adults and are potentially modifiable through targeted interventions (119,142,143). Sedentary behaviour levels have risen in recent years (479–481), typically accounting for 60% of waking time in adults (55). Sedentary behaviour is gaining recognition as a risk factor for several long-term conditions independent of physical activity (467,482,483). For example, meeting nationally recommended moderate-to-vigorous intensity physical activity guidelines per week does not necessarily ameliorate the health risks of high sedentary behaviour (139,140).

There is some evidence that high sedentary behaviour is an independent risk factor for depression and anxiety disorders in adults, but some findings have been inconsistent (142,143,145–147). Reducing sedentary behaviour is possible through increasing physical activity, which itself is associated with a lower incidence of depression and anxiety disorders (119,120,484) and can reduce depression and anxiety symptoms in adults with a disorder (75,90,457,458). However, most studies focus on moderate-to-vigorous forms of activity that typically account for around 4% of waking time in adults (55), such as running or cycling. If sedentary behaviour is an independent risk factor for depression and anxiety symptoms, more substantial changes to daily movement patterns may be necessary to mitigate these risks, such as increasing light-intensity activity as suggested in Chapters 4 and 5.

Inconsistent findings for sedentary behaviour as a risk factor for depression and anxiety symptoms could be due to methodological limitations in previous work, including the cross-sectional nature of many studies, use of self-report measures of activity that induce measurement error (192,194), and focus only on depression outcomes, despite the substantial global burden of anxiety disorders (1) and their co-morbidity with depression (6). I showed the importance of also assessing associations between sedentary behaviour, physical activity, and anxiety symptoms in Chapter 5 (Chapter 5: Device-measured physical activity and anxiety symptoms during adolescents), instead of just focusing on depressive symptoms. Previous studies have also been unable to appropriately account for the co-dependence of sedentary behaviour and physical activity (485). As time is finite in a day, time spent in sedentary behaviour will necessarily displace time in at least one other behaviour, such as physical activity or sleep. These other behaviours may also have their own positive or negative effects on mental health that I must consider when estimating the effect of reducing sedentary behaviour. Traditional analytical methods assume these are independent, such that increasing sedentary behaviour time will not influence physical activity or sleep time (485).

Advances in sedentary behaviour and physical activity research will require the use of novel methodologies for examining movement behaviours within a 24-hour cycle, including sleep (152). Compositional data analysis is a set of statistical principles and techniques for handling data representing proportions of a finite whole, such as periods of different activities within a day, recently applied to physical activity data (208,485). The method allows the assessment of associations between sedentary behaviour time and depression and anxiety disorders while accounting for all other periods of the day (e.g., physical activity and sleep), and also to estimate the potential impact of replacing sedentary behaviour with other activities. In Chapter 5, I used isotemporal substitution modelling, which partially addresses this co-dependence of time-use variables on a conceptual level. However, the exposure is still independent, absolute variables using these models, such that daily time in physical activity is not tethered to sedentary behaviour or sleep as in reality and total daily time can exceed 24 hours. Compositional methods use relative exposure variables to represent time in the day more closely.

At the time of this study, only three studies had used composition methods with mental health outcomes, each using cross-sectional designs in small samples (486–488). These studies suggest that replacing sedentary behaviour with activity of different intensities could lower mental health risks. Associations between time in sedentary behaviour and mental health may depend on how time in the rest of the day is structured (487). Not accounting for this could have contributed to the inconsistent findings of studies without compositional methods (142,143,145–147). For example, a recent systematic review of 12 prospective studies found that sedentary behaviour was associated with a higher risk of depression, but this was attenuated when adjusting for physical activity (142). Estimating the potential impact of replacing time in sedentary behaviour for activity of different intensities or sleep on the risk of depression and anxiety disorders would also directly impact public health policy. For example, it would determine the types of activities to promote to replace sedentary behaviour.

There were no prospective studies that used compositional methods to assess mental health outcomes or that examined associations between device-measured sedentary behaviour and depression and anxiety disorders. Compositional methods are most suited to analysing data from devices that continuously capture the full spectrum of activity intensities over 24-hours. The self-report measures of activity in prior prospective studies are less reliable than devices for estimating sedentary time (57,489) and tend to poorly estimate light-intensity activity, which accounts for most of daily movement (490). To address previous limitations in the field, I conducted a prospective cohort study to 1) determine how accelerometer-derived sedentary behaviour is associated with depression and anxiety symptoms while accounting for physical activity and sleep in a 24-hour period; 2) estimate the effect of replacing daily sedentary time with other movement behaviours (sleep, light, and moderate-to-vigorous activity) on the depression and anxiety symptoms.

6.3. Methods

6.3.1. Study participants

I used data from the UK Biobank (described in Chapter 2.4.2.), a prospective cohort study of 502,682 participants (5.5% response rate) aged 40 to 69 years recruited from the general population of England, Scotland, and Wales, between April 2006 and December 2010 (239). At baseline, participants completed various questionnaires, physical measures, imaging, genetic, and biological assessments in 22 research centres across the UK (241). Participants who provided a valid e-mail address at baseline, 236, 507 (47.1%) were also invited to wear an accelerometer for seven days between February 2013 and December 2015. A total of 103,706 participants (20.6%) agreed to wear the accelerometer, and 99,608 provided sufficient quality data for analysis (491). My study includes a complete case analysis of participants with full accelerometer (exposure) and covariate data measured once at baseline in 2006-2013 and Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7) (outcomes) measured once at follow-up in 2017 (n = 60,235). A flowchart of participants in this study is available in the Supplementary Materials (Figure 11).

6.3.2. Outcome(s): Depression and anxiety symptoms

Depression and anxiety symptoms were measured at follow-up using full PHQ-9 and GAD-7 scales. The PHQ-9 is a well-validated, 9-item screening tool for depressive symptoms (492), with scores ranging from 0 to 27. The GAD-7 is a 7-item scale that is a validated screening tool for symptoms of generalized anxiety disorders (493). For both scales, I used continuous symptom scores as the

primary outcome. I also estimated possible cases of depression and anxiety disorders at follow-up using established cut-off scores (scores ≥10) (492,493).

6.3.3. Exposure(s): Daily movement behaviours

From participants who provided a valid e-mail address at baseline, 236, 507 (47.1%) were invited to wear an accelerometer for seven days between February 2013 and December 2015. Researchers chose participant email addresses at random, except for those in the North West region to avoid overburdening participants who had already been recruited into trials for other new projects. A total of 103,706 participants (20.6%) agreed to wear the accelerometer, and 99,608 provided sufficient quality data for analysis (491). Participants wore an Axivity AX3 triaxial accelerometer on the wrist. The device performs similarly in estimating acceleration on multi-axis shake tests to the GENEActiv device used in other large, population-based cohort studies, including Whitehall II and Pelotas cohorts (494,495). The triaxial devices are validated with high precision in pre-living conditions for estimating activity and total energy expenditure, showing strong agreement and low population-level bias (~6%) compared with gold standard measures (doubly labelled water) in adults (247). After mailing the devices to participants, researchers initiated recording two days later at 10 am to continuously record activity at a sampling rate of 100Hz (1Hz is one sample per second) with a dynamic range of ±8*g* over seven consecutive days (491). Researchers asked participants to continue with normal daily activities during the recording period and always to wear the device, including while sleeping or bathing. Participants then returned the devices to a coordinating centre in pre-paid postage envelopes after the recording period.

Doherty *et al.* (491) processed the raw accelerometer data using protocols described in detail elsewhere (491). They calibrated raw accelerometer signals to local gravity (1*g*) to ensure consistent outputs from different devices under similar conditions and removed sensor noise. To derive movement intensity, they calculated Euclidean Norm Minus One (ENMO), by subtracting one gravitational unit (1g) from the vector magnitude of acceleration across three axes, the Euclidean norm. They defined non-wear time as periods where the standard deviation of all three axes was <13 milli-*g* for periods of ≥60 minutes and imputed non-wear time using data from similar time of day vector magnitudes and intensity distributions. Participants were excluded from the analysis if they had <72 hours of recording (n = 6,978) or poor-quality data (n = 120) to improve the reliability of estimates.

I followed protocols of previous studies (246–248) to define sedentary behaviour, light, and moderate-to-vigorous activity over 5-second epochs as ENMO values of ≤30 milli-*g* (minus self-reported sleep duration), >30 milli-*g* and <125 milli-g and ≥125 milli-*g*, respectively. I derived the sleep duration variable from a touchscreen questionnaire that participants completed at baseline. The questionnaire asked: "About how many hours sleep do you get in every 24 hours? (please include naps)". The questionnaire automatically rejected responses of less than 1 or over 23 and asked participants to confirm responses of <3 or >12.

6.3.4. Confounding variables

I selected possible confounding variables based on my understanding of their possible causal relationships with the exposure and outcome and previous literature, represented by a DAG in the Supplementary Materials (Figure 12). The confounding variables for this analysis included: age, sex, socioeconomic position (household income of <£18,000, £18,000 to £30,999, £31,000 to £51,999, £52,000 to £100,000, and >£100,0000), smoking status (current, former, or never), baseline

depression and anxiety symptom scores, education (degree, A/AS-level, O-level/GCSE, CSE, NVQ/HND/HNC, other qualifications, none), chronic illness (self-reported yes or no), and diet (portions of fruit and vegetables per day).

Baseline depression and anxiety were measured with a short version of the PHQ-9 (492). Three questions covered core features of depression (low mood, anhedonia, and lethargy), and the fourth was adapted to measure tenseness, a common feature of anxiety disorders. Participants responded on a four-point Likert scale from 0 (not at all) to 3 (nearly every day). Scores ranged from 0 to 12, in which higher scores indicated more severe symptoms. Ultra-brief adaptations of the PHQ-9 have good agreement with full scales of depression and anxiety symptoms (496). My *a priori* DAGs suggested that adjustment for these variables would be necessary to estimate causal associations between movement behaviours on depression and anxiety symptoms.

6.3.5. Analysis

I reported all descriptive variables using arithmetic means and standard deviations for normal distributions and medians and interquartile ranges for non-normal distributions. I also used geometric means to describe the daily physical activity, sedentary, and sleep time, which is a measure of central tendency that accounts for the compositional nature of the variables (497).

The main analysis used compositional data analysis to examine associations between sedentary behaviour and depression and anxiety symptoms scores while accounting for physical activity and sleep (Aim 1). Within this analysis, I estimate how replacing sedentary time with sleep, light, or moderate-to-vigorous activity affects future depression and anxiety symptoms scores (Aim 2).

6.3.5.1. Compositional data analysis

Compositional methods allow the inclusion of linearly independent variables representing time in sedentary behaviour, physical activity, and sleep over 24 hours, without inducing collinearity as in other approaches, such as standard multivariable regression. Standard approaches analyse data in real (Euclidean) space where variables are unconstrained, such as continuous regression lines representing different time-use variables. In this case, time-use variables contain absolute information about an activity without accounting for others. Compositional approaches use log transformations to move data into a geometric (Cartesian) space, where all lines representing a time-use variable are constrained by each other. This space is a ‘simplex’, where time in sedentary behaviour, physical activity, and sleep are co-dependent. I calculate log-ratio coordinates for each participant to represent each time-use variable and contain relative information, such as daily sedentary behaviour relative to physical activity and sleep. The term coordinate refers to the locations in the simplex, such that it is a particular composition of sedentary behaviour, physical activity, and sleep within a sample space of all possible variations of the composition. The coordinates essentially map compositions from Cartesian space (a simplex) to Euclidean space, which means I can enter them as exposure variables into a standard regression model while maintaining their relative information. The relative information contained within each composition means that any changes in sedentary behaviour would account for physical activity and sleep.

Each exposure of interest in my analysis is a composition of average daily sleep, sedentary behaviour, light, and moderate-to-vigorous activity across the recording period, which I normalized to the proportion of 1440 minutes (208), the total time in a day. I used a pivot coordinate approach whereby I calculated a set of three isometric log-ratio coordinates per participant that represents

their total relative time in each movement behaviour per day. The first (pivot) coordinate represents daily sedentary relative to the geometric mean of all other daily movement behaviours, i.e., sleep, light, and moderate-to-vigorous activity:

$$\sqrt{\frac{3}{4}}\ln\frac{sedentary\ behaviour}{(sleep.light.moderate\ to\ vigorous\ activity)}$$

The other two log-ratio coordinates contain relative information representing the remaining time in a participant's total daily composition, i.e., sleep over light and moderate-to-vigorous and light over moderate-to-vigorous activity. I entered these sets of coordinates as my exposure variables into the regression models with either one of the two primary outcomes (depression or anxiety). This provides a base model that allowed us to assess the overall associations of sedentary behaviour with depression and anxiety symptoms scores while accounting for all other movement behaviours in the day (Aim 1). I used negative binomial regressions for these base models due to the right skew distribution and over-dispersion of the mental health outcomes (see Figures 3 and 4 of the Supplementary Materials).

To then estimate the effect of replacing sedentary behaviour with other behaviours on depression and anxiety symptom scores (Aim 2), I used a change-matrix approach described in detail elsewhere (208). The base model's coefficients represent the estimated effect on depression and anxiety symptom scores when sedentary behaviour (numerator) changes relative to the geometric mean of all other time-use variables (denominator). The change-matrix procedure uses these base model coefficients to simulate different scenarios, such that I can theoretically reduce time in sedentary behaviour and increase time in either sleep, light, or moderate-to-vigorous activity isometrically to estimate the possible effect on depression or anxiety. I use the term theoretical replacements as the estimates are based on simulations rather than actual changes in movement behaviours in the data. I examined how theoretically replacing 1 to 60 minutes of sedentary behaviour with the other behaviours was associated with depression and anxiety symptom scores, using coefficients from the base model. I estimated replacements up to 60 minutes to align with previous studies using compositional methods with mental health outcomes (487). It is possible to estimate replacements of up to 1440 minutes, but substantial reductions in daily sedentary behaviour are less plausible in the population.

To aid interpretation of the final models, I back-transformed all log-ratio coordinates into the original units so that model coefficients represent changes in minutes per day of each movement behaviour. I presented the outputs of all negative binomial regression models as percentage changes in PHQ-9 and GAD-7 scores. I also ran logistic models using the same exposure and confounding variables, with the dichotomized outcome variables indicating new cases of either depression or anxiety (a score of ≥10 on the PHQ-9 or GAD-7). Fully-adjusted models included all confounding variables that I describe above.

6.3.5.2. Sensitivity analysis

I ran sensitivity analyses to test the robustness of my findings and alternative explanations. I repeated the main analysis and excluded all participants with a self-reported history of depression or anxiety to further reduce the risk of reverse causation. To estimate the plausibility of bias from unmeasured and residual confounding, I also calculated e-values for our main findings (466). The e-value estimates the strength of an unmeasured confounding variable would require to nullify the observed associations between our exposure and outcomes while accounting for all measured covariates (235).

All analyses were conducted in Stata 15 and R (version 4.0.0) using the Compositions (498) and zCompositions (499) packages.

6.4. Results

6.4.1. Study participants

The sample included 60,235 participants with complete exposure, outcome, and covariate data in the main analysis. Around 3,774 (6.2%) participants met the PHQ-9 threshold for depression and 2,216 (3.7%) for the GAD-7 threshold for anxiety, and 4096 (6.8%) met the criteria for both at follow-up, 2 years after baseline. Table 7 contains baseline characteristics for our subsample of participants (n = 60,235) and the remaining UK Biobank sample (n = 442,587).

Table 7. Baseline characteristics for included and remaining UK Biobank sample

Characteristic	Included (n = 60,235)	Remaining sample (n = 442,278)
Age, mean (SD)	55.9 (7.7)	56.6 (8.1)
Sex		
Female	33739 (56%)	239649 (54%)
Male	26496 (44%)	202629 (46%)
Ethnicity		
White	58649 (98%)	414054 (94%)
Mixed	282 (0.5%)	2676 (0.6%)
South Asian	409 (0.7%)	9473 (2.2%)
Black	373 (0.6%)	7688 (1.7%)
Chinese	108 (0.2%)	1466 (0.3%)
Other	281 (0.5%)	4277 (1.0%)
Household income		
Less than 18,000	8102 (13%)	89100 (24%)
18,000 to 30,999	14200 (24%)	93977 (26%)
31,000 to 51,999	17402 (29%)	93371 (26%)
52,000 to 100,000	15745 (26%)	70522 (19%)
Greater than 100,000	4786 (7.9%)	18144 (5.0%)
Education		
College or University degree	28844 (48%)	132321 (31%)

A levels/AS levels or equivalent	8237 (14%)	47086 (11%)
O levels/GCSEs or equivalent	11533 (19%)	93666 (22%)
CSES or equivalent	2036 (3.4%)	24851 (5.8%)
NVQ or HND or HNC or equivalent	2962 (4.9%)	29767 (6.9%)
Other professional qualifications e.g., nursing, teaching	2950 (4.9%)	22854 (5.3%)
None	3673 (6.1%)	81600 (19%)
Smoking status		
Never	34847 (58%)	238678 (54%)
Previous	21436 (36%)	151624 (35%)
Current	3952 (6.6%)	49027 (11%)
BMI, mean (SD)	26.6 (4.5)	27.6 (4.8)
Long-term physical illness		
Do not know	962 (1.6%)	10425 (2.4%)
No	43003 (71%)	286253 (65%)
Yes	16270 (27%)	143630 (33%)
Diet	4.94 (2.48)	4.88 (2.80)
Baseline depression and anxiety symptoms, mean (SD)	1.34 (1.80)	1.64 (2.11)
Parental depression		
No	54430 (90%)	383357 (91%)
Yes	5805 (9.6%)	36752 (8.7%)
Daily sedentary behaviour, arithmetic mean minutes (SD)	647.8 (99.2)	-
Daily light-intensity physical activity, mean arithmetic minutes (SD)	292.4 (62.7)	-
Daily moderate-to-vigorous arithmetic	65.1 (37.1)	-

activity, mean minutes (SD)		
Daily sleep, arithmetic mean minutes (SD)	434.8 (58.4)	-
Sedentary behaviour, geometric mean	0.45	-
Light activity, geometric mean	0.20	-
Moderate-to-vigorous activity, geometric mean	0.05	-
Sleep, geometric mean	0.30	-

SD = standard deviation; BMI = body mass index

6.4.2. Main analysis

In fully-adjusted, longitudinal base models, time in sedentary behaviour was positively associated with depression ($\beta = 0.49$, 95%CI, 0.44-0.54, $p < 0.001$) and anxiety ($\beta = 0.37$, 95%CI, 0.31-0.44, $p < 0.001$) symptom scores while accounting for time in light, moderate-to-vigorous activity, and sleep over 24 hours (Table 8).

Table 8. Estimates for negative binomial regression base model with depression and anxiety outcomes

		Depression (PHQ-9)				Anxiety (GAD-7)			
Model	**Log-ratio coordinates***	**exp(γ)****	**Lower confidence interval**	**Upper confidence interval**	**P value**	**exp(γ)****	**Lower confidence interval**	**Upper confidence interval**	**P value**
Unadjusted	z_1	**0.578**	**0.530**	**0.625**	**<0.001**	**0.517**	**0.453**	**0.581**	**<0.001**
	z_2	**0.247**	**0.204**	**0.290**	**<0.001**	**-0.061**	**-0.118**	**-0.004**	**<0.001**
	z_3	**0.207**	**0.172**	**0.242**	**<0.001**	**0.254**	**0.207**	**0.302**	**<0.001**
Adjusted	z_1	**0.491**	**0.442**	**0.539**	**<0.001**	**0.373**	**0.305**	**0.440**	**<0.001**
	z_2	**0.165**	**0.121**	**0.208**	**<0.001**	**-0.139**	**-0.199**	**-0.079**	**<0.001**
	z_3	**0.135**	**0.099**	**0.172**	**<0.001**	**0.136**	**0.086**	**0.187**	**<0.001**

**Log ratio coordinates representing:*

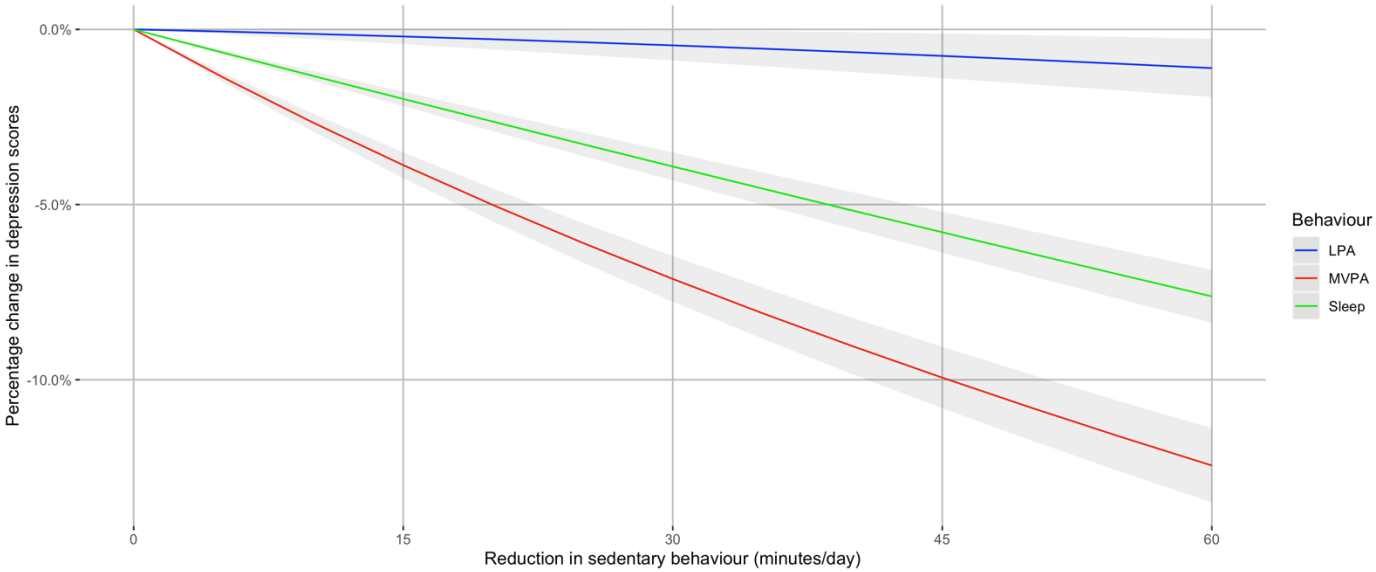
$$(z_1, z_2, z_3) = \left(\sqrt{\frac{3}{4}}\, ln \frac{sedentary\ behaviour}{(light \cdot moderate{-}to{-}vigorous \cdot sleep)^{1/3}}, \sqrt{\frac{2}{3}}\, ln \frac{light}{(moderate{-}to{-}vigorous \cdot sleep)^{1/2}}, \sqrt{\frac{1}{2}}\, ln \frac{moderate{-}to{-}vigorous}{sleep}\right)$$

In this model, only z1 is interpretable as it contains relative information for all 24h behaviours (i.e., sedentary behaviour, light and moderate-to-vigorous physical activity, and sleep). The p values indicate a statistically significant association between sedentary behaviour (z1) and depression and anxiety, after account for the time spent in the rest of the 24h movement behaviours. The direction of the coefficient indicates a positive association for both outcomes. In compositional methods, it is not possible to interpret the coefficient as the strength of association as in typical linear regression as the coefficients purposely represent ratios, not absolute values (208)*. The values for z2 and z3 are not interpretable in this table as they do not contain full data on the daily composition as in z1, such that z2 is light relative to moderate-vigorous and sleep and z3 is moderate-to-vigorous relative to sleep. However, all three variables are necessary to hold the full composition constant in the base models.*

***Exponential of regression coefficient (γ). This represents the unit change in depression or anxiety scores per unit increase in each log-ratio of the time allocated to the behaviour in the numerator against the geometric mean of the others in the denominator.*

Figure 2 shows the estimated effect on depressive symptom scores of potentially replacing sedentary behaviour with between 1 to 60 minutes of light, moderate-to-vigorous activity, or sleep. Replacing a total of 60 minutes of sedentary behaviour with 60 minutes of light-intensity physical activity, moderate-to-vigorous activity, and sleep in 24 hours was associated with lower depression symptom scores by 1.3% (95%CI, 0.4%-2.1%), 12.5% (95%CI, 11.4%-13.5%), and 7.6% (95%CI, 6.9%-8.4%), respectively.

Figure 2. Effect of replacing daily sedentary time for other movement behaviours and sleep on depressive symptoms

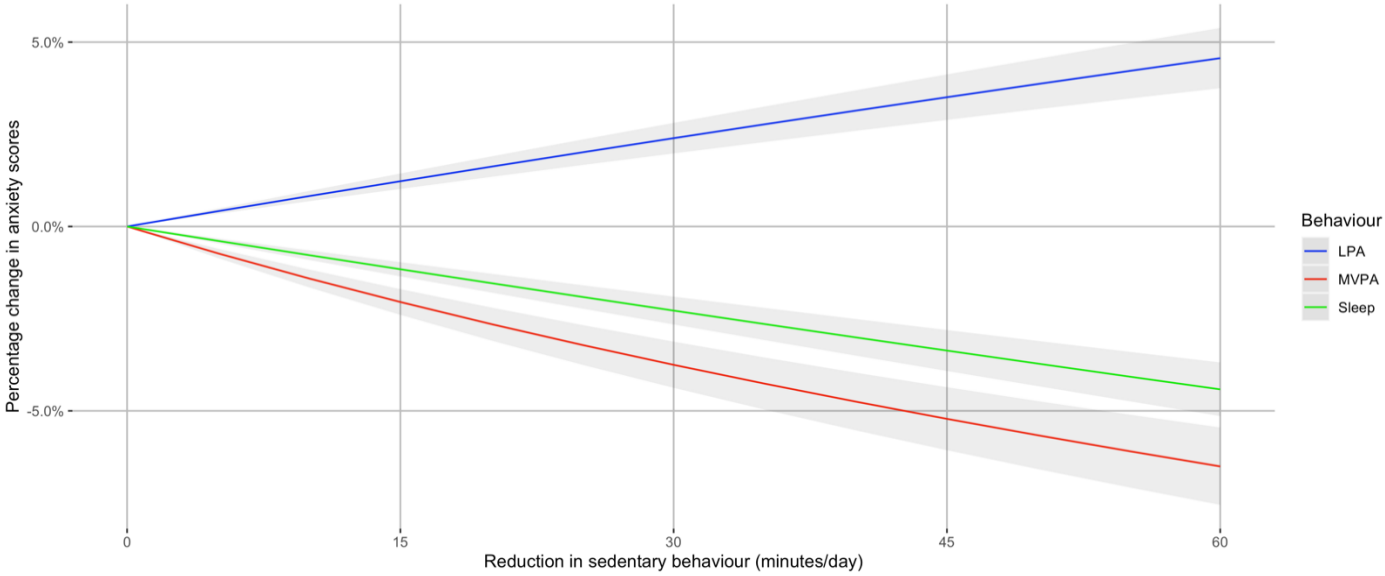


light-intensity physical activity = light physical activity; moderate-to-vigorous physical activity = moderate-to-vigorous physical activity. Models are adjusted for age, sex, socioeconomic position, smoking, baseline depression and anxiety symptoms, education, chronic illness, and diet.

In logistic models, potentially replacing 60 minutes of sedentary behaviour with 60 minutes of light, moderate-to-vigorous activity, and sleep in a 24-hour period was associated with lower odds of depression, OR = 0.95 (95%CI, 0.94-0.96), OR = 0.75 (95%CI, 0.74-0.76), and OR = 0.90 (95%CI, 0.90-0.91), respectively.

Figure 3 shows the estimated effect of replacing sedentary behaviour with activity or sleep on anxiety symptom scores. Replacing 60 minutes of sedentary behaviour with moderate-to-vigorous activity and sleep was associated with lower anxiety symptom scores by 6.6% (95%CI, 5.5%-7.6%), and 4.5% (95%CI, 3.7%-5.2%), while replacing with light-intensity physical activity was associated with higher anxiety symptom scores by 4.5% (95%CI, 3.7%-5.3%).

Figure 3. Effect of replacing daily sedentary time for other movement behaviours and sleep on anxiety symptoms



light-intensity physical activity = light physical activity; moderate-to-vigorous physical activity = moderate-to-vigorous physical activity. Models are adjusted for age, sex, socioeconomic position, smoking, baseline depression and anxiety symptoms, education, chronic illness, and diet.

In logistic models, replacing 60 minutes of sedentary behaviour with moderate-to-vigorous activity or sleep was associated with lower odds of anxiety by 0.90 (95%CI, 0.89-0.90) and 0.97 (95%CI, 0.96-0.97), while replacing with light-intensity physical activity was associated with higher odds by 1.07 (95%CI, 1.06-1.08).

6.4.3. Sensitivity analysis

I excluded participants with a history of depression or anxiety in my sample and reran the fully adjusted models in a sample of 39,973 (66% of my subsample) participants with complete data. In this subsample, substituting 60 minutes of sedentary behaviour for light, moderate-to-vigorous activity, and sleep was associated with 1.1% (95% CI 0.1% to 2.1%), 13.7% (95% CI 12.4% to 15.0%), and 9.6% (95% CI 8.7% to 10.6%) lower depression scores. Replacing 60 minutes of sedentary behaviour with moderate-to-vigorous activity and sleep was associated with 7.7% (95% CI 6.5% to 9.0%), and 5.9% (95% CI 5.0% to 6.7%) lower anxiety scores and 5.4% (95% CI 4.4% to 6.3%) higher scores with light-intensity physical activity.

The e-values estimate the required strength of an unmeasured confounding variable to nullify the observed associations between my exposure and outcomes. For depression scores, the e-values as incident rate ratios for replacing 60 minutes of sedentary behaviour with light, moderate-to-vigorous activity, and sleep were 1.13 (CI = 1.07), 1.55 (CI = 1.51), and 1.38 (CI = 1.36). For anxiety scores, the e-values for replacing 60 minutes of sedentary behaviour with light, moderate-to-vigorous activity, and sleep were 1.26 (CI = 1.23), 1.35 (CI = 1.31), and 1.27 (CI = 1.24).

6.5. Discussion

6.5.1. Main findings

This study was the first to use compositional methods to examine prospective associations between 24-hour movement behaviours and depression and anxiety symptoms in the population. This was also the first prospective study to estimate sedentary behaviour with accelerometers and determine how it is associated with depression and anxiety symptoms in adults. I found that daily sedentary behaviour time at baseline was positively associated with depression and anxiety symptom scores at follow-up, even after accounting for time spent in physical activity or sleep. Theoretically replacing periods of daily sedentary behaviour with light, moderate-to-vigorous activity, or sleep at baseline, was associated with lower depressive symptom scores and odds of depression at follow-up. Replacing sedentary behaviour with moderate-to-vigorous activity, or sleep was also associated with lower anxiety symptom scores and odds of anxiety disorders. I found that the most substantial estimated changes occurred when replacing sedentary behaviour with moderate-to-vigorous activity, where 60 minutes of replaced time resulted in 13% lower depression symptoms scores and 7% lower anxiety symptom scores. Smaller replacements with moderate-to-vigorous activity were also associated with lower depression and anxiety symptom scores. The main findings were consistent in models excluding participants with a history of depression or anxiety and are unlikely to be nullified by an unmeasured confounding variable according to the e-values.

My findings indicate that sedentary behaviour is a possible risk factor for depression and anxiety disorders, which aligns with findings from several smaller studies that use self-report activity measures (142,143,145–147). Recent meta-analyses have found that the association between sedentary behaviour and depression is attenuated when adjusting for physical activity using standard methods (142). My results contrast with these findings by showing that the association holds when using appropriate methods of accounting for physical activity and sleep over 24-hours.

I also modelled replacement effects to provide more realistic estimates of how reducing daily sedentary behaviour time might affect depression and anxiety symptom scores by considering possible replacements. For example, one recent meta-analysis found that high sedentary behaviour is associated with a 1.10 (95% CI = 1.03 to 1.19) higher risk of depression than low sedentary behaviour (142). Another meta-analysis found that high total physical activity volume was associated with 0.83 (95% CI = 0.79 to 0.88) lower odds of depression than low total physical activity (119). Whereas my results demonstrate the importance of considering how the time is replaced as reducing daily sedentary behaviour by an hour was associated with a larger effect size (odds ratio = 0.75) when replaced with moderate-to-vigorous activity and smaller effect size (odds ratio = 0.95) for light-intensity physical activity. These results also align with other studies indicating a potentially beneficial impact of light-intensity physical activity on depressive symptoms in adults (89) and adolescents (500). Replacing sedentary behaviour with activity could influence depressive symptoms through various mechanisms, such as modulating neuroplasticity, reducing inflammation, and promoting self-esteem (418).

I also found novel evidence that potentially replacing sedentary behaviour with moderate-to-vigorous activity, or sleep was associated with a lower risk of anxiety symptom scores. However, replacing sedentary behaviour with light-intensity physical activity was associated with a higher risk of anxiety symptom scores. The finding is discordant with previous studies that suggest broad increases in total physical activity volume may reduce the risk of anxiety disorders (120,122). It is also inconsistent with my findings in adolescents in Chapter 4 (Chapter 4: Device-measured physical activity and sedentary behaviour and depressive symptoms throughout adolescence). The discrepancy could be due to new triaxial devices with different processing and calibration protocols that could improve their capacity to detect light-intensity physical activity in other directional planes. Light-intensity physical activity could capture restlessness, a common symptom of anxiety disorders that may contribute to this finding. The lack of previous research using device-based measures of light-intensity physical activity and anxiety symptoms triangulates this finding with other studies challenging.

6.5.2. Strengths and limitations

I took steps to reduce the risk of several sources of bias in this study. To the best of my knowledge, the UK Biobank is the world's largest prospective cohort with accelerometer data. This sample size reduces some bias from random variability. The use of accelerometers that capture activity across the entire intensity spectrum should have lowered systematic bias due to measurement error in this domain compared with self-report measures. The use of e-values allowed me to assess the risk of bias from unmeasured confounding. I reduced the risk of reverse causation through a longitudinal design adjusting for symptoms at baseline and including a sensitivity analysis that excluded all participants with any history of depression or anxiety. I also used a compositional approach that allowed me to assess associations between sedentary behaviour and mental health while appropriately accounting for time spent the rest of the day. The method also supports the estimation of replacement effects, which accounts for the co-dependent nature of time in different movement behaviours throughout the day and provides a more realistic representation of how reducing sedentary behaviour would occur. The *a priori* use of DAGs to inform my models, a comprehensive selection of variables available in the UK Biobank, and sensitivity analyses to explore alternative hypotheses improved my ability to estimate causal associations.

There were also several limitations to the study, including the possibility of selection bias. Only 5% of participants invited to join the UK Biobank were recruited, increasing the risk of selection bias in the sample. The full Biobank cohort is comparable to the general population across several sociodemographic and health factors (239,501) but is healthier by other measures, such as smoking, obesity, or alcohol use (243). Representativeness is a major issue for estimating prevalence, which was not the aim of my study, but it can induce collider bias (238), as discussed in Section 2.3.2.2. (Section 2.3.2.2. Biobank). The extent to which this affects my results is unclear. For example, some data suggest that physical activity (my exposure) and depression and anxiety (my outcome) estimates in the UK Biobank are similar to other nationally representative samples, such as the Health Survey for England, and so appear unrelated to participation (501–503).

The risk of bias by this mechanism is unclear as physical activity (my exposure) and depression and anxiety (my outcomes) estimates in the UK Biobank are similar to other nationally representative samples, such as the Health Survey for England and so appear unrelated to participation (501–503). In my subsample, there were around 6.2% possible cases of depression and 3.7% for anxiety. These figures are comparable with nationally representative data suggesting a prevalence of 4.2% and 6.1% for depression and generalised anxiety disorders in middle-to-older adults from the Adult Psychiatric and Morbidity Survey discussed in Chapter 1 (Chapter 1: Introduction) (7). However, the comparison of physical activity data uses self-reported measures as there is a lack of nationally representative device-based estimates of this data for the UK. In my subsample, the mean daily time in moderate-to-vigorous physical activity was 65.1 minutes, which is higher than accelerometer-based estimates from middle-aged adults in the 1970 British Cohort Study of 50.4 (men) and 51.6 (women) minutes per day (504). However, direct comparisons are challenging as the cohort uses a thigh-worn accelerometer with different properties to the wrist-worn accelerometer in our sample.

The e-values indicated that the risk of unmeasured confounding nullifying my main findings is low, but it remains possible that several unmeasured confounding variables accumulate to have this effect. Sleep disturbances are also symptoms of depression and anxiety disorders, which may confound estimates of replacing sedentary behaviour with sleep. I only included measures of sleep duration but sleep quality or the timing of sleep are other relevant factors to consider for mental health. The sleep variable was also from a self-reported measure, which may be subject to greater measurement error than the accelerometer data. However, gold-standard sleep measures are

impractical for large-scale studies, such as direct observation and polysomnography, and self-reported sleep measures are common in other compositional studies (208,487,488). Novel methods for estimating sleep using accelerometer data only are promising but still require further validation for large-scale studies (505,506).

Advancing sedentary behaviour and physical activity research requires a shift to understanding behaviours within a 24-hour cycle that includes sleep (152), and improved data collection methods suitable for large-scale research will continue to develop. While the use of accelerometers is a strength of this study, wrist-worn devices could misclassify some sedentary behaviours, such as standing (194). Thigh or hip-worn devices are a useful option for assessing sedentary behaviour. For example, thigh-worn devices can measure seated, and standing postures to estimate sedentary behaviour and are feasible for use in large cohort studies, such as the 1970 British Cohort Study (504). However, the newer Axivity AX3 accelerometers in this chapter perform acceptably for estimating posture in children and adults and outperform the older ActiGraph devices in Chapter 4 and 5 (507). There is also mixed evidence as to whether 7-day measurement of activity is representative of a typical week for most adults (508,509). People wearing accelerometers may increase their activity during the study period, which could underestimate the true association between activity and depression and anxiety symptoms here.

6.5.3. Implications and future directions

My findings suggest that reducing sedentary behaviour during the day could reduce the risk of depression and anxiety symptoms and disorders in adults. However, interventions aiming to reduce sedentary behaviour must consider how different replacement activities might affect mental health. For example, I estimated that replacing sedentary behaviour with moderate-to-vigorous activity was associated with the lowest depression and anxiety symptom scores and could be a useful approach for interventions. My results indicate that even small changes of less than an hour could be beneficial. For example, 15 or 30-minutes of brisk walking (moderate-intensity activity) per day could be sufficient to reduce mental health risks and a potentially more realistic target than 60-minute changes in highly sedentary populations. Reducing sedentary behaviour with light-intensity physical activity could have a smaller effect on reducing depressive symptoms than moderate-to-vigorous activity. However, it may be more acceptable and sustainable over long periods. Light activity may be easier to implement in daily routines and is typically more pleasurable, and yields greater motivation to engage than more intense activity (478).

Further studies using objective sleep measures are necessary to assess its possible influence relative to sedentary behaviour on mental health risks. Studies should also consider concurrent uses of devices and time-use diaries that provide additional contextual information about the activity to assess how replacing specific types of sedentary behaviours or at certain times in the day affects mental health risks. There is evidence that mentally passive sedentary behaviours (e.g., watching television) are associated with greater depression risks than mentally active sedentary behaviours (e.g., reading) (448,461). Replacing 60 minutes of watching television in the evening for sleep could lower the risk of depression than replacing 60 minutes of reading.

There is a lack of movement behaviour studies that assess anxiety symptoms despite their high prevalence and physical health risks (1). My findings in that replacing sedentary behaviour with light-intensity physical activity were associated with higher anxiety symptoms highlights the need for more research, particularly given their contrast with Chapter 5's results. Future studies should consider how anxiety symptoms, such as restlessness, may produce micromovements that a wrist-worn accelerometer detects as light-intensity physical activity. The mechanisms underlying the

relationship between activity and mental health could also differ for depression and anxiety and warrant a greater focus on studying anxiety symptoms.

These findings also emphasize the nuances of understanding associations between movement and mental health in a 24-hour context, where changing time in one behaviour inherently affects the time in another. Methodologies for studying behaviour within a 24-hour time-use cycle will be necessary to advance the field of sedentary behaviour and physical activity research (152). Prospective studies should utilize compositional approaches to account for time in other behaviours during the day appropriately and estimate replacement effects, instead of only focusing on time in individual movement behaviours without appropriate adjustments. Further evidence from interventional studies will be useful in validating findings from these compositional studies.

Understanding these associations in a 24-hour context may also require studies assessing concurrent changes in dynamic aspects of mental health (e.g., mood) and movement throughout the day and their temporal relationships. For example, in Chapters 4 to 6, I have averaged movement data over a week to assess their association with future mental health. These study designs are useful for assessing the broader associations between physical activity, sedentary behaviour, and mental health over time. However, they provide limited scope for determining whether low mood or elevated fatigue increased the propensity for prolonged bouts of sitting during a day (or vice versa) and how these interrelationships develop over the week. Examining these dynamic interrelationships throughout the days and weeks could identify patterns that lead to persistent CMD symptoms and provide insights for preventing them. I return to this topic in Section 9.4.2. (Section 9.4.2. Understanding dynamic interrelationships between physical activity, sedentary behaviour, and mental health within and between days).

6.5.4. Conclusions

My findings suggest that sedentary behaviour could be a risk factor for depression and anxiety disorders in adults. More careful consideration of how best to replace sedentary behaviour is warranted. Replacing sedentary behaviour with moderate-to-vigorous activity could reduce the risk of depression and anxiety symptoms, including smaller replacements of less than 60 minutes. Replacing sedentary behaviour with light-intensity physical activity could be a sustainable and accessible approach for reducing the risk of depressive symptoms. However, whether this extends to anxiety symptoms and the extent to which sleep is beneficial over sedentary behaviour for CMD risk requires more work. Light but not moderate-to-vigorous activity was associated with CMD symptoms in Chapters 4 and 5, which suggests that physical activity intensity may differ between adolescents and adults.

7. Chapter 7: The association between cardiorespiratory fitness and the incidence of CMDs

7.1. Summary

This chapter includes my first study addressing Objective 3: Investigate the prospective associations of cardiorespiratory and muscular fitness with CMD symptoms and incidence in the population. As discussed in Section 1.6.5. (Section 1.6.5. Lack of research on associations between physical fitness and common mental health disorders), there has been a comparative lack of research on the associations of CMD symptoms with physical fitness, despite its inherent relationship with physical activity. I chose to conduct a systematic review to update a prior iteration by Schuch *et al.* that included only 2 studies in its meta-analysis (172). Since the publication of this meta-analysis in 2016, I was aware of several new cohort studies that may be eligible for review. Another motivation for conducting this review was to identify gaps in the literature and provide the foundations for Chapter 8 (Chapter 8: Individual and combined associations between cardiorespiratory fitness and grip strength with CMDs), where I conducted a new prospective cohort study on the associations between physical fitness and CMD symptoms.

In this chapter, I conducted a systematic review that included screening 6,698 studies to identify prospective cohort studies on the association between cardiorespiratory fitness and CMD symptoms. I chose to focus on cardiorespiratory fitness and my preliminary literature searches identified no prospective studies using muscular fitness as an exposure. This also coincides with the majority of physical activity-based interventions or exposures relating to aerobic activity or exercise, which primarily affects cardiorespiratory rather than muscular fitness. I used CMD incidence as an outcome in this chapter in line with the included studies. This approach differs from Chapters 4 to 6, where I included continuous symptom scores. My systematic searches and screening identified seven eligible studies for the narrative review and four studies for the meta-analysis. I pooled the hazard ratios and 95% confidence intervals of four studies, including at least 27,733,154 person-years of data. I found that low cardiorespiratory fitness (hazard ratio = 1.47, 95% CI = 1.23 to 1.76, $p < 0.001$ $I^2 = 85.1$) and medium cardiorespiratory fitness (hazard ratio = 1.23, 95% CI = 1.09 to 1.38 $p < 0.001$ $I^2 = 87.20$) are associated with a 47% and 23% greater risk of a CMDs, compared with high cardiorespiratory fitness. I found evidence to suggest a dose-response relationship between cardiorespiratory fitness and the risk of CMDs. These findings indicated an inverse association between cardiorespiratory fitness levels and the risk of a CMD. Cardiorespiratory fitness levels could be useful for identifying and preventing CMDs at a population-level.

However, another takeaway message from this study was the lack of studies investigating the association between cardiorespiratory fitness and CMD symptoms. In Section 7.5. (Section 7.5. Discussion), I discuss how this compares to the rapid growth of physical activity-related cohort studies and the relative advantages of increasing research into physical fitness-related exposures and their association with CMD symptoms in the population. This chapter highlights a need for more evidence, which I aimed to provide in Chapter 8.

A modified version of this chapter is published as:

Kandola, A., Ashdown-Franks, G., Stubbs, B., Osborn, D. P. J., & Hayes, J. F. (2019). The association between cardiorespiratory fitness and the incidence of common mental health disorders: a systematic review and meta-analysis. *Journal of Affective Disorders*, 257, 748-757.

7.2. Introduction

Novel approaches to preventing CMDs in the population are needed to reduce their global burden (1). Several meta-analyses of population-based studies have found that low physical activity is associated with a greater incidence of CMDs (119,120). Randomised control trials indicate that physical activity effectively reduces common mental health (75–86). Physical activity is a major influence on cardiorespiratory fitness levels (161), the capacity of the cardiovascular and respiratory systems to supply oxygen to muscles, and other bodily tissues, during exertion (158). There have been fewer studies assessing the associations of cardiorespiratory fitness and CMDs compared with physical activity, several population-based studies have found that low cardiorespiratory fitness is associated with a greater risk of psychological distress (166), stress (167), and CMD symptoms (168–171).

In a 2018 12-week exercise trial, Rahman *et al*. found that an increase in cardiorespiratory fitness predicted greater symptom reductions in people with depression, independently of exercise intensity, age, and body mass (173). They also found that improvements in cardiorespiratory fitness were associated with increased odds of treatment response at follow up (odds ratio = 3.73, 95% CI = 1.22 to 11.43). One systematic review in people with and without depression found a modest correlation between cardiorespiratory fitness and the severity of depressive symptoms (correlation coefficient = -0.16, 95% CI = -0.21 to 0.10), in 16 randomised controlled trials and population-based studies (174).

So far, one systematic review has attempted to quantify the prospective associations of cardiorespiratory fitness and the incidence of depressive symptoms in the general population (172). They found that compared with high cardiorespiratory fitness, people with low cardiorespiratory fitness had a 76% increase in rate of incident depression (hazard ratio = 1.76, 95% CI = 1.61 to 1.91) and people with medium cardiorespiratory fitness had a 23% increase (hazard ratio = 1.23, 95% CI = 1.20 to 1.38). However, this meta-analysis is only based on two studies with high heterogeneity, making it difficult to draw firm conclusions.

Despite the comorbidity between depression and anxiety disorders (6) and the substantial global disability burden of anxiety disorders (1), there are currently no systematic reviews that assessing prospective associations of cardiorespiratory fitness and anxiety symptoms in the general population. The purpose of this review is to describe and systematically evaluate the associations of cardiorespiratory fitness and the incidence of CMDs in the population. Since the previous systematic review on cardiorespiratory fitness and depression incidence (172), several relevant population-based studies have been published that may be eligible for inclusion which would increase the statistical power for meta-analysis.

7.3. Methods

The systematic review was conducted in accordance with the PRISMA (Moher et al., 2009) and MOOSE (Stroup et al., 2000) statement and pre-registered on PROSPERO. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=126059

7.3.1. Search procedure

I conducted searches in Medline, Embase, PsychINFO, PsychARTICLES, CINAHL, and SPORTDiscuss from inception to 23rd of May 2019. In the title, abstract, and keyword fields, I used the following

search terms: cardiorespiratory fitness OR cardiovascular fitness OR aerobic fitness OR physical fitness OR oxygen uptake OR VO_2 OR cardiopulmonary fitness OR exercise capacity OR aerobic capacity AND depress* OR anxi* OR panic disorder OR phobia OR agoraphobia. I also conducted supplementary searches using Google Scholar and reference lists of relevant review papers.

7.3.2. Inclusion and exclusion criteria

I included studies which: (1) record cardiorespiratory fitness using a measure validated against direct measures of oxygen consumption (further details in section 2.4) (2) have a prospective study design (3) measure depression, or anxiety disorders at the endpoint of the study using a clinical diagnosis, hospital admission, or a validated scale with a standardized cut off point (4) do not include participants with a prior diagnosis of any psychiatric condition at baseline

I also only considered studies that were published in peer-reviewed journals and in English. In cases where more than one study was conducted in the same cohort, I only included the study that had the most amount of data, i.e., the largest number of person-years.

7.3.3. Outcome

My outcomes were the incidence of any depressive or anxiety disorder. This included depression, major depressive disorder, dysthymic depression, generalized anxiety disorders, panic disorders, phobias, and social anxiety disorder. These were defined as a clinical diagnosis, medical or insurance record, or a validated scale with a standardised cut-off point.

7.3.4. Exposure

My exposure was cardiorespiratory fitness measured using any validated method. Gold standard measures of cardiorespiratory fitness use a maximal exercise test protocol with gas analysis (159). But these tests are expensive and difficult to administer in population-based cohorts. For this reason, I also included other validated measures of cardiorespiratory fitness, such as time-to-exhaustion protocols that are highly correlated with gas analysis (r = 0.92)(510). I also included studies that estimate cardiorespiratory fitness using algorithms based on heart rate, body composition, gender, age, smoking, and self-report responses on physical activity questions. These cardiorespiratory fitness algorithms are validated against direct measures of oxygen consumption (*r* = 0.66 to 0.83) (511–513).

7.3.5. Data extraction

In the first stage of study selection, I screened title and abstracts of all studies retrieved by the search. To minimize bias, a second author screened titles and abstracts from 30% of the search results. After this stage, both authors independently carried out full-text screening of studies that potentially met the criteria to be included in our analysis. A third author was available to review any discrepancies between the two reviewers.

After compiling a final list of studies for inclusion, both authors independently extracted data using a pre-specified form. This included information on participant demographics, study design, cardiorespiratory fitness measurement, mental health assessment, and data relating to the secondary outcomes. For any missing data, I contacted the study authors directly.

7.3.6. Data synthesis and analysis

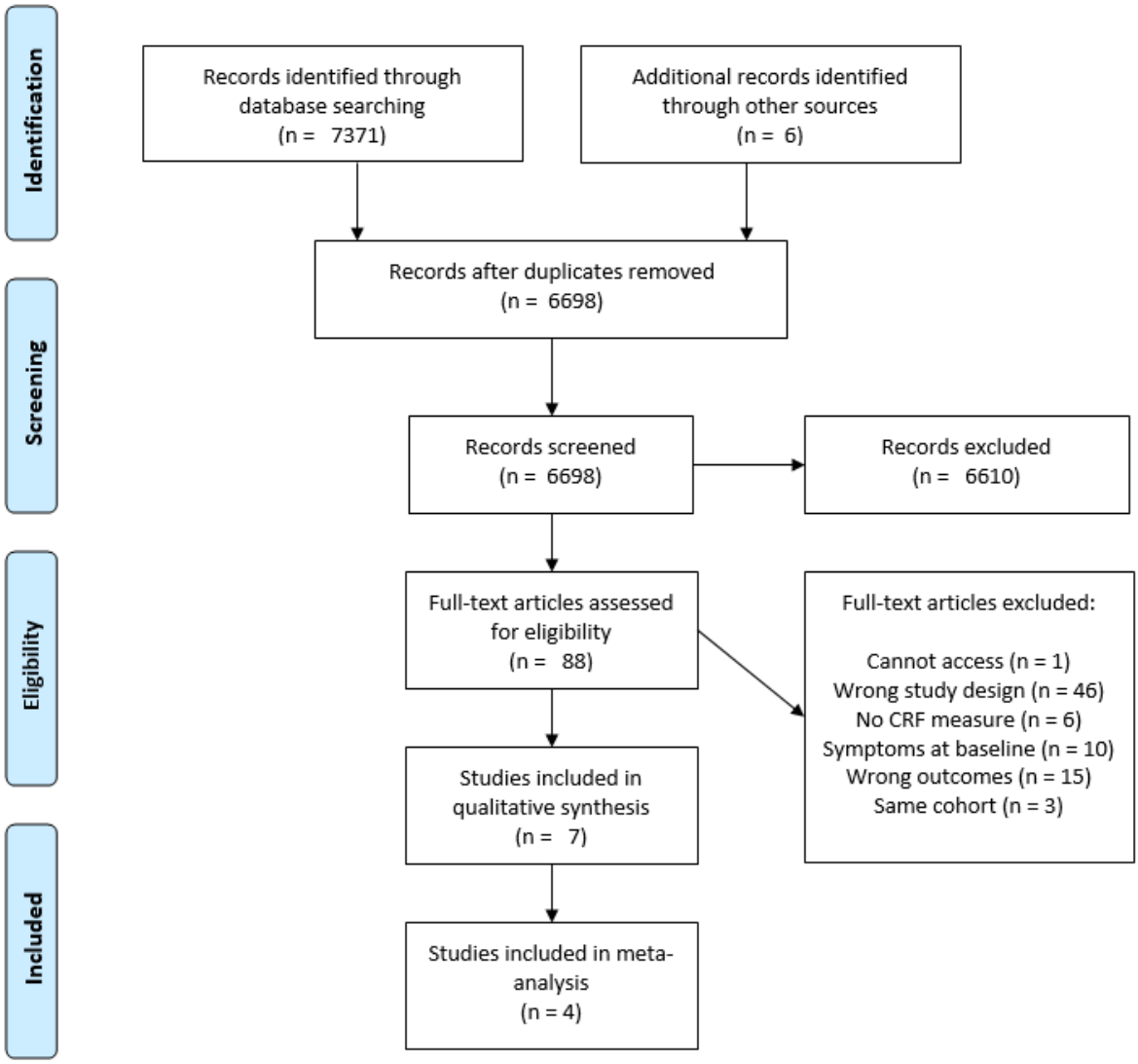
I conducted a random effects meta-analysis to calculate a pooled hazard ratio with 95% confidence intervals to investigate the relationship between cardiorespiratory fitness and incident CMDs. I first assessed the relationship between cardiorespiratory fitness and the combined risk of any CMD (either depression or an anxiety disorder), before assessing the risk for depression and anxiety individually. Based on methods used in a previous meta-analysis (172) and how studies in our final list presented their data, I categorised participants into low, medium, and high cardiorespiratory fitness groups. These groups are based on tertiles defined by the authors of each study, such as grouping by stanine scores. The details of how these groups are derived in each study are outlined in Table 1. My primary analysis focussed on comparing the risk of people in the lowest cardiorespiratory fitness group with the highest cardiorespiratory fitness (reference category), but I also compared people with medium cardiorespiratory fitness with high cardiorespiratory fitness. In cases where the study data were presented in a way that was incompatible with my analysis, I contacted authors for more information. I pooled effect size data as hazard ratio's and 95% confidence intervals reported by the authors. I used the I-squared (I^2) statistic to quantify heterogeneity between studies. I rated the quality of studies using the Newcastle-Ottawa Scale (NOS) to assess risk of bias in observational studies, which contains up to 9 points across three domains: selection of study group (3 points), comparability of groups (2 points), and ascertainment of exposure and outcomes (3 points) (514). Scores of 7-9 are considered high quality, 4-6 as fair, and 0-3 as poor.

7.4. Results

7.4.1. Search results

My search returned 7,371 studies and I identified a further 6 through manual searches of relevant reference lists. After removing duplicates, I screened the titles and abstracts of 6,698 studies and excluded 6,610. Of the 88 included in my full text screening, 81 were excluded. This left seven studies for the qualitative synthesis and four for the meta-analysis.

Figure 4. PRISMA flow diagram of study selection



I found four eligible studies from the Aerobic Center Longitudinal Studies (ACLS) cohort (168,515–517). I only included one study, which had the highest number of person-years (516). I also identified two further studies using data from the same registry of Swedish military conscripts (518,519). In this case, each study investigated different outcomes (depression or anxiety), so both studies are included in the final analysis.

7.4.2. Study characteristics

Individual study characteristics of the seven studies included in this analysis can be found in Table 6.

Table 6. Included study characteristics

Study	Cohort	N	Mean age at baseline (SD)	Female (%)	Follow-up	Peron-years	Fitness assessment	Fitness grouping	Mental health assessment	Results (95% CIs)			
										Depression	Anxiety	Other	Adjustments
Aberg et al. 2012	Military conscripts (Sweden)	1,117,292	18	0	3-40 years	Not reported	Maximal cycle ergometer with graded test protocol, using heartrate at exhaustion/body mass	Split using stanine scores	Inpatient record	High (ref) vs low HR = 1.80 (1.64-1.99)			Age, calendar year, BMI, region, conscription test centre, parental education
Baumeister et al. 2017	SHIP cohort (Germany)	4,308	20-79	50.9	1-8 years	Not reported	Maximal cycle ergometer (modified Jones protocol), using gas analysis	No grouping. cardiorespiratory fitness as a continuous variable.	M-CIDI	Per SD increase in peak VO^2 RR 0.71 (0.52-0.98)	Per SD increase in peak VO^2 RR 0.69 (0.50-0.95)	Per SD increase in peak VO^2 OR 0.45 (0.24-0.84) for combined MDD and anxiety	Age, gender, year of schooling, smoking, alcohol consumption, waist circumference
Crowley et al. 2015	Army recruits (US)	300	22 (3.7)	23.3	8 weeks	0	APFT includes measures of cardiorespiratory fitness and muscular strength	High fitness >=180 out of 300 points on APFT. Low <180 points	CES-D (>=16)	Low (ref) vs high OR 0.40 (0.19-0.84)			Age, gender, ethnicity, education, marital status, family income, army training confidence, army ID, baseline depression, baseline sleep before training

Gubata et al. 2013	Army recruits (US)	11,369	18	16.8	1 year	11,369	ARMS test including a submaximal Harvard step test and number of push ups in one minute. Only the step test is considered in this study	Two groups based on passing or failing the step test. This is defined as completing the step test for five minutes at a proper pace	Ambulatory encounter	Pass (ref) vs fail unadjusted IRR 1.40 (1.18–1.67) for mood disorders, IRR 1.32 for MDD (0.92-1.89)	Pass (ref) vs fail adjusted IRR 1.57 (1.22-2.01)	Pass (ref) vs fail adjusted IRR 1.36 (1.23-1.49) for any mental health disorder	Gender, smoking, education
Nyberg et al. 2018	Military conscripts (Sweden)	1,109,786	18 (SD)	0	3-42 years	27,528,903	Maximal cycle ergometer with graded test protocol, using heartrate at exhaustion/body mass	Split using stanine scores	Inpatient record		High (ref) vs low HR = 1.48 (1.36-1.60)		Cognitive performance, BMI, region, year of enlistment
Shigdel et al. 2019	HUNT cohort in (Norway)	14,020	52.2 (9)	52	11 years	Not reported	Estimated from physical activity questions, age, waist circumference, resting heartrate and gender	Split using quintiles	HADS (>=8)	High (ref) vs low HR = 1.28 (1.02-1.62)	High (ref) vs low HR = 1.04 (0.83-1.30)		Age, gender, marital status, smoking, alcohol intake, education, diabetes, hypertension, HADS score at baseline, limiting long term illness
Sui et al. 2009	ACLS cohort (US)	14,343	44.9 (9.7)	22	1-25 years	174,554	Maximal cycle ergometer (Balke protocol), using time to exhaustion	Split using tertiles (bottom 20% = low, middle 40% = medium and top 40% = high)	CES-D (>=16)	High (ref) vs low HR = 1.94 (1.38-2.72)			Age, baseline examination year, survey response year, stressful occupation, smoking, alcohol, BMI, hypertension, diabetes,

	abnormal exercise ECG

7.4.3. Participants

In seven studies selected, there was a total of 1,161,632 participants. As there was likely to be significant participant overlap in the two studies using the Swedish military conscript registry, this total only includes one of these studies (518). The percentage of female participants ranged from 0 (518) to 52% (520), and mean ages range from 18 (518,521) to 52.5 (520). All studies were in developed, Western countries, with most in the US (n = 3) and the others in Germany (n = 1), Sweden (n = 2), and Norway (n = 1). Follow-up periods ranged from 8 weeks (522) to 42 years (519). Of those studies reporting smoking, between 8.8% (516) and 29% (520) of participants reported that they smoked at baseline. According to their BMI, between 17.3% (521) and 26.6% (520) of participants were obese at baseline.

7.4.4. Exposure assessment

Most of the studies use a maximal exercise test with a cycle ergometer to assess cardiorespiratory fitness either through measuring heartrate at exhaustion (Aberg et al., 2012; Nyberg et al., 2018) time to exhaustion (516) or gas analysis (523). Shigdel *et al.* (2019) estimated cardiorespiratory fitness using an age-adjusted algorithm involving physical activity questions, waist circumference, resting heart-rate, and gender (520). Gubata *et al.* (2013) used an Assessment of Recruitment Motivation and Strength test involving a five-minute submaximal Harvard step test and one minute of push-ups. Crowley *et al.* (2015) used the Army Physical Fitness Test, involving push-ups, sit-ups, and a two-mile run to assess cardiorespiratory fitness and muscular fitness.

Some studies delineate low, medium, and high fitness groups by collating stanine scores (518,519), tertiles (516), or quintiles (520) from the sample data. One study did not categorise participants into groups, instead of modelling cardiorespiratory fitness as a continuous exposure (523). Gubata *et al.* (2013) split participants into pass/fail groups. The paper defines a 'pass' as performing the step test for five minutes at a proper pace and excluded the subsequent push-up test as only 4% of participants failed this part of the test. Crowley *et al.* (2015) converted raw scores from their Army Physical Fitness Test into a points-based system with 100 points per test component. High fitness was defined here as >=180 out of 300 points, and low fitness was <180 points. Unlike the other seven studies, fitness here included both cardiorespiratory fitness and muscular fitness.

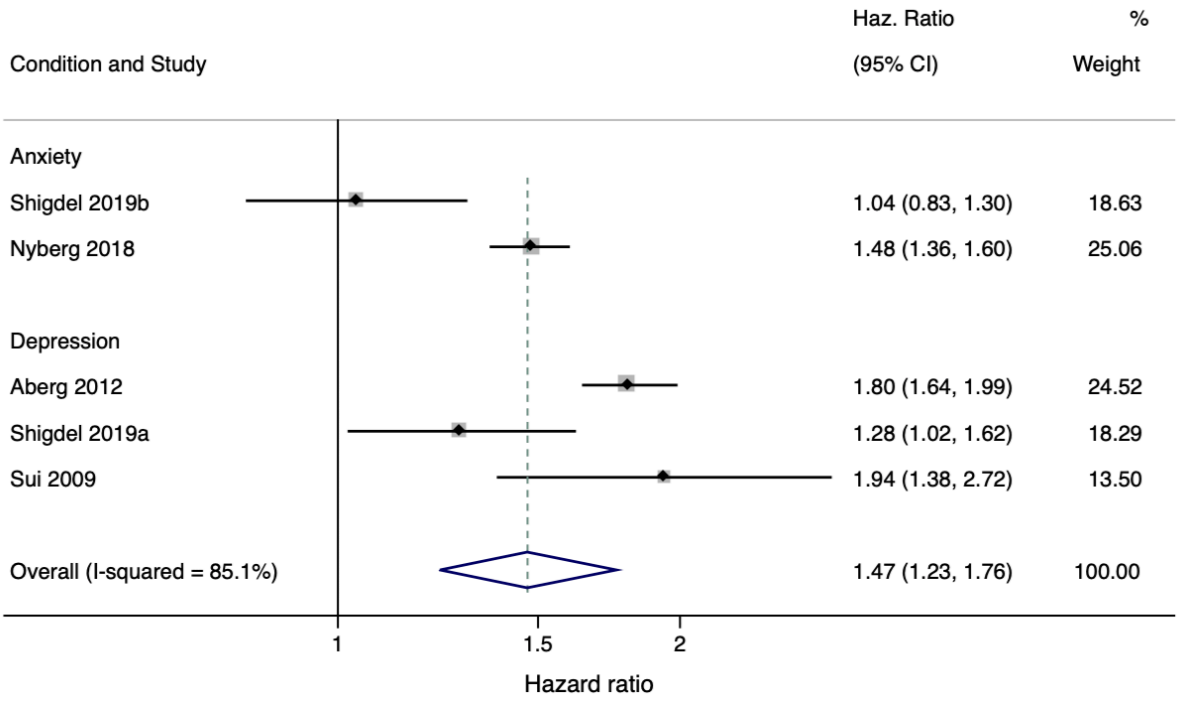
7.4.5. Outcome assessment

Some studies assessed mental health using validated scales such as the Hospital Anxiety and Depression Scale (520), Centre for Epidemiologic Studies Depression Scale (522), and clinical interviews, such as the Munich Composite International Diagnostic Interview (523). The other studies used inpatient, insurance or ambulatory records (518,519,521). Gubata *et al*. (2013) included individual categories for mood disorders and major depressive disorder using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-4). The mood disorder category includes people with major depressive disorder, dysthymia, substance-induced or medically induced mood disorder, adjustment disorder and bipolar disorder.

7.4.6. Cardiorespiratory fitness and CMDs

Of seven studies in the final analysis, it was possible to pool data from four studies, including one study that had outcomes for both anxiety and depression (520). The pooled analysis was based on data from at least 27,733,154 person-years (to avoid double counting, I calculated person-years without (518)) and suggested that low cardiorespiratory fitness is associated with a higher incidence of CMDs compared with high cardiorespiratory fitness (hazard ratio = 1.47, [95% CI 1.23 to 1.76] $p < 0.001$ $I^2 = 85.1$). Medium cardiorespiratory fitness was also associated with a higher incidence of CMDs, compared with high cardiorespiratory fitness (hazard ratio = 1.23, [95% CI 1.09 to 1.38] $p < 0.001$ $I^2 = 87.20$). There was substantial heterogeneity in both cases.

Figure 5. Comparison between low to high cardiorespiratory fitness for depression or anxiety incidence.



One study (Shigdel et al., 2019) included two separate outcomes that are both included in this table, denoted by Shigdel 2019a (depression outcome) and Shigdel 2019b (anxiety outcome).

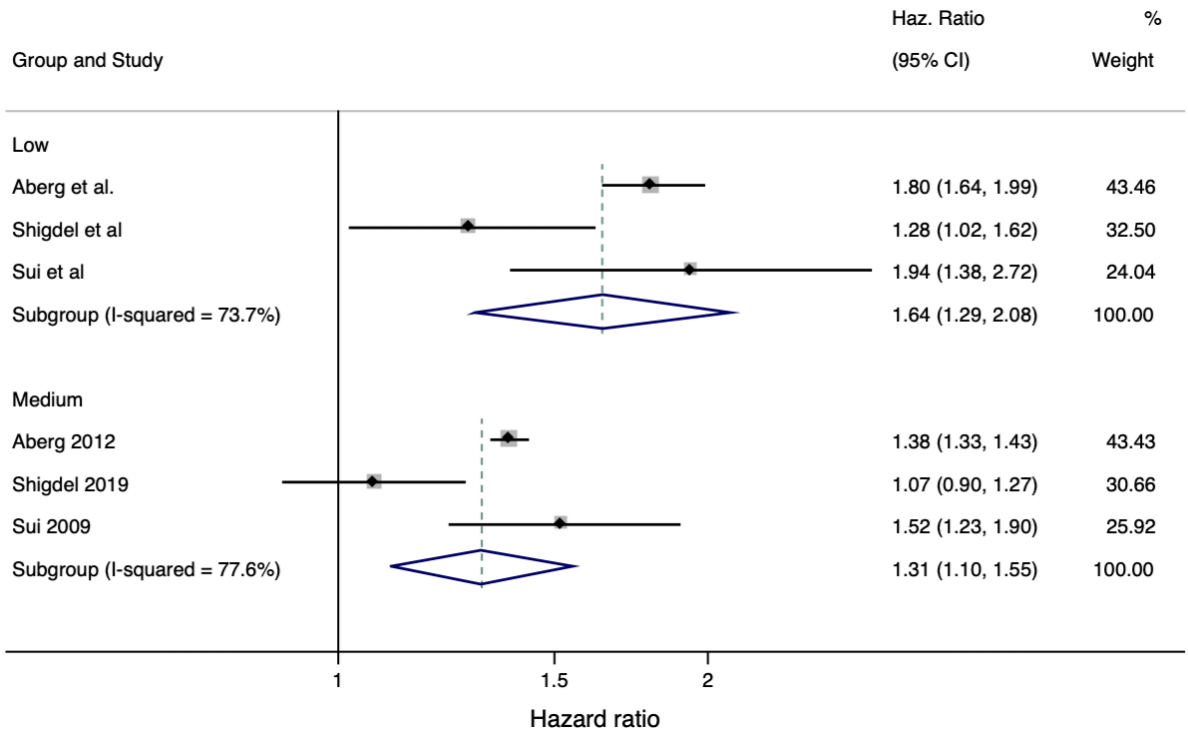
Baumeister *et al.* (2017) found that each SD increase in peak VO^2 is associated with a reduced risk of combined major depressive disorder and anxiety incidence (odds ratio = 0.45, 95% CI = 0.24 to 0.84). This association was stronger than the relationship between cardiorespiratory fitness and either single diagnosis alone.

7.4.7. Cardiorespiratory fitness and depression

Of seven studies in the final analysis, six included measures of depression (516,518,520–523). Data pooled from three of these studies (516,518,520) based on at least 3,540,450 person-years demonstrated that low (hazard ratio = 1.64, [95% CI 1.29 – 2.08] $p < 0.001$ $I^2 = 73.67$) and medium (hazard ratio = 1.31 [95% CI 1.10 – 1.55] $p < 0.01$ $I^2 = 77.60$) were associated with a greater incidence

of depression, compared to high cardiorespiratory fitness. However, there was substantial heterogeneity.

Figure 6. Comparison between low and medium to high cardiorespiratory fitness for depression incidence



It was not possible to pool data from the remaining three studies due to different analytical strategies and overlapping participant data. Baumeister *et al.* (2017) analysed cardiorespiratory fitness as a continuous variable using Poisson regression and found that each standard deviation increase in cardiorespiratory fitness (peak VO^2) was associated with a lower risk of depression by 29% (95% CI = 0.52 to 0.98). One study included in the pooled analysis above also included an analysis of cardiorespiratory fitness as a continuous variable and detected a significant linear trend ($p < 0.05$) between cardiorespiratory fitness and incidence depression (520). Each unit change in metabolic equivalent was associated with 8% lower risk of depression incidence (odds ratio = 0.92, 95% CI = 0.86 to 0.99). Another study in the pooled analysis also found a significant linear trend ($p < 0.001$) between cardiorespiratory fitness group and incidence of depression (516).

Crowley *et al.* found that participants with low fitness had higher odds of depression (odds ratio = 0.40). Using incidence rate data reported in Gubata *et al.* I manually calculated unadjusted incidents rate for both mood disorders and major depressive disorder. Participants who failed the fitness test had an increased risk of mood disorders (incident rate ratio = 1.40, 95% CI = 1.18 to 1.67]) and major depressive disorder (incident rate ratio = 1.32, 95% CI = 0.92 to 1.89), but the difference between groups for major depressive disorder was not significant. The mood disorder category also included people with bipolar disorder, which was not in my inclusion criteria and not included in my analysis.

7.4.8. Cardiorespiratory fitness and anxiety

Four studies reported anxiety as an outcome measure but only two reported data that could be pooled, which was too few to conduct a meta-analysis. In three out of four studies that included anxiety as an outcome measure, the results indicate that cardiorespiratory fitness was associated with a lower risk of anxiety (519–521,523). One study including data from 27,528,903 person-years found low cardiorespiratory fitness (hazard ratio = 1.48, 95% CI = 1.36 to 1.60) and medium cardiorespiratory fitness (hazard ratio = 1.24, 95% CI = 1.17 to 1.33) were associated with a reduction in the risk of anxiety compared to high cardiorespiratory fitness (519). Another study found that per standard deviation increase in cardiorespiratory fitness (measured in metabolic equivalents) was associated with a 31% lower risk of an anxiety disorder (risk ratio = 0.69, 95% CI = 0.50 to 0.95). Gubata *et al.* found participants who failed a cardiorespiratory fitness test had a greater risk of anxiety disorder (incident rate ratio = 1.57, 95% CI = 1.22 to 2.01). One study did not find low cardiorespiratory fitness (hazard ratio = 1.04, 95% CI = 0.83 to 1.30]) or medium cardiorespiratory fitness (hazard ratio = 0.98, 95% CI = 0.84 to 1.14) to be associated with a lower the risk of anxiety (520). This study also analysed cardiorespiratory fitness as a continuous outcome and found no association of cardiorespiratory fitness and anxiety incidence (odds ratio = 1.00, 95% CI = 0.94 to 1.07).

7.4.9. Study quality

The mean NOS score for all seven studies was 7.57 (range 6 to 9). Five studies were of good quality (516,518–520,523), one was of fair quality (522) and another of poor quality (521).

Table 6. Study quality score

Study	Selection	Comparability	Outcome	Overall
Aberg 2012	****	**	***	9
Baumeister 2017	****	**	**	8
Crowley 2015	**	**	**	6
Gubata. 2013	*	**	***	6
Nyberg 2018	****	**	***	9
Shigdel 2019	***	**	**	7
Sui 2009	****	**	**	8

7.5. Discussion

7.5.1. Main findings

This chapter aimed to systematically describe and evaluate population-based studies on the associations of cardiorespiratory fitness and CMDs. My findings suggest that low and medium cardiorespiratory fitness is associated with an increased risk of CMDs. Incremental increases in

cardiorespiratory fitness were associated with proportional decreases in associated risk of CMD incidence, indicating a dose-response relationship. This aligns with significant linear trends in studies that analysed cardiorespiratory fitness as a continuous variable (520,523) and across the different cardiorespiratory fitness groups (516).

This review's results build on the previous meta-analyses by Schuch *et al*., (172), and other cross-sectional studies (169–171) that have found low cardiorespiratory fitness is associated with a higher incidence of CMDs. These findings also align with meta-analyses suggesting that low physical activity is associated with a higher risk for CMDs (119,120). As physical activity is a major influence on cardiorespiratory fitness, the psychosocial and biological mechanisms that potentially underlie associations between physical activity and depressive symptoms discussed in Chapter 3 (Chapter 3: Physical activity and depression: Understanding the possible mechanisms of action underlying the relationship of physical activity and depressive symptoms) could contribute to these findings. For example, high cardiorespiratory fitness could stimulate angiogenesis and improve the circulation of blood in the brain. The richer supply of energy, neurotrophins and other important nutrients, could improve brain functioning in areas relevant to CMD symptoms, such as the hippocampus (see Chapter 3: Physical activity and depression: Understanding the possible mechanisms of action underlying the relationship of physical activity and depressive symptoms). People with low cardiorespiratory fitness may be forgoing these protective mental health benefits due to insufficient physical activity for improving cardiorespiratory fitness.

7.5.2. Strengths and limitations

A strength of my analysis is its inclusion of data from a large number of participants with at least 27,733,154 person-years – excluding one (518) of the two studies using Swedish conscript data. The large sample size allows me good statistical power for estimating the association between cardiorespiratory fitness and CMDs at a population level. However, there are also several limitations of this review. I was only able to identify seven studies that met the inclusion criteria for analysis. While participants were from a wide range of ages (18 to 52) and followed for up to 42 years, the small number of studies limited my ability to perform any subgroup analysis. These studies were also all from developed, Western countries, which further limits my ability to generalise these findings. I also detected substantial heterogeneity between studies. Several factors are likely to have contributed to this. The outcome measures varied from self-report questionnaires and clinical interviews to inpatient records. The different outcome measures are likely to capture different populations. For example, self-report measures may capture people with common mental health symptoms that are not receiving treatment. However, studies using inpatient records will only include people who are receiving treatment.

Methods for collecting and analysing cardiorespiratory fitness data also varied across the studies and may have contributed to the substantial heterogeneity found here. As a result, it was only possible to pool data from four of the seven included studies. Even within the four included studies, three use a maximal exercise test, and another uses a non-exercise algorithm to estimate cardiorespiratory fitness. This algorithm has been shown to have a good predictive value of cardiovascular disease and mortality in the same cohort (524,525) and the ACLS cohort (526). However, its predictive value for mental health is unknown. Just one of seven studies measured cardiorespiratory fitness using the gold standard maximal exercise test with gas analysis (523). This was not included in the meta-analysis as cardiorespiratory fitness was analysed as a continuous variable, incompatible with other studies in the meta-analysis. With fitness being an inherently

continuous outcome, it is possible that categorising cardiorespiratory fitness into low, medium and high groups inflated findings in previous studies and my results (123).

7.5.3. Implications and future directions

My findings highlight the need for more population-based studies focussing on cardiorespiratory fitness and mental health. I was only able to identify seven studies for the final analysis, with two from the same cohort. A recent meta-analysis of physical activity and incidence of depression was able to identify 49 unique prospective cohort studies (119). While recording physical activity levels is essential in public health against a backdrop of rising sedentary behaviour, measures of cardiorespiratory fitness capture broad physical activity trends with one discrete test using objective, clearly defined markers, such as oxygen consumption. Whereas researchers typically use device-based measures of physical activity in field research (e.g., accelerometers) to only record up to a week of data. They are also poor at capturing several non-ambulatory activities, such as cycling (249).

Cardiorespiratory fitness measures are not a suitable replacement for physical activity, but they have complementary benefits that warrant greater efforts to study at a population level. It is also possible that cardiorespiratory fitness has an independent predictive value from physical activity. In addition to capturing habitual physical activity, cardiorespiratory fitness also captures the complex interplay between a range of other relevant factors in mental health, such as smoking and obesity (162). The value of this is increasingly being recognised in physical health, with several studies finding cardiorespiratory fitness to be a stronger predictor of cardiovascular disease in population-based studies (164,527). While no such comparisons exist in mental health, a previous meta-analysis found high activity levels associated with a 17% depression incidence compared to low based on 1,837,794 person-years (119). Whereas in my study, data from 3,540,450 person-years indicate a much larger magnitude of effect, with low cardiorespiratory fitness being associated with a 64% higher risk of depression compared to high. While any direct comparison of these studies is difficult, such a difference could indicate that cardiorespiratory fitness has an independent predictive value for CMDs from physical activity. One study included in this review included data on physical activity levels and cardiorespiratory fitness (523). They found that leisure-time, work- and sport-based physical activity was not associated with CMD, but each standard deviation increase in cardiorespiratory fitness (measured using VO_{2peak}) was associated with a 55% lower risk.

A potential limitation of studying cardiorespiratory fitness at the population-level is the specialist equipment, training, and resources necessary to collect gold-standard physical fitness data in large groups, such as in administering exercise tests with gas analysis. These tests are uncommon in large cohort studies and potentially contributes to the lack of studies identified in this chapter. However, there are an increasing number of indirect tests of cardiorespiratory fitness that are more suitable for large-scale research in the population. For example, some tests involve walking or running pre-specified distances or times and the results correlate well with direct measures of cardiorespiratory fitness (252). I return to these indirect cardiorespiratory fitness tests in Section 9.3.2. Implementing these tests in newer data sweeps of large-scale cohort studies could be cost-effective way to increase the collection of physical fitness data in the population.

More research in this area is necessary to further explore the role of cardiorespiratory fitness as a risk factor for CMDs, which I aim to address in Chapter 8 (Chapter 8: Individual and combined associations between cardiorespiratory fitness and grip strength with CMDs). Such research could inform the development of preventative strategies designed to improve cardiorespiratory fitness. It is possible for cardiorespiratory fitness to change relatively quickly (528), including in people with

common mental health conditions (124). For example, three weekly 45-minute aerobic exercise sessions for three weeks are sufficient to improve cardiorespiratory fitness by 31% in older people (mean age = 68) and 18% in younger people (mean age = 23) with further training leading to greater improvements (528). There are also several low-cost methods of improving cardiorespiratory fitness through social prescribing frameworks, such as organised park runs (128). These properties make targeting changes in cardiorespiratory fitness a potentially useful public health approach for reducing the incidence of CMDs in the population.

These findings may also influence the way exercise-based interventions are administered. For example, there is limited information on the optimal dose of exercise for reducing CMD symptoms, but most studies use moderate-to-vigorous intensity physical activity (75–86). As higher intensity exercise is necessary to influence cardiorespiratory fitness (529–532), changes in cardiorespiratory fitness may be an important contributor to the efficacy of exercise treatments. A recent exercise trial found that increases in cardiorespiratory fitness were significantly associated with reductions in depressive symptoms, independent of the frequency and intensity of the exercise, and strongly predicted treatment response (173). Designing exercise interventions with sufficient intensity, frequency, and duration to increase cardiorespiratory fitness could be one way to promote treatment success. Recording cardiorespiratory fitness at baseline could be useful in developing exercise protocols that are tailored to individual fitness levels. Measures of cardiorespiratory fitness could also be used as a tool for monitoring and improving adherence to the intervention.

7.6. Conclusions

The results of this systematic review indicate that low and medium cardiorespiratory fitness levels are associated with a greater risk of CMDs than high cardiorespiratory fitness. I found evidence of a dose-response relationship between cardiorespiratory fitness and the associated risk of CMDs. These findings align with the results of Chapter 6 (Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms), which showed that replacing sedentary behaviour with moderate-to-vigorous physical activity was associated with lower CMD scores in adults. The limited pool of studies identified here also indicates a need for more cardiorespiratory fitness research at a population-level that I aim to address in the following chapter.

8. Chapter 8: Individual and combined associations between cardiorespiratory fitness and grip strength with CMDs

8.1. Summary

This chapter includes the final study of my thesis, which addresses Objective 3: Investigate the prospective associations of cardiorespiratory and muscular fitness with CMD symptoms and incidence in the population. Chapter 7 (Chapter 7: The association between cardiorespiratory fitness and the incidence of CMDs) provided evidence of an association between cardiorespiratory fitness and CMD symptoms. It also highlighted a paucity of prospective studies in the area, particularly in the UK population. I identified several studies from the same cohorts (e.g., military conscripts in Sweden and the ACLS cohort in the US), highlighting a lack of data sources for population-level physical fitness data. As discussed in Section 1.5. (Section 1.5. The relationship between physical fitness and physical and mental health), there were even fewer robust, prospective studies assessing the association between muscular fitness and CMD symptoms. There were also no studies assessing the association between combined cardiorespiratory and muscular fitness with CMD symptoms. I addressed these evidence gaps in this chapter using data from 152,978 UK Biobank participants. I used data from an aerobic exercise test and handgrip dynamometer to estimate cardiorespiratory fitness and grip strength, respectively. My results indicated that low and medium cardiorespiratory fitness was associated with 1.485 (95% CIs, 1.301 to 1.694, $p < 0.001$) and 1.141 (95% CIs, 1.005 to 1.297, $p = 0.041$) higher odds of depression or anxiety, compared to high cardiorespiratory fitness. These findings were broadly comparable with the effect sizes in Chapter 7 for the association between cardiorespiratory fitness and depressive. Low and medium grip strength was associated with 1.381 (95% CIs, 1.315 to 1.452, $p < 0.001$) and 1.116 (95% CIs, 1.063 to 1.172, $p < 0.001$) higher odds of CMDs compared to high grip strength. Individuals in the lowest group for both cardiorespiratory fitness and grip strength had 1.981 (95% CIs, 1.553 to 2.527, $p < 0.001$) higher odds of depression, 1.599 (95% CIs, 1.148 to 2.118, $p = 0.004$) higher odds of anxiety, and 1.814 (95% CIs, 1.461 to 2.252, $p < 0.001$) higher odds of either CMD, compared to high for both types of fitness.

These findings align with the findings in Chapter 7 to suggest that population-level cardiorespiratory and muscular fitness markers represent modifiable risk factors for common mental disorders in adults. They also highlight the importance of considering different fitness types. A combination of different types of exercise could be optimal for preventing low fitness in any domain and reducing CMD risks. The findings also align with Chapter 6 (Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms), which indicated that moderate-to-vigorous physical activity was associated with lower CMD symptoms. Physical activity of a sufficient intensity to improve physical fitness could be a useful framework for population-level strategies to reduce CMD risks in adults. It is unclear whether light activity is sufficient to substantially improve physical fitness, which limits comparisons with my findings in adolescents in Chapters 4 and 5.

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8.2. Introduction

CMDs are major contributors to the global health burden, with depression and anxiety disorders being the first and sixth leading causes of disability worldwide, respectively (1). Structured physical activity interventions have been shown to reduce common mental health symptoms with a moderate-to-large effect size (75,76,79,80,82,256,458). Low physical activity may be a modifiable, population-level risk factor for common mental disorders (119,120,122,145,146). Physical activity has a major influence on cardiorespiratory fitness and muscular strength (161,533), two related but distinct markers of physical fitness that are reliable indicators of overall health, disease risk, and mortality (157,158,163,164,534–537). Both are measurable in large groups through validated fitness tests that produce objective outputs, which may also act as surrogate markers of habitual physical activity that are not reliant on self-report measures subject to cognitive biases (161,538).

There is limited research on the associations between physical fitness markers and the incidence of common mental disorders. In Chapter 7 (Chapter 7: The association between cardiorespiratory fitness and the incidence of CMDs), I showed that low cardiorespiratory fitness was associated with a 47% (hazard ratio = 1.47, 95% CI = 1.23 to 1.76) higher incidence rate of common mental disorders. However, these results were from a small number of studies (n = 4) with substantial heterogeneity (I^2 = 85.1%), mostly focused on depression rather than anxiety. Fewer studies have focused on the role of overall muscular strength, for which grip strength is a simple clinical proxy measure (177,539,540). Some small cross-sectional (224,225) and longitudinal (181–183) studies suggest that low grip strength is associated with a higher incidence of depression and one with anxiety (226). However, longitudinal findings have been inconsistent, and more high-quality data from large samples are necessary. Most studies only focus on depression, despite anxiety disorders being another major source of global disability and highly comorbid with depression (6).

Low physical fitness, indexed by cardiorespiratory fitness or grip strength, could be a useful risk factor for common mental disorders in the population. I am not aware of any large-scale studies focusing on associations between individual and combined cardiorespiratory fitness and grip strength with the incidence of common mental disorders. Cardiorespiratory fitness and grip strength reflect different physiological profiles and indicate different types of habitual physical activity, i.e., aerobic vs. resistance training. Combined training to increase both cardiorespiratory fitness and strength leads to improved physical health outcomes than focusing on either component of fitness alone (541–544) and the same may be true for mental health. A recent cross-sectional study in adolescents found that cardiorespiratory fitness and not muscular strength was associated with fewer psychological difficulties, but did not assess the combination of cardiorespiratory fitness and muscular strength (545).

To address these knowledge gaps, I conducted a prospective study to examine associations between individual and combined markers of cardiorespiratory fitness and grip strength with the incidence of depression and anxiety. I aimed to 1) examine longitudinal associations between cardiorespiratory fitness, grip strength, and the incidence of CMDs, and 2) investigate associations between combined fitness levels with the incidence of CMDs.

8.3. Methods

8.3.1. Participants

The UK Biobank is a prospective cohort study that recruited 502,682 participants (5.5% response rate) aged 40 to 69 years from the general population that I describe in Chapter 2.4.2. My sample

included participants who had a valid measure of baseline symptoms and at least one measure of grip strength or cardiorespiratory fitness (n = 491,278) at baseline. For the longitudinal analyses, I restricted the sample to participants who also had a completed Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7) at follow up (2017) and at least one measure of grip strength or cardiorespiratory fitness (n = 152,978).

8.3.2. Exposure(s): Cardiorespiratory fitness and grip strength

A subset of Biobank participants completed fitness tests between August 2009 and December 2010. Participants completed a 6-minute submaximal exercise test on a stationary bike (eBike Comfort Ergometer, General Electric). Individualised protocols were developed to calculate an appropriate workload based on participants' age, height, weight, sex, and resting heart rate. A four-lead ECG was used to monitor heart rate before, during, and in the recovery phase following the test.

I followed protocols from previous studies to estimate cardiorespiratory fitness from the submaximal tests (546,547). I first estimated the work rate participants would have achieved in a maximal fitness test. The maximal work rate maps onto maximum oxygen consumption (VO_{2max}), which is an indicator of cardiorespiratory fitness. I estimated maximal work rate (measured in watts) from heart rate before the test, maximum heart rate during the test, and work rate at the end of the test using linear regression. I then extrapolated the regression line to participants' age-predicted maximal heart rate using the equation: 208 – 7 x age(548), assuming a linear relationship.

To estimate maximum oxygen consumption I used the equation: 7 + (10.8 x maximal work rate (in watts))/body weight (in kg))(549). Maximal oxygen consumption is a continuous measure of cardiorespiratory fitness expressed in millilitres of oxygen per kilogram of body weight per minute (ml kg-1.min-1). I used metabolic equivalents (METs) to express cardiorespiratory fitness output, where 1 MET is 3.5 ml kg-1.min-1.

Grip strength was measured using a Jamar j00105 hydraulic hand dynamometer in each hand. Participants grasp the handle sitting in an upright position and squeeze as strongly as possible for 3 seconds. The output was expressed in kilograms (kg), taking the mean value of each hand.

For the main analysis, I created age- and sex-adjusted tertiles of grip strength and cardiorespiratory fitness, in line with previous studies (547). The tertiles represent low, medium, and high fitness groups. These groupings were to aid interpretation and account for possible non-linear associations between fitness and mental health. I also used continuous cardiorespiratory fitness and grip strength exposure variables in the secondary analysis, with cardiorespiratory fitness presented in METs and grip strength in 5kg increments as in previous studies (546). I chose to focus this part of the analysis on participants with concordant low, medium, and high cardiorespiratory and muscular fitness groupings to aid interpretability and facilitate comparisons with the main analysis.

8.3.3. Outcome(s): Common mental health symptoms

At baseline (2006 to 2010), common mental health symptoms were measured using 3 questions from Patient Health Questionnaire-9 (PHQ-9) that cover core features of depression (low mood, anhedonia, and lethargy) (492). It contains an additional question adapted from the PHQ-9 to cover tenseness, a common feature of anxiety disorders. The questionnaire uses a four-point ordinal scale from 0 (not at all) to 3 (nearly every day), with scores ranging from 0 to 12. Ultra-brief adaptations of the PHQ-9 have good agreement with longer scales for both depression and anxiety symptoms (496). I used a continuous symptom score for this measure due to the lack of a valid cut-off.

At follow-up, common mental health symptoms were measured in a 2017 Mental Health Questionnaire, which included the PHQ-9 and Generalised Anxiety Disorder-7 (GAD-7) questionnaire. The PHQ-9 is a depression screening instrument with nine questions on a four-point ordinal scale from 0 (not at all) to 3 (nearly every day) (492). Total scores range from 0 to 27, with higher scores indicating greater symptom severity. I defined possible incidences of depression using an established cut-off (scores ≥10) for the main analysis, and a continuous symptom score (secondary analysis). Previous studies show that a cut-off score of ≥10 has 88% sensitivity and specificity for identifying incident major depression (492).

The GAD-7 is a 7-item anxiety scale using the same four-point ordinal scale as the PHQ-9(493). Scores range from 0 to 21. I defined possible incidences of generalised anxiety disorders using an established cut-off (scores ≥10) in the main analysis, and continuous symptom score for the secondary analysis. This cut-off has a sensitivity of 89% and specificity of 82% (493).

8.3.4. Confounding variables

I constructed a DAG of the proposed causal assumptions between exposure, outcome, and confounding variables that informed our analysis (Figure 13 of Supplementary Materials). Possible confounding variables for this analysis include: Age, sex, socioeconomic position (household income of <£18,000, £18,000 to £30,999, £31,000 to £51,999, £52,000 to £100,000, and >£100,0000), baseline mental health symptoms, smoking status (current, former, or never), total physical activity (total daily minutes spent walking and in moderate or vigorous activity from the International Physical Activity Questionnaire (IPAQ)), education level (degree, A/AS-level, O-level/GCSE, CSE, NVQ/HND/HNC, other qualifications, none), parental depression, chronic illness (self-reported yes or no), and diet (pieces of fruit and vegetable per day).

My DAG indicated that adiposity (body fat percentage) could be on the causal pathway between fitness and common mental health symptoms. To avoid over-adjustment, I only include body fat as a confounding variable in the sensitivity analysis. Other variables used in the sensitivity analyses include a self-reported indicator of having visited a doctor or psychiatrist for depression, nerves, or anxiety in the past to identify participants with a history of common mental disorders.

8.3.5. Analysis

Descriptive variables include means and standard deviations for normally distributed variables and medians and interquartile ranges for non-normally distributed variables.

8.3.5.1. Main analysis

The main analysis consists of two components. The first aimed to determine longitudinal associations between individual domains of cardiorespiratory fitness, grip strength, and common mental health symptoms and disorders (aim 1). The second aimed to determine longitudinal associations between combined fitness and the incidence of common mental disorders (aim 2).

Firstly, I used logistic regression models with depression and anxiety incidence as outcomes and grip strength and cardiorespiratory fitness as categorical exposures, in separate models. I ran crude and fully adjusted iterations of all models. Secondly, the analysis of the combined role of

cardiorespiratory fitness and grip strength derived logistic regression models with the same mental health outcomes and adjustments as my initial longitudinal models but using combined fitness as the main categorical exposure. Combined fitness includes both cardiorespiratory fitness and grip strength, which were positively correlated (r = 0.40). I compared combinations of cardiorespiratory fitness and grip strength, using the high cardiorespiratory fitness and high grip strength group as the reference category.

8.3.5.2. Secondary and sensitivity analysis

In the secondary analysis, I examined cross-sectional associations between cardiorespiratory fitness and grip strength with common mental health symptoms at baseline (n = 491,278). I used negative binomial regression models as with symptom scores on a quasi-continuous scale. I used negative binomial regression to account for the high positive skew and over-dispersion of the symptom scores. I presented the output of negative binomial regressions as a percentage change in symptom scores. High fitness was the reference category for both exposure models.

I also reran the first part of the main analysis using continuous exposure variables (per 1-MET for cardiorespiratory fitness and per 5kg for grip strength). I then created age and sex-standardised z scores for each exposure and ran the same models with age- and sex-exposure as multiplicative interaction terms to examine possible interactions.

I also carried out several sensitivity analyses determined a priori to examine the robustness of my main findings and explore alternative explanations. These included rerunning the longitudinal models from part 1 of the main analysis and in separate models: 1) excluding participants with a self-reported history of depression or anxiety prior to the baseline to further reduce the risk of residual confounding from reverse causation, 2) including adiposity as a possible confounding variable to examine the alternative hypothesis that adiposity is not on the causal pathway, and 3) using lower thresholds for defining depression (PHQ ≥8) and anxiety (GAD-7 ≥8) disorders (550,551).

I then performed an adjusted multivariate linear model with cardiorespiratory fitness and grip strength as continuous exposures and PHQ-9 and GAD-7 scores as continuous outcomes. This was to assess whether both exposures were associated with depression and anxiety outcomes independently by testing each exposure coefficient across the equations for both outcomes. I also calculated e-values to assess the plausibility of unmeasured confounding affecting my findings (466). The e-value estimates the required strength of an unmeasured confounding variable that would nullify the observed associations between our exposure and outcomes, while accounting for all measured covariates (235).

I reran the first part of the main longitudinal analysis in a full cohort with imputed missing data to assess the risk selection bias within our longitudinal sample (n = 152,978). I used multiple imputation models with chained equations to estimate missing data. I generated 50 datasets for 152,978 in the longitudinal analysis. The method uses separate distributions per imputed variable. Non-normally distributed continuous variables were imputed using predictive mean matching. The results from all 50 datasets are pooled together with corrected standard errors according to Rubin's rule. The multiple imputation model included all variables used in our analysis for the exposure, outcome, and covariates, including those in the sensitivity analysis.

8.3.6. Results

8.3.6.1. Participants

At baseline, there were 491,278 participants with complete cardiorespiratory fitness or grip strength data. For the adjusted longitudinal (main) analysis, 147,141 participants had complete data for grip strength and 22,667 for cardiorespiratory fitness. For the cross-sectional (secondary) analysis, there were 465,757 participants in the fully-adjusted analysis for grip strength and 60,838 for cardiorespiratory fitness data. According to the PHQ-9 and GAD-7 scales, 9,156 (5.99%) participants met the criteria for depression, 5,282 (3.45%) for anxiety, and 11,295 (7.39) for either common mental disorder at the 7-year follow-up. Tables 7 and 8 respectively contain baseline characteristics of participants by the cardiorespiratory fitness group and by grip strength group.

Table 7. Baseline participant characteristics by cardiorespiratory fitness groupings

			Cardiorespiratory fitness (n = 63,372)		
Variable		All	Low	Medium	High
N		491,278	17,952 (28.33)	20,257 (31.97)	25,163 (39.71)
Sex (%)	Women	267,392 (54.43)	9621 (53.59)	10991 (54.26)	13409 (53.29)
	Men	223,886 (45.57)	8331 (46.41)	9266 (45.74)	11754 (46.71)
Age	Mean (SD)	56.559 (8.090)	57.013 (7.837)	56.63 (8.10)	56.20 (8.34)
Ethnicity	White	463630 (94.72)	15221 (85.18)	18524 (91.88)	23852 (95.13)
	Mixed	2884 (0.59)	174 (0.97)	180 (0.89)	202 (0.81)
	South Asian	7732 (1.58)	933 (5.22)	635 (3.15)	359 (1.43)
	Black	1497 (0.31)	1086 (6.08)	484 (2.40)	274 (1.09)
	Chinese	9347 (1.91)	63 (0.35)	81 (0.40)	126 (0.50)
	Other	4367 (0.89)	392 (2.19)	257 (1.27)	260 (1.04)
Household income	Less than 18,000	95316 (22.86)	3807 (25.19)	3340 (19.02)	3480 (15.62)
	18,000 to 30,999	106335 (25.50)	4164 (27.56)	4399 (25.05)	5035 (22.60)
	31,000 to 51,999	108634 (26.06)	3844 (25.44)	4773 (27.18)	5844 (26.23)
	52,000 to 100,000	84405 (20.24)	2633 (17.42)	3881 (22.10)	5692 (25.55)
	Greater than 100,000	22248 (5.34)	663 (4.39)	1165 (6.64)	2229 (10.00)
Education level	None	83697 (17.35)	2701 (13.47)	2502 (10.00)	8273 (13.18)
	College or University degree	157403 (32.63)	7090 (35.36)	10741 (42.94)	22925 (36.52)
	A levels/AS levels or equivalent	54196 (11.24)	2370 (11.82)	3096 (12.38)	7489 (11.93)
	O levels/GCSEs or equivalent	103278 (21.41)	4385 (21.87)	4881 (19.51)	13298 (21.18)
	CSEs or equivalent	26339 (5.46)	1124 (5.61)	1161 (4.64)	3462 (5.51)

	NVQ or HND or HNC or equivalent	32125 (6.66)	1363 (6.80)	1380 (5.52)	4096 (6.52)
	Other professional qualifications e.g., nursing, teaching	25310 (5.25)	1020 (5.09)	1251 (5.00)	3232 (5.15)
Parental depression	No	434749 (91.14)	15991 (91.73)	17976 (91.07)	22204 (90.40)
	Yes	42248 (8.86)	1441 (8.27)	1762 (8.93)	2357 (9.60)
Chronic illness or disability	No	322634 (65.80)	11236 (62.76)	14242 (70.39)	18432 (73.29)
	Yes	156670 (31.95)	6169 (34.46)	5545 (27.40)	6294 (25.03)
Body fat %	mean (SD)	31.458 (8.545)	34.188 (8.425)	31.506 (7.958)	28.696 (7.853)
Grip strength per 5kg	mean (SD)	6.121 (2.205)	5.84 (2.105)	5.978 (2.117)	6.149 (2.118)
cardiorespiratory fitness, METs	mean (SD)	9.951 (2.971)	7.171 (1.438)	9.311 (1.519)	12.452 (2.606)
Daily minutes of physical activity	mean (SD)	125.429 (145.591)	114.057 (139.592)	127.198 (137.176)	140.215 (139.356)
Daily pieces of fruit and vegetables	mean (SD)	4.898 (2.751)	4.793 (2.835)	4.876 (2.822)	5.022 (2.747)
Smoking status	Never	35424 (56.08)	10415 (58.25)	11304 (55.97)	13705 (54.62)
	Previous	21964 (34.77)	6023 (33.68)	7032 (34.82)	8909 (35.51)
	Current	5779 (9.15)	1443 (8.07)	1859 (9.21)	2477 (9.87)

Table 8. Baseline participant characteristics by cardiorespiratory fitness groupings

			Grip strength (n = 491,108)		
Variable		All	Low	Medium	High
N (%)		491,278	151,300 (30.81)	165,629 (33.73)	174,179 (35.47)
Sex (%)	Women	267,392 (54.43)	82151 (54.30)	89563 (54.07)	95591 (54.88)
	Men	223,886 (45.57)	69149 (45.70)	76066 (45.93)	78588 (45.12)
Age	Mean (SD)	56.559 (8.090)	56.695 (8.023)	56.888 (7.853)	56.12 (8.344)
Ethnicity	White	463630 (94.72)	138717 (92.06)	157700 (95.52)	167213 (96.27)
	Mixed	2884 (0.59)	922 (0.61)	878 (0.53)	1084 (0.62)
	South Asian	7732 (1.58)	2465 (1.64)	2296 (1.39)	2971 (1.71)
	Black	1497 (0.31)	665 (0.44)	505 (0.31)	327 (0.19)
	Chinese	9347 (1.91)	5850 (3.88)	2421 (1.47)	1076 (0.62)
	Other	4367 (0.89)	2054 (1.36)	1301 (0.79)	1012 (0.58)
Household income	Less than 18,000	95316 (22.86)	36406 (29.05)	31196 (22.10)	27714 (18.41)
	18,000 to 30,999	106335 (25.50)	32921 (26.27)	36302 (25.72)	37112 (24.66)
	31,000 to 51,999	108634 (26.06)	29752 (23.74)	37150 (26.32)	41732 (27.73)
	52,000 to 100,000	84405 (20.24)	21012 (16.77)	28828 (20.43)	34565 (22.97)
	Greater than 100,000	22248 (5.34)	5214 (4.16)	7656 (5.42)	9378 (6.23)
Education level	None	83697 (17.35)	31784 (21.46)	27705 (17.02)	24208 (14.12)
	College or University degree	157403 (32.63)	43184 (29.16)	53043 (32.59)	61176 (35.67)

	A levels/AS levels or equivalent	54196 (11.24)	15741 (10.63)	18360 (11.28)	20095 (11.72)
	O levels/GCSEs or equivalent	103278 (21.41)	31392 (21.19)	35533 (21.83)	36353 (21.20)
	CSEs or equivalent	26339 (5.46)	8713 (5.88)	8835 (5.43)	8791 (5.13)
	NVQ or HND or HNC or equivalent	32125 (6.66)	9750 (6.58)	10705 (6.58)	11670 (6.80)
	Other professional qualifications e.g., nursing, teaching	25310 (5.25)	7548 (5.10)	8562 (5.26)	9200 (5.36)
Parental depression	No	434749 (91.14)	132770 (90.67)	146749 (91.11)	155230 (91.58)
	Yes	42248 (8.86)	13667 (9.33)	14317 (8.89)	14264 (8.42)
Chronic illness or disability	No	322634 (65.80)	86103 (57.04)	112045 (67.74)	124486 (71.55)
	Yes	156670 (31.95)	61022 (40.43)	49588 (29.98)	46060 (26.47)
Body fat %	mean (SD)	31.458 (8.545)	32.12 (8.679)	31.282 (8.522)	31.054 (8.421)
Grip strength per 5kg	mean (SD)	6.121 (2.205)	4.498 (1.602)	6.076 (1.709)	7.575 (2.075)
cardiorespiratory fitness, METs	mean (SD)	9.951 (2.971)	9.722 (2.887)	9.966 (3.002)	10.191 (3.002)
Daily minutes of physical activity	mean (SD)	125.429 (145.591)	113.267 (141.988)	126.639 (145.651)	133.927 (147.834)
Daily pieces of fruit and vegetables	mean (SD)	4.898 (2.751)	4.813 (2.925)	4.883 (2.691)	4.963 (2.676)
Smoking status	Never	83297 (55.32)	83297 (55.32)	90837 (55.03)	93694 (53.96)

	Previous	50129 (33.29)	50129 (33.29)	57063 (34.57)	62440 (35.96)
	Current	17153 (11.39)	17153 (11.39)	17159 (10.40)	17504 (10.08)

8.3.6.2. Main analysis

Longitudinal models for cardiorespiratory fitness and grip strength as separate exposures with incident depression, anxiety, and depression or anxiety as outcome variables are presented in Table 9. Adjusted models indicate that low cardiorespiratory fitness was associated with a 1.596 (95% CI = 1.378 to 1.849 $p < 0.001$) and medium cardiorespiratory fitness was associated with a 1.154 (95% CI = 0.999 to 1.334, $p = 0.051$) increase in the odds of depression compared with the high cardiorespiratory fitness group. Low cardiorespiratory fitness was associated with a 1.230 (95% CI = 1.020 to 1.483, $p = 0.030$) increase in the odds of anxiety compared to high cardiorespiratory fitness. Low cardiorespiratory fitness was associated with a 1.485 (95% CI = 1.301 to 1.694, $p < 0.001$) and medium cardiorespiratory fitness with a 1.141 (95% CI = 1.005 to 1.297, $p = 0.041$) increase in the odds of either common mental disorder compared to high cardiorespiratory fitness.

Low grip strength was associated with a 1.410 (95% CI = 1.355 to 1.490, $p < 0.001$) and medium with a 1.126 (95% CI = 1.066 to 1.189, $p < 0.001$) increase in the odds of depression compared with high grip strength. Compared with high, low grip strength was associated with a 1.380 (95% CI = 1.286 to 1.480, $p < 0.001$) and medium with a 1.145 (95% CI = 1.068 to 1.228, $p < 0.001$) increase in the odds of anxiety. Low grip strength was associated with 1.381 (95% CI = 1.315 to 1.452, $p < 0.001$) and medium with 1.116% (95% CI = 1.063 to 1.172, $p < 0.001$) higher odds of depression or anxiety.

Table 9. Longitudinal associations between cardiorespiratory fitness and grip strength as separate exposures and common mental disorders

		Common mental disorders												
		Crude						Adjusted						
			Depression		Anxiety		Depression or anxiety			Depression		Anxiety		Depression or anxiety	
	Fitness group	N	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P	N	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	p
Cardiorespiratory fitness	Low	23,399	1.671 (1.455, 1.919)	< 0.001	1.228 (1.027, 1.469)	0.024	1.529 (1.350, 1.732)	< 0.001	22,667	1.596 (1.378, 1.849)	< 0.001	1.230 (1.020, 1.483)	0.030	1.485 (1.301, 1.694)	< 0.001
	Medium		1.172 (1.020, 1.347)	0.025	1.072 (0.904, 1.270)	0.425	1.160 (1.027, 1.311)	0.017		1.154 (0.999, 1.334)	0.051	1.067 (0.894, 1.272)	0.427	1.141 (1.005, 1.297)	0.041
	High		Reference							Reference					
Grip strength	Low	152,853	1.538 (1.461, 1.619)	< 0.001	1.454 (1.360, 1.554)	< 0.001	1.486 (1.418, 1.556)	< 0.001	147,141	1.410 (1.335, 1.490)	< 0.001	1.380 (1.286, 1.480)	< 0.001	1.381 (1.315, 1.452)	< 0.001
	Medium		1.118 (1.061, 1.178)	< 0.001	1.123 (1.051, 1.201)	0.001	1.107 (1.056, 1.160)	< 0.001		1.126 (1.066, 1.189)	< 0.001	1.145 (1.068, 1.228)	< 0.001	1.116 (1.063, 1.172)	< 0.001
	High		Reference							Reference					

OR = odds ratio; CIs = confidence intervals; cardiorespiratory fitness = cardiorespiratory fitness

Adjusted for age, sex, deprivation, smoking status, baseline symptoms, total physical activity, education, parental depression, chronic illness, and diet.

Table 10 shows the results from the combined fitness exposures of cardiorespiratory fitness and grip strength. Compared to the high fitness group (high cardiorespiratory fitness and grip strength), low fitness (low cardiorespiratory fitness and low strength) was associated with 1.981 (95% CI = 1.553, 2.527, $p < 0.001$) and medium with 1.427 (95% CI = 1.117 to 1.825, $p = 0.004$) higher odds of depression. Low fitness was associated with 1.599 (95% CI = 1.148 to 2.118, $p = 0.004$) higher odds of an anxiety disorder, compared with high fitness. Low fitness was associated with a 1.814 (95% CI = 1.461 to 2.252, $p < 0.001$) and medium with a 1.325 (95% CI = 1.067 to 1.645, $p = 0.011$) increase in the odds of depression or an anxiety disorder, compared with high combined fitness.

Table 10. Longitudinal associations between combined fitness categories and common mental disorders

	Common mental disorders												
	Crude							Adjusted					
	Depression		Anxiety		Depression or anxiety			Depression		Anxiety		Depression or anxiety	
Fitness group (n in group)	**N**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**N**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**p**
Low both (7,054)	23,330	2.099 (1.667 2.645)	< 0.001	1.518 (1.133, 2.036)	0.024	1.866 (1.519, 2.295)	< 0.001	22,605	1.981 (1.553, 2.527)	< 0.001	1.559 (1.148, 2.118)	0.004	1.814 (1.461, 2.252)	< 0.001
Medium both (7,071)		1.389 (1.096, 1.758)	0.006	1.118 (0.833, 1.500)	0.459	1.278 (1.037, 1.574)	0.021		1.427 (1.117, 1.825)	0.004	1.209 (0.894, 1.637)	0.217	1.325 (1.067, 1.645)	0.011
High both (8,601)		Reference							Reference					

OR = odds ratio; CIs = confidence intervals; cardiorespiratory fitness = cardiorespiratory fitness

Adjusted for age, sex, deprivation, smoking status, baseline symptoms, total physical activity, education, parental depression, chronic illness

8.3.6.3. Secondary analysis and sensitivity analysis

The fully-adjusted cross-sectional analysis examining associations between cardiorespiratory fitness and common mental health symptoms included 63,372 participants. The models suggest a biological gradient with the medium cardiorespiratory fitness group associated with a 7% higher symptom score (95% CI =, 4.4% to 9.6%, p < 0.001) and low cardiorespiratory fitness associated with 17.5% higher symptom score (95% CI = 14.6% to 20.6%, p < 0.001) compared to the high cardiorespiratory fitness group. A similar association was observed for grip strength: compared to the high grip strength group, the medium group had 8.6% (95% CI = 7.7% to 9.6%, p < 0.001) higher scores and the low group had 26.8% (95% CI = 25.7% to 27.9%, p < 0.001) higher scores.

Fully adjusted longitudinal models with a continuous exposure suggest each 1 MET increase in cardiorespiratory fitness was associated with a 2.4% lower depression score (95% CI = -3% to -1.8%, p < 0.001) and a 1.22% lower anxiety score (95% CI = -2% to -0.3%, p < 0.001). Each 5kg increase in grip strength was associated with a 4.4% lower depression score (95% CI = -4.8% to -3.9%, p < 0.001) and a 4.8% lower anxiety score (95% CI = -5.4%, -4.2%, p < 0.001).

There was some evidence of an interaction between grip strength and sex (p = 0.018), and grip strength and age (p = 0.001) for anxiety disorders. For men, each 5kg increase in grip strength was associated with reduced odds of an anxiety disorder (odds ratio = 0.901, 95% CI = 0.855, 0.950, p < 0.001), for women this reduction was greater (odds ratio = 0.840, 95% CI = 0.809, 0.873, p < 0.001). In those aged <54, a 5kg increase in grip strength was associated with 12.5% reduction in odds of anxiety (odds ratio = 0.875, 95% CI = 0.826, 0.927, p < 0.001), ages ≥54 to 65 with 22.8% reduced odds (odds ratio = 0.772, 95% CI = 0.711, 0.837, p < 0.001) and those ≥65 with 27.3% reduced odds (odds ratio = 0.727, 95% CI = 0.623, 0.850, p < 0.001).

The results of these sensitivity analyses (presented in Tables 16 to 19 of Supplementary Materials) indicate no substantial differences from my main findings. The results from my analyses in a fully imputed cohort were consistent with the findings in the main analysis (Table 19 of Supplementary Materials). The results of the multivariate linear model indicate that cardiorespiratory fitness is independently associated with both PHQ-9 and GAD-7 outcomes, following a test of the coefficient across both equations ($F(2, 23{,}399) = 35.36$, $p < 0.001$). Grip strength was also independently associated with each outcome ($F(2, 152{,}853) = 207.09$, $p < 0.001$). The e-values estimates the required strength of an unmeasured confounding variable to nullify the observed associations between my exposures and outcomes. For longitudinal models of the association between low cardiorespiratory fitness (vs. high) with depression were 2.57 (CI = 2.1), with anxiety was 1.76 (CI = 1.16), and depression or anxiety was 2.33 (CI = 1.93). The odds ratios for observed confounding variables in these models ranged between 0.65 to 2.07. For associations between low grip strength (vs. high) with depression, the e-value was 2.17 (CI = 2), with anxiety it was 2.1 (CI = 1.89), and for depression or anxiety, it was 2.11 (CI = 1.96). Observed confounding variables in these models had odds ratios ranging from 0.64 to 2.16. For low combined fitness (vs high), the e-value was 3.38 (CI = 2.48) for depression, 2.49 (CI = 1.56) for anxiety, and 3.03 (CI = 2.28) for depression or anxiety. Observed confounding variables in these models had odds ratios ranging from 0.60 to 2.06.

8.4. Discussion

8.4.1. Main findings

To the best of my knowledge, this was the first prospective study to examine associations between individual and combined cardiorespiratory fitness and grip strength with the incidence of common mental disorders in the general population. Low combined fitness (low cardiorespiratory fitness and

low grip strength) was associated with 1.8 times the odds of a common mental disorder compared to high combined fitness, with the medium combined fitness group having 1.3 times the odds. Low combined fitness was associated with 2.0 and 1.6 times higher the odds of depression and anxiety disorders, respectively. When looking at cardiorespiratory fitness and grip strength as separate exposures, the effect sizes were smaller. I found that compared with high cardiorespiratory fitness, low cardiorespiratory fitness was associated with 1.5 times higher odds of a common mental disorder incidence and low grip strength with 1.4 times higher odds. There was some evidence of a dose-response relationship between fitness and the incidence of common mental disorders. I also found that associations with grip strength and anxiety disorders had higher odds ratios for women than men, and for older than younger adults.

These findings were robust to a series of sensitivity analyses. The findings are unlikely to be nullified by an unmeasured confounding variable according to the e-values. For example, the e-value for combined fitness groups indicates an unmeasured confounding variable would require an association of at least OR = 3.0 with fitness and common mental disorders to nullify the observed associations. The observed confounding variables had ORs ranging from 0.6 to 2.1, suggesting an OR of 3 for an unmeasured confounding variable is unlikely. My results were also consistent in a full cohort with imputed missing data.

My study is novel in demonstrating that the combination of low cardiorespiratory fitness and grip strength is associated with a higher risk of common mental disorders than either type of fitness alone. This finding highlights the importance of focusing on multiple components of fitness and their associations with mental health. Findings for individual exposures align with results my meta-analyses of 4 studies in Chapter 7 that suggested low cardiorespiratory fitness was associated with an increased risk of common mental disorders of similar effect size (hazard ratio = 1.47, 95% CI = 1.23 to 1.76), which also suggested a dose-response relationship. These findings build on previous prospective studies in smaller samples (181–183,226) to suggest that low grip strength is a possible risk factor for common mental disorders in adult men and women.

These findings also coincide with the results of Chapter 6 (Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms), which showed that replacing sedentary behaviour with moderate-to-vigorous activity was associated with lower CMD symptom scores in Biobank participants. Moderate-to-vigorous physical activity can be of a sufficient intensity to improve different aspects of physical fitness. However, light activity is unlikely to be sufficient to improve physical fitness, even in highly sedentary adults (529–532).

8.4.2. Strengths and limitations

This study benefitted from a large sample size and a 7-year follow-up period. It included objective measures of fitness administered by trained staff using validated protocols. The prospective study design, dose-response relationship, consistent results from several sensitivity analyses (including the removal of participants with a history of depression or anxiety), and multiple imputation models, suggest possible biases such as attrition bias, reverse causation, or unmeasured confounding are unlikely to explain our results. The use of DAGs to inform the analysis also improved my ability to estimate causal effects.

The study also had several limitations. I estimated cardiorespiratory fitness from a submaximal exercise test rather than a gold-standard maximal exercise with gas analysis (159). However, these tests are prohibitively expensive in large samples and I are aware of only one previous study (n = 1,575) in this area using these gold-standard exercise protocols, which I identified in Chapter 7

(Chapter 7: The association between cardiorespiratory fitness and the incidence of CMDs) (251). Exercise testing was a late addition to Biobank data collection protocols in 2009 and only available for ~14% of participants. These participants were representative of the wider Biobank sample in terms of sociodemographic and biological characteristics (547). However, the cohort is unrepresentative of several sociodemographic and health-related factors discussed in Chapter 6 that could affect my associations here. The lack of physical fitness data in representative cohort studies in the UK makes it difficult to determine whether fitness levels in Biobank are comparable with the wider population. While I used a sex and age-adjusted tertile-based approach from previous studies (547), it is possible that the medium fitness group is not representative of the medium or average level of fitness in the population. However, the findings should still capture broad non-linear trends from the models with categorical exposure and linear trends from the continuous exposures.

The observational nature of this study also includes the risk of unmeasured confounding biasing my results. The e-values suggest it is unlikely that a single unmeasured confounding variable would explain our main findings. However, multiple unmeasured variables together might explain the associations that I found. There may also be some measurement error in the self-reported scales used to record common mental health symptoms compared with clinical diagnoses. However, these scales allowed me to assess symptoms in people who do not seek treatment or are without a formal mental health diagnosis and are extensively validated. As highlighted in Section 1.2.1., the Adult Psychiatric and Morbidity Survey found that 39% of people who met the criteria for a CMD were not receiving treatment (7).

Another limitation is that it was also not possible to reliably estimate CMD incidence at baseline, only symptoms. CMD symptoms were measured with a shorter version of the PHQ-9 at baseline, with only 4 items. These measures differ from the full PHQ-9 and GAD-7 measures used at follow-up and may introduce measurement bias into my results. However, the brief PHQ-4 scale correlates well with full scales for CMD symptoms (496). In a community-based sample of 5,003 middle-aged adults the PHQ-4 showed good internal consistency (Cronbach's alpha = 0,82), factorial and structural validity.

I also focused one part of the analysis on people who had concordant low, medium, and high cardiorespiratory and muscular fitness to assess combined fitness, which excluded people with discordant fitness groupings, such as low-medium or high-low fitness. I chose this approach to improve the interpretability of my findings and allow direct comparison with the main analysis, but it limits how many different potential combinations of fitness I was able to assess in this study and could introduce bias. However, taken together with the main findings in the complete case analysis and fully-imputed sample using categorical and continuous exposure measures, these findings still highlight that associations between low, medium, and high fitness with CMD symptoms differ when comparing each fitness type in isolation or in combination.

8.4.3. Implications and future research

Aerobic and resistance training improves different aspects of physical fitness and randomised controlled trials have found that both types of training can each reduce common mental health symptoms (75,76,79,80,82,256,458). The findings of Chapters 7 and 8 indicate that multiple aspects of fitness are inversely associated with CMDs in the population. Population-level strategies to promote physical activities that improve cardiorespiratory and muscular fitness could reduce CMD incidence in the population. While broadly increasing physical activity will be beneficial (119,120), structured aerobic and resistance exercises with sufficient intensity to improve fitness may have a

greater effect on risk reduction. These combined approaches may also have additive benefits for reducing the physical health risks (541–544) associated with CMDs.

It is possible to modify fitness through simple, low-cost physical activity interventions, including in people with common mental health symptoms (124). Substantial improvements in fitness are possible within a short timeframe. For example, one study in previously untrained older adults suggested that 3 weeks of regular aerobic exercise was sufficient to improve cardiorespiratory fitness by 31%, which continued to increase with further training (528). My data suggest that a 31% increase would equate to moving from low to medium cardiorespiratory fitness and reduce the odds of a common mental disorder by 14.1%. Similar improvements in grip strength over the same period would further reduce the odds of a common mental disorder by 32.5%.

Future research should also examine these associations of physical fitness and CMD symptoms in adolescents. The studies identified in Chapter 7 were all in adult populations and little is known about whether physical fitness might be protective against CMD symptoms in younger age groups. My findings in Chapters 4 and 5 highlight the protective association of light but not moderate-to-vigorous activity with CMD symptoms, which could suggest physical activity for improving fitness (e.g., exercise) is more impactful in adults than adolescents. However, robust data on the associations of cardiorespiratory and muscular fitness with CMD symptoms in adolescents is necessary to examine this.

Objective markers of physical fitness approximate habitual physical activity and could also be useful population-level indicators of mental health risk in their own right. Most studies of associations between physical activity and the incidence of common mental disorders use self-reported activity data (119,120). My study suggests that objective markers of physical fitness could be useful indicators of mental health risk in the population, as they are for physical health risks (157,534). Meta-analyses suggest that high physical activity is associated with a 0.83 (95% CI = 0.79 to 0.88) and 0.74 (95% CI = 0.62 to 0.88)(119,120) lower odds of a depression and anxiety disorders respectively. However, effect sizes for low (combined or individual) physical fitness appear larger in this study and my meta-analysis in Chapter 7. Objective markers of fitness are increasingly recognised as stronger indicators of cardiovascular disease than physical activity (164,165), and the same may be true for mental health. Increased efforts to collect population-level physical fitness data could inform our understanding of mental health and the development of public health strategies.

Future studies should also consider methods that can minimise or reduce bias from confounding and reverse causation to assess associations of cardiorespiratory and muscular fitness with CMD symptoms. For example, instrumental variable analysis uses a different set of assumptions without relying on having full and accurate measures of all confounding variables. Mendelian randomisation is a form of instrumental variable analysis that uses genetic data that is randomised at birth to assess potentially causal effects in observational data without interference from confounding, including from reverse causation (552). A 2019 study used Mendelian randomisation methods to demonstrate an inverse association between total physical activity volume and depression incidence in population-based adults (484). The study also found no evidence that depression influenced total physical activity volume, suggesting that the association is unidirectional. Future studies should consider using instrumental variable analysis to determine whether similar associations exist for physical fitness and CMD symptoms. I return to instrumental variable analysis and Mendelian randomisation methods in Section 9.4.

8.4.4. Conclusions

Low cardiorespiratory fitness and grip strength are both associated with an increased incidence of common mental disorders, and the combination of low cardiorespiratory fitness and low grip strength was associated with the highest level of risk in adults. These findings align with the association between cardiorespiratory fitness and CMD symptoms that I found in my systematic review in Chapter 7 (Chapter 7: The association between cardiorespiratory fitness and the incidence of CMDs). It also relates to the finding in Chapter 6 (Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms) that replacing sedentary behaviour with moderate-to-vigorous activity was associated with lower CMD symptom scores in Biobank participants. Physical fitness could be an objectively measurable indicator and a modifiable risk factor for CMDs in the adult population. Public health approaches to improve physical fitness through combined aerobic and resistance activities could reduce the incidence of CMDs and improve physical health outcomes for people with mental health symptoms. Further research is necessary to determine whether similar associations exist in adolescents and complement the findings in Chapters 4 and 5.

9. Chapter 9: Overall discussion, implications, conclusions of this thesis

9.1. Summary

In this chapter, I summarise the main findings in Chapters 3 to 8 together and triangulate them with existing literature. I discuss how the findings fit into a broader public health narrative and the potential implications for public health policies to prevent CMDs in the population. I discuss the future directions for research to build on my findings here and the wider literature. I also highlight several key strengths and limitations of this thesis to complement earlier discussions of the individual strengths and limitations in each chapter.

9.2. Key findings of this thesis

I will outline the key findings per objectives of this thesis:

Objective 1) Develop a framework to describe the biological and psychosocial pathways through which physical activity may influence depressive symptoms (Chapter 3).

My narrative review highlights several key mechanisms that may underlie the relationship between physical activity and depressive symptoms in a novel framework to guide future research (Chapter 3). Physical activity has a substantial physiological and psychological impact that implicates a wide range of possible mechanisms. In my review, I highlighted changes in neuroplasticity, inflammation, oxidative stress, the endocrine system, self-esteem, and social support as possible mechanisms. These mechanisms likely vary across individuals and interact to produce antidepressant effects of varying magnitudes. However, it remains unclear whether these mechanisms are applicable to prevention and there was a lack of direct evidence for their mediating role in the association between physical activity and CMD symptoms, particularly for psychosocial factors.

To my knowledge, this study provided the first comprehensive overview of the potential biological and psychosocial mediators that could explain the association between physical activity and depressive symptoms. Providing a series of plausible mechanisms of action can strengthen the arguments that the associations between physical activity and CMD symptoms in this thesis and the wider literature are causal. The review may also act as a call for further research to understand these mechanisms in the context of physical activity as a preventive measure for CMD symptoms.

Objective 2) Examine the prospective association of device-measured physical activity and sedentary behaviour with CMD symptoms across the lifespan (Chapters 4, 5, and 6).

I found consistent evidence that high sedentary behaviour is a risk factor for CMD symptoms in adolescents and adults in the population. Daily time in sedentary behaviour was positively associated with CMD symptoms in all studies. However, the progression of statistical methods in Chapters 4 to 6 prohibits a succinct summary of the effect sizes and dose-response associations. An hour of daily light-intensity physical activity between ages 12 and 16 was associated with 8 to 11% lower depression scores at 18 (Chapter 4: Device-measured physical activity and sedentary

behaviour and depressive symptoms throughout adolescence). Theoretically replacing an hour of sedentary behaviour with light-intensity physical activity between 12 and 16 was associated with 12% to 16% lower anxiety scores at age 18 (Chapter 5: Device-measured physical activity and anxiety symptoms during adolescents). Theoretically replacing an hour of sedentary behaviour with light-intensity physical activity in adults at baseline (mean age = 56) was associated with 1.3% lower depression scores and 4.5% higher anxiety scores at a 2-year follow-up (Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms). There were no clear associations between moderate-to-vigorous physical activity and CMD symptoms in adolescents. However, theoretically replacing an hour of sedentary behaviour with moderate-to-vigorous physical activity was associated with 12.5% lower depression and 6.6% lower anxiety scores in adults. Replacing sedentary behaviour with sleep in adults was also associated with 7.6% and 4.5% lower depression and anxiety scores, respectively.

These findings suggest that sedentary behaviour is a risk factor for CMD symptoms, but the intensity of physical activity to replace it with may differ between ages. Some, but not all, previous epidemiological studies have broadly found an inverse association between sedentary behaviour time and CMD symptoms or incidence (142–147,150,151). My findings strengthen the evidence that high sedentary behaviour is a CMD risk factor by addressing some key limitations of previous research, such as their overreliance on self-report measures and cross-sectional study designs, particularly in adolescents. The prospective studies in Chapters 4 and 5 also advance previous work by using statistical methods that conceptualise sedentary behaviour in a 24-hour context, which allow for estimates that more closely mirror time use throughout the day.

The lack of an association between moderate-to-vigorous physical activity and CMD symptoms in adolescents aligns with another prospective device-based study in a smaller sample (n = 736) (220). However, it differs from many previous studies with mixed designs and self-report activity measures that have found a positive association between moderate-to-vigorous physical activity and CMD symptoms or incidence (119,120,142). A major limitation of my findings is the low amount of moderate-to-vigorous physical activity engagement in the wider ALSPAC sample that limited my power to detect an association. For example, only around 1.5% (n = 63) of participants in my subsample of the ALSPAC participants (n = 4,257) were meeting the physical activity guidelines of at least 60 minutes of moderate-to-vigorous physical activity per day at baseline. In the other device-based study that found no association, around 34% (n = 248) of participants met these guidelines but may still have lacked power due to their smaller overall sample size (n = 736) (220). A more recent study using device-based measures in another UK-based cohort (n = 4,763) found that participants who met these guidelines at ages 7 and 14 were less likely to experience depressive symptoms (odds ratio = 0.55, 95% CI = 0.34 to 0.88) compared with not meeting the guidelines (553). Exact figures are not reported, but around 79% of participants in this study met the guidelines at baseline or follow-up. These findings and randomised controlled trial data suggest that moderate-to-vigorous physical activity is still likely to be beneficial for reducing or preventing CMD symptoms in adolescents (90), but more device-based research is necessary to confirm this.

My findings also show novel protective associations between light-intensity physical activity and subsequent CMD symptoms in adolescents, which coincides with the growing ‘sit less, move more’ narrative in physical activity guidelines and health research that any movement can be beneficial (67,209). There is relatively little information of the mental health implications of light activity and the results in the ALSPAC analyses of Chapter 4 and 5 provide new insights suggesting that light activity is prospectively associated with lower CMD risks in adolescents. These findings are particularly important given the activity shift from light activity to sedentary behaviour that I show in the prospective studies of Chapters 4 and 5 occurs during adolescence. There is limited information on the consequences of this activity shift, but my findings suggest it could adversely affect CMD

symptoms by age 18. These findings align with some epidemiological studies using device-based measures with varying designs in adolescents (553) and adults (429–431). However, the lack of studies with device-based measures in this area means there are few research findings that allow for direct comparison. This also complicates the interpretation of my finding regarding the contrasting associations of light-intensity physical activity with depression and anxiety symptom scores in adults, as discussed in Chapter 6 (Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms).

The prospective studies of Chapters 5 and 6 also provide new insights by examining associations within a 24-hour context using continuous device-based measures of daily sedentary behaviour and physical activity with appropriate statistical methods for finite time-use data. This is an important conceptual advance on previous research that examine associations of physical activity or sedentary behaviour time in isolation, which does not reflect how changes in movement behaviours occur in reality. Canada's progressive 24-hour movement guidelines that focus on promoting combinations of optimal movement and sleep behaviours (209) indicate the future directions of the field. The guidelines highlight a growing number of studies with physical health outcomes taking this approach but few studies with mental health outcomes. Chapters 5 and 6 provide unique prospective evidence to address this evidence gap.

Objective 3) Investigate the prospective associations of cardiorespiratory and muscular fitness with CMD symptoms and incidence in the population (Chapters 7 and 8).

My findings suggest that low cardiorespiratory or muscular fitness or both are possible risk factors for CMD symptoms for adults in the population. My meta-analysis showed that low or medium cardiorespiratory fitness was associated with 47% and 23% higher risk of CMD incidence than high cardiorespiratory fitness, respectively (Chapter 7). The chapter also highlighted a lack of prospective studies examining these associations in the population. My prospective study in the UK Biobank found that low and medium cardiorespiratory fitness was associated with 1.48 and 1.14 higher odds of CMD incidence in adults, compared to high cardiorespiratory fitness (Chapter 8). Low and medium grip strength (as a proxy for muscular fitness) was associated with 1.38 and 1.12 higher odds of CMD incidence compared to high grip strength. The combination of low cardiorespiratory fitness and grip strength was associated with 1.81 higher odds of CMD incidence, compared to high for both fitness markers.

My findings in Chapters 7 and 8 suggest that physical fitness markers are novel CMD risk factors. These findings build on evidence from previous studies that show an inverse association between cardiorespiratory and muscular fitness with CMD incidence in the population (181–183,224–226). Previous studies have also found an association between cardiorespiratory fitness and depressive symptom severity (174). However, most of these previous studies on the association between either marker of fitness and CMD symptoms were cross-sectional, had a small sample size, or only focused on outcomes for depression. A 2021 meta-analysis of 11 cross-sectional studies in children and adolescence also found an inverse association between cardiorespiratory fitness and depressive symptoms (r = -0.174, 95% CI = -0.221 to -0.126) (554). The evidence of a causal association between physical fitness and CMDs is strengthened by randomised controlled trial evidence. Aerobic and resistance training improves cardiorespiratory and muscular fitness, and randomised controlled trials have found that both types of training can each reduce CMD symptoms (75,76,79,80,82,256,458). However, it is unclear whether these findings are applicable to preventive contexts in people without CMD diagnoses.

The prospective study of Chapter 8 also provides unique insights on combined associations of cardiorespiratory and muscular fitness with CMD symptoms. Previous studies have examined these associations for each exposure individually, but there are multiple, interrelated types of fitness that may vary and interact. Chapter 8 shows that cardiorespiratory and muscular fitness are each inversely associated with CMD symptoms, but the association differs when considering both exposures together. Exercise patterns that train multiple fitness types could have a greater impact on reducing CMD symptoms than training cardiorespiratory or muscular fitness in isolation.

9.3. Implications of these findings for public health

9.3.1. Approaches for reducing sedentary behaviour in the population

The findings of my thesis highlight high sedentary behaviour as a modifiable, population-level risk factor for CMD symptoms across the lifespan. Adolescence is an important window for preventing CMD symptoms (9,10) and a period in which sedentary behaviour increases and total physical activity volumes decline (132–134). Public health initiatives to target rising sedentary behaviour in adolescents could be a particularly useful component of population-level prevention strategies for CMD symptoms. International physical activity guidelines increasingly recognise sedentary behaviour as a related but distinct problem to insufficient moderate-to-vigorous physical activity (67). However, guidelines cannot provide clear targets for daily sedentary behaviour time for optimal physical or mental health as they do for moderate and vigorous physical activity as >75 or >150 per day, respectively. Clear targets facilitate self-monitoring, an increasingly common method of improving adherence to physical activity interventions (555). Robust data from prospective studies with device-based measures are still necessary to establish threshold effects and the dose-response relationships of sedentary behaviour with CMD and other health outcomes. My findings contribute some evidence for dose-response associations between sedentary behaviour and CMD symptoms, either as a single-variable exposure or when replaced by some form of physical activity.

Promoting physical activity of any intensity could be beneficial for reducing CMD risk across the lifespan. There were some inconsistencies in my findings on the presence or direction of association between light or moderate-to-vigorous physical activity with CMD symptoms in adolescents and adults that indicate a need for more research (discussed in Section 1.5. The relationship between physical fitness and physical and mental health). However, there is strong evidence for the CMD benefits of moderate-to-vigorous physical activity (75–86) and emerging evidence for light-intensity physical activity (429–431). Its low intensity and accessibility make light-intensity physical activity a practical method of substantially reducing daily sedentary behaviour. For example, replacing sedentary behaviour by an hour is more feasible with light-intensity physical activity given adults typically spend around five hours of total waking time at this intensity compared with just 14 minutes in moderate-to-vigorous physical activity per day (55).

Schools and colleges could be ideal settings to implement population-level approaches to reduce sedentary behaviour and increase light-intensity physical activity in adolescents. Targeting these settings will inherently include large, representative cross-sections of the population. These environments are amenable to regulatory frameworks that can influence physical activity in the day and monitoring that can facilitate interventions. School-based approaches to increase moderate-to-vigorous physical activity in children and adolescents have been ineffective (556) but multicomponent approaches to reducing sedentary behaviour with light-intensity could be promising (557). For example, the Transform-Us! trial included 1,200 children across 20 schools in Australia and active lessons, frequent active breaks, active homework assignments, environmental changes to support activity (e.g., physical activity equipment in classrooms), and parent newsletters to reduce sedentary behaviour (558,559).

Workplaces are a promising setting for interventions that account for most of daily sedentary behaviour in some adults (e.g., office workers) (55) and have similar benefits to intervening in schools and colleges. I recently conducted an insight analysis that included three systematic reviews on the evidence for the benefits and effective methods of reducing excessive sitting with light-intensity physical activity breaks in offices (560). After screening 3,301 systematic reviews and I included 19 reviews of 252 individual studies of workplace sedentary behaviour interventions. Many interventions reported reductions in sedentary behaviour of greater than 60 minutes per 8-hour workday. Most interventions used dynamic workstations, an individual-level environmental strategy that includes sit-stand, treadmill, or under-desk pedalling. Studies consistently found that dynamic workstations effectively reduced sedentary behaviour time by between 20 to 100 minutes per 8-hour workday.

Studies are increasingly employing multicomponent approaches that combine these environmental changes with individual, or culture and policy-level changes. For example, a cluster-randomised controlled trial of the multicomponent Stand More at Work (SMArT) intervention provided 77 employees in 19 office clusters with sit-stand desks, seminars, goal setting, self-monitoring, feedback, and coaching sessions (561). The intervention reduced occupational sitting by around 50 minutes per workday at 3 months and over 80 minutes after 12 months compared to a usual practice control group. The intervention also reduced prolonged sitting time, daily anxiety, presenteeism, fatigue, and improved job performance. However, few studies in my review included outcomes for CMD symptoms, and none included mental health-related primary outcomes.

I also identified various factors that can reduce (barriers) or increase (facilitators) the likelihood of successfully implementing these interventions that produce sustainable reductions in excessive occupational sitting time. For example, one systematic review of 32 qualitative studies found various individual, work-related, cultural, or environmental barriers and facilitators to reducing occupational sitting (562). Many key barriers were work-related factors, such as employees having insufficient tasks that allow for leaving the desk and excessive work or time pressures that prohibit interruptions for standing or moving around the office. Cultural factors were also identified as potential barriers. For example, some employees were concerned about perceptions of standing or moving as unusual by colleagues or unproductive by managers. Some individual barriers included forgetting to change posture, being unaware of time spent sitting, or lacking guidance.

I made a series of recommendations for how policymakers, employers, and employees can stimulate changes to working practices that prevent excessive sitting at work. For example, the UK's Health and Safety Executive Regulations for Display Screen Equipment already identifies principal risk factors associated with desk-based work to include musculoskeletal, postural, or visual problems and fatigue or stress. Updating these regulations to ensure that mental health issues are considered a principal risk factor can provide employees the autonomy and encouragement to take regular light-intensity physical activity breaks. The regulations also require employers to perform suitable and sufficient assessments of workstations and provide reasonable adjustments for the principal risk factors, which could be amended to include excessive sitting. For example, regulations could ensure workstations are height adjustable to encourage movement during work. Another important factor is encouraging participation from managers, leaders, and co-workers, which can overcome the perception of standing or moving at work as unusual or unproductive as a major barrier (562).

The COVID-19 pandemic accelerated the shift to remote working for many people and led to an increase in sedentary behaviour (563,564), which could have lasting consequences for CMD symptoms. These shifts highlight the importance of addressing high sedentary behaviour and adapting interventions to include remote-working environments. It also provides an opportunity to encourage working practices and environments that are amenable to physical activity. For example, employers could encourage hybrid working arrangements and reduce the number of desks in office spaces to provide room for physical activity. Employers could relocate more suburban locations with

greater green space access to encourage employees to take walking breaks. While the immediate future of educational and occupational environments remains uncertain, the findings of my thesis suggest that sedentary behaviour reduction should be a consideration for protecting CMD in any short or long-term changes to these environments.

In the insight analysis, I also highlighted evidence gaps in trials and epidemiological studies on the association between sedentary behaviour, and CMD symptoms in young adults at work. My thesis uses data from adolescents and middle-older aged adults, but these associations may differ during young adulthood, which is a period characterised by major life transitions (e.g., relationship or career decisions). Approaches for reducing workplace sedentary behaviour should actively recruit young adults to assess these associations more directly.

9.3.2. The importance of physical fitness and its mental health risks

My findings indicate the physical fitness could be useful, population-level markers of CMD risk to complement measures of physical activity, as they increasingly are for cardiovascular disease (164,165). For example, fitness data could be used to identify groups at risk of CMDs or guide interventions. Fitness tests are measures of physiological traits that are inherently more stable than physical activity behaviours. They have several other measurement features that make physical fitness markers useful population-level indicators of mental health risks discussed in Section 8.4.3 (Section 8.4.3. Implications and future directions). For example, fitness markers have clearly defined outputs (e.g., oxygen consumption) and can provide some information on habitual physical activity trends in a single assessment. Activity monitoring devices are poor for measuring resistance training or cycling (57), influencing cardiorespiratory and muscular fitness. These forms of activity could account for most of daily moderate-to-vigorous physical activity for some people.

Collecting population-level fitness data could complement existing physical activity data, but administration of gold-standard fitness testing is challenging, particularly for cardiorespiratory fitness. This may partially explain why I was only able to identify six cohorts with cardiorespiratory fitness and depression data. In contrast, a recent systematic review of physical activity and depression included 49 unique cohorts (119). For example, cardiorespiratory fitness tests require specialised equipment to measure respiration, and maximal tests (to exhaustion) could be inappropriate in some population groups, such as those with some cardiovascular diseases. However, there are a growing number of indirect cardiorespiratory fitness tests that require minimal equipment. They commonly involve walking or running for prespecified distances or times, and the results correlate with direct measures of oxygen consumption. A 2016 meta-analysis of 122 studies assessing various walk or run tests and found that the 1.5-mile test (r = 0.79, 95% CI = 0.73 to 0.85) and the 12-minute test (r = 0.78, 95% CI 0.72 to 0.83) outputs have moderate to high correlations with direct measures of oxygen consumption, based on 18 and 26 studies respectively (252). These test variants involve either walking or running for 1.5-miles or 12 minutes, using time to completion or distance travelled to estimate cardiorespiratory fitness. Approximate measures of muscular fitness are also implementable in large groups with minimal equipment, such as grip strength tests with hand dynamometers (177,539,540). My results in Chapter 8 indicate that collecting multiple fitness markers could have greater benefits for assessing CMD risk than one marker alone.

The association between physical fitness and CMD symptoms here and in children and adolescents (554) also reinforces the importance of incorporating moderate-to-vigorous physical activity alongside light-intensity physical activity into daily routines across the lifespan. Light intensity physical activity is a practical method of reducing daily sedentary behaviour that may reduce CMD risk. However, light-intensity physical activity alone may be insufficient for avoiding low cardiorespiratory fitness in adolescents and adults, even in highly sedentary or obese adults (529–

532). Movement-based approaches to preventing CMD should prioritise light-intensity activity for reducing and breaking up daily sedentary behaviour but ensure sufficient moderate-to-vigorous physical activity across the week to avoid low fitness. The combination of maintaining moderate or high fitness and low sedentary behaviour could have a larger impact on reducing CMD risk than either approach alone at any age. Maintaining this approach may also reduce the long-term risks of physical health complications associated with CMDs (18–22) as high sedentary behaviour (67,138–141) and low cardiorespiratory or muscular fitness (157,158,163,164,534–537) are each associated an increased risk of cardio-metabolic diseases and premature mortality.

However, integrating light and moderate-to-vigorous physical activity into the day will require different approaches. Global public health interventions and strategies to increase moderate-to-vigorous physical activity have had little effect on adults, adolescents, and children (69,70). Interventions that focus on promoting moderate-to-vigorous physical activity in structured environments have produced mixed results so far, such as in schools or workplaces (556,565,566). There are many practical limitations of focusing on these environments. For example, the activity could cause sweating that requires people to bring changes of clothes to work and access to shower facilities. The physical constraints of work or educational environments may prohibit sufficient space for the activity, which may also require specialised equipment, such as exercise bikes or weights.

These limitations are not insurmountable. For example, a 2021 scoping review highlighted the potential of brief, incidental bouts of vigorous-intensity physical activity throughout the day as a mean to improve health (567). For example, promoting stair climbing breaks at work is one method of promoting more intense physical activity in brief bouts that partially overcome some practical limitations of work-based approaches. These approaches could be extended to non-work domains, such as carrying shopping bags or walking up hill. If a clear dose-response relationship between vigorous activity bouts and CMD symptoms is established, this is one possible approach to complement interventions to increase light-intensity physical activity.

9.4. Future research directions

My thesis presents a series of findings from robust epidemiological investigations that outline some fundamental aspects of the associations between sedentary behaviour, physical activity, fitness, and CMD symptoms in the population. I have primarily focused on reducing key sources of bias in previous observational studies to strengthen the causal evidence for existing research questions, such as measurement error or confounding due to reverse causation. For example, I provide clear and consistent evidence that high sedentary behaviour is a CMD risk factor in adolescents and adults, reinforcing previous findings. I have also contributed new studies to other relevant research questions lacking in evidence, such as examining associations with fitness or light-intensity physical activity. For example, I have shown that low cardiorespiratory fitness is another possible risk factor for CMD in adults.

The associations of sedentary behaviour, physical activity, fitness, and CMD symptoms that I present in this thesis still require more evidence to strengthen the cause for causality. I will discuss some limitations of my research that need to be addressed in Section 9.5. (Section 9.5. Strengths and limitations). Future research should examine the nuances of associations between sedentary behaviour, physical activity, fitness, and CMD symptoms in more detail to guide interventions and advance knowledge of how and why CMD symptoms might develop. I discuss some possible nuances for future research to investigate in this section.

9.4.1. Moving beyond energy expenditure to examine behaviour types and domains

My research focuses on quantifying sedentary behaviour and physical activity exposures as daily time at different energy expenditure thresholds. However, the type of sedentary behaviour or physical activity may modify its association with CMD symptoms. For example, time in sedentary behaviour during adolescence is largely due to the use of screen-based devices (137). Different uses of screen-based devices provide distinct user experiences that may affect mental health differently.

For example, social media and video gaming provide platforms for social interactions, which are absent from watching television, could reduce feelings of isolation or loneliness associated with the risk of depressive symptoms in adolescents (568). Among adults, spending more time in mentally-passive sedentary behaviours (e.g., watching television) is associated with an increased risk of depression, but there is no or an inverse association with mentally-active behaviours (e.g., computer use) (142,448,449,461). However, studies comparing different types of screen time in adolescents have been scarce and inconsistent. Studies in adolescents have found that high social media, computer, or television use is associated with poorer mental health outcomes (151,221,569,570), but not always video game use (151,221,571). The factors underlying the relationship between screen time with mental health in adolescents can be complex (572,573), likely extend beyond lower energy expenditure levels (418), and warrant a more nuanced investigation into different screen time modalities.

Clarifying associations between different types of sedentary behaviour or physical activity with CMD symptoms is important for informing guidelines and targeted interventions. For example, international activity guidelines are increasingly making strong recommendations to limit all screen-use in adolescents based on low certainty of evidence (67), which overlooks these nuances. I recently published a prospective study with data from 11,341 population-based adolescents from the Millennium Cohort Study to examine associations of frequency of video game, social media, and internet use at age 11 with depressive symptoms at age 14 (444). I found that regular video game use at age 11 was associated with 24% to 31% (95% CIs = 9% to 43%) lower depressive symptom scores at age 14 in boys, compared with less frequent use. These associations were only present in boys with low self-reported physical activity. Girls who reported using social media most days at age 11 were associated with 13% (95% CIs = 5% to 22%) higher depressive symptoms in girls, compared to those reporting none or less than once a month use.

These opposing associations highlight how associations between specific sedentary behaviour types and CMD symptoms may differ in a way that the device-based exposures in my thesis overlook. As discussed in Chapter 1.6.3, considering the replacement activity for a sedentary behaviour is important to interpreting its association with CMD symptoms in a 24-hour context. The extent to which physical activity influences CMD symptoms may also differ by its type. For example, team sports incorporate cooperative and potentially more sociable elements that may have additional benefits for reducing depressive symptoms than individual exercise does (574–576).

I conducted another study in 4,599 adolescents from the Millennium Cohort to examine how theoretically replacing daily television, video game, social media, or general computer use with individual exercise or team sports at age 14 may affect emotional distress at age 17, using compositional data analysis (under review at the Journal of Affective Disorders). I derived emotional distress from a Strengths and Difficulty Questionnaire emotional symptom subscale, which are a component of internalising symptoms associated with mood disorders in adolescents (577–579). In this study, I found that theoretically replacing 60 minutes of total screen time with any exercise at age 14 was associated with a 0.05 (95% CI = -0.08 to -0.02) lower emotional symptom score at 17. However, only replacing 60 minutes of television or social media use with team sports was associated with lower emotional symptom scores. There were no estimated changes in emotional

symptom scores when replacing video game or general computer use with team sport, or when replacing any screen time with individual exercise.

By virtue of facilitating sedentary behaviour, excessive use of screen-based devices could increase the risk of CMD symptoms. However, my findings in these two studies suggest possible benefits for reducing daily time spent using television or social media and not video gaming or computer use in adolescents. The thresholds at which time spent using a screen-based device becomes harmful to mental health may differ by modality. For example, video games can provide a stimulating experience, where users can interact with a complex environment, follow immersive storylines, and solve problems. They also offer a platform for social interactions in a cooperative or competitive environment. Fewer of these mentally-active and social features are available when watching television, which may have a lower threshold than video gaming for when the behaviour starts to increase mental health risks. Screen-based devices typically function as tools for engaging in various activities, and more detail is needed on the nature of screen-use beyond how much time is spent. For example, an hour of using social media to interact with peers could be beneficial. In contrast, an hour of passively scrolling through activity feeds may be less stimulating, potentially even indicating subclinical CMD symptoms.

Advancing knowledge on the associations of sedentary behaviour and CMD symptoms will require a more nuanced approach that incorporates these contextual factors about individual behaviours. A similar level of detail is necessary for investigating the types of physical activity to best replace sedentary behaviour. For example, a recent exposure-wide Mendelian randomisation study in adults highlighted the importance of social support as a protective factor and television watching as a possible risk factor for depressive symptoms (580). Physical activities that encompass social and cooperative elements, such as team sports, could be most impactful on CMD symptoms when replacing sedentary behaviours that lack social or cooperative elements, such as television watching.

Future research should investigate these associations using a combination of activity monitoring devices (e.g., accelerometers to quantify daily movement patterns) and self-report measures (e.g., diaries or questionnaires to examine behaviour types). I have focused on behaviour type in this section, but future research should also consider other contextual factors may also modify associations of sedentary behaviour, physical activity, and CMD symptoms. For example, a 2017 systematic review of 98 studies with varying study designs found different associations with mental health across multiple physical activity domains (581). For example, the study found indicators of poor mental health (e.g., depression symptoms) were inversely associated with leisure-time and school sport-based physical activity but positively associated with work-related physical activity. Future research could use self-report alongside device-based measures to examine these domain-specific associations. Device-based measures could also incorporate geo-location data to estimate domain, such as smartphone-based global positioning system data to identify work-based or non-work-based movement.

9.4.2. Understanding dynamic interrelationships of physical activity, sedentary behaviour, and mental health within and between days

In this thesis, I have assessed associations between averaged exposure data at baseline (e.g., mean daily sedentary behaviour time) and averaged outcome data at follow-up (e.g., mean PHQ-9 scores). This approach is useful for addressing population-level questions that require comparisons between persons, such as whether people who typically spend a relatively high proportion sitting down are more likely to develop CMD symptoms in the future. However, these absolute exposure variables overlook the reality that sedentary behaviour and physical activity occur in dynamic patterns through the day that can vary throughout the week. They are also unlikely to capture the cumulative

effects of physical activity over time due to the typical observation periods of up to one or two weeks. The outcome variable is typically an absolute value representing the number and severity of possible CMD symptoms. These absolute outcome variables overlook the reality that some central features of CMD symptoms also vary throughout the day and week, such as mood, fatigue, or stress.

These exposure and outcome variables provide a cross-sectional snapshot of inherently dynamic processes that could interact on an hourly or daily basis. Intensive repeated measures that simultaneous assess movement and central CMD feature (e.g., mood) patterns over time could provide novel, within-person insights to inform prevention. For example, consecutive hours of sitting could increase fatigue and reduce resilience to a workplace stressor, which has a more lasting effect on mood. In some people, these everyday experiences may develop into CMD symptoms over weeks or months. This within-subject data characterises the full subclinical spectrum (e.g., daily mood) to CMD symptoms (e.g., persistent low mood for two weeks). It also captures how movement patterns can influence this subclinical spectrum or the development of CMD symptoms on a daily basis.

Capturing this rich, within-person data is possible through smartphone and wearable devices. Smartphone and wearable devices are increasingly accessible, amounting to around 1.5 billion and 305.2 million global sales in 2019 (582,583), respectively. They provide a real-time platform for passively monitoring continuous movement through sensors (e.g., accelerometers) and actively collecting mood, stress, fatigue, or other CMD features using smartphone-based ecological momentary assessment. A growing number of studies are employing these measures to examine relationships of movement patterns and mental health in over 200 community-based participants with mood disorders (584), over 100 to 700 adolescence and young adults without symptoms (585,586), and over 2000 medical students (587). Analysing these dynamic associations typically requires new approaches, such as multi-level functional models for intensive repeated measures or fragmentation modelling of emotional state stability.

These methods have already produced new insights into mental health treatment. For example, Merikangas *et al.*'s 2019 study in 242 people with bipolar disorder assessed dynamic associations between movement, energy, and mood to suggest that interventions targeting daily movement and subjective energy could be more impactful on psychiatric symptoms than current approaches that focus on mood (584). The data could also support pragmatic just-in-time interventions to deliver real-time behaviour change support (588). For example, a wearable sensor may trigger more frequent reminders to engage in light-intensity physical activity after detecting consecutive nights of low-quality sleep to reduce feelings of persistent fatigue. Employing these methods to focus on preventing CMDs would require large samples of people without or with subclinical symptoms, ideally monitored over long periods to characterise CMD symptom development and the influence of movement on this transition. However, the approach could add important nuances on the daily interactions between movement patterns and the development of CMD symptoms over time to inform prevention.

9.4.3. Utilising genetic methods in epidemiology and examining genetic influences

Recent advances in genetic methods and big data resources have accelerated the use of genetically-informed study designs in epidemiology and insights from population genetics in mental health (589). Genetically informed study designs can improve our capacity to make causal inferences from observational data, primarily through enabling instrumental variable analysis. Most statistical models used in observational research assume that all confounding variables are measured, and the exposure is randomly allocated to participants conditional on these confounding variables, which is rarely the case. Instrumental variable analysis does not require the measurement of all confounding variables. The method instead conditions on an 'instrument' that is associated with the exposure has

no common cause with the outcome and does not directly affect the outcome. An individual's genotype is randomly allocated at birth and can be associated with an exposure without having a common cause or directly affecting an outcome.

Mendelian randomisation is a form of instrumental variable analysis that uses genetic variants as the instrumental variable, which reduces the influence of confounding and reverse causation compared to most other observational analysis methods (552). These methods more closely assess causal effects in observational data by minimising the risk of confounding and reverse causation, two major sources of bias in observational research. For example, as people with CMD symptoms typically engage in less physical activity and more sedentary behaviour than the general population (204,590,591), reverse causation is a major caveat to observational studies in this area. Poor health behaviours (e.g., low physical activity) and CMD symptoms also typically cluster within specific population groups, such as people with low socioeconomic status (592,593). In this thesis, I have partially addressed these issues through statistically adjusting for baseline CMD symptoms or socioeconomic in my analysis. However, these biases can still affect my associations to limit causal inferences, such as measurement error or unmeasured confounding variables.

These genetically informed designs can produce more robust evidence on the causal relationships of sedentary behaviour, physical activity, and CMD symptoms in the population to advance knowledge in prevention without the practical or financial barriers of running a large-scale randomised controlled trial. For example, a Mendelian randomisation study in 2019 used data from the UK Biobank and the Psychiatric Genomics Consortium to assess bidirectional associations between self-reported and accelerometer-measured physical activity with major depressive disorder incidence (199). The study provided robust evidence of a unidirectional, protective association between accelerometer-based total physical activity volume and major depressive disorder, but not with self-reported physical activity. These findings align with my results from Chapter 6 (Chapter 6: Impact of replacing sedentary behaviour with other movement behaviours on CMD symptoms), which show inverse associations of light and moderate-to-vigorous physical activity with depressive symptoms in UK Biobank participants. Similar studies could investigate the risks associated with sedentary behaviour or low physical fitness, including identifying dose-response associations to inform national guidelines or interventions. They could also assess effect modifiers and moderators discussed in Section 9.4.1, such as sedentary behaviour type or domain. For example, another 2020 study in the UK Biobank using genetically informed methods assessed associations between 106 modifiable lifestyle and environmental factors and depressive symptoms before using Mendelian randomisation to examine possible causal effects (580). The study concluded that television watching was the only risk factor for depressive symptoms that may be causal.

Genetic methods can also help to identify potential mediators or confounding factors for the associations of sedentary behaviour, physical activity, and CMD symptoms. In my narrative review in Chapter 3, I highlighted a paucity of research on causal mechanisms underlying the relationship between physical activity and depression. Much of the available evidence was from randomised controlled trials and experimental studies that collect neuroimaging or biomarker data in assessing a physical activity intervention. This evidence is important for establishing treatment effects and assessing causality but randomised controlled trials and experimental studies using these measures can be resource-intensive, time-consuming, and potentially statistically underpowered to detect changes in secondary outcomes. Population genetic studies in large, existing data resources (e.g., UK Biobank) are an increasingly important tool for assessing the shared genetic aetiologies between two traits (pleiotropy) and identifying associated physiological mechanisms. For example, a 2016 study in 112,151 UK Biobank participants derived genetic correlations to share substantial overlaps between cognitive ability and several mental and physical health-related traits, including depression (594).

Physical activity, sedentary behaviour, and CMD symptoms could share genetic aetiologies that underlie their association. For example, physical activity (exposure) could influence CMD symptoms relating to fatigue and sleep problems (outcome) through energy metabolism pathways (mediator). A study could use co-localisation methods (595) to assess genetic overlap between physical activity and CMD symptoms, including genetic variants associated with energy metabolism. The shared genetic aetiologies could also represent confounding influences that partially explain the associations between physical activity and CMD symptoms (596). For example, energy dysregulation (confounding variable) could be a common cause of high sedentary behaviour (exposure) and increased fatigue (outcome). Population genetic and genetically informed study designs utilise existing data resources to examine the structure and causality of sedentary behaviour, physical activity, and CMD symptoms associations to advance knowledge and inform interventions.

9.5. Strengths and limitations of this thesis

An overarching strength of this thesis is that the findings from each chapter are broadly consistent internally and externally with the wider literature. I have selected study designs and methods for each chapter to reduce systematic and random biases and strengthen causal inferences. Where possible, I have sought to use large cohort studies to reduce error from random variation that can cause imprecise estimates and improve statistical power to appropriately assess possible associations. For example, the UK Biobank is the world's largest prospective cohort with accelerometer data. My ALSPAC analyses (Chapters 4 and 5) included three accelerometer assessment points and four mental health assessments over six years, with complete exposure and outcome data in >1000 participants at each time point. These repeated measures allowed me to assess changes over time and changes with age with reasonable statistical power. I have used prospective study designs that reduce the risk of reverse causation by allowing baseline adjustments for CMD symptoms or diagnoses. They also help to ensure that the exposure is temporally before the outcome, which strengthens causal inferences.

I have also aimed to quantify systematic biases existing in the cohorts or in the way I have selected participants into my subsample from the cohorts. For example, I assessed selection bias due to attrition and missing data by comparing models with imputed missing values in Chapters 4 to 6 and 8. In each chapter, the main findings are broadly comparable with the results of models with fully imputed data. While this comparability does not eliminate the risk of selection bias in these chapters, it suggests that the bias due to attrition within my subsamples of ALSPAC and Biobank may not nullify my main findings.

I aimed to reduce measurement bias by using device-based measures (accelerometers) to quantify time in sedentary behaviour or physical activity in Chapters 4, 5, 6, and 8, compared with previous studies that have used self-report measures. I addressed confounding by using *a priori* DAGs to outline my proposed causal associations and inform stratification-based adjustments to my final models (Chapters 4, 5, 6, and 8). I also used statistical methods to account for the co-dependence of time-use variables in the day, such as iso-temporal modelling and compositional data analysis in Chapters 5 and 6, respectively. The combination of continuously measured physical activity and sedentary behaviour data with these statistical methods represents an important conceptual advance in understanding their relationship with CMD symptoms within a 24-hour context. I also calculated e-values to estimate the potential risk of unmeasured confounding variables that could nullify my observed associations in the prospective studies of Chapters 5, 6, and 8. Each chapter also includes several sensitivity analyses to assess my main findings' robustness, such as excluding participants with a history of CMDs to reduce the risk of reverse causation or including potentially confounding variables that were measured after baseline.

Limitations of this thesis include the reliance on observational data to assess causal associations. Recent advances in causal inference methods are have provided a language to describe causality, which enables a clearer identification of biases to causal evidence in observational data and methods to reduce or eliminate these biases (187). I have applied these principles of causality throughout this thesis, but several biases remain across all chapters. For example, the presence of unmeasured confounding variables, measurement biases within confounding variables, and interactions between confounding variables prohibit the exchangeability assumption to make causal inferences in Chapters 4 to 8. DAG-informed models and calculating e-values help to limit or quantify the risk of confounding but do not eliminate it. For example, chronic physical illness or experiences of bullying could increase the risk high sedentary behaviour and CMD symptoms, representing possible unmeasured confounders in the ALSPAC analyses of Chapters 4 and 5. Selection bias is a consistent issue in Chapters 4 to 8. For example, there is data suggesting that the ALSPAC and Biobank samples are not representative of the general population across several sociodemographic and health-related variables, as discussed in Chapters 4, 5, 6, and 8. This is particularly problematic in the Biobank sample, where there may be differences with the general population in the physical activity and sedentary behaviour exposure variables (see Section 6.5.2. Strengths and limitations). This could introduce a collider bias into my final results for the prospective Biobank study of Chapter 8. However, there is a lack of nationally representative accelerometer-measured physical activity and sedentary behaviour data for a direct comparison, as discussed in Section 6.5.2. (Section 6.5.2. Strengths and limitations).

As participants are not 'exchangeable', comparing their CMD outcomes cannot represent a causal effect. Other methods that avoid conditioning on confounding variables (e.g., instrumental variable analysis) or can theoretically assume exchangeability (e.g., randomised controlled trials) are still necessary to validate my findings. I have selected the exchangeability assumption as an example here. However, similar arguments could be made for other assumptions that are difficult to meet within my thesis but are necessary for identifying causal effects in observational data, such as consistency or positivity (187). However, most of my findings align with existing evidence from studies that can more closely estimate causal effects, such as Mendelian randomisation studies of highlight sedentary behaviour (television watching) as a depression risk factor (580) or randomised controlled trials that show physical activity can reduce anxiety symptoms (81). While these studies address overlapping but different research questions (e.g., by focusing on treatment), triangulating evidence from studies with varying study designs, populations, and methods in this way can partially overcome the limitations of individual studies and strengthen the overall causal assumptions.

While the use of accelerometer data is a key strength of the prospective studies in Chapters 4, 5, and 6, they are most suitable for measuring quantitative aspects of sedentary behaviour and physical activity, such as daily time at each intensity threshold. Focusing on daily physical activity and sedentary behaviour time as my exposure variables in these chapters is an important step in establishing their association with CMD symptoms, but this approach potentially overlooks other relevant details. Advancing knowledge of these relationships will require capturing and analysing qualitative aspects of physical activity and sedentary behaviour, such as the type of behaviour or domain (see Section 9.4.1. Moving beyond energy expenditure to examine behaviour types and domains).

Incorporating data from self-report or other sensors (e.g., geo-location) could provide important nuances to the associations of sedentary behaviour, physical activity, and CMD symptoms that are not possible with accelerometers alone. For example, the type of light-intensity physical activities could modify its association with anxiety symptoms and partially explain the contrasting findings in the ALSPAC and Biobank studies of Chapters 5 and 6. I also used different generations of accelerometers between Chapters 4 and 5 (ALSPAC, uniaxial) with Chapter 6 (Bioabank, triaxial). The ALSPAC devices in Chapters 4 and 5 measure acceleration across a single directional plane (uniaxial)

and produce different outputs (counts) than the Biobank's triaxial devices in Chapter 6, which measures acceleration in three directions and outputs milli-gravities. The different units of measurement and number of directional planes could limit comparisons between the exposure variables in Chapters 4 and 5 (ALSPAC) with Chapter 6 (Biobank). For example, additional directional planes could increase the sensitivity of triaxial accelerometers to restlessness (e.g., fidgeting), which may be classified as light activity and contribute to the difference in its association with anxiety symptoms in Chapters 5 (ALSPAC) and 6 (Biobank).

Wrist-worn accelerometers have measurement issues (see Section 2.3.3. Overview of exposure variables) that include the inability to assess posture, which may result in the misclassification of standing as a sedentary behaviour (194). It is also unclear whether a 7-day measurement of activity is representative of a typical week (508,509), and longer periods could provide further insights. For example, real-time activity and CMD symptom monitoring over several weeks could provide more nuanced detail on their interrelationships over time, as discussed in Section 9.4.2. (Section 9.4.2. Understanding dynamic interrelationships between physical activity, sedentary behaviour, and mental health within and between days) Using averaged activity data (e.g., average daily minutes of physical activity) that is only recorded at one point in time limits my capacity to assess the temporality of the associations of physical activity, sedentary behaviour, and mental health as they develop over several weeks. Similarly, mental health is only assessed at a single time point and generally covers a two-week period, several years after the exposure measurement. Real-time or more frequent and longer physical activity, sedentary behaviour, and mental health data collection protocols could provide more nuanced information on their relationships over time. However, my findings are still informative given the scarcity of device-based measures in prospective studies assessing associations of physical activity, sedentary behaviour, and CMD symptoms.

My investigations of associations between physical fitness and CMDs largely focus on cardiorespiratory fitness. I did not use gold-standard cardiorespiratory fitness measures in the prospective study of Chapter 8 (Biobank), which include graded exercise tests with gas analysis. However, the evidence of its association with CMD incidence is stronger in combination with the evidence I identified in my systematic review of Chapter 7. I have included indirect measures of muscular fitness (grip strength) as an exposure in Chapter 8. The findings of this chapter highlight the importance of considering multiple aspects of fitness and how they combine to potentially influence the risk of CMDs. Other forms of heart-related fitness include flexibility and body composition, which could influence CMD symptom risk individual and in combination.

9.6. Conclusions

I aimed to assess prospective associations of physical fitness, sedentary behaviour, physical activity, and CMD symptoms in the population and identify possible causal mechanisms underlying these associations in this thesis. I found consistent evidence that high sedentary behaviour is a risk factor for CMD symptoms in the population. Replacing daily sedentary behaviour with light or moderate-to-vigorous intensity physical activity could reduce CMD risks. The optimal intensity of physical activity for reducing sedentary behaviour and CMD risks could vary by age or other factors not assessed in this thesis, such as activity type or domain. I proposed a conceptual framework of biological and psychosocial mechanisms that could underlie the association of physical activity and depressive symptoms. I also found that theoretically replacing sedentary behaviour with light-intensity physical activity was associated with higher anxiety symptom scores in adults. This finding and the paucity of research in this area highlight the association between light-intensity physical activity and CMD symptoms, an important area for future research. I also found consistent evidence

for low cardiorespiratory fitness as a risk factor for CMD symptoms in the population. There was some evidence for low muscular fitness as another possible CMD risk factor and the combination of low muscular and cardiorespiratory fitness being associated with the highest degree of risk.

My findings suggest that population-level sedentary behaviour reduction approaches could reduce CMD risk in the population. Targeting structured environments that are conducive to excessive sitting could be a practical method of reducing sedentary behaviour, such as schools and workplaces. Interventions to increase school and work-based physical activity have produced mixed findings but have largely aimed to increase moderate-to-vigorous activity. Light activity could be more acceptable and sustainable in schools and workplaces than higher intensity activity. The COVID-19 pandemic likely increased sedentary behaviour with remote working and schooling environments. This highlights the importance of addressing of utilising sedentary behaviour reduction techniques that are adaptable to remote environments. It also provides an opportunity to implement or trial changes that can increase school and work-based physical activity during the transition back to workplaces and schools, such as changing office designs. My findings also show the potential importance of physical fitness as a population-level marker of CMD risks. Increasing the collection of fitness data in cohort studies can improve our understanding of its relationship with CMD symptoms and potential utility as a population-level marker of CMD risk.

My thesis advances knowledge by providing evidence of consistent and prospective associations between sedentary behaviour and CMD symptoms across the lifespan using device-based measures. Previous studies have used self-report activity measures to assess these associations. It also collates existing data and provides new evidence in a large, prospective cohort of associations between multiple physical fitness markers and CMD symptoms in the population. Future research should build on my thesis by examining these associations in more detail, including how activity types and domains modify the potential effects. Genetic studies can also strengthen causal evidence and identify potential mechanisms underlying associations of physical fitness, sedentary behaviour, physical activity, and CMD symptoms in the population. Real-time monitoring of daily movement and central features of CMD symptoms (e.g., mood) could also provide novel insights into how these dynamic relationships develop and interact over time. The nuances of these associations require further investigation. However, my findings and others in the field increasingly highlight the possible dangers of rising sedentary behaviour on mental health and the importance of promoting daily movement in different forms and physical fitness to mitigate these risks.

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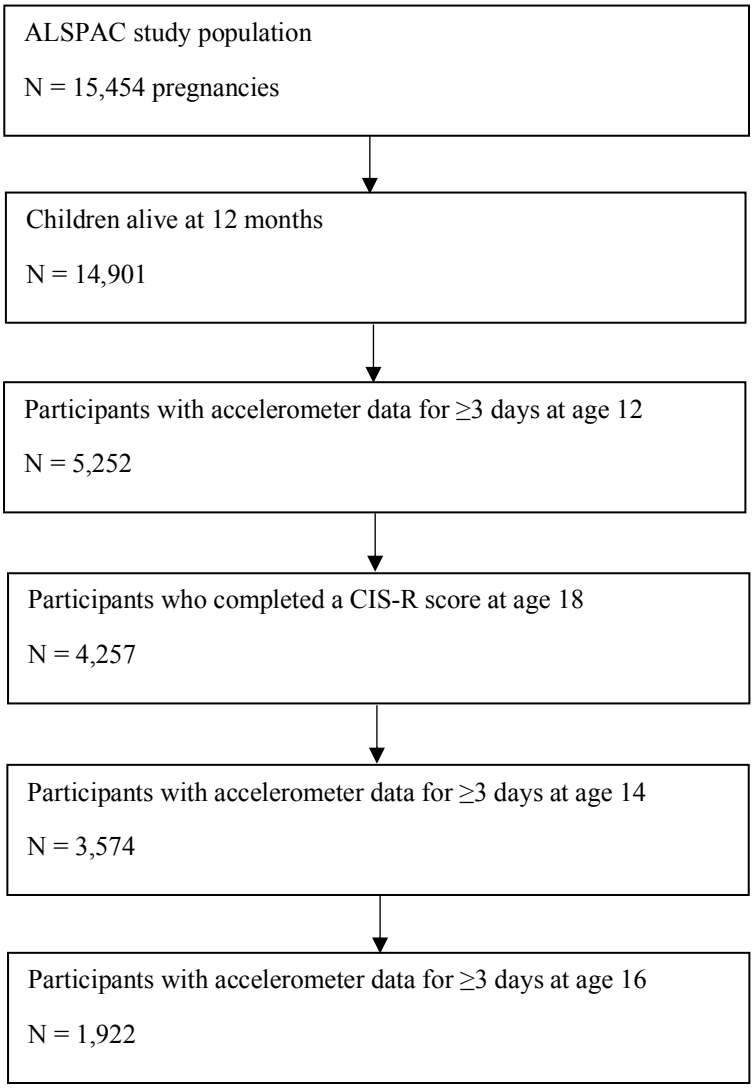
11. Supplementary materials

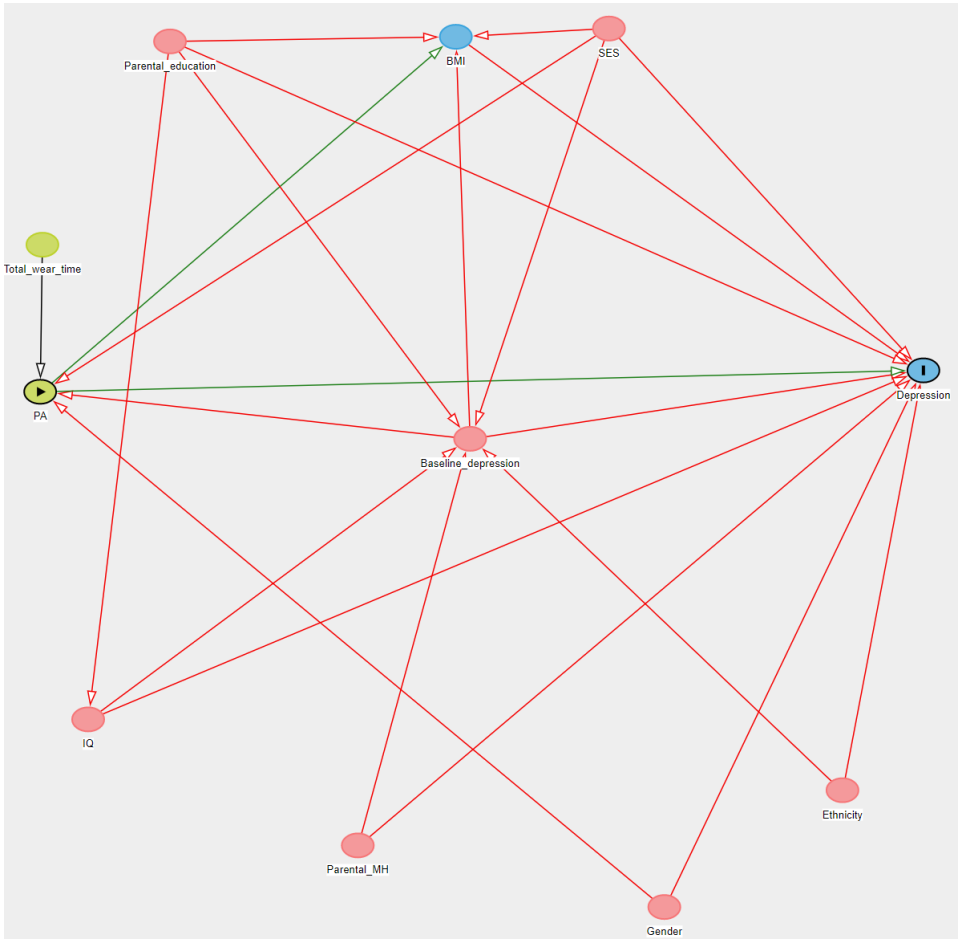
Thesis Supplementary Materials

Figure 1. Flow chart of participants



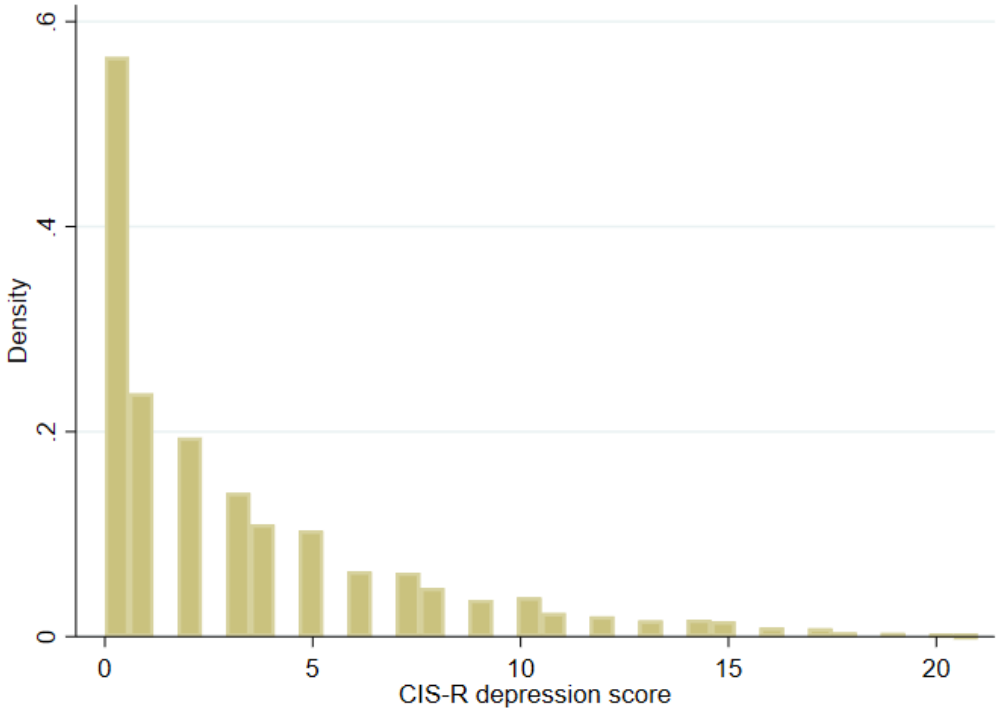
ALSPAC = Avon Longitudinal Study of Parents and Children.

Figure 2. PA, depression, and covariates Directed Acyclic Graph (DAG)



The following DAG was made using the online resource DAGitty (http://www.dagitty.net/dags.html#).

Figure 3. CIS-R distribution



Group based trajectory modelling

Using the trajplot command in STATA, I generated the following figures to illustrate the trajectory subgroups used in my models. I created Group based trajectory models for total PA (CPM), sedentary, light activity and MVPA time, and baseline depression (MFQ scores).

Figure 4. Total PA (CPM) trajectories

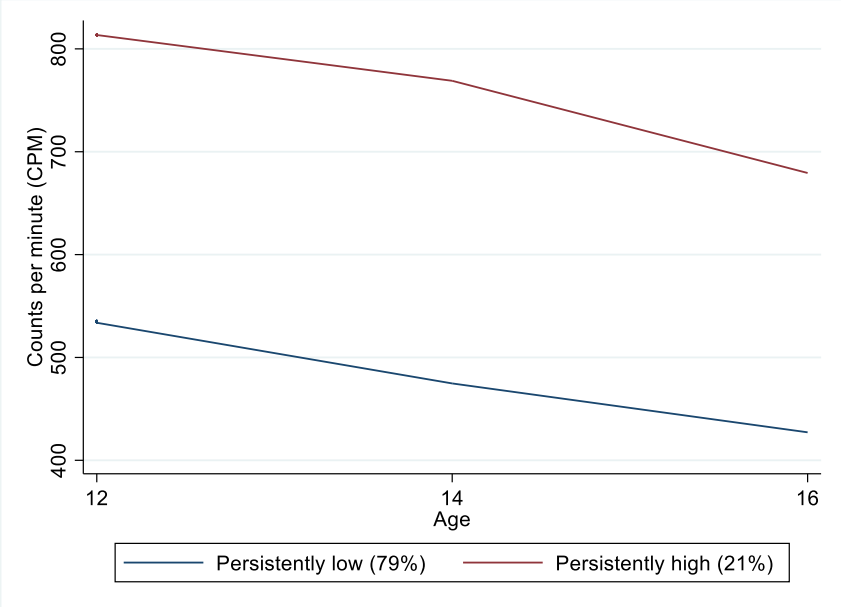


Figure 5. Sedentary time trajectories

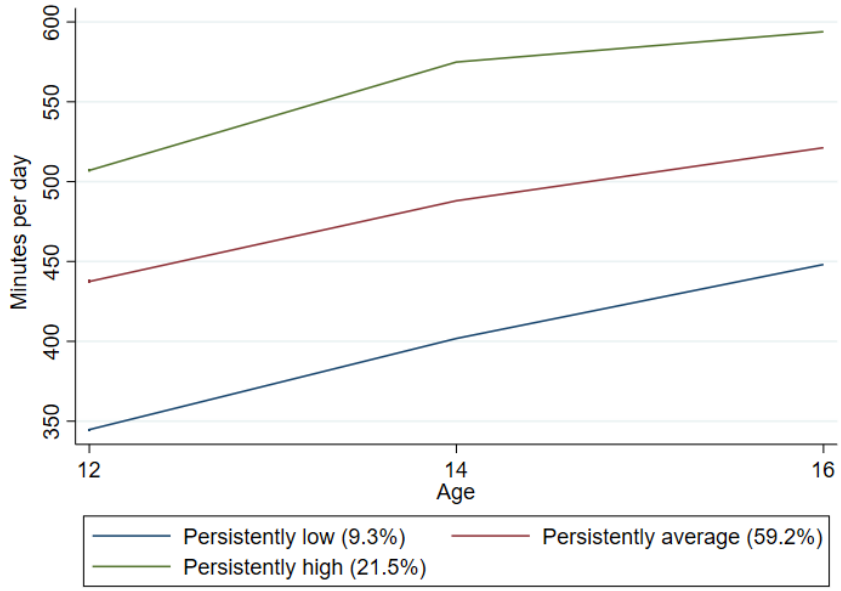


Figure 6. Light time trajectories

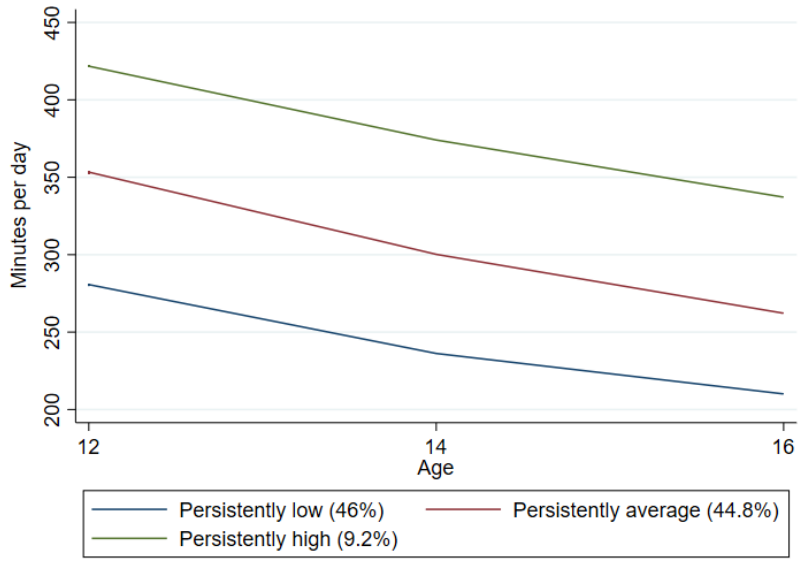


Figure 7. MVPA time trajectories

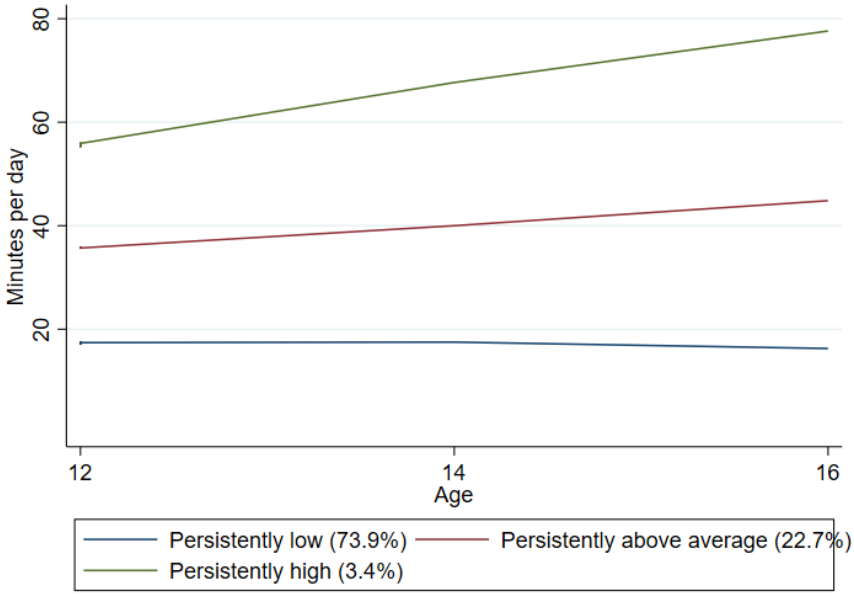


Figure 8. Baseline depression trajectories (MFQ)

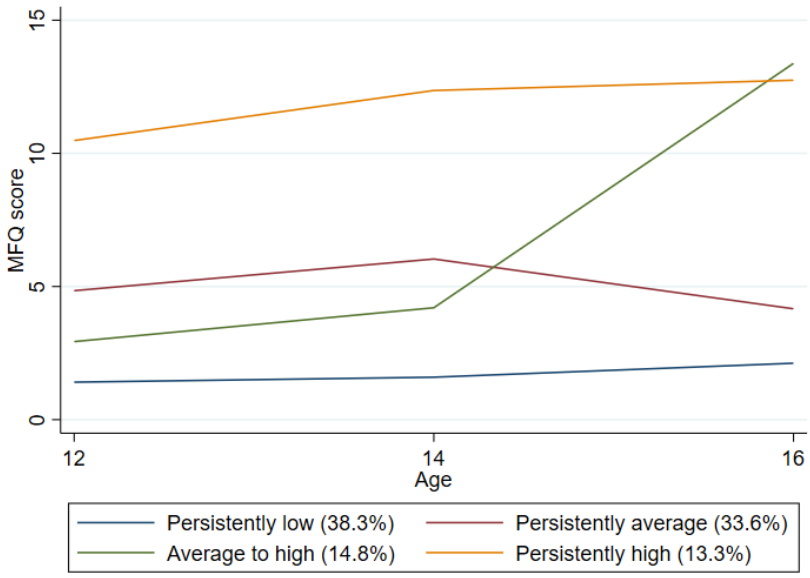


Table 1. Baseline characteristics of included and excluded participants

Baseline characteristic		**Incidence/total no. of participants with available data (%)**		***P***
		Included (n = 4,257)	**Excluded (n = 10,664)**	
Sex	Female	2,390/4,257 (56.14)	4,351/10,664 (40.80)	<0.001

Ethnicity	Non-white	173/4062 (4.26)	429/7,912 (5.42)	0.006
Parental education	Higher (degree)	1,207/4,257 (28.35)	1,328/10,664 (12.45)	<0.001
Maternal social class	Manual	553/3626 (15.25)	1,435/6,354 (22.58)	<0.001
Parental psychiatric diagnosis	Severe depression or schizophrenia	422/4257 (9.91)	1,117/10,664 (10.47)	0.065
BMI	Overweight or obese	270/3671 (7.35)	263/2602 (10.11)	<0.001
Baseline depression	MFQ > = 10	344/3,683 (9.34)	227/2600 (8.73)	0.408

OR: Odds ratio; CIs: Confidence intervals

Table 2. Physical activity at ages 12, 14, and 16

Age (years)	**Physical activity variable**	**Boys**		**Girls**		**All**	
		Mean or median (SD or IQR 25-75)	**% of total wear time**	**Mean or median (SD or IQR 25-75)**	**% of total wear time**	**Mean or median (SD or IQR 25-75)**	**% of total wear time**
12	Total activity (CPM)	662.04 (184.92)	n/a	547.97 (151.51)	n/a	603.33 (177.62)	n/a
	Sedentary activity minutes	421.61 (66.13)	53.74	439.53 (64.35)	56.66	430.99 (65.80)	55.26
	Light activity minutes	334.28 (59.09)	42.59	317.82 (56.02)	41.01	325.66 (58.09)	41.76
	MVPA activity minutes	25.67 (16.29, 38.67)	3.25	15.59 (9.67, 24.29)	2.01	20 (11.86, 31.21)	2.55
14	Total activity (CPM)	598.61 (192.38)	n/a	486.67 (153.15)	n/a	539.12 (181.43)	n/a
	Sedentary activity minutes	471.35 (70.16)	59.40	500.22 (63.66)	63.62	486.69 (68.30)	61.64
	Light activity minutes	293.04 (59.10)	36.94	265.93 (51.30)	33.85	278.63 (56.72)	35.29
	MVPA activity minutes	25.82 (15.34, 38.69)	3.29	16.8 (9.67, 27)	2.15	20.71 (12, 32.8)	2.63
	Total activity (CPM)	529.90 (166.35)	n/a	430.60 (137.16)	n/a	474.83 (158.68)	n/a

16	Sedentary activity minutes	515.60 (68.27)	64.43	528.99 (62.13)	67.51	523.02 (65.25)	66.14
	Light activity minutes	255.67 (58.32)	31.90	236.31 (50.76)	30.13	244.94 (55.08)	30.92
	MVPA activity minutes	25.69 (16.8, 39.86)	3.22	15 (7.17, 25.71)	1.90	19.5 (10.25, 33.34)	2.47

SD: Standard deviation; IQR: Interquartile range; CPM: Counts per minute

Table 3. Model iterations for group-based trajectory models, according to number of groups and trajectory shapes

Variable	Number of groups	Trajectory shape (0 = zero order, 1 = linear, 2 = quadratic)	BIC for total number of observations (N = 3519)	% group membership				
				1	2	3	4	5
CPM	2	0 0	-46321.36	79.48	20.52			
	2	0 1	-46244.02	73.60	26.40			
	2	0 2	-46244.53	78.99	21.01			
	2	1 1	-46027.21	73.79	26.21			
	2	1 2	-46027.33	79.04	20.96			
	2	2 2	-46029.34	78.98	21.02			
	3	0 0 0	-46246.71	66.10	29.53	4.37		
	3	0 1 1	-46227.35	67.21	30.01	2.78		
	3	0 1 2	-46225.30	62.04	31.45	6.51		
	3	0 2 2	-46211.46	66.85	33.15	2.36		

	3	1 1 1	-46111.89	67.53	29.26	2.61
	3	1 1 2	-46109.52	67.88	28.94	3.18
	3	1 2 1	-46104.72	69.33	25.68	4.99
	3	1 2 2	-46107.39	70.45	25.62	3.93
	3	2 1 1	-46189.43	65.69	28.65	5.66
	3	2 2 1	-46080.71	75.56	19.35	5.09
	3	2 1 2	-46071.41	70.58	21.12	8.3
	3	2 2 1	-46246.71	66.65	30.22	3.13
Sedentary	2	0 0	-40580.56	32.34	67.64	
	2	0 1	-39663.92	11.47	88.53	
	2	0 2	-39639.21	12.23	87.76	
	2	1 1	-39478.15	36.95	63.05	
	2	1 2	-39451.10	37.15	62.87	
	2	2 2	-39453.79	37.41	62.59	
	3	0 0 0	-40581.83	20.99	71.43	7.57
	3	0 1 1	-39477.44	1.46	41.63	56.90
	3	0 1 2	-39449.30	1.54	41.84	56.60

	3	0 2 2	-39451.10	1.68	42.65	55.65	
	3	1 1 1	-39438.30	20.64	60.47	18.89	
	3	1 1 2	-39414.33	16.29	54.21	29.48	
	3	1 2 1	-39418.11	24.89	63.89	11.22	
	3	1 2 2	-39410.23	19.26	59.23	21.50	
	3	2 1 0	-39470.96	34.25	64.59	1.14	
	3	2 1 1	-39439.66	21.53	60.64	17.82	
	3	2 1 2	-39416.15	17.02	54.36	28.61	
	3	2 2 1	-39421.50	25.13	63.94	10.91	
	3	2 2 2	-39413.45	19.52	59.24	21.22	
	4	0 0 0 0	-40589.08	2.56	27.29	66.18	3.94
Light	2	0 0	-39499.75	77.69	22.30		
	2	0 1	-38643.13	8.59	91.40		
	2	0 2	-38633.93	8.30	91.69		
	2	1 1	-38272.04	69.78	30.21		
	2	1 2	-38271.05	69.18	30.81		
	2	2 2	-38258.23	69.64	30.35		

	3	0 0 0	-39499.39	68.25	29.66	2.09
	3	1 2 1	-38196.20	43.53	46.27	10.18
	3	2 1 1	-38256.63	7.51	66.73	25.74
	3	2 2 1	-38189.06	46.05	44.78	9.15
	3	2 2 2	-38182.65	46.01	44.80	9.17
MVPA	2	0 0	-29158.27	83.03	16.96	
	2	0 1	-29111.67	81.84	18.15	
	2	0 2	-29115.15	81.85	18.14	
	2	1 1	-29115.61	81.80	18.19	
	2	1 2	-29119.06	81.81	18.18	
	2	2 2	-29121.40	81.83	18.16	
	3	1 1 1	-28991.31	73.90	22.66	3.42
	3	1 1 2	-28995.14	74.10	22.61	3.27
	3	1 2 2	-29007.30	76.67	16.91	6.40
	3	2 1 0	-29008.14	74.10	21.94	3.95
	3	2 1 1	-29124.31	25.64	58.14	16.21
	3	2 1 2	-29007.30	16.91	76.67	6.40

	3	2 2 1	-29122.26	32.28	52.92	14.79
	3	2 2 2	-29000.97	74.30	22.50	3.19
MFQ	2	0 1	-44943.13	76.88	23.11	
	2	0 2	-44917.35	77.10	22.89	
	2	1 1	-44836.23	78.54	21.45	
	2	1 2	-44808.87	78.70	21.29	
	2	2 2	-44810.34	78.76	21.23	
	3	0 0 0	-45175.98	63.51	28.90	7.57
	3	0 1 1	-44611.78	55.92	33.81	10.26
	3	0 1 2	-44584.65	53.83	35.07	11.08
	3	0 2 2	-44582.67	54.15	35.03	10.80
	3	1 1 1	-44552.03	62.24	28.64	9.10
	3	1 1 2	-44531.05	60.12	29.86	10.01
	3	1 2 1	-44538.40	63.51	27.85	8.63
	3	1 2 2	-44536.99	60.95	29.49	9.55
	3	2 1 0	-44594.72	70.65	10.98	18.35
	3	2 1 1	-44553.37	62.54	28.40	9.04

3	2 1 2	-44532.65	60.47	29.58	9.93		
3	2 2 1	-44541.50	63.61	27.78	8.60		
3	2 2 2	-44529.85	61.11	29.35	9.52		
3	1 2 3	-44528.25	60.69	29.53	9.77		
4	0 0 0 0	-46198.98	22.13	39.82	27.55	10.47	
4	0 1 1 1	-44905.80	34.39	27.02	16.80	21.77	
4	1 1 1 1	-44727.95	36.54	20.35	15.92	27.17	
4	1 1 1 2	-44618.05	21.10	36.80	25.90	16.19	
4	1 1 2 2	-44551.40	21.27	37.17	26.17	15.37	
4	1 2 2 2	-44426.99	38.51	33.40	14.92	13.33	
4	2 2 2 2	-44501.21	20.41	36.98	27.17	15.42	
5	0 0 0 0 0	-48793.35	20.24	17.50	36.77	10.41	15.05
5	1 1 1 1 1	-48568.81	20.11	16.82	36.30	14.79	11.96
5	1 2 2 2 2	-482715.69	17.00	20.37	37.07	15.10	10.44
5	2 2 2 2 2	-47715.18	37.06	16.67	10.78	15.32	20.15

BIC: Bayesian Information Criterion; CPM: Counts per minute; MVPA: Moderate to vigorous physical activity; MFQ: Moods and Feelings Questionnaire.

Table 4. Cross-sectional and longitudinal associations between PA and depression scores from imputed sample (n = 4,257)

	Age	CPM (per 100)			Time spent at different intensities								
					Sedentary (per 60 mins)			Light (per 60 mins)			MVPA (per 15 mins)		
		IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*
Cross-sectional	12	0.966	0.948, 0.984	<0.001	1.038	1.007, 1.068	0.014	0.947	0.917, 0.979	0.001	0.947	0.917, 1.021	0.001
Longitudinal	12	0.950	0.925, 0.976	<0.001	1.048	1.008, 1.091	0.020	0.946	0.990, 0.904	0.016	0.915	0.873, 0.960	<0.001
	14	0.964	0.939, 0.989	0.006	1.083	1.040, 1.129	<0.001	0.957	0.906, 1.011	0.114	0.971	0.933, 1.119	0.158
	16	0.973	0.942, 1.005	0.095	1.054	1.001, 1.113	0.046	0.928	0.875, 0.985	0.014	0.839	0.936, 1.030	0.474

All models are fully adjusted for sex, ethnicity, maternal social class, paternal psychiatric history, paternal education,, and baseline depression.

Table 5. Logistic models with depression as a dichotomous outcome

Age (years)	Model (n)	CPM (per 100)			Time spent at different intensities								
					Sedentary (per 60 mins)			Light (per 60 mins)			MVPA (per 15 mins)		
		OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
12	Fully adjusted (2,486)	0.93	0.87, 0.99	0.049	1.15	1.02, 1.30	0.022	0.83	0.77, - 0.99	0.039	0.89	0.78, 1.01	0.078
14	Fully adjusted (1,938)	0.91	0.84, 0.98	0.017	1.24	1.08, 1.42	0.002	0.80	0.69, - 0.93	0.004	0.90	0.79, 1.02	0.108
16	Fully adjusted (1,220)	1.02	0.91, 1.14	0.771	1.10	0.90, 1.33	0.352	0.88	0.71, - 1.08	0.225	1.05	0.91, 1.22	0.505

Table 6. Longitudinal models excluding participants with elevated depressive symptoms (MFQ >= 10)

Age (years)	Model (n)	CPM (per 100)			Time spent at different intensities								
					Sedentary (per 60 mins)			Light (per 60 mins)			MVPA (per 15 mins)		
		IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*
12	Fully adjusted (2,163)	0.937	0.904, 0.970	<0.001	1.075	1.017, 1.136	0.011	0.904	0.850, 0.961	0.001	0.900	0.844, 0.959	0.001
14	Fully adjusted (1,760)	0.960	0.925, 0.997	0.034	1.080	1.017, 1.180	0.012	0.931	0.864, 1.004	0.064	0.964	0.906, 1.026	0.251
16	Fully adjusted (1,062)	0.972	0.922, 1.024	0.286	1.087	1.008, 1.172	0.031	0.905	0.825, 0.993	0.034	0.992	0.924, 1.065	0.829

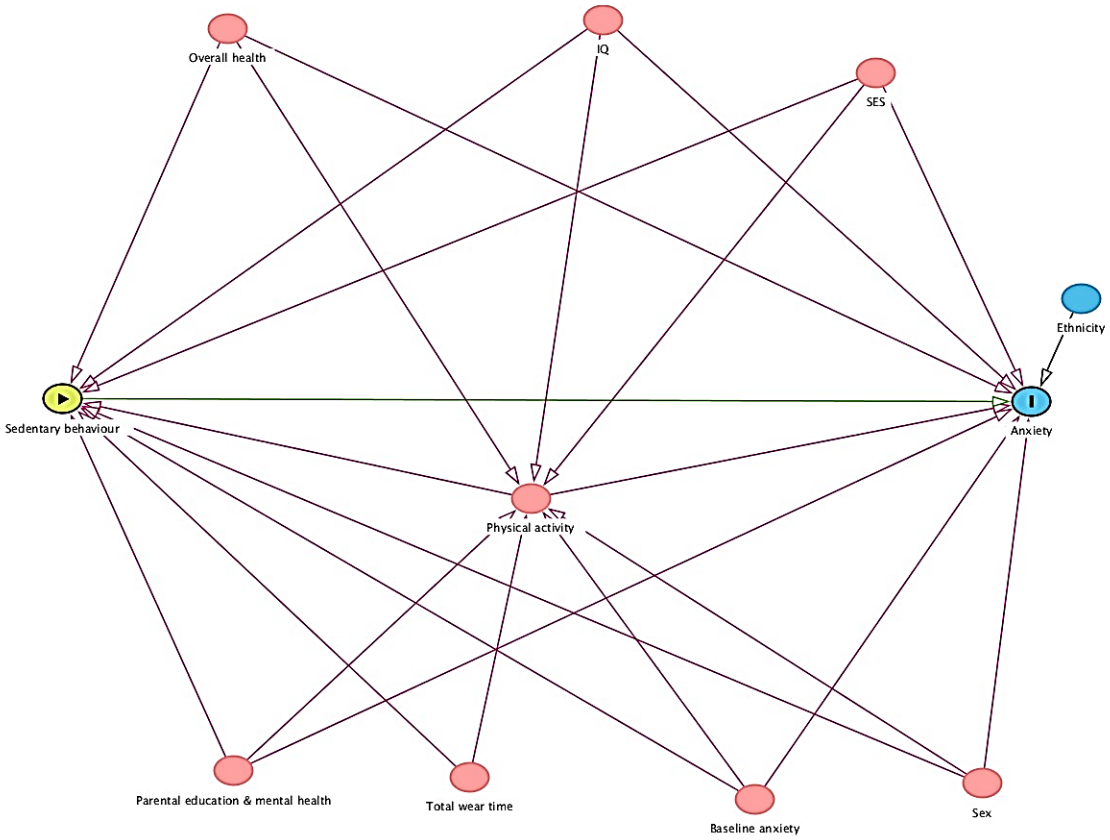
Table 7. Longitudinal models including BMI

Age (years)	Model (n)	CPM (per 100)			Time spent at different intensities								
					Sedentary (per 60 mins)			Light (per 60 mins)			MVPA (per 15 mins)		
		IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*
12	Fully adjusted (2,348)	0.946	0.916, 0.978	0.001	1.070	1.017, 1.127	0.010	0.923	0.871, 0.977	0.006	0.904	0.848, 0.964	0.002
14	Fully adjusted (1,916)	0.966	0.933, 1.001	0.056	1.072	1.014, 1.133	0.014	0.952	0.890, 1.019	0.159	0.966	0.911, 1.023	0.241
16	Fully adjusted (1,151)	0.985	0.938, 1.034	0.548	1.077	1.004, 1.116	0.038	0.919	0.844, 1.001	0.053	1.005	0.942, 1.073	0.874

Table 8. Longitudinal models excluding participants with smoking at 16 and alcohol use at 15 as confounding variable

Age (years)	Model (n)	CPM (per 100)			Time spent at different intensities								
					Sedentary (per 60 mins)			Light (per 60 mins)			MVPA (per 15 mins)		
		IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*
12	Fully adjusted (1,799)	0.955	0.920, 0.992	0.019	1.050	0.991, 1.113	0.101	0.926	0.868, 0.988	0.021	0.908	0.843, 0.977	0.010
14	Fully adjusted (1,536)	0.970	0.933, 1.008	0.128	1.076	1.011, 1.145	0.021	0.955	0.885, 1.030	0.237	0.970	0.909, 1.003	0.348
16	Fully adjusted (1,019)	0.984	0.932, 1.038	0.549	1.043	0.968, 1.124	0.269	0.920	0.840, 1.001	0.069	0.990	0.922, 1.062	0.777

Figure 9. A Directed Acyclic Graph (DAG) of associations between sedentary behaviour and anxiety



NB, I constructed this DAG using the online resource: http://www.dagitty.net/dags.html#. Discussions between co-authors produced the causal assumptions underlying my analysis, which are graphically represented in this DAG. For simplicity, I have omitted arrows between covariates except for physical activity.

Figure 10. Distribution of anxiety scores (CIS-R)

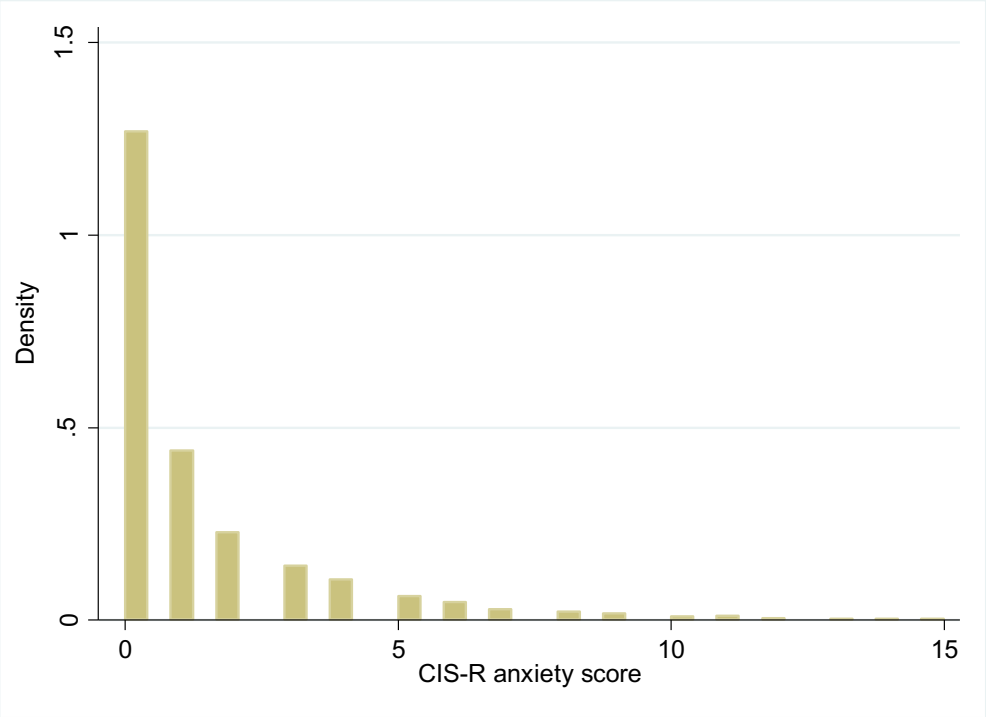


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Table 9. ISM in full cohort with imputed data

Age	Activity category	Activity category			
	Activity category	Light		MVPA	
		%Δ	95% CI	%Δ	95% CI
12	**Sedentary**	-10.29	-16.02, -4.17	-25.90	-43.50, -2.87
14		-9.78	-16.71, -2.27	8.37	-16.70, 2.27
16		-9.06	-17.61, 0.36	-10.40	-32.53, 19.00

Table 10. ISM with depressive symptoms as a confounding variable

Age		Activity category			
	Activity category	Light		MVPA	
		%Δ	95% CI	%Δ	95% CI
12	Sedentary	-15.81	-22.36, -8.66	-12.33	-35.92, 19.99
14		-11.22	-19.27, -2.37	5.70	-22.1, 43.42
16		-9.58	-20.07, 2.28	-3.38	-32.30, 36.17

Table 11. ISM with smoking and alcohol use (age 16) as confounding variables

Age		Activity category			
	Activity category	Light		MVPA	
		%Δ	95% CI	%Δ	95% CI
12	Sedentary	-16.41	-22.79, -9.49	-7.62	-32.42, 26.38
14		-12.17	-20.11, -3.46	-10.99	-17.71, 49.53
16		-9.72	-21.45, 3.77	-4.50	-34.92, 40.14

NB smoking and alcohol are entered into the model at age 16.

Table 12. ISM with physical illness as a confounding variable

Age		Activity category			
	Activity category	Light		MVPA	
		%Δ	95% CI	%Δ	95% CI
12	Sedentary	-16.32	-22.74, -9.38	-7.52	-32.40, 26.49
14		-11.71	-19.72, -2.91	12.28	-16.74, 51.41
16		-14.26	-23.86, 3.44	-3.35	-30.95, 35.27

NB physical illness was entered into all models as it was not possible to determine when the illness occurred.

Table 13. ISM excluding anyone with a possible anxiety disorder at baseline

Age	Activity category	Activity category			
	Activity category	Light		MVPA	
		%Δ	95% CI	%Δ	95% CI
12	**Sedentary**	-16.02	-22.47, -9.04	-8.15	-32.94, 25.82
14		-12.09	-20.07, -3.31	-12.60	-16.55, 51.96
16		-14.65	-24.18, -3.93	-5.88	-32.66, -31.55

Table 14. ISM using linear regression

Age	Activity category	Activity category			
	Activity category	Light		MVPA	
		β	95% CI	*β*	95% CI
12	**Sedentary**	-0.22	-0.32, -0.12	-0.09	-0.48, 0.31
14		-0.16	-0.28, -0.04	0.12	-0.26, 0.49
16		-0.17	-0.31, -0.03	-0.08	-0.49, 0.32

Table 15. ISM with BMI as a confounding variable

Age	Activity category	Activity category			
		Light		MVPA	
		%Δ	95% CI	%Δ	95% CI
12	**Sedentary**	-15.71	-22.32, -8.454	-10.73	-35.17, 22.92
14		-12.06	-20.01, -3.32	-10.83	17.73, 49.29
16		-14.97	-24.51, -4.23	-4.45	32.60, -33.48

Figure 11. Flow of participants included in this study

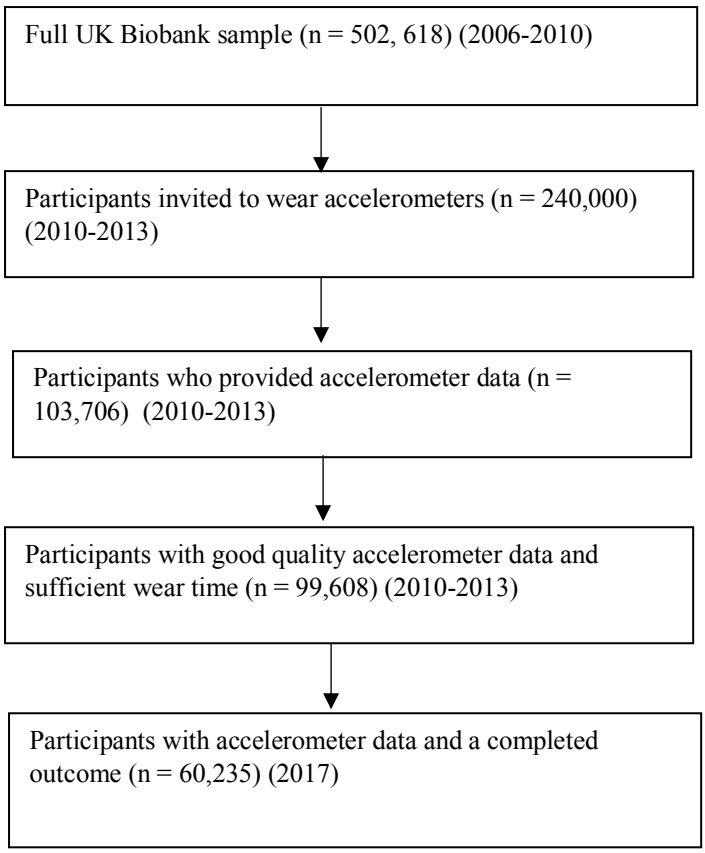
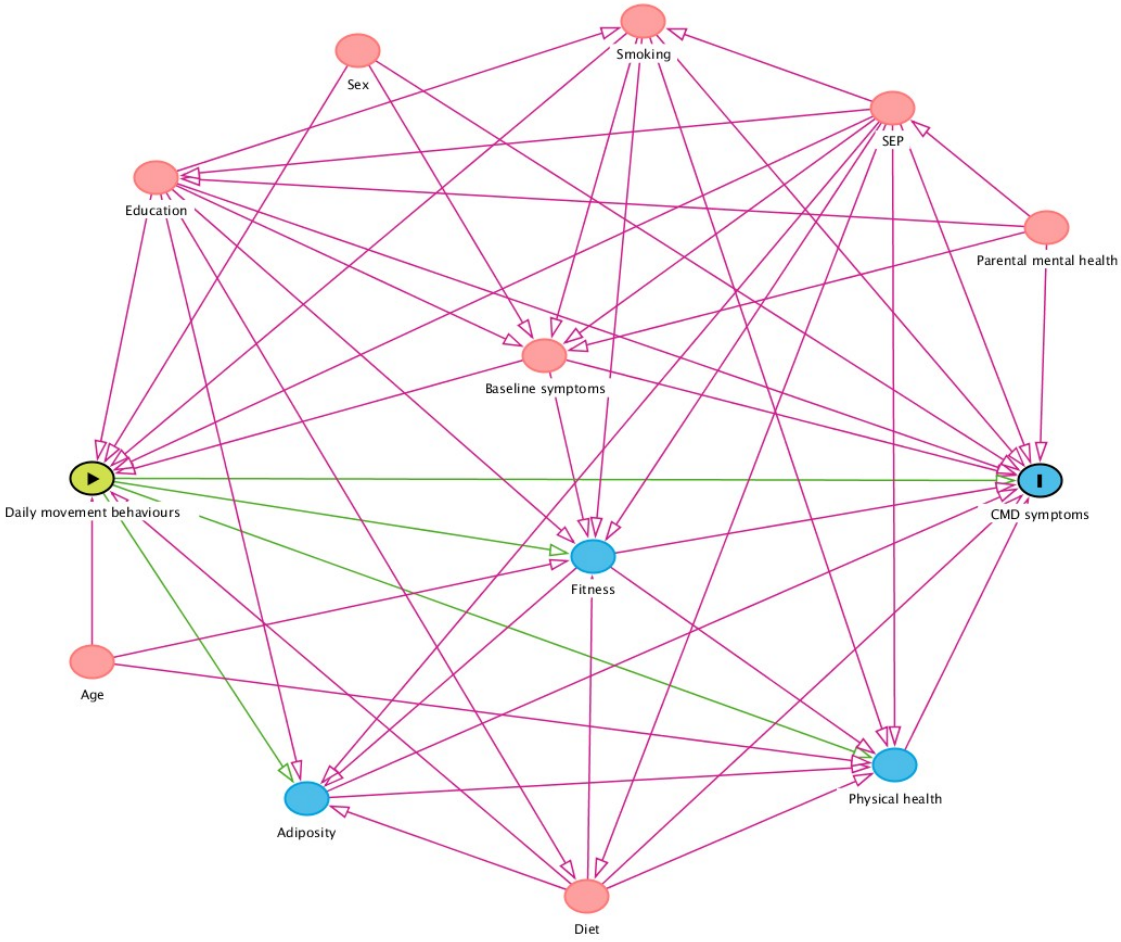
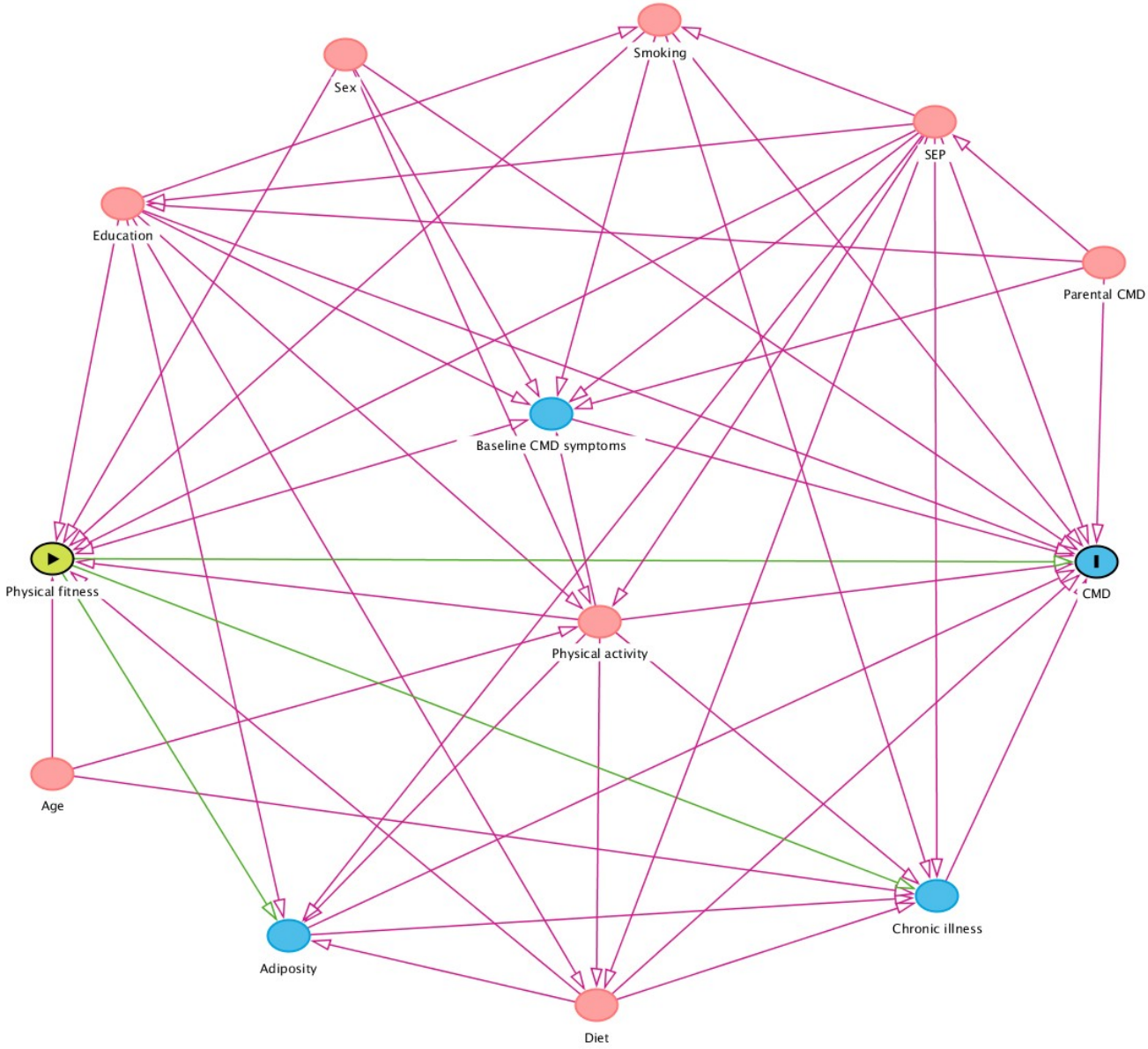


Figure 12. Directed acyclic graph of causal associations between covariates in this analysis



I used an online software package to generate this figure from Dagitty.net.

Figure 13. DAG of proposed causal associations between fitness, common mental disorders, and covariates



CMD = common mental disorder; SEP = socioeconomic position

Table 16. Longitudinal models with participants with a history of depression or anxiety excluded

			Common mental health disorders					
			Adjusted					
			Depression		Anxiety		Depression or anxiety	
	Fitness group	N	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P
CRF	Low	15,363	1.75 (1.143, 1.905)	0.003	1.339 (0.964, 1.858)	0.081	1.522 (1.220, 1.900)	< 0.001
	Medium		1.371 (1.082, 1.736)	0.009	1.120 (0.822, 1.153)	0.471	1.308 (1.062, 1.611)	0.011
	High		Reference					
Grip strength	Low	97,880	1.409 (1.285, 1.545)	< 0.001	1.358 (1.196, 1.115)	< 0.001	1.393 (1.284, 1.514)	< 0.001
	Medium		1.110 (1.013, 1.215)	0.0024	1.125 (1.115, 1.417)	< 0.001	1.134 (1.046, 1.229)	0.002
	High		Reference					

Table 17. Longitudinal models adiposity included as a covariate

			Common mental health disorders					
			Adjusted					
			Depression		Anxiety		Depression or anxiety	
	Fitness group	N	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P
CRF	Low	23,399	1.328 (1.131, 1.559)	0.001	1.180 (0.961, 1.446)	0.115	1.281 (1.110, 1.480)	0.001
	Medium		1.044 (0.900, 1.213)	0.566	1.050 (0.876, 1.206)	0.596	1.056 (0.925, 1.203)	0.423
	High		Reference					
Grip strength	Low	152,853	1.366 (1.296, 1.444)	< 0.001	1.356 (1.262, 1.456)	< 0.001	1.343 (1.278, 1.413)	< 0.001
	Medium		1.112 (1.063, 1.444)	< 0.001	1.142 (1.064, 1.224)	< 0.001	1.112 (1.058, 1.168)	< 0.001
	High		Reference					

Table 18. Longitudinal models lower thresholds for defining depression (PHQ ≥8) and anxiety (GAD-7 ≥8) incidence

		Common mental health disorders						
		Adjusted						
			Depression		Anxiety		Depression or anxiety	
	Fitness group	N	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P
CRF	Low	23,399	1.475 (1.309, 1.660)	< 0.001	1.351 (1.159, 1.570)	< 0.001	1.485 (1.302, 1.695)	< 0.001
	Medium		1.195 (1.067, 1.337)	0.002	1.157 (1.002, 1.337)	0.046	1.141 (1.005, 1.296)	0.041
	High		Reference					
Grip strength	Low	152,853	1.354 (1.286, 1.405)	< 0.001	1.402 (1.322, 1.486)	< 0.001	1.381 (1.315, 1.452)	< 0.001
	Medium		1.116 (1.068, 1.165)	< 0.001	1.140 (1.076, 1.207)	< 0.001	1.112 (1.061, 1.173)	< 0.001
	High		Reference					

Table 19. Longitudinal models in full cohort with imputed missing data

Fully imputed		**Common mental health disorders**						
		Adjusted						
			Depression		**Anxiety**		**Depression or anxiety**	
	Fitness group	**N**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**
CRF	Low	152,978	1.628 (1.436, 1.846)	< 0.001	1.256 (1.072, 1.472)	< 0.001	1.489 (1.332, 1.664)	< 0.001
	Medium		1.252 (1.133, 1.384)	< 0.001	1.102 (0.982, 1.238)	0.096	1.198 (1.096, 1.307)	< 0.001
	High		Reference					
Grip strength	Low	152,978	1.385 (1.312, 1.460)	< 0.001	1.356 (1.266, 1.452)	< 0.001	1.359 (1.294, 1.426)	< 0.001
	Medium		1.122 (1.064, 1.183)	< 0.001	1.140 (1.065, 1.220)	< 0.001	1.115 (1.063, 1.170)	< 0.001
	High		Reference					