SYSTEMIC INFLAMMATION, EXECUTIVE FUNCTION & MENTAL HEALTH: BRIDGING RESEARCH AND CLINICAL PERSPECTIVES

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Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

Signed: 

Karolina Tothova

Date: 04.05.2025

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Abstract

This thesis investigates how systemic inflammation interacts with cognitive, psychological, and physical health outcomes, reflecting a growing recognition of its role across multiple domains of health. Systemic inflammation refers to a chronic, low-grade immune response that can influence brain function, behaviour, and physiology. While its role in physical conditions such as obesity, cardiovascular disease, and metabolic disorders is well established, increasing evidence also links systemic inflammation to mental health difficulties and impaired executive functioning. Such findings carry implications for many disciplines, including clinical psychology, highlighting the potential value of inflammation-informed approaches to case formulation, assessment, and intervention—particularly in complex, comorbid presentations.

This thesis comprises of two studies. Study 1 is a qualitative study which explored general practitioners' (GPs') experiences of supporting patients with concurrent obesity and common mental health conditions, such as depression and anxiety. Addressing existing research gap, this study focused particularly on how GPs understand, deliver, and communicate lifestyle-based interventions, such as dietary changes and physical activity, that have potential to reduce inflammation.

Study 2 is a scoping review mapping current empirical literature on the association between systemic inflammation and executive function in childhood and adolescence. explore which biopsychosocial moderators have been studied in relation to this association, and consider gaps and future directions to help inform early intervention and future clinical research.

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List of Abbreviations

ACEs - Adverse childhood experiences

BMI – Body mass index

CBT – Cognitive behavioural therapy

CNS – Central nervous system

CRP- C-reactive protein

EF – Executive function

ELA- Early life adversities

GP – General practitioner

HPA axis – Hypothalamic-pituitary-adrenal axis

HSE – Health Executive Service

IL-6 - Interleukin-6

MDD – Major depressive disorder

NICE- National Institute for Clinical Excellence

MH – Mental health

PTSD – Post-traumatic stress disorder

SES – Socio-economic status

TNF-α- Tumour necrosis factor alpha

Overview of Thesis Structure

This thesis is structured across four main chapters. Chapter 1 presents the Integrative Introduction, which provides a comprehensive overview of the background literature that informed both studies. Chapter 2 details the qualitative study which explored General Practitioners' perspectives and experiences in supporting patients with concurrent obesity and mental health difficulties. Chapter 3 comprises a scoping review investigating the association between systemic inflammation and executive function in children and adolescence. Finally, the Chapter 4 provides an Integrative Discussion, considers implications for future research and clinical psychology practice, and includes a reflective account of the researcher's role in the qualitative study as well as a discussion of recruitment challenges encountered during the research process.

Chapter 1: Integrative Introduction

Understanding Systemic Inflammation

Physical, cognitive, and psychological health are shaped by the complex and constantly changing interactions between biological, psychosocial, and environmental factors. With research progress, that has been increased recognition of how physiological systems, such as the immune, nervous, and endocrine systems, interact to influence wellbeing. Within this context, inflammation has emerged as one of key mechanism linking physical and mental health across the lifespan.

Overview of Inflammation

In broad terms, inflammation is a universal physiological reaction of the immune system in response to various insults and harmful stimuli. This includes infections, physical tissue damage, psychological stress and other environmental stimuli which are deemed dangerous or harmful (Black, 2002; Calder et al., 2009). While the processes implicated in the activation of immune responses are complex and outside the scope of this thesis, inflammatory processes are generally thought of as an effective response to facilitate healing (Pahwa et al., 2022). However, it is important to distinguish between acute and chronic inflammation. While acute inflammation is understood as a short-lasting response which is resolved after harmful stimuli has been attended to, chronic inflammation persist past the resolution of an insult or injury and is increasingly associated with a range of adverse physical and psychological effects (Raiten et al., 2015; Kanterman et al., 2012). Chronic, low-grade inflammation has been traditionally linked to various chronic diseases and health conditions, including cardiovascular diseases, some cancers, obesity etc. (Cifuentes et al., 2025) has been increasingly studied in relation to

psychosocial processes and psychiatric disorders (Ferat-Osorio, Maldonado-García, & Pavón, 2024). The majority of biopsychosocial research is focused on the effects of systemic inflammation, as characterised by elevated circulating markers of inflammation. In the wider literature, the term systemic inflammation is often used interchangeably with peripheral inflammation. These terms typically refer to inflammatory processes occurring in peripheral tissues and the bloodstream, rather than within the central nervous system, where inflammation would be classified as neuroinflammation. Neuroinflammation differs from the peripheral one largely by the types of cells involved and their communication mechanisms (Ransohoff & Brown, 2012). Peripheral inflammation can trigger neuroinflammatory processes through several mechanisms, such as disruption of the blood-brain barrier, activation of glial cells triggered by systemic immune responses, and modulation of autonomic pathways involved in organ-to-brain signalling (Sun, Koyama, & Shimada, 2022). The precise mechanisms through which psychosocial factors trigger inflammatory responses, and how these responses subsequently lead to structural and functional brain changes, remain subjects of ongoing research.

Inflammatory Markers in Research Settings

A number of inflammatory markers are traditionally being used in studies evaluating systemic inflammation. The most commonly used ones in the research of chronic inflammation are C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) (Cullen et al., 2017). These have distinct roles in the inflammatory response and might have varied effects on different brain regions. CRP is a liver-synthesised protein, the levels of which increase in response to inflammation (Nehring, Goyal, & Patel, 2017). CRP has been frequently used in research settings with the typical concentration levels being established to be normally below 3mg/L (MacGiollabhui et al., 2020), whereas most studies of chronic inflammation would

exclude participants with levels above 10mg/L as this might indicate acute inflammatory nature and therefore acute illness or infection). Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) are pro-inflammatory cytokines—signalling proteins secreted by immune and other cells that contribute to the initiation and regulation of inflammatory responses (Bawer & Kuhlman, 2023). Cytokines are key regulators of inflammatory responses. Beyond facilitating communication between immune cells, they can also influence neurochemical and neuroendocrine pathways, leading to broad effects on physiological functions and behaviours (Curfs, Meis, & Hoogkamp-Korstanje, 1997). Due to the complexity of the cytokine network and their production in response to diverse stimuli (Bawer & Kuhlman, 2023), determining the precise role and origin of these markers is challenging.

Building on the understanding of inflammatory processes and markers, psychobiological research has significantly advanced our understanding of the complex interplay between systemic inflammation and a range of biological, psychological, and social factors. Over the past two decades, there has been growing interest in the role of inflammation as a potential underlying mechanism contributing to the development, maintenance, or exacerbation of physical and mental health difficulties, as well as cognitive impairments.

The following sections provides an overview of key evidence and theoretical models linking systemic inflammation to specific biopsychosocial factors relevant to this thesis. First, the relationship between inflammatory processes and common non-communicable diseases is outlined, with particular emphasis on obesity, given its central relevance to Study 1. This is followed by a review of chronic stress and early life adversities and its link to immune functioning. This leads into an overview of the current understanding of the role of inflammation in common mental health problems, particularly depression. Finally, the focus

turns to the association between cognitive function and inflammation, with the particular emphasis on executive function (EF) as this topic is central to Study 2 (Scoping Review) of this thesis.

Systemic Inflammation and Physical Health

Systemic Inflammation and Chronic Diseases

While acute inflammatory responses are essential for survival, facilitating the elimination of pathogens or other harmful stimuli, ongoing activation of immune system can lead to a range of physical health conditions. Systemic inflammation has been implicated in the pathophysiology of a range of non-communicable (i.e., non-infectious, not directly transmittable for a person to person) diseases, including cardiovascular disease, diabetes, certain cancers, autoimmune and neurodegenerative conditions - collectively representing a major global burden of morbidity and mortality (Furman et al., 2019).

The mechanisms underlying both the initiation and perpetuation of systemic inflammation as well as its particular role in the development or progression of individual disease are complex and multifactorial. However, broadly speaking, chronic inflammatory states can arise from unresolved infections, or they can be driven by an exposure to environmental and lifestyle-related factors. The examples of these include dietary factors (such as high-fat, low fibre diet), smoking, physical inactivity and chronic psychosocial stress (Clader et al., 2017). Unlike acute inflammation, which resolves once the harmful stimulus is eliminated, many of these environmental/ lifestyle-related factors can inherently persistent over longer time. This ongoing exposure continually stimulates the immune system, preventing the resolution of inflammation and promoting a chronic low-grade systemic inflammatory state that contributes to metabolic, vascular, and other disease processes (Calder et al., 2017; Furman et al., 2019).

Importantly, inflammatory activation is accompanied by a range of behavioural and physiological changes which are often referred to as sickness behaviour (Dantzer et al., 1993; Dantzer & Kelly, 2007). These include fatigue, anhedonia, sleep disturbances, social withdrawal etc. (Straub, 2017; Dantzer et al., 2008). While these responses are adaptive in acute settings, facilitating energy conservation and promoting recovery, in long term they may further exacerbate inflammatory processes, for example, through sleep disruption and reduced physical activity, thereby establishing a self-perpetuating cycle of inflammation and detrimental effects on health. Understanding these dynamic interactions between chronic inflammation, sickness-related behaviours and disease progression is important for development and improvement of effective disease management as well as preventative approaches. Taking into consideration the somewhat cyclical nature of these interactions is particularly relevant when interpreting findings from Study 1 (GP Study) of this thesis, as it explores GPs' experiences of supporting patients with concurrent obesity and MH difficulties- two conditions frequently associated with chronic systemic inflammation.

Obesity, Allostatic Load & Inflammation: A Physiological Pathway

Obesity has become a large focus of multidisciplinary research over the years, reflecting its high global health significance. Given its rising global prevalence (Haththotuwa, Wijeyaratne, & Senarath, 2020), obesity has become a major focus of research into physiological, psychological, and immune-related processes. The health-related complications associated with obesity are well recognised and documented, including cardiovascular disease, increased stroke risk, type 2 diabetes, and certain types of cancer (Calle et al., 2003; Versini et al., 2014). Obesity is also associated with elevated risk of depression, anxiety, and other psychiatric conditions including schizophrenia (Leutner et al., 2023). The relationship between obesity and

mental health is likely multifactorial and bidirectional, involving a complex interplay between individual, behavioural, and systemic factors (Swallen et al., 2005; Luppino et al., 2010). Systemic inflammation has been implicated as one of the potential mechanisms linking obesity and MH problems, particularly depression and anxiety, relevant for a subset of people experiencing these concurrent conditions. The association between inflammation and mental health will be further explored in a subsequent section.

In efforts to successfully address the ever-increasing rates of obesity worldwide, research attention has turned to better understand the physiological mechanisms underlying obesity and its commonly associated comorbidities. Among these, systemic inflammation has been highlighted as an important pathway, potentially connecting obesity with adverse cognitive and mental health outcomes. Unlike other inflammation-inducing conditions, obesity-related inflammation originates in adipose tissue, which—despite being primarily composed of fat cells—functions as an active endocrine organ (Balistreri et al., 2010; Greenberg & Obin, 2006). When body fat ratio increases substantially, adipose tissue releases pro-inflammatory cytokines and chemokines, perpetuating a state of chronic, low-grade systemic inflammation (Ferrante, 2007).

This chronic low-grade inflammatory state has been increasingly linked to structural and functional brain alterations, particularly in prefrontal regions involved in executive functioning (Guillemot-Legris & Muccioli, 2017), and is viewed as a potential shared physiological mechanism underlying (at least partially) the association between obesity and certain mental health outcomes. Chronic stress likely contributes to this inflammatory cascade and may influence both obesity and mental health. These processes are explored further in subsequent sections.

Psychosocial Pathways to Inflammation

Chronic stress & Immune Dysregulation

Chronic psychosocial stress refers to the sustained experience of stressors perceived as uncontrollable or overwhelming, particularly in the context of limited coping resources (Cohen, 1995). Chronic stress has long been studied in relation to immune system functioning. There is extensive evidence indicating that prolonged psychological distress is linked to elevated inflammatory markers (e.g., Kiecolt-Glaser et al., 2020; Slopen et al., 2013). For instance, previous studies have explored this association between increased inflammation and interpersonal stress, highlighting the adverse impact of inflammatory processes on relationships marked by ongoing conflicts, trust issues and instability (Fulgini et al., 2009; Miller, Rohleder & Cole, 2009). Similarly, Kiecolt-Glaser, Gouin, and Hantsoo (2010) suggested that close interpersonal relationships characterised by high conflict and low social support can activate the production of proinflammatory cytokines.

Beyond relational stress, broader social determinants such as socioeconomic status have also been linked to systemic inflammation. In fact, the relationship between low socioeconomic status and systemic inflammation has been recognised across all ages (Milaniak & Jaffee, 2019; Muscatell et al., 2020). In a retrospective birth cohort analysis, Tabbasum et al. (2008) found that both childhood and early adulthood socioeconomic status predicted CRP levels in middle age, even after controlled for variables including smoking, levels of physical activity and weight status. However, in general, longitudinal studies that account for key confounders remain limited, making it challenging to clarify the specific role of socioeconomic status in these processes. This is important to further determine due to the association between low SES and chronic stress, a significant driver of systemic inflammation.

Socioeconomic status, understandably, does not operate in isolation, but rather is closely linked to other contextual factors, including race, ethnicity, and gender. All of these factors have previously been associated with differential exposure to and experiences of chronic stress, which in turn have implications for systemic inflammation. More specifically, racial and ethnic differences in inflammatory markers are well documented. For instance, higher levels of C-reactive protein (CRP) and other pro-inflammatory markers have frequently been observed among Black, Hispanic, and Asian minorities compared to White majorities (Farmer et al., 2020; Nazmi & Victora, 2007). Herd, Karraker, and Friedman (2012) reported that racial disparities in CRP levels persisted even after accounting for socioeconomic and behavioural factors, with Black men showing substantially higher levels than White men. Such findings are typically understood as reflecting broader inequities, including differential access to health-promoting resources, greater exposure to environmental stressors, and the cumulative impact of social disadvantage. Some evidence suggests that such disparities may be compounded by gender, with women from racial or ethnic minority backgrounds showing particularly elevated inflammatory profiles (Farmer et al., 2021), even after controlling for body mass index and health behaviours (Herd et al., 2012; Khera et al., 2005).

In this context, discrimination has previously been identified as a one of important pathways through which structural inequities give rise to chronic stress and, in turn, elevated systemic inflammation. For instance, a prospective study of women found that daily experiences of discrimination predicted higher CRP levels over a seven-year period (Beatty Moody et al., 2014). More broadly, perceived discrimination across multiple domains, including racial, gender and sexual identity has been consistently linked to heightened systemic inflammation de Castro, Gee, & Takeuchi, 2010; Guyll et al., 2001; Meyer et al., 2008), likely reflecting the chronic stress burden imposed by these experiences. Together, these findings suggest that discrimination, frequently experienced by racial/ethnic minorities, contributes to sustained stress exposure that is associated with higher inflammatory risk

In addition to various social determinants, factors of physical environment exposure have also been increasingly suggested to play an important role in shaping inflammatory processes. Differences between rural and urban populations have been noted, with studies reporting variation in CRP levels linked to lifestyle and environmental exposures (Yajnik et al., 2008; Ye et al., 2007). Recent research has highlighted the protective effects of green spaces and outdoor environments, with greater residential greenness and more time spent outdoors

associated with lower allostatic load and reduced inflammatory activity (Egorov et al., 2024). By contrast, both short- and long-term exposure to environmental pollutants, such as air pollution and toxins more prevalent in deprived urban settings have been linked to elevated systemic inflammation (Hajat et al., 2015; Liu et al., 2019).

Taken together, these accounts illustrate examples of how various social and environmental conditions shape cumulative stress burdens across the life course. Biological embedding offers one account of how such burdens are translated into changes in neuroendocrine and immune regulation. According to the biological embedding hypothesis, chronic stress exposure can lead to prolonged stimulation of the sympathetic nervous system, enhancing inflammatory cytokine production (Segerstrom & Miller, 2004; Glaser & Kiecolt-Glaser, 2005; Fagundes & Way, 2014). Furthermore, persistent stress disrupts anti-inflammatory pathways, notably the HPA axis, reducing the body's ability to regulate inflammation effectively (Minihane et al., 2015; Segerstrom & Miller, 2004). Additionally, chronic stress-induced suppression of parasympathetic activity further diminishes the body's anti-inflammatory mechanisms (Kuhlman et al., 2017). Collectively, these alterations result in physiological wear-and-tear known as allostatic load, which can maintain chronic inflammatory states with long-term consequences for health (McEwen & Gianaros, 2010).

Allostatic Load in chronic stress

Allostasis refers to a range of physiological processes in the body in response to stress exposure (Sterling & Eyer, 1988). During these processes, there is a cascade of biological mechanisms being activated which aim to mobilise body to respond promptly to danger (Juster et al., 2010). While these complex mechanisms are adaptive in short term, a prolonged, chronic activation can lead to a number of adverse health effects. This wear-and-tear (i.e. allostatic load) can lead to disruptions to metabolic, immune and cardiovascular systems (Korte et al., 2005; Lupien & Schramek, 2006). As the perception of perceived stress is influenced by a combination of one’s genetic predisposition, past lived experiences and behaviours, the extent of allostatic load will differ from individual to individual. Overall, the increasing allostatic load, particularly in a

chronic nature, may ultimately result in adverse consequences for health and disease through over-activation of both immune and neuroendocrine systems (McEwen, 1998). As the allostatic load/ overload is associated with dysregulation of the immune system, and thus systemic inflammation (McEwen & Stellar, 1993), it could be seen as a mechanism linking chronic psychosocial stress with systemic inflammation (Kuhlman et al., 2020; Glaser & Kiecolt-Glaser, 2005). Given the growing evidence showing an association between increased inflammatory markers and psychosocial adversities as well as mental health difficulties, allostatic load theory can provide valuable insights into these complex biopsychosocial mechanisms.

Early life adversity and immune system

Early life adversity (ELA) describes childhood or adolescence' experiences that place considerable demands on a child's capacity to adapt emotionally, behaviourally, or biologically to their environment (Duffy, McLaughlin & Green, 2018). This includes experiences such as abuse, neglect, family dysfunction etc. These experiences are relatively common, with prior research indicating than approximately one in ten children with a history of ELA will experience long term physical or mental health consequences (Felitti et al., 1998; Kalmakis & Chandler, 2015). These include am increased risk of psychiatric disorders, substance use problems, cardiovascular disease and premature mortality (Evans & Whipple, 2013; Hughes et al., 2017). While the psychological consequences of ELA are well documented, growing evidence also highlights the physiological impact of early adversities. The growing evidence that early adversity can impact neurodevelopment and immune function (Duffy, McLaughlin & Green, 2018) highlights its relevance across both clinical psychology and medical disciplines. In particular, research suggests that such experiences may disrupt the development of neurobiological regulatory systems—especially during sensitive periods in early life—

contributing to long-term alterations in immune functioning (Gabard-Durnam & McLaughlin, 2020). neuroimmune models propose that early adversity may heighten inflammatory responses and intensify neuroimmune signalling, thereby increasing susceptibility to later psychiatric disorders (Miller et al., 2011; Nusslock & Miller, 2016). Accordingly, it has been suggested that exposures to early life adversities might impact the immune system both at the time of exposure and is thought to influence immunological processes in the long term (Hennessy et al., 2010, 2011). Moreover, Boyce et al. (2021) proposed that the frequency and intensity of early life stressors influences the extent of subsequent inflammatory responses, indicating a potential dose-response relationship between psychosocial stressors and systemic inflammation. However, more research is needed to clarify the nature and boundaries of this relationship. For instance, it is unclear whether inflammatory responses are shaped more by the duration, severity or specific characteristics of early adversity. Similarly, there is currently a lack of understanding of how different forms of adversities interact in their effects on immune system activation, and to what extent the protective factors, such as individual resilience or supportive figure in child's life, might serve as buffers against heightened inflammatory risk.

Inflammation & Mental Health

Inflammation & Common mental health problems- overview

Common mental health problems like depression and anxiety have been increasingly linked to elevated levels of pro-inflammatory cytokines. A substantial body of literature has associated chronic low-grade inflammation with depression in both children and adults (e.g., Berk et al., 2013; Dantzer et al., 2008; Mössner et al., 2007; Toenders et al., 2022). Elevated inflammatory activity has also been identified in post-mortem brain tissue of individuals diagnosed with depression (Miller & Raison, 2016). Longitudinal studies further support this relationship, with

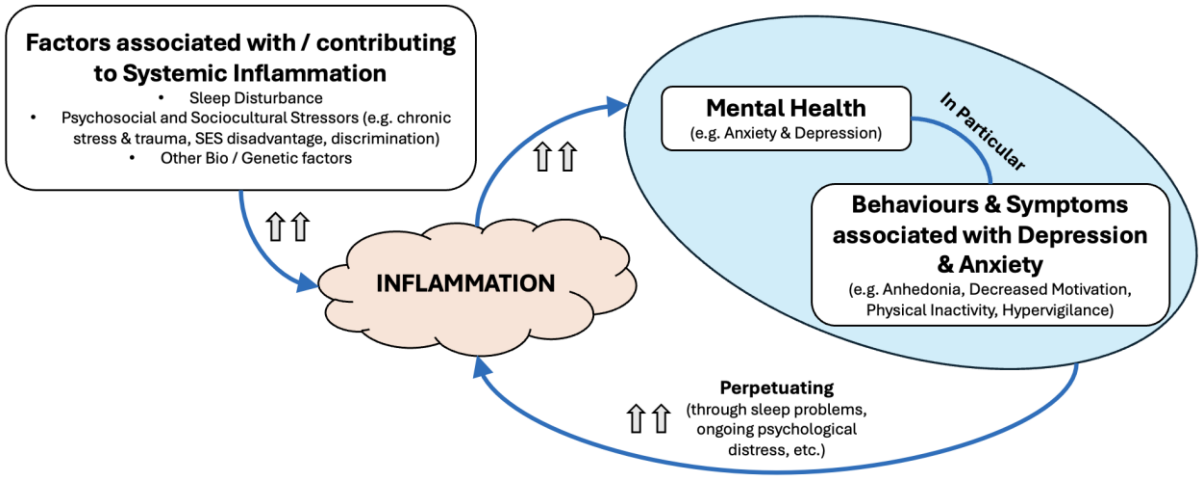
findings indicating that the presence of elevated inflammatory markers prospectively predicts the onset of depressive symptoms (Khandaker et al., 2014; Valkanova, Ebmeier & Allan, 2013).

Moreover, research suggests a bidirectional relationship between inflammation and mood disorders, where inflammation may contribute to and also result from psychiatric symptoms (e.g., Dowlati et al., 2010; Miller & Raison, 2015). Kiecolt-Glaser, Derry & Fagundes (2015) highlighted that while inflammation seems to play a significant role in the development of depression for a subset of the clinical population, depression can, in turn, contribute to a feedback loop that further amplifies inflammation. They further discussed that certain childhood factors, such as obesity and childhood adversity, might mediate the ongoing inflammatory responses.

Overall, while depression has received the most attention in this field, studies have also demonstrated increased inflammatory activity in conditions such as anxiety, post-traumatic stress disorder (PTSD), and schizophrenia (Michopoulos et al., 2017; Miller & Raison, 2016).

Figure 1.

Illustrative model of systemic inflammation as a physiological mediator and perpetuating factor in mental health problems among a subset of the population.



Note. The figure outlines how lifestyle, psychosocial, sociocultural and biological factors can initiate and sustain systemic inflammation, which is bidirectionally linked to mental health problems such as depression and anxiety. One proposed pathway involves behaviour changes triggered by immune system activation, such as social withdrawal and anhedonia, which in turn contribute to the maintenance of elevated inflammatory states and persistence of mental health problems. Certain factors, particularly lifestyle factors (e.g., poor sleep and physical inactivity), can act both as contributors to systemic inflammation and as perpetuating mechanisms once inflammation and mental health difficulties are established. This figure is not exhaustive but highlights the main categories most relevant to the focus of this thesis.

Neuroimmune Interactions in Mental Health

A substantial body of research has focused on exploring the mechanisms implicated inflammatory-moderated effects on the brain that are particularly relevant for clinical population, especially in relation to depression and anxiety. For instance, Felger (2018) reviewed existing evidence on both clinical and translational studies which explored how

peripheral inflammation affects brain regions and neurotransmitter activity in individuals with mood and anxiety disorders. He noted that inflammatory cytokines may more strongly affect brain regions involved in processing reward and detecting threats, such as amygdala and basal ganglia. This may clinically translate into behaviours commonly observed in mood and anxiety disorders, such as hypervigilance, reduced motivation, motor slowing and anhedonia. Further evidence points to changes in reward circuitry and dopamine functioning in basal ganglia (e.g., Brydon et al., 2008; Capuron et al., 2012; Felger & Miller, 2012). Additionally, heightened amygdala activation in response to inflammation—associated with symptoms of anxiety and PTSD—has been linked to increased cytokine production, potentially creating a self-reinforcing cycle of neural and immune dysregulation (Felger, 2018; Harrison et al., 2009; Muscatell, 2015).

The Partial Role of Inflammation in Depression

When discussing the links inflammation and depression, it is important to highlight the heterogeneity of depression, both clinically and physiologically. Current evidence suggests that elevated inflammatory responses are implicated only in a subset of individuals with depression, indicating that immune dysregulation is not universally present across all presentations. For instance, in a large sample of 5579 participants, 47% of those who reported high depressive symptomatology had elevated levels of CRP (above 3.0 mg/L) and 41% also met criteria for metabolic syndrome (Rethorst, Bernstein & Trivedi, 2014). Similarly, Raison & Miller (2011) suggested that elevated inflammatory markers can be observed in about one third of clinical population compared to controls, and Osimo et al. (2018) reported that up to 40% of an inpatient psychiatric sample exhibited markers of systemic inflammation.

Altogether, these findings highlight the heterogeneity of inflammatory profiles among individuals with depression and raise additional questions for future research. In particular, it is important to determine whether or which characteristics, such as genetic susceptibility, psychosocial context, or behavioural patterns, differentiate inflammation-linked depression from non-inflammatory subtypes. It also remains unclear how these factors may interact, either independently or in combination, to influence inflammatory processes.

Nevertheless, there is sufficient evidence supporting a strong and potentially self-perpetuating relationship between inflammatory processes and depression. This makes the topic highly clinically relevant, pointing to the potential for inflammation-targeted and multidisciplinary interventions.

Early Adversity, Inflammation, and Mental Health Risk

One emerging direction here is the role of early life adversity and chronic psychosocial stressors in shaping inflammation-related risk for depression. As noted earlier, ELA may contribute to inflammation-related depression via neuroimmune mechanisms (Miller et al., 2011; Nusslock & Miller, 2016), potentially helping explain variability in inflammatory profiles among individuals with depression. Supporting this, patients with major depressive disorder (MDD) and a history of adverse childhood experiences (ACEs) have been found to exhibit higher levels of inflammatory markers compared to participants with MDD but no reported history of ACEs (De Punder et al., 2018).

In a longitudinal study of adolescents, Miller and Cole (2012) found that in participants with childhood adversity, the onset of depression was accompanied by increases in CRP and IL-6, and the elevated CRP persisting even after symptoms subsided. Notably, higher inflammatory markers also predicted later depression—an effect not observed in those without early

adversity—suggesting that inflammation may play a greater role in the pathogenesis of depression among individuals with such histories. Similarly, a review of 15 studies by Maayan & Maayan (2024) found that depressed individuals with a history of early adversity exhibited higher inflammatory markers compared to non-depressed individuals with history of ELA. Eight of these studies showed that inflammation served as a mediator between early adversity and later depression.

Together, these findings highlight the relevance of considering early psychosocial context when investigating biological and physiological mechanisms underpinning depression and potentially other MH presentations.

Inflammation & Cognition

Executive Function: Development and Influences

Executive function (EF) refer to a set of top-down cognitive processes, which play crucial role in everyday life as they allow us to plan forward, respond flexibly to the changing environment and purposefully focus our attention (Ferguson, Brunsdon & Bradford, 2021). Executive function play a crucial role in behavioural and emotional regulation (Calkins & Marcovitch, 2010; Romero-López, 2018). They have been extensively studied in relation to a range of life outcomes, including academic success, cognitive development, and psychosocial adjustment (Diamond, 2005; Miller et al., 2011; Borella et al., 2010; Willoughby et al., 2012a). Previous research has consistently shown that executive skills support effective learning, emotional resilience, and social competence throughout childhood and adolescence (e.g., Benavides-Nieto et al., 2017; Pearce & Davis, 2021; Schmeichel, Volokhov & Demaree, 2008). Conversely, difficulties in executive functioning have been linked to increased risk for both

internalising symptoms such as anxiety and depression, and externalising behaviours such as impulsivity and aggression (Thorell & Wåhlstedt, 2006; Brocki et al., 2010; Hughes & Ensor, 2011) and adverse physical health outcomes (Crescioni et al., 2011; Miller et al., 2011; Riggs et al., 2010).

While various theoretical models of executive functions have been proposed, a tripartite framework remains widely adopted in developmental and lifespan research. Miyake et al. (2000) initially identified three distinct but interrelated executive functions—inhibition, shifting, and updating—emphasising their shared reliance on working memory processes. However, in developmental psychology, the tripartite model most commonly referenced is that of Diamond (2013), who conceptualised the three core executive functions as inhibition, working memory, and cognitive flexibility. Inhibition, or inhibitory control, refers to the ability to regulate one's attention, behaviour or emotions in order to suppress an automatic impulse or resist an external temptation, enabling a more appropriate or goal-directed response (Diamond, 2013). Working memory involves the ability to temporarily hold and mentally process information to carry out tasks or solve problems (Baddeley, 2000). Lastly, cognitive flexibility refers to the capacity to adapt one's cognitive strategies or mental processes in response to new or unexpected environmental demands (Cañas et al., 2003). Inhibitory control and working memory, foundational elements of executive functions, tend to emerge early in childhood, with finer refinement happening throughout adolescence. These abilities lay the groundwork for more complex cognitive operations. Similarly, working memory continues to develop throughout adolescence and into early adulthood, often reaching its peak performance in the mid-20s (e.g. Best & Miller, 2010; Schweinsburg et al., 2005). In contrast, cognitive flexibility, which entails the ability to shift between tasks or mental sets, sees its most pronounced maturation during mid to late adolescence. This delayed development is consistent with the protracted maturation of the prefrontal cortex, a region essential for task-switching and

adaptability. While individual factors play crucial role, previous studies underscored the ongoing maturation of white matter tracts in the prefrontal regions, supporting the notion of enhanced cognitive flexibility throughout adolescence and into late twenties (Reichelt, 2016). This is supported by the evidence that during adolescence and early adulthood, EFs undergo both linear and non-linear morphological brain changes (Tayler et al., 2015). From a perspective of developmental neuroscience, it has been proposed that the brain circuits underpinning cognitive flexibility mature later compared to those for inhibitory control and working memory (Diamond, 2013). Brain imaging studies seem to support the differential maturation of EF components, further strengthening the idea that separate components of EFs might develop along different timelines (e.g. Mills & Tamnes, 2014; Rosen et al., 2018). There is some evidence that while inhibition and working memory follow comparable developmental pathways, cognitive flexibility follows a distinct developmental trajectory (Ferguson, Brunsdon & Bradford, 2021).

Previous evidence shows that influences such as chronic stress, early life adversities, socioeconomic deprivation, and obesity can significantly impact these cognitive processes (e.g., Girotti et al., 2024; Hackman & Farah, 2009; Yang et al., 2018). For example, there is a well-established link between lower socioeconomic status (SES) and poorer executive function performance. This association is often attributed to chronic stress and environmental factors prevalent in lower socioeconomic environments (Blair & Raver, 2016; Hackman, Farah & Meaney, 2010). Similarly, adverse childhood experiences (ACEs) have been associated with deficits in executive function. Studies have shown that children experiencing ACEs often exhibit greater difficulties in working memory and impulse control (Bucker et al., 2014; Hughes et al., 2017). Furthermore, ACEs have been linked to an increased risk of cognitive impairment in older adults (Halpin et al., 2022), potentially due to the cumulative and lasting effects of psychological effects of psychological stressors on the body and brain. As described

earlier, many of these biopsychosocial risk factors are also closely intertwined with inflammatory pathways across the lifespan. Similarly, growing evidence suggests that systemic inflammation is associated with poorer executive function performance in both clinical and general population samples (Goldsmith et al., 2016; Mac Giollabhui et al., 2020; McAfoose & Baune, 2009). The next section explores the broader links between inflammation and cognitive functioning, positioning EF within a complex network of biological and environmental influences.

Systemic Inflammation and Cognitive Function – Overview

Systemic inflammation has been increasingly investigated in relation to cognition and cognitive deficits, with most studies traditionally focused on adults and older adults. Indeed, systemic inflammation has been linked to cognitive decline and dementia processes (e.g. Lai et al., 2017; Stacey et al., 2017; Weninger & Yanker, 2001) and elevated inflammatory markers have been linked to a more rapid deterioration across various cognitive domains (Lai et al., 2017; Stacey et al., 2017). Prolonged systemic inflammation may adversely affect cognitive performance in healthy middle-aged adults (Marsland et al., 2015). Similar findings emerge from studies in which experimental manipulation of cytokine levels have demonstrated negative impacts on executive functions, learning, and memory in adults of various ages (Krabbe et al., 2005; Paine et al., 2015; Reichenberg et al., 2001). Evidence supporting an inflammatory basis for cognitive impairment in adults and older population stems from postmortem brain analyses, observational epidemiological research, and, to an extent, clinical trials (Gorelick, 2010). While research on inflammation-related cognitive deficits in childhood and adolescence is less extensive, a growing body of work indicates that systemic inflammation is associated with aspects of cognitive performance from very early life. For example, elevated inflammatory markers have been tied to poorer outcomes in various cognitive domains (Cullen

et al., 2017; Kyriklaki et al., 2019; Mac Giollabhui et al., 2024). Kuban et al. (2017) found that extremely preterm babies with elevated inflammatory markers during their first month of life exhibited worse executive function performance at age ten, compared to preterm babies without increased inflammatory markers. Overall, while exploration of this relationship has gained momentum in recent years, much remained to be explored, especially in the context of childhood and adolescence, in both clinical and community settings.

Proposed mechanisms of the impact of inflammation on cognitive development

While the mechanisms by which systemic inflammation affects cognitive development are not fully understood (Bach et al., 2022), several mechanisms have been proposed. One proposed mechanism is through the influence of inflammation on neuromodulatory pathways. Inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha, can affect neurotransmitter systems, particularly the serotonergic and dopaminergic systems, which play crucial roles in cognitive processes (Capuron & Miller, 2011). It has also been suggested that these cytokines can pass the blood brain barrier, allowing systemic inflammatory signals to interact directly with the central nervous system (Banks, Lynch & Price, 2009). Once in the brain, inflammatory mediators may also be produced locally by astrocytes, microglia, neurons, or endothelial cells in response to injury or infection (McAfoose, & Baune, 2009).

C-reactive protein has also been linked to alterations in brain function and structure, potentially leading to cognitive decline in certain populations (Wang et al., 2023). Additionally, inflammation can impact synaptic plasticity, potentially leading to alterations in neural connectivity and function (Yirmiya & Goshen, 2011). Recent neuroimaging studies further indicate that higher peripheral levels of pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α) correlate with structural and functional alterations, such as changes in cortical thickness and

surface area in particular brain regions (Marlsand et al., 2017; Prats-Soteras et al., 2020). It has also been suggested that the effects of inflammatory processes on the brain may differ depending on a developmental stage of an individual (Prats-Soteras et al., 2020). More research is required to explore the longitudinal effects of inflammation on cognition across lifespan.

Currently, research is starting to also consider whether and how these inflammatory processes impact on brain functionality and structure differently depending on a particular developmental period. It has been proposed that certain developmental periods, specifically the first trimester of pregnancy, the first year of life, and adolescence, might represent times when brain is particularly sensitive to environmental influences such as systemic inflammation. This increased sensitivity is thought to reflect distinct neurodevelopmental processes occurring at each stage: migration of microglia into the central nervous system during the first trimester, initial synaptic during infancy, and continued pruning and myelination of cortical and subcortical regions throughout adolescence (Dziabis & Bilbo, 2022). Overall, childhood and adolescence are periods marked by considerable neural reorganisation, including synaptic pruning, neurogenesis, and the maturation of inhibitory neurotransmitter systems (Liston et al., 2009; Hanson et al., 2012; Teicher et al., 2016). Microglia, the brain's resident immune cells, are central to these processes, facilitating synaptic pruning and modulating neurotransmission. When inflammation is elevated during these periods, it may impair microglial functioning, potentially altering developmental trajectories and contributing to long-term cognitive deficits (Miller & Spencer, 2014). However, further longitudinal and translational research is needed to clarify the timing, mechanisms, and long-term outcomes of such disruptions across the lifespan.

Nevertheless, these insights together highlight the clinical relevance of systemic inflammation as a shared physiological mechanism across many physical, cognitive, and mental health

domains, prompting further consideration of how such understanding informs real-world intervention strategies.

Systemic Inflammation as a Shared Mechanism: Implications and Lifestyle-Based Approaches

The earlier sections of this chapter were informed by research intersecting psychology, immunology, and cognitive neuroscience, illustrating how systemic inflammation may serve as one potential framework to better understand and connect a range of biopsychosocial phenomena. While other relevant mechanisms and theoretical perspectives exist and have not been addressed here, the two empirical studies presented in the subsequent chapters are grounded in the theoretical assumption that systemic inflammation plays a meaningful role in both cognitive and mental health outcomes. Up to this point, the focus has been on presenting relevant research evidence and important concepts. However, some crucial questions remain regarding the clinical relevance and real-world application of such findings. Specifically, to what extent is the evidence linking inflammation with executive function and mental health being translated into clinical settings? What is currently known about the effectiveness of interventions that target systemic inflammation in order to improve physical, cognitive, and psychological outcomes? And what are the challenges associated with implementing such approaches in routine clinical practice?

While the biopsychosocial model of physical and mental health has been recognised since at least the mid-twentieth century (Lugg, 2022), it is most widely associated with Engel (1977), who conceptualised health as a "continuum of natural systems." Despite being accepted across disciplines and endorsed by organisations such as the World Health Organisation, its core principles are often not reflected in wider healthcare. In practice, healthcare delivery remains

largely compartmentalised, and the model has had limited influence on the broader structure and funding of health services (Wade & Halligan, 2017). Earlier literature argued that the concepts of seeing body and mind as separate entities are largely present in modern healthcare structures (Menninger, 2006; Wade, 2006), whereas more recent research continues to support these notions. For instance, Cormack et al. (2023) highlighted that where the biopsychosocial model is applied, it is often interpreted in a reductionist manner, limiting its potential to inform holistic and personalised care. Similarly, a systematic review by Ng et al. (2021) highlighted an existing gap between research evidence and clinical practise relating to the implementation of biopsychosocial approach in relation to musculoskeletal pain. They identified multilayer barriers preventing practitioners from effectively implementing this model. These included time constraints, lack of interdisciplinary collaboration, insufficient clinicians' knowledge and training, as well as several systemic and structural factors, such as particular healthcare infrastructure and broader policies in place. While the review focused exclusively on musculoskeletal pain, these barriers most likely span across numerous clinical presentations and are particularly relevant for people with multiple comorbidities.

Insights from psychoneuroimmunology may offer a valuable opportunity to re-emphasise biopsychosocial principles by targeting shared physiological mechanisms, potentially shifting the focus from symptom management to more integrated care approaches. Research into interventions that reduce systemic inflammation is growing, with promising implications for physical, cognitive, and mental health outcomes. Although this area, and particularly the evaluation of its clinical application is still relatively new, it may be especially beneficial for individuals with complex comorbidities, where traditional care pathways are often fragmented and resource intensive. Considering the previously described links between systemic inflammation and both physical and mental health difficulties, lifestyle-based interventions may offer dual benefits for individuals with such comorbid presentations. Obesity and mental

health comorbidity represent one example where such an approach may be particularly relevant. How such interventions are perceived and implemented by general practitioners in primary care is explored in Study 1 of this thesis.

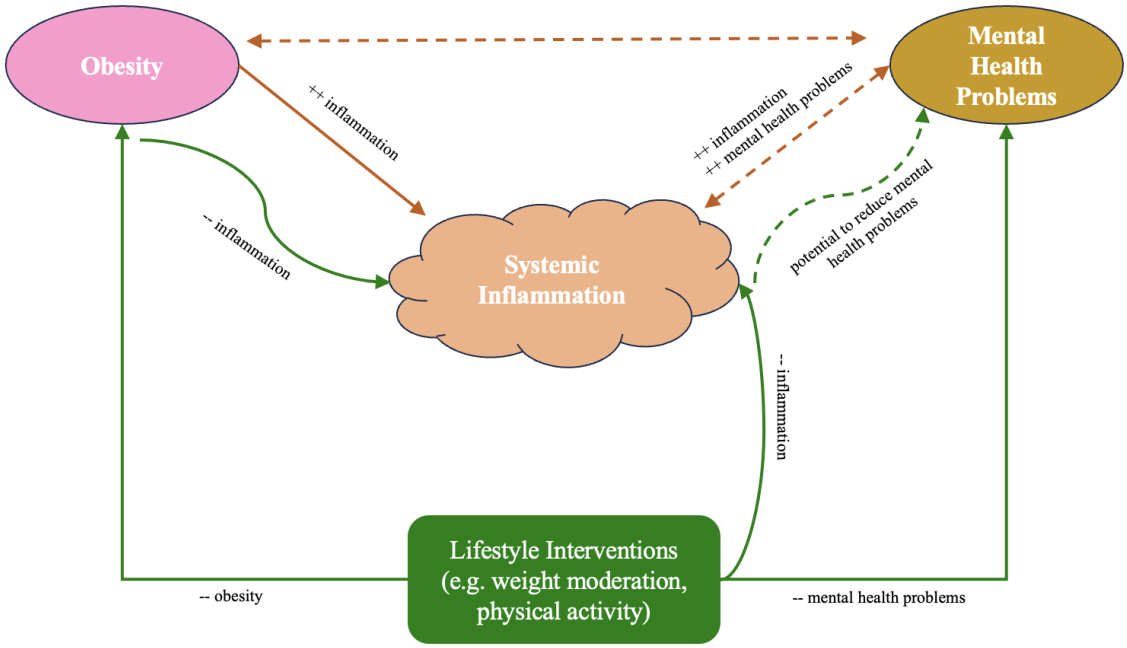
Lifestyle-Based Interventions: Targeting Inflammation to Improve Physical and Mental Health

Lifestyle-based interventions refer to a broad range of behavioural approaches aimed at reducing systemic inflammation. These are typically categorised into three main types: dietary interventions, physical activity or exercise-based programmes, and combined approaches. Additionally, some interventions may focus more directly on improving sleep hygiene or mindfulness-based stress reduction. While such strategies have long been recommended to promote general health and wellbeing, recent research increasingly frames them as targeted interventions - rather than primarily preventive measures- with inflammation reduction as a core target. These approaches are grounded in evidence suggesting that lowering inflammatory markers can lead to improved physical health outcomes, such as reduced blood pressure and decreased risk of cardiovascular disease and metabolic syndrome, while also potentially mitigating the development of comorbidities. As the associations between elevated inflammation and health risk appear to follow a linear pattern, even minor reductions in inflammation achieved through behavioural interventions may produce clinically relevant benefits (Nicklas, You & Pahor, 2005).

Figure 2 below presents a conceptual model illustrating how lifestyle interventions based on reducing inflammation may support complex concurrent presentations. It specifically focuses on the link between obesity-mediated inflammation and mental health difficulties, as this forms the theoretical basis of Study 1.

Figure 2

Conceptual model of systemic inflammation as a shared mechanism linking obesity and mental health, and the potential moderating role of lifestyle interventions.



Note. The figure presents a conceptual model of the bidirectional relationship between obesity and inflammation alongside the proposed link between inflammation and mental health difficulties. Systemic inflammation is recognised as a shared physiological mechanism between the two. While lifestyle-based interventions are often recommended for each condition independently, the model suggests that by targeting systemic inflammation directly may lead to improvements in both physical and psychological health outcomes.

Overall, with the growing appreciation of the role of inflammation in the subset of population presenting with mood or anxiety problems, interventions aimed at reducing systemic inflammation are being increasingly considered as relevant treatment options (Felger, 2018).

Such approached could be particularly relevant for depressed individuals with known increase of inflammatory markers (Kiecolt-Glaser, Derry & Fagundes, 2015). Within this context, a range of non-pharmacological, lifestyle-based interventions have been explored, including dietary changes, exercise-based interventions and mind-body practices. Prior research in this area has shown promising results in both the reductions of inflammation and improvements in symptoms of depressive and anxiety following both weight reducing and increased physically activity interventions (e.g., Bower & Irwin, 2016; Fabricatore et al., 2011; Schuch et al., 2016). Additionally, compassion-based meditation has been shown to modulate stress-related physiological responses via the HPA axis and sympathetic nervous system leading to lower inflammatory responses (Pace et al., 2009). Naturally, the relevance and effectiveness of these interventions are likely to vary depending on the underlying condition and the extent to which systemic inflammation is implicated. For instance, in the context of mental health, given that only a subset of individuals with depression exhibit elevated inflammatory markers (Osimo et al., 2018), the clinical benefits of anti-inflammatory interventions may be most evident in this subgroup (Rapaport et al., 2016). The subsequent sections provide an overview of evidence base for main types of lifestyle-based interventions aimed at reducing inflammation, with the first two groups being particularly relevant for Study 1.

Diet-based interventions

Dietary interventions aimed at reducing systemic inflammation typically involve either the reduction of food intake associated with pro-inflammatory effects, such as red meat (Calder et al., 2011) or the increased consumption of foods associated with anti-inflammatory effects, such as high-fibre diets (Barbaresko et al., 2013; King, 2005). For instance, adherence to a Mediterranean-style diet has consistently been associated with lower levels of inflammatory biomarkers and a reduced risk of cardiovascular disease (Raffaele & Miryam, 2004; Tsigalou

et al., 2020). Moreover, previous studies have indicated the potential protective effects of anti-inflammatory diets on age-related cognitive decline (Martínez-Lapiscina et al., 2013; Valls-Pedret et al., 2015). While further research is needed to clarify the underlying mechanisms, accumulating evidence suggests that reductions in inflammation may contribute to improvements in cognitive function (Scarmeas, Anastasiou, & Yannakoulia, 2018; Vauzour et al., 2017). These dietary interventions are particularly common in the context of obesity and obesity-related inflammation. For instance, short-term intensive dietary restrictions—especially those targeting fat intake—have been shown to reduce inflammatory markers in both children and adults (Bastard et al., 2000; Heilbronn, Noakes, & Clifton, 2001; Gallistl et al., 2001). In the general population, a meta-analysis of nine randomized controlled trials found that 6- to 12-week consumption of whole grains was associated with reduced levels of pro-inflammatory biomarkers (Xu et al., 2018). Moreover, longitudinal data from a large community cohort indicate that low-inflammatory diet was linked to a reduced risk of developing multiple comorbidities and/or a slower progression of developing new comorbidities, especially in older adult population (Maimaitiyiming et al., 2024).

Interventions based on physical activity

Sedentary lifestyle and a lack of physical activity increase a risk of various chronic conditions, including cardiovascular diseases, types of cancer, diabetes etc.- all of which inflammation have been linked to elevated systemic inflammation (Rook & Dalgleish, 2011; Pedersen, & Saltin, 2006). Therefore, a considerable amount of research has explored the potential anti-inflammatory effects of exercise. A systematic review and meta-analysis of twenty randomised control trials found that exercise produced significant reductions in C-reactive protein (CRP) and tumour necrosis factor-alpha (TNF-α), although no significant effect was observed for

interleukin-6 (IL-6). Exercise was also associated with increased levels of the anti-inflammatory cytokine IL-10 (Alizaei Yousefabadi et al., 2021).

The anti-inflammatory effects of exercise may not be limited to the indirect mechanism of adipose tissue reduction (which itself is linked to lower pro-inflammatory activity). Exercise also appears to have direct immunomodulatory effects, including the stimulation of anti-inflammatory cytokine production by contracting skeletal muscles (Mathur & Pedersen, 2008; Petersen & Pedersen, 2005). While there is evidence supporting anti-inflammatory effects of different types and intensities of physical activity, it is yet unclear which modality, duration and frequency would be optimal for people with different inflammation-related conditions (Gleeson et al., 2011). Nevertheless, physical exercise has shown to be a promising for both the prevention and management of inflammation-related disorders.

Inflammation has also been implicated as one of the potential mechanisms linking exercise and favourable cognitive outcomes, although most research has focused on older adults, particularly with existing cognitive impairment. For example, Chupel et al. (2017) found that 28-week resistance training increased levels of pro-inflammatory cytokines and improved cognitive performance (compared to controls) in older women with cognitive impairment. In general, regular physical activity has been shown to contribute to various neuroprotective effects on the brain, partially through the downregulation of pro-inflammatory cytokines and increase of anti-inflammatory agents such as interleukin-10 (IL-10) (Flynn et al., 2007; Kohman & Rhodes, 2013).

Yoga & mindfulness practices

Related to the general benefits of physical activity, different yoga practises have recently received increasing attention for their potential to improve physical and psychological wellbeing through a number of ways. While yoga has been widely incorporated to many

therapeutical practices due to its recognised effect on stress reduction, studies have also investigated the possibility of yoga practices on reduction of systemic inflammation. A systemic review of 15 studies concluded that yoga represents a solid option for interventions aimed at reducing inflammation, thus indirectly positively impacting a range of health outcomes (Djalilova et al., 2019). In addition to the general benefits associated with physical activity, various yoga practices have received increased research interest for their potential to enhance both physical and psychological well-being. While yoga has been widely incorporated to many mindfulness practices due to its recognised effect on stress reduction, emerging evidence also supports its role in modulating systemic inflammation. A systematic review of 15 studies concluded that yoga might be an effective intervention for lowering inflammatory markers, thereby contributing indirectly to improved physical and mental health outcomes also through physiological mechanisms (Djalilova et al., 2019). Similarly, mindfulness-based interventions which are well established psychological interventions for a range of clinical population, some studies found evidence for reductions of pro-inflammatory markers following mindfulness-based interventions in participants with depression and anxiety. However, despite promising findings, high-quality evidence on the broader impact of these interventions on inflammation remains limited, warranting further research (Andrés-Rodríguez et al., 2019).

Conclusion – Chapter 1

This chapter provided an overview of key evidence and theoretical models underlying the interplay between the immune system, neurodevelopmental processes, and key psychological and cognitive outcomes. Systemic inflammation was positioned as a proposed physiological pathway linking physical health, mental health, and cognitive functioning, offering a foundation for the relevance of interventions aimed at reducing inflammation. The chapter outlined how biopsychosocial factors and experiences, including chronic psychosocial stress

and early life adversity, may shape neuroimmune trajectories, with possible long-term consequences for mental and physical health, as well as cognitive development.

These mechanisms are of clinical relevance for multiple disciplines, including psychology and medicine. Although several lifestyle-based interventions have been proposed for individuals with comorbid inflammatory-related conditions—such as concurrent obesity and mental health problems—less is known about how these interventions and underlying concepts are understood or applied in everyday clinical practice. Existing research highlights persistent challenges in implementing biopsychosocial models in primary care. Increasing recognition of the role of systemic inflammation across a range of conditions indicates a clear need to better understand how such insights translate into routine care, particularly in relation to lifestyle-based approaches. To this end, study 1 addresses this gap by exploring general practitioners' experiences of supporting individuals with co-occurring obesity and mental health difficulties, both common and often intertwined conditions, previously associated with systemic inflammation. The study uses thematic analysis to examine perceived barriers, opportunities, and current approaches in this context. Study 2 complements this by focusing on the other end of the inflammation-outcome continuum: the association between systemic inflammation and cognitive development. It synthesises the current evidence on inflammation and executive function in children and adolescents—an area that remains underexplored to provide clearer directions for future research and provide clearer evidence towards possible intervention strategies in children and adolescents.

Together, these studies offer a complementary perspective on the biopsychosocial impact of inflammation. While one explores how (and to what extent) emerging knowledge is integrated into clinical care and what are the barriers and difficulties supporting physical & MH conditions connected through systemic inflammation, the other maps an evolving research

landscape focused on intricate relationship between developing executive functioning and inflammatory processes. Collectively, the findings aim to inform future research and contribute to more integrated and potentially preventative approaches in clinical practice.

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Chapter 2. Study 1: Exploration of general practitioners' perspectives and experiences of patients with concurrent obesity and MH difficulties. Thematic analysis.

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Abstract

Background

Obesity and common mental health (MH) conditions, particularly depression and anxiety, frequently co-occur and together are associated with poorer outcomes than either condition alone. These complex presentations share overlapping psychosocial and physiological mechanisms, including systemic inflammation. Lifestyle-based interventions targeting inflammation, such as diet, exercise, sleep, and stress reduction, are increasingly recognised as promising strategies to support both physical and mental health outcomes. General practitioners (GPs), being often the point of contact for patients with concurrent obesity and MH problems, are well placed to deliver such integrated care. However, little is known about how GPs perceive, implement, or communicate these approaches for this patient group. This study aimed to explore GPs' experiences in managing these complex cases, with a particular focus on lifestyle-based interventions.

Methods

A qualitative mixed-methods approach was used, combining semi-structured interviews and open-ended survey responses. Eight GPs participated in the study. Data were analysed using Braun and Clarke's thematic analysis framework, guided by a contextualist epistemological framework.

Results

Eight themes were identified across two overarching domains: GPs' perspectives on supporting patients with concurrent obesity and mental health difficulties, and their experiences of delivering lifestyle interventions. Key findings included the emotional and relational intensity

of consultations, the challenge of addressing obesity without reinforcing stigma, and systemic pressures that constrained care. Mental health concerns were often prioritised in consultations, particularly when symptoms were severe, which limited opportunities to introduce or implement lifestyle changes. Lifestyle recommendations were often seen as clinically important yet difficult to implement, especially in the absence of clear guidance and structural support. GPs emphasised the importance of person-centred care, shared goal setting, and the need for psychoeducational resources that communicate the rationale for lifestyle change—particularly in relation to systemic inflammation.

Conclusions

The findings highlight the complexities GPs face when delivering lifestyle interventions to patients with co-occurring obesity and mental health conditions. Addressing these challenges will require system-level changes, clearer clinical resources, and enhanced support for integrated, person-centred care. The study provides practical directions for improving the implementation of inflammation-informed lifestyle interventions in primary care.

Keywords

General Practitioners, Inflammation, Lifestyle Interventions, Obesity, Mental Health

Title Page

Title: Exploration of general practitioners' perspectives and experiences of patients with concurrent obesity and MH difficulties. Thematic analysis.

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1. Introduction

Both obesity and mental health conditions have received extensive research attention over the decades, owing to their high prevalence and significant impact on various health outcomes, psychological wellbeing and overall quality of life. Historically, these conditions have been treated separately. However, there has been a growing drive toward integrated clinical approaches, aiming to improve translation of research evidence demonstrating their frequent co-occurrence in order to provide more holistic and effective support in clinical practice.

1.1. Obesity and Mental Health in Primary care

Obesity is now understood as a chronic disease significantly associated with reduced quality of life and increased mortality [1]. In Ireland, approximately 60% of adults are overweight or obese [2]. Obesity is associated with a wide range of chronic diseases, including type 2 diabetes, cardiovascular disease, certain cancers, and musculoskeletal disorders [3, 4]. As such, obesity significantly contributes to global morbidity and mortality [5, 6, 7]. Beyond its link to a range of physical diseases, growing evidence is highlighting the association between obesity and different mental health (MH) difficulties.

Obesity has been linked to a number of MH conditions—including anxiety, schizophrenia, and bipolar disorder [8, 9, 10]. So far, research has been most focused on obesity's relationship with depression. For example, Carrey et al. [11] identified a U-shaped relationship between body weight and depression, with highest depression rates among both underweight and obese individuals. The relationship between obesity and depression has been shown to be bidirectional in nature [12, 13], as also demonstrated by findings from a meta-analysis of longitudinal studies [14]. Obesity may increase the risk of depression through mechanisms such as weight-related stigma, chronic inflammation, and impact on self-image and self-esteem

[15, 16]. Conversely, depression can contribute to or perpetuate obesity via changes in appetite, reduced physical activity, as well as through weight-promoting effects of certain medications [17, 15]. These reciprocal influences can present challenges for treatment and highlight the need for integrated care approaches.

Notably, individuals who experience concurrent obesity and MH difficulties are at increased risk of poorer health outcomes than those experiencing either condition alone [18, 19]. Additionally, people living with co-occurring obesity and MH difficulties tend to experience increased psychosocial strain and have higher need of healthcare services [20, 21]. Moreover, they frequently present with additional comorbidities, such as diabetes or metabolic syndrome, further complicating their overall care and contributing to reduced quality of life [22, 23].

It is also important to recognise that these clinical patterns are embedded in wider social and cultural determinants. For example, lower socioeconomic status and area deprivation have been associated with higher obesity prevalence and worse MH outcomes via mechanisms and factors such as material constraints, chronic stress, reduced access to supportive environments, and cumulative adversity [24-27]. In practice, this translates to limited access to affordable, nutritious food, fewer safe or convenient opportunities for physical activity, and competing financial and caregiving demands that constrain the capacity to engage in health-promoting behaviours. Food poverty and food insecurity constrains dietary quality and is associated with higher risk of depression and increased chronic stress [28]. On the other hand, inexpensive energy-dense foods are more accessible and affordable than healthier options [29, 26].

Additionally, work related pressures and characteristics (e.g., shift work, irregular hours) can contribute to disrupted sleep through alterations in the circadian rhythm, which has been associated with increased risk of obesity [30]. Moreover, cultural norms can significantly shape eating practices and body ideals with stigma; influencing how individuals perceive and respond

to weight-related health recommendations [31]. Within healthcare settings, weight stigma is an important sociocultural consideration.

1.2. Weight Stigma and Consequences on Health Care Engagement

Evidence suggests that weight stigma can negatively impact health, even after controlling for BMI [32]. Weight discrimination has been linked to increased physiological dysregulation, including elevated inflammation, blood pressure, and cholesterol levels, as well as increased risk of mortality [33]. Puhl et al. [34] further demonstrated that obesity stigma can undermine motivation to engage in physical activity and promote maladaptive eating behaviours, thus reduce the effectiveness of lifestyle interventions. In healthcare settings, previous experiences of judgment or shame can discourage individuals with obesity from seeking help. Similarly, HSE Model of Obesity Care [2] highlighted how weight stigma in healthcare can prevent providers from delivering supportive, non-judgemental care, contributing to underdiagnosis and suboptimal treatment outcomes. This is particularly concerning for individuals living with both obesity and mental health conditions, who are likely to face compounded stigma.

1.3. Obesity & Mental Health – Shared Physiological Mechanisms and the Role of Inflammation

Obesity and mental health conditions share overlapping risk factors and may involve common physiological mechanisms, such as chronic stress and systemic inflammation. Systemic inflammation, in particular, has been identified as a key factor in the pathophysiology of both conditions [35]. Obesity is characterised by a state of chronic low-grade inflammation [36-38], which is triggered by excessive adipose tissue and marked by elevated pro-inflammatory cytokines and adipokines [39]. This inflammatory response is one of several mechanisms—

alongside hormonal, metabolic, and psychosocial factors—implicated in the development of obesity-related comorbidities such as insulin resistance and cardiovascular disease [40].

Similarly, increased markers of systemic inflammation have been associated with depression, anxiety, post-traumatic stress disorder (PTSD), and schizophrenia [35, 41]. Out of these, depression has received most attention, with inflammatory markers found consistently in a significant subset of depression, estimated at around 40% [42, 43]. A meta-analysis performed by Miller & Raisin [44] found that compared to controls, people with depression exhibited higher levels of inflammatory markers—such as IL-6, TNF-α, and CRP—compared to those without depression.

This evidence, supporting a significant role of immune system alterations in both obesity and depression indicates a need for a shared treatment target. Interventions that reduce inflammation, such as lifestyle-based interventions and pharmacological measures have a potential to improve outcomes in both conditions [44]. In particular, a growing body of research shows support for a range of lifestyle-based interventions, including dietary changes, exercise regimes and stress reduction, in improving increased inflammatory states for patients with concurrent obesity and depression [15, 45-47]. Additionally, interventions that improve sleep disturbance (which is frequently associated with depression) and reduce stress can lower inflammation, hence support both mental and metabolic health [48].

1.4. Current Clinical Guidelines and Gaps in guidelines

Traditionally, many healthcare systems tended to rely on single-disease oriented models of care that are poorly equipped to support patients with multiple, co-occurring conditions [49-51]. More recent national and international guidance have recognised the problematic nature of such approaches, owing to the high comorbidity rates in general populations. Currently, obesity

guidelines highlight the importance of addressing both physical and mental health needs in the clinical management of overweight and obesity at all levels of care. For instance, NICE Guideline NG246 [52] emphasises person-centred care, recommending that clinicians consider the potential impact of adverse experiences, weight stigma, and comorbid mental health conditions. Further, NICE Guideline QS111 [53] reinforces the need for coordinated care pathways that integrate mental health support into weight management, especially for individuals presenting with concurrent psychological difficulties. In the Irish context, the Association for the Study of Obesity on the Island of Ireland [54] positions mental health as central to effective obesity care, recommending proactive screening for psychological conditions such as depression, anxiety, binge eating disorder and trauma. They also advocate a stepped care approach, tailoring mental health input to the individual's level of need. HSE Model of Care of Obesity [2] states that coordinated input from obesity, mental health, and eating disorder services is required to establish consistent screening, defined care pathways, and accessible treatment options.

Alongside evolving guidelines, growing evidence has examined the effectiveness of lifestyle-based interventions targeting inflammation, offering a promising approach for patients with concurrent obesity and mental health difficulties to address both presenting concerns together.

1.5. Lifestyle based interventions targeting inflammation

Although the field is still developing, several modifiable lifestyle factors—particularly those related to physical activity and diet—have been shown to reduce systemic inflammation. Accordingly, a number of recent interventions have focused on these factors. These include increased fibre intake, Mediterranean-style dietary patterns, and both aerobic and resistance-

based exercise programmes. A Mediterranean-style diet in particular has been linked to improvements in both metabolic and mental health outcomes, likely through its effects on inflammatory markers such as CRP and IL-6 [15, 45]. Moreover, regular moderate-intensity exercise has also been shown to reduce systemic inflammation, support weight regulation, and alleviate symptoms of depression [46, 47]. Together, these approaches are increasingly recognised for their potential to simultaneously support both physical and mental health [55-57].

Given their dual impact, lifestyle-based interventions may be particularly relevant in primary care, where general practitioners (GPs) are expected to provide comprehensive support for patients with co-occurring obesity and mental health difficulties. However, despite growing evidence, there remains limited understanding of how such strategies are implemented in routine general practice.

1.6. Role of General Practitioners in Managing Co-occurring Obesity and Mental Health Difficulties

In Ireland and many other countries, primary care is typically the initial point of access for individuals with obesity and common mental health difficulties. General practitioners (GPs) are expected to lead on early detection, deliver initial advice and management, and coordinate follow-up or referrals to specialist services as needed [2]. Given the frequent co-occurrence of obesity and mental health conditions such as depression and anxiety, GPs are often tasked with supporting patients presenting with both physical and psychological challenges. Their dual role places them in a strong position to facilitate integrated care; however, limited research has explored how they navigate these complex presentations in practice. Greater attention is needed to understand their experiences and identify the structural and clinical supports required to deliver effective, sustainable care for this population.

While this paper focuses on general practitioners, the insights are directly relevant to clinical psychology. Because GPs are frequently the first point of contact for people with co-occurring obesity and mental health difficulties, understanding how they frame and deliver lifestyle advice highlights where psychological expertise can complement medical care and support integrated, patient-centred pathways.

1.7. Study rationale

Previous literature provides some insights into GPs' perspectives on managing obesity in primary care, highlighting common challenges such as limited time, insufficient training, perceived stigma, and the absence of multidisciplinary support [58, 59]. Similarly, some prior studies explored the role of primary care professionals in mental health care—particularly regarding depression. These reported diagnostic uncertainty and variability in GPs' confidence in managing these conditions [60]. While a small number of studies have explored GPs' general experiences with multimorbidity management, [61, 62], these do not specifically consider obesity and mental health together. Furthermore, although some qualitative studies investigate the use of lifestyle-based recommendations in primary care [63, 64], these address physical or mental health in isolation and do not consider systemic inflammation as a shared mechanism or treatment target for these presentations.

To date, no known qualitative studies have focused specifically on how GPs manage co-occurring obesity and depression or anxiety, nor how they understand or apply lifestyle interventions aimed at addressing systemic inflammation in such cases. This represents a critical gap in research, particularly in light of increasing evidence highlighting the physiological and psychosocial overlap between obesity and mental health conditions, and the growing recognition of lifestyle-based strategies as a promising treatment avenue.

In addition to exploring how GPs understand and implement lifestyle-based interventions for patients with concurrent obesity and mental health difficulties, the current study will also focus on examining GPs' perceptions of how such recommendations may be received by patients. By investigating how GPs anticipate and make sense of patient responses, the study can contribute to the development of more person-centred, responsive communication practices in primary care. While patient perspectives on weight stigma and healthcare avoidance have been widely explored, there is limited research capturing how GPs themselves reflect on these dynamics in the context of these complex presentations.

1.8. Specific study aims

The aim of this study was to consider GPs' perspectives and experiences of supporting this patient group. Using semi-structured interviews and open-ended surveys, the investigation focused on the challenges clinicians face and strategies they find effective in relation to lifestyle-based interventions. Specifically, the study explored several key areas: the perceived prevalence of concurrent obesity and MH difficulties in GPs' clinical practice; how GPs approach lifestyle-based recommendations for patients experiencing concurrent obesity and MH difficulties; the challenges encountered in offering combined MH and obesity-related guidance; the strategies they find helpful; and GPs' perceptions of how patients view lifestyle-based recommendations, including how encouraging or discouraging they may find them.

2.Methods

2.1.Study Design

This qualitative study employed a mixed-methods approach, combining semi-structured interviews and open-ended survey responses to explore general practitioners' (GPs) experiences and perspectives on supporting patients with concurrent obesity and common MH

problems. Particular attention was given to GPs' views on the role and implementation of lifestyle recommendations in clinical practice for this population. Ethical Approval was granted from the University College Cork Clinical Psychology Research Ethics Committee (CPREC).

2.2.Recruitment and Participants

Participants were eligible to take part if they were either qualified GPs or in the final year of GP training, and were currently involved in direct patient care, either independently or under supervision. Inclusion criteria specified that participants must be English-speaking and regularly seeing patients in general practice settings. Practitioners were excluded if they worked exclusively with children or in specialist area where contact with patients experiencing both obesity and mental health difficulties was unlikely. Recruitment strategies included outreach through professional networks, direct invitations to GP practices, snowballing and dissemination of the study invitation via a national GP forum in Ireland. Initially, data were collected via semi-structured interviews. However, due to limited uptake, an option was introduced to allow participation through an open-ended online survey format with a choice of an audio or written format. No demographic or professional background data were collected, as this could have increased the risk of participant identification due to the use of professional networks and snowball sampling.

The development of the topic guide was informed by a review of relevant literature and structured to enable both consistency across interviews and sufficient flexibility for participants to express their individual experiences and reflections. The topic guide (see Appendix 4) was structured around three broad areas: (1) general experiences and perspectives on supporting patients with concurrent obesity and common MH problems; (2) clinical experiences with delivering lifestyle recommendations in this context; and (3) GPs' perceptions on how patients

engage with and respond to lifestyle advice. Where appropriate, follow-up prompts and clarifying questions were used to explore further participants' experiences and cover all topics.

The open-ended survey followed the same structure as the interview guide, with minor adaptations to accommodate the written format. These changes were limited to phrasing and layout, ensuring consistency across both data collection methods.

Three semi-structured interviews were conducted between October 2024 and January 2025; one in person and two via Microsoft Teams. The interviews lasted between 35 to 55 minutes and were audio-recorded. The remaining data (N=5) were obtained through open-ended surveys, one of which included audio-recorded responses, while the others provided written responses.

2.3.Analysis

Interviews were transcribed verbatim into a Word document, and open-ended survey responses were similarly compiled into a single dataset for analysis. Thematic analysis (TA) was selected as the most appropriate qualitative analytic method, as it offered flexibility to explore GPs' perspectives in depth and to identify broader patterns of meaning across a relatively novel area of clinical interest. The analysis followed the six-phase framework outlined by [65]: (1) familiarisation with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) producing the report. To ensure analytical rigour and quality throughout the process, Braun & Clarke's [65] 15- point checklist for thematic analysis was used as a guiding tool. This helped support internal coherence, consistency in theme development, and analytical depth.

The analysis was conducted from a contextualist epistemological approach, which positions itself between essentialist and constructionist perspectives. This approach acknowledges that

participants' accounts reflect both individual experience and the broader social and structural contexts in which those experiences are embedded [65-67]. Following this approach, GPs' accounts were understood primarily as expressions of their individual clinical experiences, but also as shaped by the wider healthcare environment, institutional structures, professional norms, and social expectations surrounding obesity and MH care. The researcher's role in shaping the analytic process was acknowledged, including reflecting on how differences in professional background and disciplinary training may have informed the researcher's position in relation to the participant group.

Coding was primarily inductive, with a focus on capturing semantic-level patterns across the dataset, while also considering underlying latent meanings where relevant. The data were printed and manually coded. Both transcripts and codes were reviewed by a second researcher to ensure the credibility and consistency of the coding process. Codes, along with their accompanying extracts, were subsequently organised into a table to support transparency and facilitate theme development. Theme identification was iterative and interpretive, involving the development and refinement of themes and subthemes through repeated engagement with the codes. During the theme refinement stage, [68] dual criteria of internal homogeneity and external heterogeneity were used to assess the coherence and distinctiveness of themes. Themes were then incorporated into the final report to present the key patterns identified in the data.

To support rigour and transparency, a number of quality assurance processes were implemented throughout the analysis. These included maintaining a clear audit trail of coding decisions and theme development, using [65] 15-point checklist for quality thematic analysis, and involving a second researcher (SD) independently reviewed all interview transcripts, initial codes, and developing themes. The main researcher (KT) also engaged in ongoing reflexivity,

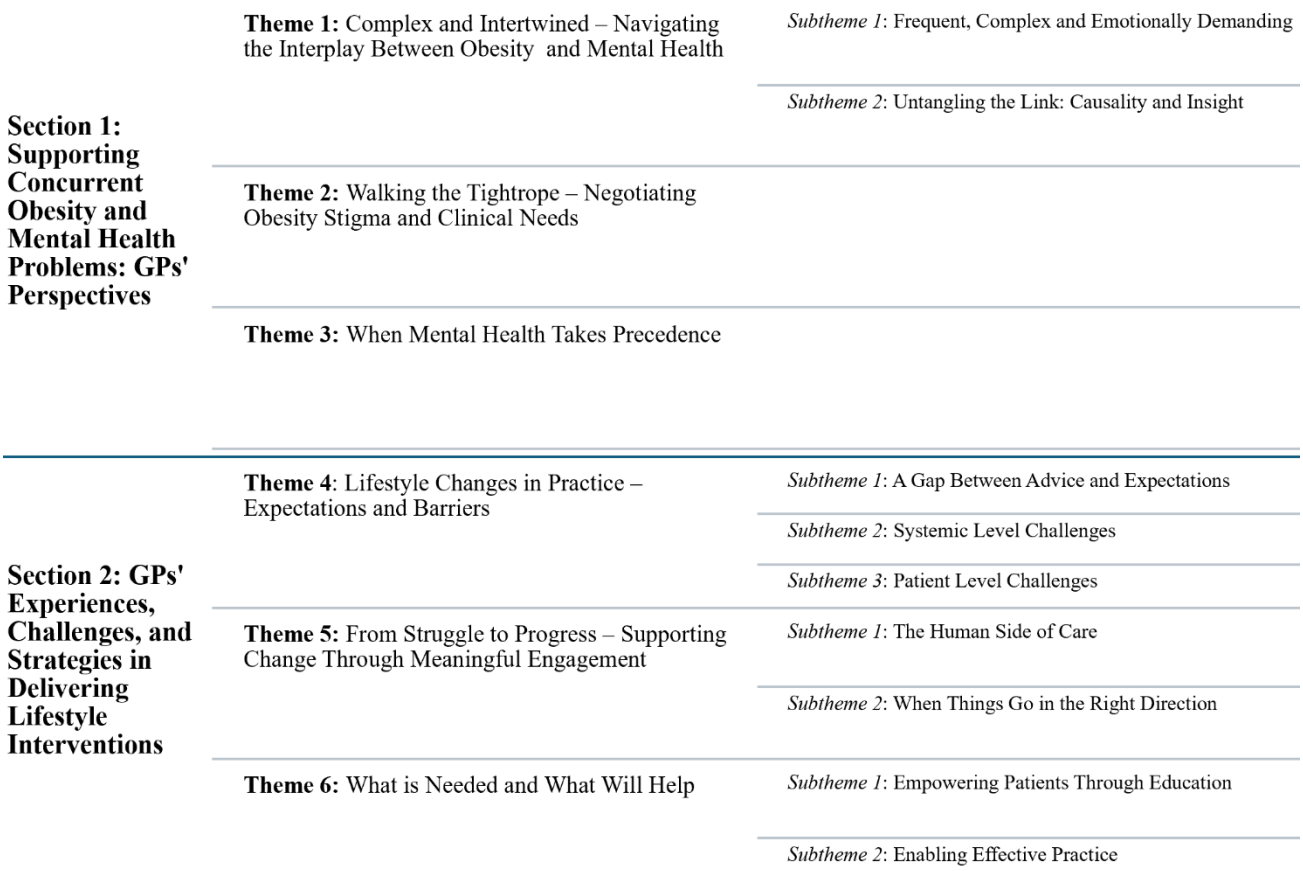
keeping a reflective journal throughout the research process keeping examining the influence of their professional background and assumptions. A more in-depth reflexive account is presented in Chapter 4.

3.Findings

In total 6 themes were identified with multiple subthemes. A conceptual map of themes is presented in **Figure 1** below. An additional theme (Theme 7: Quick Fix or a Stepping Stone) can be accessed in Appendix 1 of this thesis. This theme was included in full in the appendix as it provided valuable contextual insights but was considered less central to the primary goals and objectives of this study. While both interviews and surveys contributed to the thematic analysis, the nature of responses differed by mode of data collection. Interview participants generally provided longer, more detailed accounts, often illustrated with examples, whereas survey responses tended to be shorter and more concise. Despite this variation in depth, the same overarching themes were identified across both data sources, providing confidence in the consistency of the findings.

To depict the complex narrative, the Findings section is organised into two sections to map onto the overall research questions as following (1) Supporting patients with concurrent obesity and MH problems – GPs' perspectives, and (2) GPs' experiences, challenges and strategies in delivering lifestyle interventions.

Figure 1. Conceptual map of themes



Section 1. Supporting Concurrent Obesity and Mental Health Difficulties: GPs' Perspectives

Theme 1: Complex and intertwined – navigating the interplay between obesity and mental health

The first theme captures GPs' views on the prevalence and complexity of managing concurrent obesity and MH difficulties in primary care. GPs highlighted the clinical and relational intensity of these presentations and reflected on the challenges associated with the interconnection between the two conditions.

Subtheme 1: Frequent, complex and emotionally demanding

Participants frequently encountered patients presenting with obesity and concurrent mental health difficulties. These presentations were viewed as routine: “I would see at least one or two people per week with both [conditions]” (P4), “At least once a week” (P3). However, these difficulties were not always a presenting complaint: “Obese patients can appear in clinic daily, but they come in with another problem” (P5).

Alongside their frequency, GPs highlighted the clinical complexity of these consultations. Due to the competing demands of these concurrent presentations, some participants remarked that: “[It is] challenging to support these patients” (P3).

Reflecting on the complexity of managing comorbid obesity, mental health difficulties, and other commonly co-occurring conditions such as metabolic syndrome, Participant 7 stated, “It’s very hard to treat” (P7).

Several GPs described the emotional intensity of these consultations, noting that due to visible distress of many patients, greater time and sensitivity is required. As participant 4 explained:

> But when people are also quite depressed, that can be quite difficult for them. And so, it’s a very long and very difficult conversation and it often needs a couple of consultations… It’s not a quick fix, people are generally very upset and quite tearful and anxious.

Some GPs also associated this intensity with delayed help-seeking: “by the time they come and see their GP, let’s be honest, the things are already slightly more serious... they are low and they are looking for help” (P6).

Subtheme 2: Untangling the Link: Causality and Insight

GPs' accounts reflected the clinical interconnectedness of obesity and MH difficulties. This relationship was often described as difficult to navigate, particularly when trying to determine which issue should be prioritised in a consultation. As one participant noted: "Obesity and mental health are all interlinked" (P7). Another GP described obesity as "linked to overall health, either mental or physical" (P6), highlighting its broader implications for patient wellbeing.

These presentations were seen as particularly difficult to explore given the constraints of a typical consultation. As P4 explained, "there is a lot to ask and a lot of things to tease out." Similarly, another GP reflected on the nature of consultations: "very challenging, the two conditions are intertwined and in my experience it's very difficult to address them separately" (P2).

Some participants spoke about a difficulty of establishing causal connection between the two conditions*:* "It's often hard to tease out, have they put on weight and now they feel depressed or the other way round?" (P4), "It's not obesity itself that brings depression but it can go the other way," and further noted, "Inflammatory markers definitely interact with depression" (P7). Overall, these accounts highlighted the complexities of concurrent presentations, placing demands on GPs and their limited consultation time to determine next steps and agree a treatment plan.

Conversations around clinical priorities and collaborative goal setting were further complicated, in some cases, by differences in patients' insight into the relationship between their mental and physical health. Participant 6 reflected on the observed ambiguity of patients' consultation reasons: "Sometimes people know why they seek consultation with their GP, but

more often than not, they are not even sure… It's usually kind of like [focus on] mental health and on the side note, you notice that they have a raised BMI and they might not have a good insight into it." They further noted that "sometimes the factor they think they are looking to get help for is not necessarily consistent with what they need." In contrast, another participant described: "a lot of people come in and say they've put on weight and now they feel depressed because of it, or they know it is that they have become depressed and then they end up putting on weight" (P4).

Taken together, these accounts portray a consultation process shaped by both the intertwined nature of obesity and mental health difficulties and the variability in patients' awareness of this connection, creating additional layers of complexity in reaching agreement on priorities and next steps.

Theme 2: Walking the Tightrope – Negotiating Obesity Stigma and Clinical Needs

This theme captures how GPs navigated the delicate balance of addressing obesity in consultations, weighing concerns about reinforcing stigma against recognition of its impact on both mental and physical health.

Overall, GPs narratives indicated the discomfort surrounding obesity-related conversations, supporting previously reported accounts in healthcare settings and obesity care. For instance, participants spoke about approaching weight discussions with caution, expressing concern about the potential to cause emotional harm and further reinforce the stigma of obesity. As participant 6 noted: "It's almost a shame to talk about it [BMI]… So just trying to be gentle, not to insult people, especially if they are presenting with both mental health problems and obesity." Some expressed concern that raising the issue might unintentionally reinforce patients' past negative experiences and perpetuate existing stigma. As Participant 7 noted:

"You need to be very careful with language – patients could have been bullied in past or so." Such concerns led some GPs to question whether to raise these discussions, with co-occurring mental health difficulties heightening caution due to fears of emotional impact and damage to the therapeutic alliance. As P4 reflected: "They are difficult conversations and there's also the element if someone is coming with mood [problems], but you notice they might be overweight… a lot of people can find it hurtful…accusatory if you are bringing up their weight. The awareness of these challenges was often accompanied by a clear recognition of the condition's broader implications for both mental and physical health.

Although concerns about raising obesity were common, some GPs drew attention to how obesity is conceptualised more broadly, both in the medical settings and in wider societal narratives, and how these framings can impact on their efforts to support patients with concurrent obesity and mental health difficulties. In fact, the way obesity was framed clearly played a critical role in shaping clinical dialogue. Some GPs reflected on the distinction between clinically significant obesity-related concerns and the reasons patients sometimes raised weight-related topics themselves—often influenced by aesthetic or cultural factors. As Participant 4 explained:

> There is obviously a certain idea of how someone should look, especially in younger age group and if people are maybe not exactly that slim they might feel that they are not healthy, which is generally not the same… A lot of people who might be a bit overweight might be very healthy from a metabolic perspective.

However, even within healthcare settings, the clinical status of obesity continues to be debated, perpetuating ambiguity about how best to approach the topic with patients. For instance, Participant 6 pointed to a broader debate within the medical community regarding how obesity

is, or should be, conceptualised: "… but the other thing is, that, you know, you have to bear in mind that obesity itself is not addressed as an illness… and there's actually a huge discussion around that" (P6).

While some GPs reported focusing primarily on obesity-related complications and comorbidities, others framed obesity as a medical condition in its own right. For instance, Participant 5 noted: "Support we provide consist of explaining health risks of obesity as a serious civilisation disease and its impact on mental and physical health" (P5).

This participant further reflected on how the perceived psychosocial impact of obesity often remains unspoken: "The paradox is that obese patients don't confide that their obesity bothers them or that they have anxiety, social isolation, frustration or depression because of it" (P5).

This highlights that despite widespread recognition among GPs of obesity's psychosocial consequences, these concerns might not be explicitly raised in consultations. This silence may be influenced by how obesity is framed and the extent to which GP and patient share a common understanding of its relevance.

Theme 3: When Mental Health takes precedence

A recurring narrative in GPs' accounts was that, when patients presented with both obesity and MH difficulties, the MH component often took precedence — both in initial and ongoing consultations. In such instances, GPs described how the severity of MH problems shaped clinical priorities, making it difficult to address both conditions simultaneously. Several participants reflected that, in these contexts, MH problems were seen as a considerable barrier to effective implementation of lifestyle interventions.

GPs generally agreed that promoting physical activity was a key component of managing concurrent obesity and MH difficulties. However, they also recognised that the impact of depressive symptoms, particularly low energy and motivation, posed practical challenges for these patients.

Participant 6 described a concern highlighted across multiple accounts:

> …but how easy it is for patients to implement this? If you ask most people what's good for their health, everyone would be able to tell you like going for a walk etc... but how many people would actually implement those changes when they are feeling low? (P6)

GPs noted that encouraging physical activity was difficult when patients were already struggling with daily tasks. As Participant 4 expressed: "People who are depressed generally don't want to exercise or do physical activity. They might not even want to get dressed, so going out and exercising would be like climbing Mount Everest." This reflects a shared observation that at times, low mood and its accompanied presentation might more directly perpetuate the obesity cycle.

In light of these difficulties, some GPs viewed practical lifestyle changes alone as insufficient or unlikely to work without attending more broadly to the MH needs. For instance, Participant 2 noted, "[lifestyle recommendation] rarely works, the underlying mental health struggles make it very challenging to encourage this patients' cohort to undertake sustainable and significant lifestyle changes."

Section 2: GPs experiences, challenges and strategies in delivering lifestyle interventions

Section two explores GPs' perspectives on delivering lifestyle-based interventions to this patient group. The themes here highlight three interrelated areas: the challenges GPs identified in delivering such care; the barriers they perceive patients encounter when attempting lifestyle change; and their experiences of what has been helpful. These accounts illustrate both the complexity and importance of integrating lifestyle recommendations into everyday primary care practice.

Theme 4: Lifestyle Change in Practice- Expectations and Barriers

Subtheme 1: A Gap Between Advice and Expectations

When exploring GPs' views on how patients perceive lifestyle-based recommendations, varied reactions were acknowledged. As Participant 8 observed: **"**They can be mixed, I suppose patients might have mixed reviews as regards [to] lifestyle changes and the way they're recommended."

Nevertheless, several GPs felt that patients often hoped for quick or simple solutions, which stood in contrast to the longer-term effort required for lifestyle-based interventions. As a result, some GPs described limited patient enthusiasm or motivation for such approaches. As Participant 3 noted: "Lifestyle recommendations are perceived as demotivating. They usually want a quick fix" (P3).

This perceived mismatch between patients' expectations and clinical recommendations was understood as a barrier to engagement and at times, contributed to frustration for both patients and doctors. One GP reflected on how in their view, this approach is common in the cultural context of the UK and Ireland: "Most people are looking for a medication to fix all their

problems. That's my general impression, and I think especially in UK and Ireland, I think" (P6).

Some GPs offered additional insights into what might shape these differing expectations. For instance, one participant noted that: "[Patients] usually tell you they are doing their best" (P3), suggesting that some patients may already feel they are taking the necessary steps for their wellbeing. In this context, being recommended lifestyle-based interventions might be perceived as insufficient. Some reports indicate that GPs are aware of patients' potentially feeling like they did not receive what they came for, and some questioned whether they were offering enough support.

As Participant 4 explains:

> …recommending lifestyle measures can feel like you're not giving them enough... I feel like they might be hoping for more than that and I often find that I might not be able to give them. That can end up being a less satisfactory consultation for both, because patient might go away a bit disheartened (P4).

This account highlights how differing expectations can lead to patients' dissatisfaction with the consultations, as well as affect GPs' own experience of the encounter.

Subtheme 2: Systemic level challenges

This subtheme captures GPs' perspectives on systemic barriers impacting their ability to effectively support patients with concurrent obesity and mental health difficulties. A recurring concern was the limited availability of community-based services, particularly psychology and dietetics, which were viewed as essential for addressing the dual needs of this patient group. Long waiting lists and limited availability of community-based services were frequently cited:

"[Biggest challenge is] lack of services in the community" (P3); "Main challenge is access to services, mainly psychotherapy, dietetics" (P2), "We can refer them to dietitians for which of course [there] is probably long waiting list" (P4). In some cases, service fragmentation further complicated multidisciplinary input: "Community GPs have very challenging job. It can be very difficult to get support from [the Health Service Executive, Ireland's national health service], it's all very restrictive, it's not acting like a team" (P7).

Participants described time constraints, a well-known challenge in primary care, as a particularly significant barrier to delivering meaningful lifestyle-based interventions in the context of concurrent obesity and mental health difficulties. While all participants regarded such interventions as important, they emphasised that exploring the complex social and psychological factors shaping these presentations often exceeded the capacity of a standard consultation. For some, this translated into a shared sense of frustration between doctors and patients: "…they are waiting for psychology… for a dietitian… or they are waiting for their referral that was made years ago. So I think like the frustration is mutual" (P6).

Beyond the availability of clinical time and appropriate services, GPs often reflected on economic constraints when considering lifestyle-change recommendations for this patient group. It was acknowledged that, due to the strained public healthcare system, many of these patients might need to rely on paid services and resources. However, the ability to access these depends on patients' ability to afford care, including their insurance status. As one participant expressed: "I think finances will inevitably limit your access to resources as well. Getting a private counsellor, psychologist, dietitian…" (P6). This was echoed by another GP, who noted: "The first issue would be if a patient was private or public, which would then limit their access to particular services." (P8).

The financial aspects were especially pertinent to lifestyle-based recommendations, with participants highlighting two main areas: the costs associated with engaging in physical activity and the affordability of healthier food choices. As one GP explained: “Where I am working at the moment is a fairly low socioeconomic class and high levels of poverty and people might not be able to afford healthy foods because cheaper foods are often processed and higher in fat and calories… so their priorities are probably just to feed themselves and their families” (P4). While such barriers were commonly described in relation to low-income backgrounds, one participant also reflected on how healthcare access challenges may affect middle-income groups, underscoring the additional complexities of financial circumstances shaping access to care: “One of the biggest factors, I hate to say it, is finances. There is an unequal distribution from socioeconomic status and quality of health you get. … but it’s actually very complicated. It’s the middle class who can’t afford a private health insurance, but they don’t have the medical card. So, they are actually highly compromised in the middle” (P6).

Overall, participants emphasised that while lifestyle-based care was valued, systemic pressures such as limited services, time, and financial barriers shape the successful implementation of lifestyle interventions in practice.

Subtheme 3: Patient level challenges

When discussing the effective implementation of lifestyle-based interventions for this patient group, GPs often reflected that, from their perspective, patients’ success depends largely on their own resources — namely readiness, motivation, and perseverance. More specifically, GPs acknowledged that dietary and exercise changes require substantial commitment. This was illustrated in the following examples: “Patients’ motivation and discipline is crucial” (P5). “In community, it’s very difficult unless patient has good insight and motivation” (P7). Some

highlighted that patients may not always be ready or able to make such commitments, particularly since their personal resources might already be taxed by co-occurring mental health difficulties.

Overall, GPs varied in views on how motivated patients tend to be when lifestyle changes are being recommended. While some considered low motivation as a significant barrier, others observed a strong willingness among certain patient groups. The diversity of views was captured in comments like: “Biggest challenge is convincing and motivating these patients to change and improve their eating habits, guiding them towards regular physical activity” (P5). For Participant 3, “lack of motivation to change their bad habits” was seen as a main barrier in their clinical experience. In contrast, Participant 1 noted: “The vast majority, especially among the younger generations, are motivated to adopt lifestyle changes, often driven by the desire for better opportunities in life.”

Some participants described a pattern of a fear-based motivation. GPs shared experiences of patients receiving negative news, such as abnormal tests results, which then served as external motivators for adopting lifestyle recommendations. In this way, tangible evidence was seen to encourage patients to take lifestyle recommendations more seriously. As some explained:

> … let’s say you could tell someone that your cholesterol is raised and they are so alerted because they are very worried and concerned. And you tell them about lifestyle. So, I find in those contexts they are more likely to be motivated… so when they see something objectively measurable, there is almost kind of like, scaring them. In a sense, I think it’s a fear motivation (P6).

> …some people take them on board [lifestyle recommendations] and go with them, and it's almost like a motivation if their blood tests are abnormal or they are obese they take it on board and actively do something about it (P8).

While fear-based motivation was sometimes effective, participants noted that motivation alone did not always lead to successful lifestyle changes.

Some GPs highlighted several psychosocial factors that, from their perspective, influence patients' capacity to adopt lifestyle changes. For instance, one participant reflected on how the level of social support can influence patients' ability to incorporate lifestyle changes into their daily routines: "Limited support from their social environment, whether in their community, workplace or sometimes within their own family is a challenge" (P1).

Participant 5 similarly emphasised, "Support from loved ones, family, and a coach is also very important." Another GP described how lifestyle-based interventions often require substantial time and energy from patients, highlighting the need to consider how such changes can realistically be integrated into individual circumstances*:* "…people obviously live very busy lives, they might have young children etc. and find it difficult to exercise" (P4). These reflections underscored that lifestyle recommendations had to be understood in the context of patients' wider lives, not just their individual motivation.

As discussed, while patient motivation was seen as central to effective lifestyle change, it was recognised that it does not operate in isolation; rather, the availability of psychosocial supports and personal circumstances play a key role. Nevertheless, many GPs emphasised that motivation and social context alone cannot capture the full picture. A recurring theme was the

need to account for the wide range of physical health comorbidities so common in this population:

> It can be quite easy to advise patients they need to increase their physical activity. But in theory, it can be quite difficult for patients because there might be barriers to them actually being physically active (P8).

Comorbidities frequently highlighted included metabolic syndrome, diabetes, and high blood pressure, as well as high incidence of chronic pain. These comorbidities were seen as further complicating an already complex area, requiring careful consideration when recommending lifestyle-based interventions. In particular, pain and mobility-related conditions were often described as significant barriers to increasing physical activity. GPs shared reflections on how such conditions can reinforce the cycle of inactivity, which might in turn perpetuate or worsen MH difficulties. As Participant 4 described:

> There is a lot of people who have obesity and mental health issues and there can often be comorbidities involved, they might have pains that can prevent them from doing things which in turn make things worse for them and make their mood worse.

This aligns with broader shared narratives emphasising that comorbidities not only pose physical limitations but can also exacerbate MH challenges. As one GP observed, "Comorbidity of obesity, diabetes, insulin resistance, metabolic syndrome – this increases mental health problems" (P7).

These challenges were recognised as particularly relevant for older adults, who are more likely to experience conditions further limiting their mobility. As a result, GPs acknowledged that for this group, implementing lifestyle-based interventions could be even more difficult. Participant

4 summarised: “People, especially older people who are obese and might have also arthritis in the knees/hips... that might prevent them from doing a lot of physical activity.”

Theme 5: From struggle to progress- Supporting change through meaningful engagement

From struggle to progress captures GPs’ accounts of how meaningful engagement supported positive lifestyle changes among patients. Empathy, trust, and clear, professional communication were seen as key ingredients to meaningful progress. GPs reflected on what helped foster engagement and shared examples of how lifestyle-based interventions improved both physical and MH outcomes.

Subtheme 1: The Human Side of Care

GPs described several communication strategies they used when approaching sensitive topics of MH and weight. These were seen as essential for encouraging patient engagement and supporting lifestyle change. Many participants highlighted the role of honesty, appropriate tone of language and professional approach: “I feel like if you are very genuine and honest with them, even the things that might seemingly insult people... it might not be as insulting if it’s coming from a doctor...” (P6). “One needs to use very tentative language, talking from your medical expertise and being sensitive” (P7). “...has to be expressed in a very professional way, for instance explaining that overweight may be contributing to your depression” (P5).

Maintaining a non-judgemental stance was considered important for encouraging continued engagement with interventions. Participant 5 reflected on how these principles informed their own clinical approach:

> I always stick to the approach of motivating, supporting, explaining, and dedicating the time I can, even if it often seems like it's in vain or a waste of time. We never know if our motivation, support, and advice might just bring the right direction for one patient (P5).

Trust and rapport were seen as essential foundations for collaboration. As described, a strong therapeutic relationship increased the likelihood of patients disclosing relevant concerns and being receptive to lifestyle-based recommendations. As one participant reflected: *"*Personal contact with an adequate amount of time for conversation has a positive impact on the patient's confidence and their willingness to cooperate and engage in activities" (P1).

Despite the rise in online care options, some GPs highlighted the continued value of in-person contact in fostering trust and openness. For instance, one GP explained: "[We have] online options but I think that meaningful bond, you know, connections that you make with other human beings is probably different" (P6).

Another participant offered a reflection on how their praise can support ongoing progress: "For these patients, the results eventually come... we naturally praise them. This is also another motivation for them to keep progressing and maintaining good condition" (P5).

While most reflections focused on strategies to support patients, one GP also highlighted the personal value of these relationships: "It's a very privileged job. You establish a bond with your patients" (P6).

Subtheme 2: When things go in the right direction

The second subtheme captures GPs' experiences of times when things began to move in the right direction for patients; patients made progress, and positive changes were seen across both

physical and MH domains. Though less frequent than reports of barriers, these reflections illustrate clear and, at times, lasting positive effects on patients' overall wellbeing. For instance, Participant 7 described positive impact of combined lifestyle changes: "Exercise regime and healthy diet reduces metabolic syndrome and tends to improve mood...What I am saying is, it should be small but persistent steps. No need for big expensive equipment etc..."

A few GPs offered more specific accounts of patients' progress. Participant 5 shared general reflections on cases where lifestyle changes had been successfully implemented:

> I can confirm from my own clinical practice that patients who have accepted these recommendations achieved very good and visible results, and their health has significantly improved in many ways. Their immune system has strengthened, they are less frequently affected by acute respiratory illnesses, and their doctor visits have been greatly reduced…Mentally, they are more stable, and they are less often on sick leave. I can say they are happier, smile more and I see increased self-confidence in them.

Likewise, another GP offered an example from their clinical practice, emphasising the value of small but consistent progress and a collaborative approach:

> I will give you an example of this young woman, she was a professional sports person who suffered an injury. Subsequently, she started suffering from depression and then obesity followed. I started her on sertraline and referred to psychology. She then started exercising again, in small doses, not competitively and as a result, lost weight. This impacted positively on her mood, and she is much happier now" (P7).

Theme 6: What is needed and what will help

The final theme brings together GPs' forward-looking reflections on what could help them better support patients with concurrent obesity and MH difficulties. Building on earlier accounts of systemic and individual-level barriers, this section focuses on several practical priorities GPs felt could make a meaningful difference. These include clearer clinical guidance, accessible patient education, and support from multidisciplinary teams.

Subtheme 1: Empowering Patients Through Education

Education—both in terms of health literacy and clinical understanding—was described as a cornerstone for engaging this patient group with lifestyle-based interventions. As one participant summarised, "I think the most important thing with obesity and mental health problems is education" (P6).

Specific emphasis was put on improving patients' understanding of how their mental and physical health difficulties interact: "…we need to include them [patients] in their disease management, help them understand and motivate them. They should know how their overweight connects to insulin issues, cortisol, mental health" (P7).

A few GPs specifically noted the value of explaining physiological links between mental and physical health as a way of reinforcing the rationale behind lifestyle-based interventions. One participant discussed the difficulty of relaying such information to patients in an accessible way:

> I am yet to find a way of explaining it to people…if there was some clear kind of evidence on how it causes inflammation in a relatable way for the patient, a lay-person

> way or a non-medical way of explaining it that might help make sense to the patient…and just so people can understand…I think if maybe we were to give it in a more confident and structured way then it might be received better (P4).

Offering this type of education was described not only as a way to improve patient understanding of lifestyle-based interventions, but also to support more confident, collaborative participation in their care. As Participant 4 emphasise*d,* "In general, there is increasing awareness and education around obesity management but it's not very clear."

As some GPs suggested, better informed patients may be more willing to take shared responsibility for their health. Two participants articulated further on the concept of shared responsibility: "We are more and more pushed towards individuals not taking full responsibility for their own health, which is an absolute must" (P6). "Doctors are a pivotal support pillar—but not the only one. We need to divide responsibility—can't tell patients 'Don't worry, we will mind you,' — I will help you, with your help we need to go 50:50 with patients" (P7).

Subtheme 2: Enabling Effective Practice

Alongside improving education and sharing responsibility, GPs also emphasised that achieving these goals is dependent on a supportive clinical context. Participants described practical supports which could help facilitate the translation of lifestyle advice into lasting change for this patient group. This included multidisciplinary input, clearer guidance, and sustained follow-up could help translate lifestyle advice into more effective, long-term positive outcomes for patients.

For instance, participant 2 emphasised the need for coordinated, multidisciplinary support*:* "…from my experience, it usually doesn't work well without structure, guidance and support from professionals: dietetics, psychologists, physiotherapists."

Another GP spoke about the type of engagement that is required:

> It's quite important to address these issues and not just use them as flippant, throwaway comments, but... to actually engage with and try to encourage it or to set up programs for people or to point them in the right direction (P8).

Others expressed a desire for clearer clinical guidance in relation to supporting patients with concurrent obesity and MH difficulties, and a few GPs recognised that they would benefit from access to clear, practical, evidence-based resources in relation to lifestyle-based recommendation for this complex population. As participant 4 noted, "It's certainly a difficult area for us and we could certainly do with any help or advice or evidence that might be available… There is definitely a lack of effective recommendations that we have at the moment."

Overall, a few core needs stood out across accounts: more time, sustained follow-up, and a collaborative environment that empowers patients through understanding and shared responsibility. As one participant concluded: "Repeated consultations, explaining procedures and the need for patience and willingness on the part of the patient lead to overall, albeit slow, improvement" (P1).

4.Discussion

This study examined GPs' perspectives on supporting patients with concurrent obesity and mental health difficulties, with a particular focus on the experiences of supporting these patients with lifestyle-based interventions. The themes presented throughout highlight both practical and relational complexities of supporting this patient group. GPs described these co-occurring conditions as frequent and clinically relevant yet challenging to assess and manage—particularly due to their intertwined biopsychosocial nature, the emotional intensity of consultations, and time-limited primary care settings. Clinicians often faced challenges in balancing the need to establish clinical priorities with efforts to maintain a collaborative, person-centred approach. This study extends existing literature by providing insight into how GPs make sense of and apply lifestyle-based interventions in the context of these conditions thereby offering practical insights into the barriers and strategies involved in delivering lifestyle interventions in this group. This can help inform future clinical training and resource development.

Success of these interventions was seen as being shaped not only by clinical guidance but by patients' motivation, understanding, and contextual realities. Motivation was often described as reactive—emerging in response to health concerns—rather than sustained, pointing to a need for more proactive engagement strategies to support sustained behavioural change. This pattern underscored the need for clearer psychoeducation materials for patients about the links between mental and physical health, including systemic inflammation -something GPs felt ill-equipped to provide due to a lack of accessible resources. Such resources can support GPs' explanations of complex and intertwined conditions, for instance help explain the interplay between obesity-related inflammation and mental health and through that support GP's

rationale for recommending lifestyle interventions for example. However, such resources need to be accessible and carefully designed to avoid overwhelming patients, particularly those experiencing significant emotional or cognitive burden (e.g., in major depression). The aim should be to provide supportive, empowering information that may enhance motivation for lifestyle change—without inadvertently conveying blame or judgement.

The current findings suggest that GPs experienced weight-related conversations as particularly delicate when supporting patients with concurrent obesity and mental health difficulties and shared a fear of offending patients or exacerbating weight-stigma. This concern was echoed in previous research, where clinicians reported avoiding weight discussions unless deemed medically required [69].

Concerns with sensitivity surrounding weight-related conversations was also reflected in the language used by some participants. Notably, the terms obesity and overweight were at times used in a seemingly interchangeable way. Several explanations may account for this pattern. One possibility is that GPs deliberately avoided the term obesity, aware of its strongly stigmatised connotations, and instead opted for what may be perceived as a less judgmental term. Prior research has highlighted that patients often experience terms such as obese as stigmatising across various healthcare settings, expressing preference for more neutral language [74]. Awareness of this might have led GPs to adjust their terminology, in efforts to minimise the possibility of offending their patients and maintaining good rapport. At the same time, it is possible that some participants may have purposefully broadened the definition of obesity to include overweight in order to acknowledge that the lifestyle-based interventions are relevant and should be considered at earlier stages of weight gain, before the onset of more severe health risks. Beyond questions of intentionality in the choice of terminology, the variability in the chosen language can also mirror a broader lack of consensus in how obesity

is defined and understood beyond strict diagnostic thresholds such as BMI or body mass index, both among clinicians and the general public. From this perspective, some GPs appeared to conceptualise obesity as existing on a continuum rather than as a discrete diagnostic category. Moreover, participants' narratives conveyed hesitation, and in some cases apparent discomfort, in explicitly naming obesity as a medical condition, despite acknowledging its associated risks. This reluctance may reflect wider cultural shifts in how weight is discussed, particularly the influence of social media and the body positivity movement, which have reframed norms around what constitutes a healthy body. These changes may contribute to heightened awareness among clinicians of the need for more patient-centred terminology. Nevertheless, the current findings also raise the possibility of unintended consequences, as some participants appeared to allude to. Specifically, if clinicians substitute the terms overweight when they in fact mean obese, they may inadvertently minimise the perceived severity of risk and reduce patients' engagement with lifestyle interventions. Furthermore, unclear or inconsistent terminology may heighten the risk of misalignment between patient and GP understandings, thereby complicating already sensitive consultations. Thus, while efforts to promote patient-centred communication are essential, there is also a pressing need to ensure accuracy and clarity in how obesity is addressed as a clinical risk.

Additionally, while a sensitive, empathetic, and professional approach was consistently described as essential for supporting this patient group, these accounts also raise broader questions about the clinical focus of such discussions. Specifically, GPs' reflections point to the potential benefit of shifting away from weight-centric goals toward health-related outcomes that address both physical and psychological wellbeing. This perspective aligns with previous critiques of weight-normative care, which had been associated with limited long-term success and increased risk of weight cycling, stigma, and patient disengagement [70, 71]. Obesity has been extensively linked to increased shame, stigma, and body dissatisfaction, particularly in

childhood and adolescence [72, 73]. Obesity-related stigma operates on multiple systemic levels, with research consistently reporting its presence and impact across the lifespan and across different domains, including educational, workplace, and healthcare settings [74, 75]. Extensive evidence links obesity with experiences of discrimination, social rejection, and increased barriers to appropriate healthcare [76, 77]. From a psychological perspective, these experiences have far-reaching consequences for wellbeing, including lowered self-esteem, social exclusion, and greater vulnerability to mental health difficulties. For individuals already experiencing mental health difficulties, such as those discussed by GPs in the current study, these effects may be particularly salient, with the potential to compound psychological distress, exacerbate mood or anxiety symptoms, and complicate engagement with lifestyle-based care. The effects of weight stigma have also been proposed to manifest behaviourally. For instance, Lee et al. [78] found that weight stigma was associated with disordered eating, comfort eating, and sleep disturbance- behaviours that may further impact both mental and physical health and hinder lifestyle change.

A whole-person model of care may offer a more constructive framework for guiding lifestyle-based interventions in this context. Rather than focusing narrowly on weight reduction, this approach encourages goal setting around broader wellbeing indicators—such as mood improvement, increased energy, or improved physical endurance. These goals can be shaped collaboratively to align with each patient's individual circumstances. In line with the current findings, such an approach also emphasises the value of psychoeducation, shared responsibility, and ongoing therapeutic contact in supporting engagement with lifestyle interventions.

This approach could help address several barriers identified in this study, such as difficulties with sustaining patient motivation and communicating the rationale for lifestyle changes. Many

GPs highlighted the need for accessible psychoeducational materials that help patients understand how their mental and physical health are interconnected, including through mechanisms like systemic inflammation [15]. Clearer resources of this kind could empower patients to take a more active, collaborative role in their care. However, participants also emphasised that implementing such care models would require structural support—including protected time for follow-up, clinical guidance, access to multidisciplinary teams, and opportunities to build trust through consistent therapeutic contact.

Although the study is centred on general practice, the findings are also informative for clinical psychology. Firstly, GPs frequently framed depression and anxiety as obstacles to lifestyle change, which could inadvertently lead to deferring intervention. In this context, psychological input can help teams address these difficulties by supporting mood, sleep, and motivation alongside lifestyle advice, using realistic goals and non-stigmatising language within time-limited consultations.

Secondly, several participants explicitly asked for more guidance, training, and practical resources to support these conversations. This points to a role for clinical psychology in contributing to education for current and future GPs or potentially creating reflective spaces for clinicians to navigate sensitive discussions. Such collaboration can build confidence and promote more consistent, person-centred care within primary care pathways.

Although not specific to lifestyle recommendations, GPs' broader accounts of supporting this patient group also underscored a shifting landscape in weight management. This shift is being driven, in part, by the growing availability of pharmacological options, notably GLP-1 receptor agonists (e.g., semaglutide). These medications, while still relatively new in clinical practice, may further contribute to the reported discrepancy between patient expectations—seeking, at times, rapid solutions—and GPs' recommendations of longer-term lifestyle-based approaches.

Several participants' reflections suggested that the differences in expectations could make it more challenging to engage patients in sustained behavioural change, as lifestyle interventions may be perceived as less appealing when compared to medication. Theme 7 in the Appendix 1 further discusses GPs' perspectives on pharmacological treatments relevant to patients with concurrent obesity and mental health difficulties. As these medications become more widely available and utilised over time, future research should consider both their impact on patient–clinician interactions and how clinicians can be best supported in continuing to promote lifestyle-based approaches alongside the rise in pharmacological options.

4.1. Limitations and Future Research

The use of two different modes of data collection by semi-structured interviews and open-ended survey responses introduces certain limitations. These formats are not interchangeable and tend to yield differing levels of depth and detail, as noted in qualitative research literature [58]. In the present study, interview data generally produced richer, more detailed accounts, likely due to the opportunity for follow-up prompts and extended engagement, compared to the more concise responses generated via the survey format. A further difference was observed in the tone of responses. While challenges and systemic pressures were identified across both sources, survey responses at times conveyed a slightly more pessimistic outlook, particularly in relation to patients' perceived receptivity to lifestyle recommendations, with GPs more often describing them as favouring quick solutions or losing motivation. Although these issues were also discussed in interviews, they were presented in a somewhat softer, more balanced manner. This difference is consistent with previous research suggesting that anonymous survey formats can reduce social desirability bias and thus can at times elicit more critical accounts compared to face-to-face interviews [66- 68]. Recognising such differences is important, as it points to

both the added value of combining survey and interview methods and the influence of data collection format on how participants frame their responses.

Additionally, no demographic or contextual data were collected from participants. While this was decided to mitigate the risk of participant identification, particularly given the use of professional networks and snowball sampling, this may limit the wider interpretability of the findings. As such, it is not possible to assess the representativeness or diversity of the sample in terms of factors such as geographical location, years of clinical experience, or type of practice. Having this information could provide further useful insights into how these factors may shape GPs' views, particularly in relation to complex, comorbid presentations such as concurrent obesity and mental health difficulties.

Future research could also benefit from purposefully including culturally and contextually diverse participants. As both obesity and mental health are shaped by sociocultural norms and values, this might influence how these conditions are perceived, discussed, and managed in clinical settings. Including participants from more varied cultural backgrounds could offer deeper insight into how such perspectives shape engagement with lifestyle-based interventions. Similarly, clinicians' experiences may vary depending on the socioeconomic profile of their patient populations, particularly in disadvantaged or underserved areas, where barriers to implementation may be more pronounced.

5. Conclusion

The current study examined general practitioners' experiences and perspectives on supporting patients with concurrent obesity and mental health difficulties**.** The study was informed by a growing body of research on systemic inflammation, particularly in relation to interventions aiming to reduce inflammatory processes as a means to improve overall health outcomes.

This study sought to contribute to the efforts of improving effective implementation of such interventions in clinical practice by exploring the perspectives and experiences of general practitioners, who routinely encounter these complex presentations—an area that remains under-researched to date. While some previous research has examined GPs' views on obesity or mental health separately, this is, to our knowledge, the first study to qualitatively explore GPs' experiences of supporting patients with both conditions through lifestyle-based interventions in primary care. In addition to capturing GPs' concerns, perceived challenges, and strategies related to lifestyle interventions, this study uniquely explored their perspectives on patients' struggles, encouraging reflection on the lived experiences of those attempting to implement such changes and potentially fostering greater clinical compassion and understanding. From a research standpoint, this dual perspective contributes to the existing literature by enhancing our understanding of the practical and psychological considerations involved when supporting these patients to adopt lifestyle changes.

Through identifying several actionable areas for improvement, including a need for psychoeducational materials, system-level supports and more integrated care, this study may help inform policy and service development/ improvement. On a practical level, this study could also support the development of patients' psychoeducational materials to assist primary care practitioners, bringing us one step closer to translating emerging research on systemic inflammation into routine clinical practice.

Disclosure of conflicts of interest

None of the authors have any conflicts of interest to disclose.

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Chapter 3. Study 2: Exploring the association between systemic inflammation and executive function in childhood and adolescence (Scoping Review)

Prepared in accordance with the submission guidelines for the Journal:

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Abstract

Background

Systemic inflammation has been increasingly linked to a range of cognitive and mental health outcomes across the lifespan, including executive functioning (EF). While this relationship is well-documented in adult population, less is known about how systemic inflammation may influence EF during childhood and adolescence—a period of heightened neurodevelopmental sensitivity. This scoping review aimed to map and synthesise current empirical evidence on the association between systemic inflammation and EF in children and adolescents, while further exploring biopsychosocial moderators or mediators identified in the included studies.

Methods

The scoping review followed Arksey and O'Malley's (2005) framework, enhanced by Levac et al. (2010) and used PRISMA-ScR checklist to conduct a systematic search across five electronic databases and six grey literature sources. Inclusion criteria encompassed quantitative studies published in English from 1994 onwards that examined the association between systemic inflammation and executive function in children and adolescents. Sixteen studies met eligibility criteria. The protocol for the review was registered with the Open Science Framework.

Results

Included studies comprised both cross-sectional (n = 9) and longitudinal (n = 7) designs, spanning community and clinical samples. Most reported negative associations between inflammatory markers—such as CRP, IL-6, and TNF-α—and executive function, particularly working memory, and inhibition. Longitudinal studies suggested that chronic inflammation may affect the developmental trajectory of executive functions, with several indicating cumulative or worsening effects over time. Obesity, socioeconomic status, and mental health

emerged as the examined moderators, with obesity-mediated inflammation showed most consistent links with EF. Methodological heterogeneity and limited use of repeated measures constrained direct comparisons and broader generalisability.

Conclusions

This review underscores an important emerging area that suggests systemic inflammation may negatively influence executive function development in childhood and adolescence. Future research should incorporate repeated biomarker assessments, multimodal executive function measures, and developmentally informed designs to better understand causal pathways and inform targeted early interventions.

Keywords: Inflammation, Childhood, Executive Function, Scoping Review

Title Page

Title: Exploring the association between systemic inflammation and executive function in childhood and adolescence (Scoping Review)

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Introduction

Background and Rationale

Childhood and adolescence represent important developmental stages characterised by biological growth, cognitive maturation, significant psychological changes evolving social roles across home, school, and peer environments. These transitions shape long-term cognitive, emotional, and physical health outcomes (Sawyer et al., 2018). Reflecting their complexity and developmental significance, this period has attracted growing interest from researchers across different disciplines (Lerner et al., 2005). Similar to the rapid brain development seen in infancy, adolescence marks a second major wave of neurodevelopment, characterised by heightened neuroplasticity, synaptic pruning, and maturation of key brain regions such as the limbic system and prefrontal cortex (Giedd, 2008; Gogtay et al., 2004; Paus, 2005). The development of the prefrontal cortex, in particular, facilitates the refinement of higher-order cognitive processes such as decision-making, impulse control, and goal-directed planning. These skills essential for navigating complex social environments and regulating emotional responses. These cognitive abilities collectively fall under the umbrella of executive function- a set of top-down processes involved in the regulation of behaviour, attention, and cognition (Diamond, 2013; Miyake et al., 2000).

Research increasingly highlights how various biopsychosocial influences, such as chronic stress, socioeconomic deprivation, early life adversity, cognitive deprivation, malnutrition, and obesity—can negatively affect the development of executive functions. These factors are thought to impact brain maturation by interacting with underlying genetic and hormonal processes, together shaping the trajectories of neurodevelopment. One key pathway involves chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis, often triggered by

prolonged exposure to stress or adversity. Sustained elevations in glucocorticoids such as cortisol can alter neuronal structure and function, particularly in brain regions rich in glucocorticoid receptors, including the prefrontal cortex, hippocampus, and amygdala (Lupien et al., 2009; McEwen & Morrison, 2013). These neurobiological effects include reduced dendritic branching, impaired synaptic pruning, and disrupted myelination, a process essential for the development of efficient executive functioning (Liston et al., 2009; Hanson et al., 2012; Teicher et al., 2016). For instance, prior research shows that children from socioeconomically disadvantaged backgrounds might be particularly vulnerable to such mechanisms, with lower socioeconomic status (SES) consistently associated with both heightened exposure to stressors and poorer executive functioning outcomes (Blair & Raver, 2016; Hackman, Farah, & Meaney, 2010). Similarly, adverse childhood experiences (ACEs) have been linked to persistent difficulties in areas such as attention, working memory, and impulse control (Hughes et al., 2017; Lund et al., 2020), with some evidence suggesting that these effects may extend into later life and contribute to increased risk of cognitive decline (Halpin et al., 2022). While existing research offers valuable insights into the factors affecting executive function development, the precise nature of the relationships between the immune system, mental health outcomes, and executive function deficits remains debated. Understanding the underlying physiological mechanisms that may underpin these relationships is crucial for developing more effective prevention and intervention strategies. In this context, systemic inflammation has become a particularly prominent focus in biopsychological research, as it may hold important insights into these complex interrelations.

Systemic inflammation and cognition

One potential pathway through which physical health, environmental adversity, and psychosocial factors may influence cognitive development is systemic inflammation. Systemic inflammation refers to a prolonged, low-grade immune response triggered by a variety of

factors, including infections, tissue damage, chronic psychological stress, and unhealthy lifestyle behaviours (Black, 2002; Calder et al., 2009). Unlike acute inflammation, which is a protective and time-limited response to injury or infection, systemic inflammation persists over time and has been implicated in the pathophysiology of several chronic physical conditions. A growing body of research has demonstrated that systemic inflammation is associated with cognitive impairment and neurodegenerative processes in adulthood, particularly in relation to memory and executive functioning. For instance, elevated levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) have been linked to cognitive decline and dementia (Lai et al., 2017; Lin et al., 2018; Stacey et al., 2017). Accumulating evidence also suggests that dysregulated inflammatory physiology is associated with poorer cognitive functioning in both clinical populations (Goldsmith et al., 2016) and general population samples (Mac Giollabhui et al., 2021). In adults with generalised anxiety disorder, a meta-analysis found significantly elevated CRP levels compared to healthy controls (Costello et al., 2019), further pointing to the interplay between immune dysregulation and mental health-related cognitive difficulties.

More recently, studies have begun to explore how systemic inflammation may affect executive functions across the lifespan, including in children and adolescents. This represents an emerging area of research with growing empirical support. Inflammatory processes are thought to interfere with neuronal signalling, synaptic plasticity, long-term potentiation, neurotransmitter metabolism, and neurogenesis, potentially impacting brain regions responsible for executive functioning, such as the prefrontal cortex and anterior cingulate cortex (Haroon et al., 2012; McAfoose & Baune, 2009). While the evidence for adults is well-established, findings are less conclusive in younger populations, where research remains in early stages and sometimes yields inconsistent results. Nonetheless, several studies point to a potentially meaningful association. For instance, Cullen et al. (2017) found that inflammatory

markers were associated with impairments in cognitive flexibility and inhibition in adolescents with psychiatric symptoms. Other studies suggest that chronic inflammation may negatively influence the developmental trajectory of working memory and other executive functions in young people (Mac Giollabhui et al., 2024; Caldú et al., 2023). In addition, systemic inflammation is increasingly understood as a mediator linking social and environmental risk factors with neurodevelopmental outcomes. Socioeconomic disadvantage, for example, is consistently associated with elevated inflammatory biomarkers across the lifespan—even after controlling for health-related behaviours such as BMI and smoking (Malfertheiner & Schutte, 2006; Park et al., 2005; Muscatell et al., 2018). These associations are particularly relevant for childhood and adolescence, given the heightened neuroplasticity and sensitivity to environmental inputs during this period.

Despite substantial knowledge regarding the diverse factors contributing to systemic inflammation, less is known about how these factors interact and ultimately result in systemic inflammation associated with executive function difficulties. The current scoping review is based on the hypothesis that inflammation may serve as a mediator between various biopsychosocial contributors (e.g., obesity, autoimmune diseases, chronic sleep problems, early life adversities, chronic stress) and executive function impairments (Bach et al., 2022). Gaining a deeper understanding of these underlying physiological mechanisms is crucial for developing more effective prevention and intervention approaches. While research on systemic inflammation has grown substantially, much of the focus remains on adult population, with limited number of studies addressing children and adolescents. Nevertheless, greater attention to youth is essential, as systemic inflammation during childhood and adolescence may have profound and lasting effects on cognitive and executive functions. A deeper understanding of these impacts could inform early interventions to potentially mitigate long-term consequences and improve biopsychosocial outcomes across the lifespan.

This review addresses an existing gap in systematically and comprehensively exploring the link between systemic inflammation, executive function, and previously suggested key mediators of inflammation in childhood and adolescence. While a few prior reviews have examined associations between systemic inflammation and some individual factors such as childhood adversity or obesity, to our knowledge, no review has specifically investigated the broader connection between systemic inflammation (as driven by various biopsychosocial factors) and executive function in children and adolescents.

By providing an up-to-date, comprehensive review of the literature on this topic, we aim to address outstanding questions, identify specific gaps in knowledge, and suggest directions for future research. As this remains a developing field with limited synthesis of existing findings, a scoping review is considered the most suitable approach for achieving these objectives. In this way, a scoping review will allow for the mapping of key concepts, identification of the types of evidence available, and clarification of working definitions, which is particularly beneficial when the topic has not been extensively reviewed or is complex and heterogeneous (Arksey & O'Malley, 2005; Levac, Colquhoun, & O'Brien, 2010).

Objectives

The overall objective of this scoping review is to systematically map the extent and nature of primary published and unpublished studies to identify the themes and associations present in the existing literature on the relationship between systemic inflammation and executive function in children and adolescents. More specifically, this scoping review aims to examine the nature, range, and extent of empirical research investigating the relationship between systemic inflammation and executive functions in childhood and adolescence. It also seeks to identify and evaluate which mediating or moderating factors previously associated with inflammation—such as socioeconomic status and lifestyle factors—are most well-studied and

documented in the context of this relationship. Furthermore, the review highlights key gaps in the literature and identifies areas where further research may be directed. Finally, it provides a critical overview of empirical findings to inform future studies.

In this review, the population of interest comprises children and adolescents. Systemic inflammation, influenced by various biopsychosocial factors, serves as the condition of focus, while the primary outcomes relate to executive function impairments or deficits.

Methods

This scoping review was conducted using Arksey and O'Malley's (2005) methodological framework, with enhancements from Levac, Colquhoun, and O'Brien (2010) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist. A protocol for this review was registered on the Open Science Framework and is available at https://doi.org/10.17605/OSF.IO/57HY8.

Inclusion/Exclusion Criteria

The inclusion criteria were as follows: (1) empirical studies employing quantitative methodologies examining the relationship between the relationship between systemic inflammation and executive functions in children and/or adolescents; (2) published and unpublished (grey literature) sources will be included to capture a broad range of relevant data; (3) studies published in the past 30 years (since 1994) to ensure data reflects current methodologies in inflammation measurement ;this timeframe has been deemed appropriate as core biomarkers of systemic inflammation (e.g., CRP, IL-6) have been assessed with consistent immunoassay principles over this period, supported by international reference standards ensuring methodological comparability; (4) studies focusing on children and adolescents where at least one measure of systemic inflammation (e.g., CRP, IL-6) and at least one executive

function measure (cognitive flexibility, working memory, inhibition) were empirically assessed; (5) studies available in English language.

The exclusion criteria were as follows: (1) studies involving animal models; (2) studies that explore systemic inflammation or executive functions independently without examining their relationship; (3) studies that cannot be accessed in full-text or retrieved in English language.

Search Strategy

A comprehensive literature search was conducted on 19th and 24th of November in the following databases: (1) PubMed, (2) Embase, (3) Scopus, (4) PsycINFO, (5) ProQuest. In addition, the following Grey Literature sources were searched: (1) BASE, (2) Clinicaltrials.gov, (3) Clinicaltrailsregister.eu, (4) Cochrane, (5) World Health Organisation (WHO); (6) Google Scholar. The search terms were defined as follows:

("systemic inflammation" OR "chronic inflammation" OR "C-reactive protein" OR "Tumor Necrosis Factor") AND ("executive function*" OR "working memory" OR "cognitive flexibility") AND ("child*" OR "adolescents" OR "youth" OR "teenager" OR "paediatric") NOT ("Alzheimer" OR "dementia").

Results obtained from the systematic search were stored in Rayyan software to assist organisation and screening of articles. Title and abstracts were reviewed by the primary researcher, with a secondary reviewer screening 20% of abstracts to verify accuracy and consistency, yielding a 90.1% inter-rater agreement rate. Articles that met inclusion criteria were subsequently reviewed in full text. Any discrepancies were resolved through consensus between the primary researcher and the secondary reviewer.

Data Extraction

The following data were extracted from the included studies:

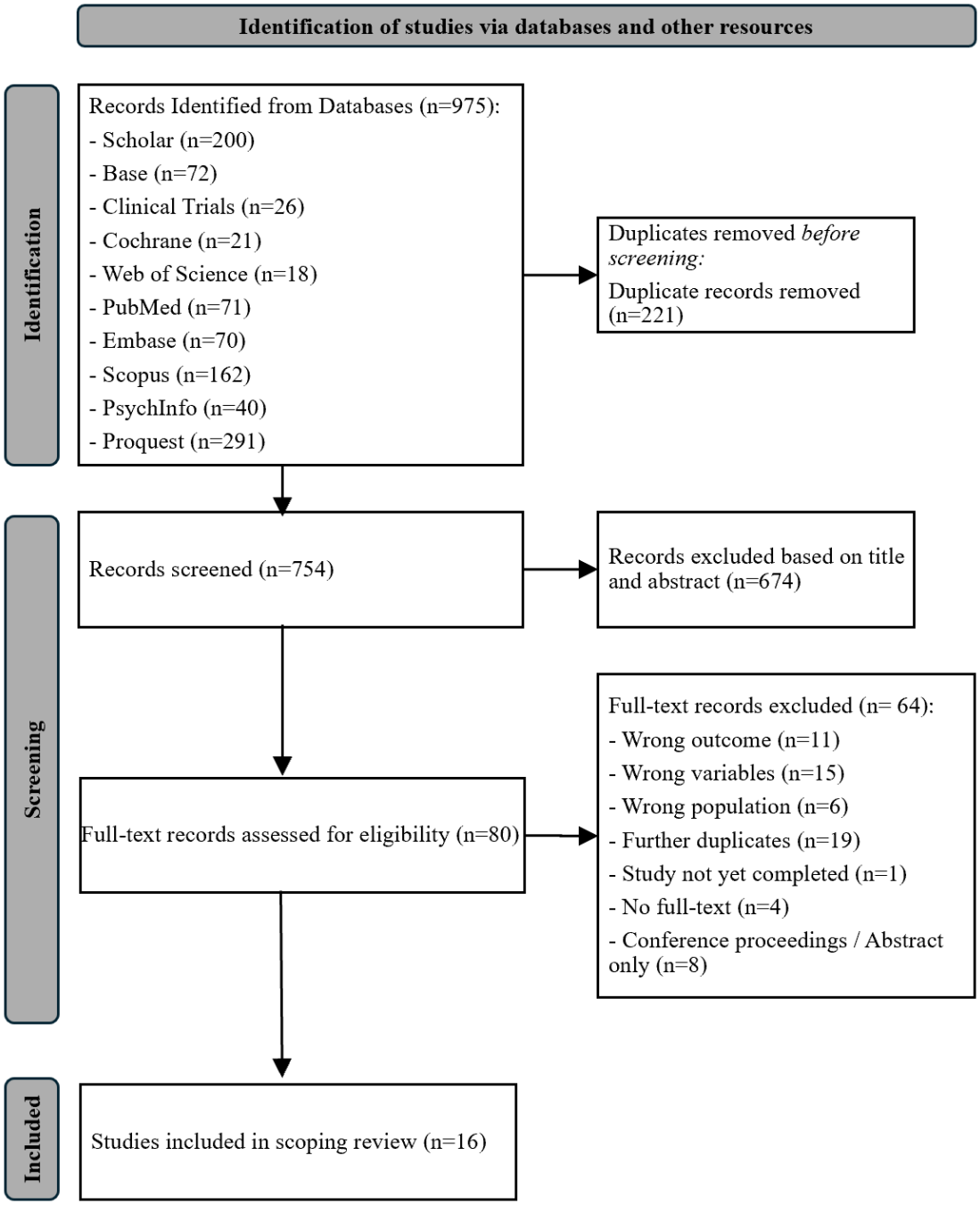
Study title, authors, publication year, country, age, sample size, sex, setting, design, relevant demographic information (gender, ethnicity, race), type of data collected, inflammatory markers measured including collection method and levels, executive function assessment method, reported IQ/ estimates, any physical conditions reported, any adverse childhood experiences and mental health variables, socioeconomic status, main findings on executive function- inflammation, findings on biopsychosocial mediators, main study limitations and future research recommendations as per authors.

Results

The literature search identified 975 studies, 80 remained following de-duplication and abstract and title screening. A full-text review resulted in 16 articles for inclusion in the review. Figure 1 below presents a PRISMA flowchart illustrating the literature search and study selection process.

Figure 1

Prisma Flowchart



Study population and characteristics

All studies were published between 2014 and 2025 with 63 % published between 2020 and 2025. Sample sizes ranged from 14 to 8,536 participants, with a combined total sample size of 17,178 across all studies. The unique sample size consisted of 10,536 children and adolescents, following accounting for overlap of participants from the same longitudinal cohorts or retrospective databases; two studies used the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort and three utilised data from the Tracking Adolescents' Individual Lives Survey (TRAILS) study. Nine studies employed a cross-sectional design, while seven used a longitudinal approach and two included a mix of cross-sectional and longitudinal design. The characteristics of the 16 included studies are presented in **Appendix 6.**

Participants' age ranged from 8 to 22 years, but most participants were in middle to late adolescence with older ages more likely to be in studies with a longitudinal design. Three studies (King et al., 2024; King et al., 2023; Peters et al., 2019) included both pre- and post-adolescent participants and collected biological measures of puberty. Most studies had a gender balance, but there was more variation in sample diversity with respect to race and ethnicity representation. Geographically, there was a clear prevalence of studies conducted in Western Europe and the Northern America (N= 8 and 6, respectively). One study took place in Asia (Japan) and one took place in Africa (Uganda). Just over one third of the studies included exclusively non-clinical samples, which—based on the stated exclusion criteria—can be assumed to represent a healthy general youth population.

There was a balanced mix of clinical and community samples, with a predominant focus on depression, other mood disorders, and obesity/overweight. Interestingly, only one study

purposefully recruited participants with known neurodevelopmental diagnosis (Sasayama et al., 2017) and no other studies describe inclusion of neurodiverse participants.

Overall, the studies employed one of three approaches to assess executive function: clinician-administered performance-based assessment, parent-reported measures, or computer-based assessments. Only two studies incorporated two assessment methods (i.e., clinician-administered performance-based assessment and parent-reported measure). For the purposes of this review, executive function measures were classified into three broad subdomains, working memory, inhibition, and cognitive flexibility, following the frameworks of Diamond (2013) and Miyake et al. (2000). Nine studies (predominantly longitudinal studies) measured a single subdomain of executive function. Different inflammatory markers were used in the studies, with the most prevalent being CRP, TNF-α and IL-6. Slightly over one-third of the studies relied on a single inflammatory marker, with blood sample assay analysis being the most commonly used measurement method. To facilitate synthesis, the results are presented thematically in line with the review's primary and secondary objectives. Additionally, the first two paragraphs are organised by study design (i.e., cross-sectional vs. longitudinal).

Cross-Sectional Perspectives: The Inverse Relationship Between Executive Function and Inflammation

The review includes 9 studies reporting on cross-sectional data and two studies with a longitudinal design with cross-sectional analyses. While there was a range of age groups, most studies focused on middle to late adolescence. Sample sizes varied from 14 to 134 participants, encompassing both community and clinical populations. Clinical samples included individuals with mood disorders (depression, bipolar disorder), asthma, and perinatally acquired HIV with controlled viremia, while one study specifically examined children and adolescents with autism or pervasive developmental disorder.

Table 1

Summary of cross-sectional studies examining the association between inflammation and executive function

Study	N (Age Range)	Type of sample	Inflammatory markers	Executive function - subdomains	Statistically significant association	Effect sizes
Dirajlal-Fargo et al., 2022	111 (10-18 years)	Clinical (PHIV with controlled viremia)	T cell activation	Inhibition*, Cognitive flexibility* Working Memory*	✓	small
Caldú et al., 2023	105 (12-21 years)	Community (includes obesity)	TNF-α	Inhibition	✓	small
Adelantado-Renau et al., 2019	107 (8-11 years)	Community (includes obesity)	TNF-α, CRP, white blood cell count	Inhibition, Cognitive Flexibility, Working Memory	X	
King et al., 2024	35 (8-12 years)	Community	IL-6*, hsCRP*, TNF-α	Inhibition*, Cognitive Flexibility*, Working Memory*	✓	small to large
Laubacher, 2024	134 (9-13 years)	Community (includes asthma)	Neutrophil to lymphocyte ratio	Inhibition	X	
Cullen et al., 2017	107 (11-14 years)	Community	CRP (salivary)	Inhibition*, Working memory*	✓	small
Rahmani et al., 2021****	111 (13-20 years)	Clinical (Bipolar Disorder) * & Community	IL-6*, CRP*, IL-1β, TNF-α, IL-4, IL-6, IL-10	Cognitive flexibility	✓	small to medium
Sasayama et al., 2017	14 (9-14 years)	Community (Autism)	INF-y	Inhibition, Cognitive flexibility Working Memory*	✓	medium to large

Study	N (Age Range)	Type of sample	Inflammatory markers	Executive function - subdomains	Statistically significant association	Effect sizes
Peters et al., 2019	70 (12-17 years)	Clinical (mixed mood disorders) + Community	IL-1β, TNF-α*, IL-6	Inhibition*, cognitive flexibility	✓	small to medium
King et al., 2023	68 (7-14 years)	Community (includes obesity)	IL-6, hsCRP*, TNF-α	Inhibition, Cognitive flexibility* Working Memory	✓	medium
Mac Giollabhui et al., 2024	76 (12-22 years)	Clinical (Depression) & Community	CRP	Working memory	X	

Note: Where multiple measures are reported within the same variable, * indicates significant associations reported, $p \leq 0.05$

Most of the results from cross-sectional studies, as outlined in **Table 1**, show negative association between pro-inflammatory markers and executive function (on single or multiple domains). However, effect sizes varied considerably, ranging from small to large and there was substantial heterogeneity in the measurement of executive function, encompassing computerised tasks, parent-reports, and clinician-administered assessments. The studies included participants from different stages of childhood and adolescence.

All three subdomains of executive function—working memory, cognitive flexibility, and inhibition—were represented, with inhibition being the most frequently studied. Specifically, five studies identified significant associations between inhibition and various inflammatory markers, while four studies reported significant relationships between inflammation and both working memory and cognitive flexibility. The most frequently assessed inflammatory markers across the included cross-sectional studies were two pro-inflammatory cytokines, TNF-α and IL-6, along with CRP, a commonly used general marker of systemic inflammation. Their association with poorer executive function performance was observed across both clinical and community population. Three studies specifically examined participants with mental health diagnoses, while two focused on particular physical health conditions (asthma and perinatally acquired HIV).

Longitudinal Insights: The Association Between Executive Function and Inflammation Over Time

Seven studies with longitudinal design were included, with participants aged 7–22 years. All but one measured CRP, with five studies assessing CRP exclusively. Two studies also included IL-6, and one measured TNF-α. Working memory was assessed in all studies, while cognitive flexibility and inhibition were both examined in a single study (King et al., 2024). Similarly,

this was the only study to employ a combination performance-based measures and parent-reported measure (BRIEF). **Table 2** below outlines the overview of longitudinal studies, inflammatory markers, executive function subdomain measured and the main findings.

Table 2. Overview of included longitudinal studies.

Study	N (Age Range) *	Type of sample	Inflammatory markers (age when measured)	Executive function - subdomains	Main Findings	Effect Size	Directionality and Coefficients	Direct or Mediator	N (Waves)	Duration between measurement points (months)
Shields et al., 2021	8536 (9-15 years)	Community (includes obesity)	CRP (age 9 & 15.5)	Working Memory (age 10)	Higher CRP (age 9) prospectively predicted worse working memory (age 10). Worse WM (age 10) predicted higher CRP (age 15.5)	Medium to Large (Adiposity-CRP age 9) Small (CRP age 9 on WM age 10) Small (WM age 10 on adiposity age 15.5) Medium (adiposity age 15.5 on CRP age 15.5)	Adiposity → CRP → WM: indirect β = -0.021; WM → Adiposity → CRP: β = -0.005	CRP as Mediator (both directions)	2	78
Jonker et al., 2014	1084 (10-18 years)	Community	hsCRP (age 16)	Working Memory (age 18)	hCRP not associated with working memory	Not significant	EF: B = -0.013 (ns); Memory: B	Direct (no significant effect)	4	24

Study	N (Age Range) *	Type of sample	Inflammatory markers (age when measured)	Executive function - subdomains	Main Findings	Effect Size	Directionality and Coefficients	Direct or Mediator	N (Waves)	Duration between measurement points (months)
							= -0.002 (ns)			
Mac Giollabhui et al., 2024	76 (12-22 years)	Community & Clinical (Depression)	CRP (yearly over 6 years)	Working Memory (first testing age unclear, mean age follow up 22.6)	Chronic inflammation associated with worsening WM over time	Small (chronic CRP on WM)	Chronic CRP × Time → WM: β = -0.12	Direct (longitudinal predictor)	WM yearly CRP repeated (not specified)	N/A
Mac Giollabhui & Hartman, 2022	1029 (11-19 years)	Community	CRP (mean age 16.17)	Working Memory (age 19)	CRP mediated the association between lower SES and WM	Small (SES on EF via CRP)	SES → CRP → EF: indirect β = 0.10 (CI [0.007, 0.252])	CRP as Mediator	4	30
Mac Giollabhui, Alloy & Hartman, 2021	1066 (11-19 years)	Community & Clinical (Depression)	hsCRP	Working Memory	Higher levels of CRP were associated with worse future WM	Small (CRP age 16 on EF age 19)	CRP → EF: β = -0.11 (Model 2)	Direct	4	30

Study	N (Age Range) *	Type of sample	Inflammatory markers (age when measured)	Executive function - subdomains	Main Findings	Effect Size	Directionality and Coefficients	Direct or Mediator	N (Waves)	Duration between measurement points (months)
Kokosi, Flouri & Midouhas, 2021	4525 (0-10 years)	Community	CRP, IL-6 (age 9)	Working memory	Elevated CRP predicted worse WM	Small (IL-6 age 9 on WM age 10) Small (Financial difficulties on WM via IL-6)	CRP → WM: β = -0.06; IL-6 mediation: indirect β = -0.002	IL-6: Mediator; CRP: Direct	3	112
King et al., 2023	39 (7-14)	Community (includes obesity)	IL-6, hsCRP, TNF-α	Inhibition, Cognitive flexibility, Working Memory	higher hsCRP had a small non-significant effect on lower cognitive flexibility	Large (%BF on hsCRP) Small (self-reported physical activity on hsCRP)	N/A	Longitudinal: Tested only	2	24

**age range at first testing

WM = working memory, SES= socioeconomic status, %BF = percentage body fat

As presented in **Table 2** above, most studies reported a negative association between higher systemic inflammation and working memory performance. Specifically, Kokosi, Flouri, & Midouhas (2021) highlighted the role of elevated CRP in predicting worse working memory in early adolescence (age 9). In this study, inflammatory markers (CRP and IL-6) were measured at age 9, and working memory was assessed one year later at age 10 using the Counting Span Task. Shields et al. (2021) provided further insight into this association, demonstrating a prospective relationship between inflammation and working memory, where higher CRP levels predicted worse working memory a year later, which in turn predicted elevated CRP levels five years later. These findings might suggest a reinforcing cycle of inflammation and executive function deficits during critical developmental periods in childhood. Similarly, Mac Giollabhui et al. (2024) found that chronic inflammation was associated with worsening working memory over a six-year follow-up. Based in these findings, the authors indicated that inflammation may have cumulative effects on working memory performance over time. In contrast, Jonker et al. (2014), with comparatively older participants (aged 16-18) found no significant relationship between hsCRP and working memory, possibly reflecting variability in associations during later adolescence or other factors. Further, King et al. (2024) reported a small-sized effect of higher hsCRP on reduced cognitive flexibility, while other inflammatory markers did not yield significant effects.

Lastly, Mac Giollabhui & Hartman (2022) demonstrated that CRP mediated the relationship between SES and working memory, with participants being in late adolescence during the follow-up assessments. In this study, SES was measured at age 11 (Wave 1), CRP and potential mediators were measured at age 16 (Wave 3), and working memory and other cognitive outcomes were assessed at age 19 (Wave 4), thus spanning early to late adolescence. This finding suggests that lower SES may contribute to poorer working memory indirectly through

increased systemic inflammation, as indicated by higher CRP levels. A closer examination at the key reported biopsychosocial factors linked to inflammation and executive function deficits is discussed later.

Overview of the key biopsychosocial moderators and covariates (across all studies)

The majority of all included studies reported some demographic, physical and clinical information about their participants, andcross both cross-sectional and longitudinal designs, the following were treated as either covariates or hypothesised mediators: socioeconomic status, obesity/adiposity and mental health diagnosis. The following section briefly outlines these variables in relation to common associations and trends reported.

Socioeconomic Status (SES)

Socioeconomic status was hypothesised as a significant covariate in several studies. This is unsurprising, given prior research demonstrating associations between inflammation and SES and between SES and cognitive deficits independently (Muscatell, Brosso, S& Humphreys, 2020). The included studies varied in their definitions of SES, with most using combined measures of parental educational attainment, occupational level, and annual household income as a proxy. In addition, some studies also incorporated parent-reports of perceived economic hardship, subjective financial difficulties and housing tenure. Overall, in the studies included in this review, lower SES was consistently linked to worse executive function, mostly as indicated by measures of working memory, with some studies identifying inflammation as a mediating factor. Specifically, lower SES was found to be directly and indirectly associated with worse executive function via increased CRP levels in a study by Mac Giollabhui & Hartman (2022). Similarly, Mac Giollabhui, Alloy & Hartman (2020) found an inverse relationship between SES and inflammatory marker (CRP) as well as between SES and

performance across measures of all three EF subdomains. Kokosi, Flouri & Midouhas (2021) reported that in a large sample of 4525 children and adolescents, financial difficulties during early childhood (as reported by mothers) were associated with increased levels of inflammatory marker (IL-6) as well as worse working memory. They further revealed that IL-6 at age 9 mediated part of the effect of early financial difficulties on working memory a year later. In contrast, only one study (King et al., 2024, N= 68) reported that SES demonstrated no significant effect on inflammation (as measured by hsCRP).

Obesity and Adiposity

Eight studies included weight status and reported a consistent relationship between BMI/adiposity and systemic inflammation, as indicated by CRP, IL-6, IL-10, and/or TNF-α (Caldú et al., 2023; King et al., 2023; Kokosi, Flouri & Midouhas, 2021; Mac Giollabhui, Alloy & Hartman, 2021; Mac Giollabhui & Hartman, 2022; Sasayama et al., 2017; Shields et al., 2021; Peters et al., 2019). Interestingly, Mac Giollabhui, Alloy & Hartman, 2021 found that after adjusting for BMI, alongside sedentary behaviour, and substance use, the association between higher inflammatory levels and poorer executive function was no longer significant. King et al. (2023) observed that greater adiposity was associated with elevated markers of inflammation (IL-6, TNF-α), which in turn were linked to lower executive function in domains such as working memory and cognitive flexibility, suggesting a potential cumulative effect of inflammation on cognitive outcomes. Similarly, Caldú et al. (2023) found that higher BMI was associated with poorer inhibition performance, and that inflammatory marker levels (e.g., TNF-α) were inversely related to inhibition, suggesting that aspects of executive function may be influenced by inflammation linked to elevated weight status.

In addition, Shields et al. (2021) found that greater adiposity at age 9 was associated with higher CRP levels at that time and 5.5 years later. Their results indicate that higher adiposity (age 9) predicted worse working memory a year later, which in turn predicted greater adiposity at age 15.5. These findings contribute to the broader research by providing evidence of a reinforcing link between adiposity, certain aspects of executive function, and inflammation over time.

Mental Health and Childhood Trauma

Five studies included various mental health variables; symptoms of depression were measured in 3 studies, while bipolar disorder and self-reported psychotic experiences were each examined in a single study. One study (Peters et al.,2019) also explored childhood trauma within depressed participants. The studies reported mixed findings. Some observed higher inflammatory markers, while others found no significant effect of psychiatric diagnosis on the relationship between inflammation and executive function.

Higher inflammatory markers in clinical groups, compared to healthy controls were specifically reported in three studies. Namely, Peters et al. (2019) found higher IL-6 levels in both depressed adolescents and depressed adolescents with a history of trauma, while TNF-α was specifically elevated in the depression group. Higher TNF-α levels were significantly associated with poorer inhibitory control, suggesting that inflammation may contribute to executive function impairments in this population. Similarly, Rahmani et al. (2021) found that both symptomatic and asymptomatic adolescents with bipolar disorder had higher CRP levels than healthy controls, though the effects on executive function were seen only in symptomatic BD individuals. Depressive symptoms were associated with CRP and in turn elevated depression was associated with worse performance on working memory measures (Mac Giollabhui, Alloy & Hartman, 2020).

Nevertheless, three studies found that clinical symptoms had no significant impact on the relationship between inflammation and various executive function subdomains. For instance, Cullen et al. (2017) reported that psychotic-like symptoms (as reported by the Youth Self Report) did not affect the significant association between inflammation and inhibition. Similarly, Rahmani et al. (2021) found no significant interaction between CRP levels and bipolar disorder diagnosis in predicting cognitive flexibility. Moreover, in a longitudinal study by Mac Giollabhui et al. (2024), chronic inflammation was associated with worsening memory over time, independent of depression status. However, Peter et al. (2019) found the deficits in inhibitory control only to be the most pronounced in depressed adolescents with a history of trauma. Further, Rahmani et al. (2021) suggested that neurocognitive flexibility in BD adolescents might follow an inverted U-shaped pattern, where an optimal balance of pro- and anti-inflammatory markers is necessary for cognitive performance.

Discussion

This review provides a synthesis of research examining the association between inflammation and executive function in childhood and adolescence. Most of the included studies, with a few exceptions (Adelantado-Renau et al., 2019; Jonker et al., 2014; Laubacher, 2024; Mac Giollabhui et al., 2024) support prior lifespan research (primarily conducted in adult populations) by indicating a consistent link between elevated inflammatory markers and poorer executive performance in younger populations. In addition, the review presents a systematic narrative of several biopsychosocial factors (e.g., obesity, mental health, socioeconomic status) that were examined as potential mediators or moderators of this relationship.

Summary of Main Findings

Overall, the findings from the majority of cross-sectional studies included reinforce the likelihood of link between systemic inflammation and executive function in children and adolescents, suggesting that inflammatory processes, previously primarily connected to cognitive decline and deficits in adult population (Marsland et al., 2015) and preterm infants (Kuban et al., 2017) may be at play much earlier—during critical periods of executive function development. This is consistent with theoretical frameworks suggesting that inflammatory activity may disrupt executive function by affecting the structure and function of the prefrontal cortex (Hostinar et al., 2018; McAfoose & Baune, 2009; Shields et al., 2017).). While three studies reported no significant associations, the considerable heterogeneity of the methods used limits the ability to draw particular conclusions regarding these discrepancies. Given the limitations of cross-sectional studies in establishing causality, these results should be interpreted in conjunction with longitudinal evidence.

Collectively, the findings from longitudinal studies highlight a complex interplay between inflammation, age, and developing executive functions. Most studies, except for Jonker et al. (2014), reported significant associations between inflammation and working memory, with evidence suggesting progressive worsening over time. Apart from King et al. (2024), all studies measure exclusively working memory, so whether other components of executive function present similar patterns in relation to inflammation remains to be investigated in future studies. Overall, the current studies indicate that prolonged exposure to inflammation may impact the developmental trajectory of working memory, with some findings suggesting that these effects may be cumulative and unfold progressively over time (Mac Giollabhui et al., 2024; Shields et al., 2021).

Role of obesity and adiposity in the inflammation- executive function relationship

The relationship between obesity and executive function has been well documented in both adult and paediatric populations. Previous studies have reported worse executive function performance linked to obesity, particularly in the domains of inhibition and working memory (O'Brien et al., 2017; Lavagnino et al., 2016; Cheke et al., 2016). More recently, an obesity-related inflammation has been examined as a potential mediator of this relationship, with research in adult population demonstrating that obesity-related increases in inflammatory markers may contribute to executive dysfunction (Yang et al., 2018; Spyridaki et al., 2016). In the last decade, the research has extended to explore childhood overweight and its association with cognitive deficits. However, only a few have directly explored the link between obesity, inflammation and cognitive function in childhood and adolescence. In the current study, eight studies included weight variables, all reporting significant association between weight status and inflammatory markers. In these studies, these inflammatory profiles were in turn linked to poorer performance across multiple executive function domains, particularly working memory, inhibition, and cognitive flexibility. These findings align with previous research in adult populations, which has identified systemic inflammation as a potential mediator between increased adiposity and cognitive deficits (Yang et al., 2019, 2018; Spyridaki et al., 2016).

Notably, King et al. (2023) suggested a bidirectional relationship, where greater adiposity predicted increased inflammation and reduced executive functioning over time, which may subsequently contribute to further weight gain primarily via changes in weight-related behaviours such as reduced self-regulation of eating and physical activity- highlighting a potential reinforcing cycle between adiposity, inflammation, and cognitive development. Similarly, Shields et al. (2021) suggested that adiposity, inflammation, and executive functioning may interact dynamically over time. The bidirectionality of the relationship

between obesity and brain structure and function was previously indicated by a meta-analysis of 21 neuro-imaging studies conducted by García-García et al. (2019). They concluded that obesity-related measures were associated with structural and functional alterations in brain regions implicated in executive functioning, such as the prefrontal cortex, suggesting a neurobiological pathway through which obesity may influence cognitive processes.

Socioeconomic status, Mental Health and Childhood trauma exposure

Socioeconomic status, mental health problems and exposure to childhood trauma have all been extensively studied in relation to cognitive performance and inflammation (Hackman et al., 2015; Duncan & Magnuson, 2012; Goldsmith et al., 2016), albeit mostly independently of each other. This review for the first time summarised research evidence where these factors were examined in relation to inflammatory processes and executive function in childhood and adolescence. Only five of the included studies examined mental health-related outcomes, with even fewer involving participants with confirmed clinical diagnoses of depression and bipolar disorder (Peters et al., 2019 & Rahmani et al., 2021). This limited representation may reflect the relatively early stage of research examining how mental health variables intersect with inflammation and cognitive development during childhood and adolescence. The results of these studies were mixed, with some reporting elevated inflammatory markers and associated executive function impairments in adolescents with depression and trauma exposure (Peters et al., 2019), bipolar disorder (Rahmani et al., 2021), and depressive symptoms (Mac Giollabhui, Alloy & Hartman, 2020). These findings are consistent with broader literature linking elevated inflammatory biomarkers with poorer cognitive functioning, including worse executive function performance, in clinical populations with depression (Chang et al., 2012; Krogh et al., 2014; Goldsmith et al., 2016). Some theoretical models suggest that rather than depression directly causing cognitive dysfunction, inflammation may impair executive functioning, which

in turn increases vulnerability to depression via stress generation (Shields et al., 2017; Snyder & Hankin, 2016). This hypothesised link is supported by findings of one study from the current review (Mac Giollabhui et al., 2024), who observed that chronic inflammation predicted worsening working memory over time, independent of depression status.

In contrast, others found no significant effects of clinical symptoms—such as psychotic-like experiences (Cullen et al., 2017), bipolar disorder diagnosis (Rahmani et al., 2021), or depressive status (Mac Giollabhui et al., 2024)—on the relationship between inflammation and executive function. It is worth noting that none of the studies reported on anxiety disorders despite growing emerging evidence linking anxiety with systemic inflammation (Sah & Singewald, 2025). These mixed findings may be partly explained by the heterogeneity of clinical presentations and in how clinical conditions were assessed, with some studies relying on self-reported symptoms and others using confirmed clinical diagnoses.

Socioeconomic status has long been recognised as a significant determinant of both physical and cognitive health, with lower SES consistently associated with elevated inflammatory markers and poorer executive functioning (Muscatell et al., 2020). In the present review, five studies included some measures of SES. Collectively, the studies included in this review reinforced these associations, demonstrating that lower SES was frequently linked with poorer executive function—particularly working memory—and in several cases, this relationship was partially mediated by elevated inflammatory markers. Only one study (King et al., 2024) did not observe a significant association between SES and inflammation.

It is worth noting that socioeconomical hardship, mental health problems and childhood trauma do not operate it isolation; rather, they frequently co-occur and are likely to exert a combined

influence on developmental outcomes. However, none of the included studies examined how such interacting factors may jointly shape the relationship between inflammation and executive function. Future research should explore how these biopsychosocial influences intersect—whether their effects are cumulative, interactive, or whether they operate through shared mechanisms, as suggested by individual studies that examined these pathways separately (e.g., SES and inflammation, mental health and executive function).

Strengths and Limitations

Key strengths of the current review include a rigorous search strategy, the inclusion of both cross-sectional and longitudinal studies, and the incorporation of a broad set of variables previously linked to inflammation and cognitive outcomes. This approach enabled a comprehensive overview of the current evidence on the relationship between systemic inflammation and executive function in childhood and adolescence. The included studies covered multiple developmental stages, primarily late childhood and adolescence, and a range of demographic characteristics.

Methodological heterogeneity, particularly in the assessment of both executive functions and inflammatory markers, limited the ability to draw direct comparisons across studies or to synthesise findings in a standardised manner. Additionally, the majority of the longitudinal studies relied on single point sample for inflammatory measures. As stated by Caldú et al. (2023), reliance on single testing makes it difficult to ascertain whether the observed inflammation is enduring or episodic in nature, and others (Sergerstrom & Laudenslager, 2009) have emphasised the importance of repeated measurements for reliable assessment of immunological processes.

Future directions and implications from current review

Future research would benefit from incorporating repeated measures of both inflammatory markers and executive function and a longitudinal design. As previously noted, most included studies used only single-timepoint measures of inflammation, which limits the ability to examine developmental trajectories or determine whether observed associations reflect transient or more persistent patterns. Longitudinal designs with multiple measurement points could clarify whether these relationships are threshold-dependent, dose-responsive, or developmentally sensitive—offering deeper insight into how inflammatory processes and cognitive functioning interact over time.

This review could not explore developmental differences in the inflammation–executive function association as none of the included studies systematically examined age as a moderating or mediating factor in the relationship. Future studies would benefit from directly investigating developmental stage differences, by age, or other indicator of development, such as pubertal stage, particularly given the protracted maturation of executive functions into early adulthood (Zelazo & Carlson, 2012). It is therefore plausible that inflammatory processes may differentially influence the developing brain depending on the stage of maturation at which inflammation is high, or as the detrimental impact of inflammation on cognitive functioning may be more pronounced during early and late developmental windows (Adelantado-Renau et al., 2019).

Additionally, while three studies collected measures of puberty, these were either not integrated into the main analyses or not reported. There is an increasing recognition that puberty, a period of significant hormonal and neurodevelopmental changes, may influence both inflammatory processes and cognitive development (Paus et al., 2008). Pubertal maturation could affect

immune system functioning and interact with neuroendocrine pathways, potentially modulating the relationship between systemic inflammation and executive functioning. Future studies would benefit from incorporating pubertal measures more systematically to control for and better understand the moderating role of pubertal status.

Finally, all studied measured peripheral markers of inflammation. Blood or saliva-based measures are commonly used in research, particularly if involving children and adolescents due to their non-invasive nature and established utility in psychoneuroimmunological studies. However, this means that the findings cannot directly inform on the specific neurobiological processes underpinning executive function difficulties in the context of inflammation. A more complete understanding of how peripheral inflammation translates into central nervous system (CNS) inflammation is needed to refine theoretical models linking systemic inflammation to cognitive development and impairment, and in turn, help inform more targeted interventions. Thus, future research should consider incorporating methods of assessing CNS inflammation in addition to peripheral markers, for instance by structural or functional neuroimaging.

Conclusions

This scoping review synthesised existing evidence on the relationship between systemic inflammation and executive function in children and adolescents. Across the 16 included studies, most findings reported some negative association between elevated inflammatory markers and executive function performance, with the domain of working memory being the most extensively studied. Longitudinal findings further suggested that chronic inflammation may affect the developmental trajectory of executive functions, with some studies indicating cumulative or worsening effects over time. The review also examined potential mediators and moderators of this relationship. Obesity and adiposity emerged as particularly relevant to this

association, with several studies pointing to a bidirectional cycle involving inflammation, executive function, and obesity. Socioeconomic status and to an extent mental health variables were also associated with both inflammation and executive function, although no study explored their combined or interactive effects. Methodological limitations were identified, including the frequent use of single inflammatory markers and limited repeated measures of all key variables in longitudinal designs. Moreover, age and pubertal development were often underexamined despite their relevance to both inflammation and EF development.

Collectively, the findings support the emerging view that systemic inflammation may play a significant role in shaping executive function during childhood and adolescence, but further research—particularly longitudinal, developmentally informed, and methodologically rigorous studies—is needed to advance the field and inform intervention development.

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None of the authors have any conflicts of interest to disclose.

Chapter 4. Integrative Discussion

Summary of Key Findings

This thesis examines the interplay of inflammation and mental health, and is comprised of two studies examining systemic inflammation in relation to mental health and obesity in adults (Study 1) and separately, executive function in children and adolescents (Study 2). The first study explored general practitioners' perspectives on supporting patients with concurrent obesity and mental health (MH) difficulties, with a particular focus on lifestyle-based interventions that may help reduce systemic inflammation. The second study was a scoping review mapping the existing literature on the association between systemic inflammation and executive function in childhood and adolescence.

Findings from Study 1 highlighted the clinical complexity of managing concurrent obesity and mental health problems in primary care settings. GPs reported that these presentations were common in practice but often difficult to support, particularly within time-limited consultations and in the absence of more integrated care pathways. While lifestyle-based interventions were generally recognised as relevant and beneficial, their successful implementation was frequently challenged by a number of patient-related, structural, and systemic barriers. Notably, GPs expressed a need for greater psychoeducational resources to help communicate the rationale for recommending lifestyle-based interventions for this patient group, including explaining connected mechanisms such as systemic inflammation in accessible form. Importance of person-centred care which simultaneously addresses both physical and psychological aspects was emphasised.

The scoping review provided further support for the high relevance of systemic inflammation to executive functioning, synthesising evidence from 16 studies that investigated this relationship in children and adolescents. Most of the included studies (13 of 16) reported some

significant associations between elevated inflammatory markers and poorer executive function, particularly in working memory domain. Several biopsychosocial factors, including obesity, socioeconomic status, and mental health, were commonly examined within the included studies as potential moderators or mediators of this relationship. Of these, obesity-related inflammation showed the most consistent association with worse executive functioning, while socioeconomic disadvantage was consistently linked to elevated inflammatory markers and poorer working memory. Longitudinal findings suggested that sustained inflammation may disrupt the developmental trajectory of executive functioning over time, but more research is needed, particularly using repeated measures of both executive function and inflammation at multiple time points.

While inflammation has already been proposed as a shared physiological mechanism, the current findings contribute to this literature by bringing together clinical perspectives and up to date research evidence from childhood and adolescence. Focusing on obesity and mental health, the GP study highlighted challenges and opportunities for translating inflammatory theory into person-centred care, while the scoping review expanded and synthesised existing understanding of the inflammation–executive function relationship in children and adolescent population. It also identified key methodological and conceptual gaps, offering direction for future research. Together, these findings reinforce the relevance of systemic inflammation across clinical and developmental contexts and support the integration of psychologically informed approaches with biological insights—particularly for individuals experiencing overlapping mental, and physical health difficulties.

Methodological challenges in examining inflammation and executive function

Examining both the inflammatory processes and executive function presents a number of methodological challenges owing to the complexities of both constructs. While both have been a subject to extensive research interest and scrutiny, there is a lot that we still do not fully understand and as with everything, the measures currently used come with their own complications. As highlighted in the Scoping Review in Chapter 3, researchers assessing the relationship between inflammation and executive function have utilised a broad range of assessment tools and methodologies. Hence, this methodological variability makes it difficult to compare the findings together and draw more definite conclusions. Therefore, it is difficult to determine whether, or to what extend are the heterogeneity in results are contributable to real differences and which part is determined by the variability in assessment techniques. To help address some of these methodological challenges, a number of recommendations should be considered. Firstly, incorporating multiple tasks within each executive function domain can improve construct validity, particularly in studies aiming to explore complex associations with physiological processes such as systemic inflammation (e.g., Baggetta & Alexander, 2016; Friedman & Miyake, 2017). Similarly, it is advisable to integrate both performance-based and rating-based measures to enhance ecological validity (Toplak, 2013). In developmental research, adopting repeated measurement designs can help track individual changes in executive function across developmental trajectories. This longitudinal approach is also important when investigating inflammatory markers, as it can better capture the dynamic nature of inflammatory activity over time. Such designs also allow for a more nuanced understanding of how biopsychosocial factors interact and influence the inflammation–executive function relationship across developmental periods. Where feasible, employing multi-marker inflammatory panels is recommended to reflect the multifaceted nature of immune system

functioning (Khandaker et al., 2014; Thomas et al., 2025). Challenges in measuring EF and inflammation are further discussed below.

Challenges in measuring executive function

Executive function (EF) refers to a broad and multifaceted construct, rather than a single, unified ability. Various definitions of EF exist reflecting a more generalised lack of agreement on many aspects of EF (Banich, 2009; Miyake & Friedman, 2012) and ongoing debate persists regarding how its core domains are interrelated and best conceptualised (Diamond, 2013). This conceptual complexity is mirrored in the empirical literature, where studies often vary in how they define and operationalise EF, making comparisons across studies particularly challenging.

One common methodological issue is the reliance on single-task assessments to measure complex EF domains. While widely used, this approach may limit the validity of findings, particularly when results are generalised as reflecting global EF performance. For example, studies frequently report executive function impairments based on performance on a single task intended to measure a specific domain, such as working memory or inhibition. This reliance on a single indicator can oversimplify a multifaceted construct and reduce the reliability of conclusions (Baggetta & Alexander, 2016; Snyder et al., 2015). A related but distinct concern is the issue of task impurity—i.e., the fact that most neuropsychological tasks engage multiple cognitive processes simultaneously, making it difficult to isolate and measure a single executive function component in a pure form (Miyake et al., 2000; Friedman & Miyake, 2017). Additionally, many studies use or at least report only global EF scores, potentially missing domain-specific effects. This can be particularly problematic when the research is focused on developmental perspectives or attempts to compare differences between age groups, as evidence suggests that different EF components may follow distinct developmental trajectories across childhood and adolescence (Best & Miller, 2010; Zelazo & Carlson, 2012; Anderson,

2002). For instance, research suggests that working memory and inhibitory control might mature earlier and follow parallel developmental pathways, while cognitive flexibility continues to develop for much longer (Best & Miller, 2010; Zelazo & Carlson, 2012). However, these developmental differences are often not explicitly accounted for in study designs or data interpretation, especially when broad age ranges are included.

Another source of variability in the literature stems from the range of measurement approaches employed. Performance-based neuropsychological tasks and rating scales (e.g., teacher or parent reports) each offer unique strengths and limitations. While performance tasks may be regarded as more objective, they are often criticised for their reduced ecological validity. Conversely, rating scales may better reflect real-world functioning but are susceptible to subjective bias (Toplak, West & Stanowich, 2013). Despite these differences, studies frequently rely on only one method, limiting the ability to compare across measurement types. Taken together, these challenges contribute to significant heterogeneity in the EF literature and complicate the interpretation of findings, particularly in relation to complex mechanisms such as systemic inflammation.

Examining inflammation in a research context

As with executive function, measuring systemic inflammation in research presents several methodological challenges that have important implications for interpreting findings and for the comparability of studies. The challenges most relevant to the current thesis are outlined below.

Firstly, as demonstrated in the scoping review, there is considerable variability in the inflammatory markers used across studies. This heterogeneity complicates data synthesis and limits comparability. For example, one study may report a significant association between

interleukin-6 (IL-6) and cognitive outcomes, while another using C-reactive protein (CRP) may not find the same relationship. Given that inflammatory markers have overlapping but distinct physiological roles (Germolec et al., 2018; Medzhitov, 2008), generalising findings across studies using different markers may obscure specific immunological mechanisms risks overgeneralised conclusions. Additionally, many studies rely on single inflammatory markers. In the current scoping review, this was particularly evident in longitudinal studies. While frequently used for practical purposes, this approach may fail to capture the complexity of systemic inflammation. For instance, null findings based on a single inflammatory marker may not necessarily indicate the absence of an association, but rather that the selected biomarker may not be the most appropriate or sensitive indicator for capturing the specific physiological process under investigation. Using multiple markers may provide a more comprehensive picture of inflammatory activity and its relationship with the variables of interest (Khandaker et al., 2014). Another notable challenge relates to the lack of standardised thresholds for defining elevated inflammation. Some studies adopt clinical cut-offs (e.g., CRP >3 mg/L) while others use sample-specific percentiles or continuous scores. The use of clinical thresholds may not be sensitive enough to detect subclinical variation that is relevant for research investigations (Monastero, & Pentyala, 2017). The variability in used cut-offs can limit cross-study comparability and poses challenges for clear synthesis and generalisation of results. Moreover, recent findings suggest that different inflammatory markers or marker profiles may vary in their associations with cognitive domains and rates of decline, and it is important to consider how individual markers interact or impact each other in relation to changes of cognitive performance (e.g., Thomas et al., 2025). While this remains a new and developing area of research, such findings highlight important implications for interpreting findings of inflammatory effects on cognition, not only in the context of cognitive decline, but also with relevance for childhood and adolescence. To date, most insights into individual

markers and their interactions stem from studies in adult populations. Future research would benefit from investigating whether and how developmental processes in childhood and adolescence, such as neuroendocrine changes, may further influence these associations.

Considering the challenges across both executive function and inflammation domains, several suggestions have been recommended to be considered for future research. For example, in the context of research examining the relationship between systemic inflammation and executive function, some recommendations include using multi-method assessments of executive function (e.g., combining performance-based tasks with self- or informant-reports), measuring multiple inflammatory markers where feasible to better capture the complexity of systemic inflammation, and collecting repeated measures of both variables at multiple time points in longitudinal designs. Together, these strategies may enhance construct validity and provide a more comprehensive understanding of the associations under investigation.

Reducing inflammation through psychological approaches

As outlined earlier, chronic inflammation has been increasingly implicated in the development and progression of many non-communicable diseases, which are rising globally and are now recognised as leading contributors to morbidity, disability, and reduced quality of life worldwide (Furman et al., 2019). Therefore, the importance of incorporating effective strategies which target inflammatory processes, and thus support the associated conditions is being increasingly recognised. While these strategies might often require multidisciplinary or layered approach, general practitioners might be the first point of contact for many patients who could benefit from such interventions. The current study examined the experiences of these clinicians in relation to supporting patients with concurrent obesity and mental health problems to implement such lifestyle interventions to provide better insights into associated clinical challenges and strategies. Such insights can be beneficial for wider teams of

professionals who are likely to support people with these presentations in both medical and therapeutic contexts, including psychologists. The link between inflammation and several mental health difficulties, such as depression, PTSD or anxiety has been discussed earlier, particularly in the context of lifestyle-based interventions. Thus, it is important to discuss a role of clinical psychology in this context and how can psychological interventions contribute to the regulation of inflammatory processes.

Over the past two decades, research has increasingly explored how psychological interventions may contribute to the reduction of systemic inflammation. A foundation for the use of psychosocial interventions to support immune function and improve related health outcomes is provided by the extensive body of research showing that biopsychosocial factors shape immune system processes (Sternberg, 2006; Slavich, 2013). Thus, psychosocial interventions are increasingly studied for their potential to counteract the impact of chronic stress and psychological dysregulation, and associated health behaviours on inflammatory processes (Irwin, 2008; Kiecolt-Glaser et al., 2002; Rohleder, 2019). As a growing evidence base supports the use of specific psychological approaches in this context. For example, a systematic review of cognitive behavioural therapy (CBT) for individuals with depression and co-occurring physical health conditions found that 14 of 23 studies reported reductions in at least one inflammatory marker (Lopresti, 2017). Similarly, a meta-analysis by O'Toole et al. (2018) found that various psychological interventions—including CBT, mindfulness-based stress reduction, and grounding techniques—were associated with significant reductions in C-reactive protein (CRP) across both clinical and non-clinical populations. Moreover, a large meta-analysis of 56 randomised controlled trials (Shields et al., 2020) showed that psychosocial interventions could improve immune function with the effects persisting for at least six months post-trial CBT-based and integrative interventions (those incorporating mindfulness or stress reduction components) demonstrated the most consistent effects.

Although the precise mechanisms remain under investigation, the growing body of evidence collectively supports the use of psychological interventions for their combined benefits on psychological and immunological outcomes. Accordingly, therapeutic models commonly employed in clinical psychology may be more routinely incorporated into broader treatment or intervention plans for individuals with elevated inflammatory profiles. As systemic inflammation is commonly present in individuals with multiple comorbid physical health conditions, an awareness and better understanding of these conditions by all healthcare professionals who might provide therapeutic support, including psychologists, is desirable. Additionally, these findings further emphasise the importance of integrated, team approach to care, where psychological interventions can be integrated into person-centred treatment plans to promote immune health and subsequently reduce adverse health consequences.

Taken together, the evidence highlights the role of psychological approaches in addressing both mental and physiological aspects of comorbid conditions. A growing body of evidence suggests that in populations with such comorbidities, psychological interventions might not only improve depressive/ anxiety symptoms but also reduce inflammation, and so in turn potentially leading to improvements in physical health outcomes. Thus, these interventions should be considered for this clinical population already on a primary care level. However, despite the promising results, future research is needed to better determine how individual differences (such as levels of inflammation) may influence outcomes and whether or when should psychological interventions be considered as an initial or combined (with pharmacological interventions aimed at reducing inflammation) approaches here. Moreover, given the existing focus primarily on CBT, future studies should explore other psychological approaches and modalities. For instance, acceptance-commitment therapy (ACT) may be a promising candidate, as is has already been applied across various primary care and hospital

settings, enabling shorter-term intervention plans that could complement broader multidisciplinary efforts (e.g., as part of integrated treatment approach).

While these findings highlight the potential of psychological interventions more broadly, it is important to consider how lifestyle-based interventions sit within the specific remit of clinical psychology, and the challenges this raises for therapeutic work.

Clinical Psychology and Lifestyle-Based Interventions

From a clinical psychology perspective, understanding how GPs approach concurrent obesity and mental health difficulties offers an important window into systemic care processes. As highlighted earlier, GPs are often the first point of contact for this patient group, yet psychologists may contribute by translating medical perspectives into psychologically informed insights that integrate physical and mental health care. Traditionally, lifestyle and behaviour change interventions have been closely aligned with health psychology, which emphasises overt behaviour modification and health promotion. Clinical psychology, by contrast, has been centred on mental health problems. However, lifestyle interventions are increasingly recognised as integral to mental health outcomes, bringing them more within the remit of clinical psychology. In this context, clinical psychology's role lies primarily in addressing the psychological and relational contexts in which lifestyle-based changes occur. For example, clinical psychologists can support difficulties relating to self-esteem, identity, and stigma that often accompany obesity, while simultaneously supporting concurrent depression or anxiety. In parallel, they can support multidisciplinary teams by fostering psychological mindedness, encouraging sensitive communication, and highlighting the heightened risk of mental health difficulties among people with obesity. In this way, clinical psychology complements rather than duplicates health psychology.

At the same time, working with lifestyle interventions raises dilemmas for the therapeutic relationship that are important to consider. If the focus shifts too strongly toward weight, diet, or exercise, therapy risks becoming medicalised, prescriptive, or even a space of judgement and shame. This is particularly relevant given the stigma reported in both obesity and mental health. In the current GP study, participants highlighted how lifestyle advice might sometimes feel invalidating for patients. Clinical psychologists might therefore work towards achieving a balance between supporting behaviour change in a collaborative, values-based way, while protecting the therapeutic alliance and the client's sense of autonomy.

Overall, this thesis, and particularly the findings from the GP study, also underscore the importance of recognising the bidirectional relationship between lifestyle factors and mental health. As described earlier, on the one hand, lifestyle changes such as increased physical activity or dietary improvements can reduce systemic inflammation and enhance mental health outcomes. On the other, mental health difficulties, including low motivation, cognitive impairments, and emotional dysregulation, can act as barriers to engaging in precisely those changes, as described by participants in the first study. Clinical psychology is well placed to intervene here by framing depression less as an obstacle to lifestyle change, but as part of the change process itself. Techniques such as behavioural activation, motivational work, and emotion regulation strategies can help patients increase psychological resources needed to engage with health behaviours.

In summary, clinical psychology has an expanding and complementary role in supporting lifestyle-based interventions. Its contribution lies in ensuring that lifestyle interventions are framed within individuals' values, goals, and lived experiences, thereby protecting the therapeutic relationship while supporting both psychological and physical health.

Challenges related to the recruitment of healthcare professionals

It can be a challenge to recruit general practitioners (GP) into research projects, and these challenges are well-documented (Asch et al., 2000; Brodaty et a., 2013) and were experienced in this research. Low participation rates are often attributed to time constraints, high clinical workloads, he perception that research topics are not directly relevant to medical practice and concerns about the time burden of participation (Brodaty et al., 2013; Kaner et al., 1998; Stocks et al., 2004). Additionally, other barriers identified in previous studies include healthcare professionals' perceived lack of research expertise, as well as a belief that their clinical role limits the value or necessity of their contribution to research (Nkrumah et al., 2018; Rosemann & Szecsenyi, 2004; Williamson et al., 2007). Previous research has also highlighted specific challenges related to recruiting GPs. For instance, Hummers-Pradier et al. (2008) found that in a sample of 96 GPs in Germany, over half had never participated in a research study, and an equal number stated they would decline future participation offers. The main reasons included lack of time, concerns about the additional administrative burden, and fears that participation would interfere with the demands of routine clinical practice. Poor engagement of GPs may affect the representativeness and validity of primary care research findings (Barclay et al., 2002; Wetzel et al., 2005).

Nevertheless, for the current research, major recruitment difficulties were not initially anticipated considering the small target sample and planned use of snowball sampling supported by initial networks. However, these difficulties emerged and persisted resulting in the introduction of online surveys were introduced as an alternative participation method, based on the assumption that their lower time demands would enhance response rates. This facilitated the achievement of the sufficient number of participants; however, the introduction of the

survey method partially affected the richness and depth of data compared to interview responses. Ultimately, additional professional networks proved instrumental in facilitating participant recruitment. Similar conclusions were reached by previous studies, with additional factors enhancing participation being an interest in the research subject to assist in research, to advance patient care, and the opportunity for learning were incentives for the participating HCPs (Browne et al., 2022). Similarly, Williamson et al. (2007) found that GPs were motivated by minimal time demands of research and the opportunity to gain Continuing Professional Development (CPD) credits as a form of professional recognition (Williamson, 2007).

In conclusion, recruitment challenges involving GPs appear to remain a persistent barrier, with the potential to limit the diversity and representativeness of these participant groups. This, in turn, may constrain the extent to which findings reflect the realities of clinical practice-particularly when the aim is to inform or improve patient care.

Reflexivity and Researcher Position

As the first study presented in this thesis was qualitative in design, it is important to briefly consider the role and position of the researcher in this process, as in line with Braun & Clarke's (2006; 2013) recommendations.

Conducting qualitative research with medical practitioners from the perspective of a Trainee Clinical Psychologist offered opportunities for valuable insights but also presented certain complexities worth reflecting on. Firstly, being trained primarily outside the medical model, I approached the interviews from a different professional background, asking GPs to reflect on their clinical experiences within a field where I have no professional experience in, therefore might not understand or be familiar with the medical context within which they work or which

they are referring to during the interviews. I was aware of my limited knowledge regarding some of the topics participants raised, such as specific physical comorbidities and their management. Additionally, although systemic inflammation, the physiological mechanism underlying the study focus is typically situated within the medical domain, my understanding of it and the association with mental health derives exclusively from academic literature rather than clinical experience. It is interesting to consider how this dynamic may have influenced the interview process and my engagement with the data. In some ways, occupying a "novice" position allowed me to approach the topic with a fresh perspective, which may have helped in drawing together the challenges described by GPs, particularly those related to broader systems and healthcare organisation. The psychological training often emphasises the importance of positioning individual within the larger systems they operate within, and this perspective likely influenced the epistemological stance taken in this study – that of a contextualist nature which assumes that while people construct meaning based on their experiences, the meaning-making is also influenced by their broader social contexts. At the onset of the interview processes, I was generally curious to better understand how GPs navigate the complexities of concurrent physical and mental health difficulties within the constraints of short appointment times and high service demands. While many participants spoke about these systemic limitations, I was also struck by the extent to which some described their efforts to maintain a person-centred approach in their consultations. This emphasis on individualised care—despite structural and time-related pressures—offered valuable insight into how GPs navigate these values in primary care settings and what systemic supports are necessary.

I also found it encouraging that many participants—especially those interviewed—described their approaches to co-occurring conditions in ways that reflected person-centred principles, aligning with clinical psychology's emphasis on individualised approaches to formulation and treatment planning. However, the contrasts in training and professional orientation prompted

ongoing consideration of my role in this research. At times, participants focused predominantly on the physical aspects of patients' presentations, with mental health concerns receiving less emphasis. This prompted some internal reflection- as a clinician, I felt an inclination to explore mental health issues in more depth, while my role as a researcher required me to maintain a neutral stance and allow participants to share accounts of what they considered most important or relevant. I remained mindful of these dual perspectives during both the interview and analysis phases. A related point arose in response to participants' frequent references to pharmacological treatment, which featured prominently across both surveys and interviews. While reviewing the data, I became aware of a sense of internal hesitation when medication was positioned as the principal form of intervention- particularly in response to questions intended to elicit broader reflections on support strategies. Personally, engaging with the data highlighted how medical and psychological disciplines at time differ in their approaches to wellbeing, yet in other ways share the goals of improved health and wellbeing and how they often rely on each other – particularly in cases of concurrent physical and mental health difficulties, such as the ones explored in this study.

Thesis Conclusions

This thesis explored the role of systemic inflammation in shaping physical, psychological, and cognitive health across two studies. Study 1 qualitatively examined general practitioners' experiences of supporting patients with concurrent obesity and mental health difficulties, highlighting particular challenges of supporting these conditions together in a primary care setting. Uniquely, study examined GPs own perspectives and their views on how patients perceive and engage with lifestyle-based interventions. Findings underscored the importance of multidisciplinary care, patient-centred communication, and the need for clearer resources to better translate inflammation-informed research findings into clinical practice into

comprehensive information for patients. Study 2 then mapped, for the first time, existing evidence linking systemic inflammation and executive function in children and adolescents. The study complimented previous findings from adult research, identifying consistent associations across cross sectional and longitudinal studies between inflammation and poorer executive function performance, particularly in working memory.

Together, the findings offer clear directions for future research aimed at clarifying complex biopsychosocial pathways, while also highlighting the relevance of physiological processes—such as inflammation—for clinical psychology. By examining current clinical applications, this thesis aims to help bridge the gap between research and practice.

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Appendices

Appendix 1: Theme 7: Quick fix or a stepping stone? The role of medication in managing concurrent obesity and mental health problems

Discussions around pharmacological treatment in supporting patients with concurrent obesity and MH difficulties featured prominently in both interviews and survey responses. GPs commonly reflected on the importance and relevance of such measures when discussing their experiences with this patient group and their perceptions of lifestyle interventions. These accounts often reflected a pattern concurrent with a medical model of care, where pharmacological intervention- both for management of obesity and MH was often positioned by GPs as a key component of care, though not consistently as the first-line approach.

The relevance of pharmacological options was amplified by recent developments, such as the recent introduction of weight-loss medications like semaglutide, a GLP-1 receptor agonist. As the topic of this theme suggests, there were contrasting views on the purpose of medication for this patient group, with some relying on it more heavily than others. Some GPs positioned it as a central, ongoing component of care whereas others viewed medication as a temporary aid or a stepping stone that enabled patients to more fully engage with subsequent lifestyle-based interventions.

Subtheme 1: Benefits of medication – a tool for buying more time

This subtheme reflects perceptions held by some participants, where pharmacological treatment was seen as a helpful intervention in managing concurrent obesity and MH problems. Some participants regarded the use of medication as a part of an initial management plan. Often, medication for mental health difficulties was viewed as a short-term solution that

allowed patients time and space to begin engaging with longer-term lifestyle changes, as illustrated by Participant 6:

> I am not a big advocate or fan of medication over long term, but I feel like, in this short amount of time they buy you some time, they buy patients some time to enable them to work a bit more on other factors in their lifestyle.

While all GPs reflected on the role of medication in management of these patients, their narratives revealed two distinct approaches to the use of pharmacological intervention, yet oriented toward the same clinical goal. Some GPs regarded MH medication as relevant and worthwhile despite negative side effects of weight gain, others discussed the benefits of weight loss medication on the overall management of concurrent obesity and mental health difficulties. For instance, Participant 8 perceived positive secondary effects on mood: "Benefits of medications may be there in the medium or long term to help with weight loss, which in turn can help with mood and depressive symptoms." Together, these accounts illustrate how medication was not typically viewed as a standalone solution, but as a supportive tool within a broader therapeutic approach.

Subtheme 2: Medication without broader support: a risky solution

Beyond recognising the utility of pharmacological interventions, GPs expressed concerns about the limitations and potential risks of relying on medication alone, often weighing its benefits against the need for more holistic care approach. GPs described how the increased availability of weight-loss medications has influenced clinical encounters, with some noting a direct impact on patients' help-seeking behaviours. As illustrated by Participant 6: "Since the introduction of the new medication for weight loss, you are seeing more and more people on

the files with the past history of mental health problems seeking to lose weight at the same time."

Nevertheless, several participants voiced concern about the reliance on weight loss medication as a stand-alone approach, highlighting the risk of overlooking or failing to address underlying psychological distress. For instance, one participant stated, "Newer medication can help many people losing weight, but sometimes this backfires if the underlying mental health struggles were not addressed appropriately as new dysfunctional coping behaviours might emerge" (P2).

Others expressed clear scepticism toward pharmacological approaches for this population, advocating more strongly for lifestyle-based strategies: "Some patients ask for shortcuts, like the new medication [Ozempic]. I think this practise should be discouraged" (P7).

This trade-off was also evident in GPs' reflections on MH medications, where benefits were weighed against side effects, particularly weight gain. As Participant 8 noted:

> [….] and, obviously, there is different types of medications that can promote weight gain as well. So when you are trying to manage your mental health issues, it can be difficult, and a side effect of that can be problems with weigh gain and obesity.

This observation further reinforces the cyclical relationship between obesity and depression described by many GPs.

Appendix 2: Author guidelines for submission to BMC – Primary Care Journal

(https://bmcprimcare.biomedcentral.com/submission-guidelines)

Research article

Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research will not be considered. Studies reporting descriptive results from a single institution or region will only be considered if analogous data have not been previously published in a peer reviewed journal and the conclusions provide distinct insights that are of relevance to a regional or international audience.
BMC Primary Care strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's data repository guidance. Where a widely established research community expectation for data archiving in public repositories exists, submission to a community-endorsed, public repository is mandatory. A list of data where deposition is required, with the appropriate repositories, can be found on the Editorial Policies Page.
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Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports

- list the full names and institutional addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
    - Large Language Models (LLMs), such as ChatGPT, do not currently satisfy our authorship criteria. Notably an attribution of authorship carries with it accountability for the work, which cannot be effectively applied to LLMs. Use of an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript.
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses

- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner.

See our editorial policies for more information.
If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).
See our editorial policies for more information on consent for publication.
If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Authors are also encouraged to preserve search strings on searchRxiv https://searchrxiv.org/, an archive to support researchers to report, store and share their searches consistently and to enable them to review and re-use existing searches. searchRxiv enables researchers to obtain a digital object identifier (DOI) for their search, allowing it to be cited.
Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.
BioMed Central strongly encourages the citation of any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare.
2014. http://dx.doi.org/10.6084/m9.figshare.853801
With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]
If you wish to co-submit a data note describing your data to be published in *BMC Research Notes*, you can do so by visiting our submission portal. Data notes support open data and help authors to comply with funder policies on data sharing. Co-published data notes will be linked to the research article the data support (example).

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.
Please use the authors initials to refer to each authors' competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. If the funder has a specific role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript, this should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.
Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

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Group authorship (for manuscripts involving a collaboration group): if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the “Acknowledgements” section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.

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Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

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Examples of the Vancouver reference style are shown below.

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Article within a journal
Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

Article within a journal (no page numbers)
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Article within a journal by DOI
Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement
Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Appendix 3: Letter of Ethical Approval

UCC
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Coláiste na hOllscoile Corcaigh

Coláiste na nEalaíon, an Léinn Cheiltigh agus na nEolaíochtaí Sóisialta
College of Arts, Celtic Studies and Social Sciences

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http://www.ucc.ie/en/apsych/

14th December 2023

Dear Karolina,

Clinical Psychology Research and Ethics Meeting 12.12.23

Thank you for presenting your research proposal to the Research and Ethics panel.

Based on your written proposal and further clarification and discussion during the meeting the decision of the panel was:

Approved

Ethics Feedback:

This is a very well-constructed study, designed with appropriate ethical oversight. Well done.

Research Proposal Feedback:

This is a well-written proposal. Some minor amendments are recommended. See the attached annotated draft.

Yours sincerely,

Dr Samantha Dockray
Chair Clinical Psychology Research and Ethics Panel

Dr Chris McCusker
Head of School of Applied Psychology

Coláiste na hOllscolie Corcaigh
University College Cork

Appendix 4: Study Invitation Letter/Email & Research Poster

Dear [General Practitioner's Name/Title],

I hope this email finds you well.

My name is Karolina Tothova, I am Trainee Clinical Psychologist at University College Cork. I am conducting a research study titled "*Exploration of healthcare professionals' perspectives and experiences of supporting patients with concurrent obesity and mental health difficulties*," and I am reaching out to invite you to participate.

About the Study: This study aims to understand the experiences of General Practitioners like yourself in managing patients with concurrent obesity and mental health issues, such as depression and anxiety. We are particularly interested in your approaches, challenges, and strategies regarding these dual conditions.

Your Role: Should you choose to participate, you will be asked to engage in a one-to-one interview (online or in person) which will last approximately 25 minutes. The interview will focus on your professional experiences and perspectives in this area.

Your insights will help gain a deeper understanding of the practical challenges and strategies in clinical practice related to these dual conditions and can guide future comprehensive healthcare interventions and policymaking in this field.

Your participation in this study would be entirely voluntary, and all information you provide will be kept confidential and anonymous. You have the right to withdraw from the study at any time.

Next Steps: If you are interested in participating or have any questions, please feel free to contact me at 122105132@umail.ucc. Please find an attached information sheet for further information.

Your expertise and experience would be a tremendous asset to this study, and I sincerely hope you will consider this invitation.

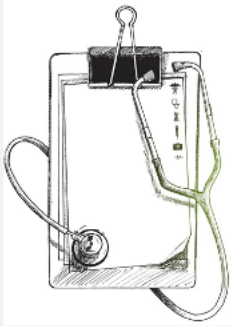
Thank you for your time and consideration.

Best regards,

Karolina Tothova, Trainee Clinical Psychologist
University College Cork

UCC
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Research Participants Needed



Dear (Trainee) General Practitioner

Please consider your participation in this doctoral research

Exploration of general practitioners' perspectives and experiences of supporting patients with concurrent obesity and common mental health difficulties.

Research Aims

- Understand your perspectives and experiences of supporting patients with concurrent obesity and mental health difficulties
- Explore challenges and strategies used to support this population
- Explore your insights into your patients' struggles with these conditions

Contact details
Karolina Tothova
Trainee Clinical Psychologist
122105132@umail.ucc.ie

Why take part?

Help us enhance meaningful application of research into clinical practice

- Your views and expertise is crucial to enhance our understanding of current biopsychologically-informed support in clinical practice
- Insights from this study have the potential to inform and shape future treatments and policymaking in this field

Participation options

Option 1 – Online 1:1 Interview -	**Option 2 - Online questionnaire (Standard)**	**Option 3 – Online questionnaire with Audio responses**
contact me directly via email to arrange a suitable time		

Ethical approved provided by the UCC Clinical Psychology Research Ethics Committee (CPREC). Study is part of the doctoral thesis in Clinical Psychology.

Appendix 5: Topic Guide

Pre-Interview:

Introduction and Consent

- Brief introduction of the researcher and the study purpose.
- Confirmation that the participant has understood the information sheet and consent form.
- Confirmation of the participant's agreement to audio record the interview and addressing any initial questions.
- Explanation of the interview structure and reminder of the approximate time the interview will take

Interview stage

Series of open-ended questions will be asked according to the key research themes/ research objectives. Opportunities will be provided to clarify any questions and relevant follow-up questions might be asked to elucidate further information.

<u>Key research themes:</u>

1.Prevalence and experience of concurrent obesity and common mental health difficulties in own clinical practice

- In your clinical practice, how often do you encounter patients who are dealing with both obesity and mental health difficulties like anxiety or depression?
- What is it like to support patients who experience both obesity and mental health difficulties?

2.Recommendation practices

Considering the recognised link between obesity and mental health difficulties, physical and lifestyle changes have been shown, in certain instances, to have positive impact on the experienced mental health difficulties. These could include weight management, increase of physical activity etc. -

- Are such recommendations relevant to your own clinical practice?
- What is your experience of such recommendations for this patient group up to date?
- If relevant, can you briefly share your experience with providing lifestyle/ physical change recommendations to your patients?

3.Challenges and strategies

- If relevant to your own practice, what are some of the biggest challenges of supporting patients with concurrent obesity and common mental health difficulties?
- On the contrary, is there anything you found helpful in supporting these patients?

4.Clinicians'perceptions of patients experience and challenges

- From your perspective, what are the main challenges your patients face when dealing with both obesity and mental health difficulties?
- In your view and from your own experience, how are physical/ lifestyle changes recommendations perceived by patients? (motivating/demotivating/why)

Post-interview stage

Following the interview stage, participants will be thanked for their participations and an opportunity will be provided to ask any questions/ follow up on any topic discussed.

Participants will be encouraged to provide feedback on their experience of the interview process. If distress or discomfort has been observed or indicated, support will be provided, including signposting if relevant. The right to withdraw from the study for up to two weeks post-interview will be reiterated.

Appendix 6. Author guidelines for submission

Introduction

Psychoneuroendocrinology publishes papers dealing with the interrelated disciplines of psychology, neurobiology, endocrinology, immunology, neurology, and psychiatry, with an emphasis on multidisciplinary studies aiming at integrating these disciplines in terms of either basic research or clinical implications. One of the main goals is to understand how a variety of psychobiological factors interact in the expression of the stress response as it relates to the development and/or maintenance of neuropsychiatric illnesses. The journal is international and comprises original research papers, reviews of an area of the literature, or at an appropriate stage in the development of the author's own work, commentaries in areas of current interest, short communications and book reviews. Other forms of publication (e.g., editorial, opinion, news, perspective) are up to the editors' discretion.

Types of Contributions

Original research papers: An original research paper should not exceed 6000 words. For the introduction there is a maximum of 1000 words and for the discussion a maximum of 2000 words. There should be no more than 6 illustrations, figures and/or tables (combined total). The reference section is limited to 50 references for the initial submission, subsequent revisions may have more references if necessary.

Review papers: Review papers of specialized topics within the scope of the journal should not exceed 8000 words. There should be not more than 6 illustrations, figures and/or tables (combined total). The reference section is limited to 100 references for the initial submission, subsequent revisions may have more references if necessary.

Short communications: describe new methods or the results of experiments that can be reported briefly. A short communication is 2000 words or less with a maximum of two illustrations (figures or tables). The reference section is limited to 15 references for the initial submission, subsequent revisions may have more references if necessary.

Book Form: Books for review may be sent to Dr. Robert Dantzer. Authors interested in reviewing a particular book should communicate directly with him.

Letters to the Editor: Submission of correspondence that provides a forum for the discussion of recent articles published in *Psychoneuroendocrinology* should not exceed 500 words (including references). Tables and/or figures should not be used. Letters critical of an article published in the Journal must be received within 8 weeks of the article's publication; letters from outside the United States must be received within 12 weeks. Letters received after the deadline will not be considered for publication and those accepted will be sent to the authors of the target article for reply.

Submission checklist

Authors are asked to use the Submission Checklist to carry out a final check of their submission before sending it to the journal for review. This checklist must be included with the cover letter.

One author should be designated as the corresponding author with contact details, but all co-authors should indicate that they approve of the cover letter's statements and should also give their complete affiliation and their electronic address:

• E-mail address

• Full postal address

All necessary files have been uploaded:

Manuscript:

• Include keywords

• All figures (include relevant captions)

• All tables (including titles, description, footnotes)

• Ensure all figure and table citations in the text match the files provided

• Indicate clearly if color should be used for any figures in print

Graphical Abstracts / Highlights files (where applicable)

Supplemental files (where applicable)

Further considerations

• Manuscript has been 'spell checked' and 'grammar checked'

• All references mentioned in the Reference List are cited in the text, and vice versa

• Permission has been obtained for use of copyrighted material from other sources (including the Internet)

• Manuscript does not contain any instance of plagiarism including self-plagiarism

• A competing interests statement is provided, even if the authors have no competing interests to declare

• Journal policies detailed in this guide have been reviewed

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Review and Appeal Procedures

Most editorial decisions are based on the results of reviews by one or more referees. However, if in the judgment of the editor a manuscript is clearly unsuitable for the journal, it will be rejected without referee review. Authors may appeal a rejection of their manuscript by the editor if they believe a pertinent point was overlooked or misunderstood by the reviewers, or the editor misinterpreted the reviewers' comments. Authors need to do so by contacting the editor and providing him with the relevant documentation. If they still believe they have received an unfair decision they can appeal to the other editor of the journal after having informed the initial editor of their decision, in which case the editor initially in charge of the manuscript will forward the file to the editor having received the appeal. Such an appeal must be based on the fairness of the procedures followed, and must not be a request for another scientific review. The questions to be answered in this review are: Were the editorial procedures followed appropriately and did the paper receive a fair hearing? A decision by the editor having received the appeal is the final level of review.

Before you begin

General Reporting Guidelines

Authors are encouraged to follow published standard reporting guidelines for the study discipline. Many of these can be found at the EQUATOR website

Other guidelines

Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Authors must disclose any interests in two places: 1. A summary declaration of interest statement in the title page file (if double anonymized) or the manuscript file (if single anonymized). If there are no interests to declare then please state this: 'Declarations of interest: none'. 2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important for potential interests to be declared in both places and that the information matches. More information.

Declaration of generative AI in scientific writing

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3. *Three or more authors:* first author's name followed by 'et al.' and the year of publication.

Citations may be made directly (or parenthetically). Groups of references can be listed either first alphabetically, then chronologically, or vice versa.

Examples: 'as demonstrated (Allan, 2000a, 2000b, 1999; Allan and Jones, 1999)... Or, as demonstrated (Jones, 1999; Allan, 2000)... Kramer et al. (2010) have recently shown...'

List: References should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters 'a', 'b', 'c', etc., placed after the year of publication.

Appendix 7.

List of studies included in the scoping review

Title	Authors	Publication Year	Country	Study Participants (N)
Association between exposure to HSV1 and cognitive functioning in a general population of adolescents. The TRAILS study	Jonker et al	2014	The Netherlands	1084
Negative Correlation between Serum Cytokine Levels and Cognitive Abilities in Children with Autism Spectrum Disorder	Sasayama et al.	2017	Japan	14
The relationship between salivary C-reactive protein and cognitive function in children aged 11-14years: Does psychopathology have a moderating effect?	Cullen et al.	2017	United Kingdom	107
Interplay between pro-inflammatory cytokines, childhood trauma, and executive function in depressed adolescents	Peters et al.	2019	USA	70
Inflammatory biomarkers and brain health indicators in children with overweight and obesity: The ActiveBrains project	Adelantado-Renau et al.	2019	Spain	107
Adiposity, Inflammation, and Working Memory: Evidence for a Vicious Cycle	Shields et al.	2021	United Kingdom	8536
Investigating whether depressed youth exhibiting elevated C reactive protein perform worse on measures of executive functioning, verbal fluency and episodic memory in a large, population based sample of Dutch adolescents	Mac Giollabhui, Alloy & Hartman	2021	The Netherlands	1066
The role of inflammation in the association between poverty and working memory in childhood	Kokosi, Flouri & Midouhas	2021	United Kingdom	4525
Lower pro- to anti-inflammatory ratios associated with reduced neurocognitive flexibility in symptomatic adolescents with bipolar disorder	Rahmani et al.	2021	Canada	111

Title	Authors	Publication Year	Country	Study Participants (N)
Examining inflammation, health, stress and lifestyle variables linking low socioeconomic status with poorer cognitive functioning during adolescence	Mac Giollabhui & Hartman	2022	The Netherlands	1029
Towards a biobehavioral and social-structural model of inflammation and executive function in pediatric obesity: A pilot longitudinal study	King et al	2022	USA	68
Inflammation, executive function, and adiposity in children with or at risk for obesity	King et al.	2023	USA	35
Body mass index, systemic inflammation and cognitive performance in adolescents: A cross-sectional study	Caldú et al.	2023	Spain	105
Chronic inflammation is associated with worsening working memory performance: Preliminary evidence from a diverse, longitudinal cohort of adolescents and young adults	Mac Giollabhui et al.	2024	USA	76
Brain Structural Correlates of Cognitive and Emotional Differences Comparing Youth With and Without An Asthma History in a Large Periadolescent Cohort	Laubacher	2024	USA	134
Immune Activation Is Associated With Neurocognitive Performance in Ugandan Adolescents Living With HIV	Dirajlal-Fargo et al.	2024	Uganda	111

Appendix 8. Methodological Reflections

Choice of Scoping Review Approach

Prior empirical research examining the association between systemic inflammation and executive functioning in childhood and adolescence is limited. Existing studies often focus on specific aspects of executive function or examine links in relation to isolated biopsychosocial factors, such as socioeconomic status or obesity. Although a growing understanding of the physiological effects of systemic inflammation has led to increased research attention in these younger populations over the past decade, a systematic synthesis of the scope and focus of current research in this area is lacking.

In preparing for this project, it was considered what methodology would most effectively address this gap and systematically map the current body of literature while identifying areas for future investigation. A scoping review methodology was selected as best suited to these purposes, allowing for the broader mapping of available evidence in this relatively new and conceptually complex field (Arksey & O'Malley, 2005; Levac et al., 2010; Munn et al., 2018). As described by Armstrong et al. (2011), scoping reviews are particularly valuable for synthesising emerging evidence when more specific questions, such as those typically addressed by systematic reviews, are yet to be determined. In the current study, a scoping review enabled an up-to-date, comprehensive overview of the literature with wider inclusion criteria to include a range of studies which used various assessment tools and examined various relevant moderators/ mediators of the proposed relationship. The main objective was to explore the breadth of available research, to describe patterns of investigation, and highlight conceptual gaps to inform future research directions. This is consistent with the purpose of scoping reviews as outlined by Peters et al. (2015), who emphasised their value in summarising and disseminating research findings and clarifying areas where knowledge is still developing.

Another objective of this review was to broadly explore which biopsychosocial factors have been investigated as potential mediators or moderators of the association between systemic inflammation and executive functioning in childhood and adolescence. Rather than applying predetermined criteria regarding which factors were important, the review sought to identify which variables prior empirical research had focused on, how frequently they were studied, and how they were conceptually positioned within existing models. Given the emerging nature of this research area, a scoping review was therefore considered the most appropriate strategy to capture the diversity and complexity of available evidence.

As the included studies comprised a mix of designs (i.e., cross-sectional, longitudinal, or mixed methods), findings were summarised according to study design category to enhance clarity and readability. To promote transparency and facilitate the identification of emerging patterns, the reported findings include information on the strength of associations and predictive relationships where available. However, the purpose of reporting these characteristics was not to formally assess the methodological quality of individual studies, but rather to systematically describe the available evidence in this field. This approach aimed to provide a clearer overview of prevailing trends in the current literature and support identification of critical gaps that can be addressed in future research.

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