Outrunning a bad diet: interactions between exercise and a Western-style diet for adolescent mental health, metabolism and microbes

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Abstract

Adolescence is a period of biological, psychological and social changes, and the peak time for the emergence of mental health problems. During this life stage, brain plasticity including hippocampal neurogenesis is increased, which is crucial for cognitive functions and regulation of emotional responses. The hippocampus is especially susceptible to environmental and lifestyle influences, mediated by changes in physiological systems, resulting in enhanced brain plasticity but also an elevated risk for developing mental health problems. Indeed, adolescence is accompanied by increased activation of the maturing hypothalamic-pituitary-adrenal axis, sensitivity to metabolic changes due to increased nutritional needs and hormonal changes, and gut microbiota maturation. Importantly, dietary habits and levels of physical activity significantly impact these systems.

In this review, the interactions between exercise and Western-style diets, which are high in fat and sugar, on adolescent stress susceptibility, metabolism and the gut microbiota are explored. We provide an overview of current knowledge on implications of these interactions for hippocampal

function and adolescent mental health, and speculate on potential mechanisms which require further investigation.

Keywords: Western diet, Exercise, Adolescence, Behaviour, Mental health, Stress, Metabolism, Gut microbiota

1. Introduction

Adolescence is a period of the lifespan between childhood and adulthood during which changes in physiological, sexual and neurological processes occur that are essential for long-term health (Best and Ban, 2021). Social, cultural and biological evidence now indicate that adolescence in humans extends from age 10 (with the onset of puberty) to age 24 (with the onset of adulthood) (Sawyer et al., 2018), while in rodents, the adolescent timespan extends between post-natal day (PND)21 and approximately PND60 (Spear, 2000). During adolescence, the brain undergoes significant restructuring (Giedd et al., 1999) which shapes and controls executive function (Li et al., 2022) and social cognitive processes (Andrews et al., 2021), essential for life-long brain function (Sawyer et al., 2012). These changes are associated with maturation of the prefrontal cortex (Calabro et al., 2020), amygdala (Zimmermann et al., 2019) and hippocampus (Zhou et al., 2022). A major component of brain changes during adolescence is heightened brain plasticity, particularly in the hippocampus, where new neurons are generated at a higher rate than in adulthood, in a process called hippocampal neurogenesis (Kozareva et al., 2019; Moreno-Jiménez et al., 2019). Preclinical studies have shown that hippocampal neurogenesis is necessary for cognitive functions with a high cognitive load such as pattern separation (Zhao et al., 2008), as well as for antidepressant action (David et al., 2009). Importantly, the neurogenic niche of the hippocampus is extremely responsive to positive stimulation by environmental and lifestyle factors such as mental activity, exercise and diet (Hueston et al., 2017).

While the heightened level of brain plasticity during adolescence facilitates enhanced learning and adaptation to new environments, the extensive brain changes can also leave the adolescent brain susceptible to developing mental disorders, which can be provoked by negative influences such as stress, social anxiety, a sedentary lifestyle or poor diet (Reichelt and Rank, 2017; Rodriguez-Ayllon et al., 2019; Romeo, 2013). A recent report by the Global Burden of Disease Study noted that mental disorders are among the top ten leading causes of burden worldwide, and there has been no reduction in the burden since 1990 (GBD 2019 Mental Disorders Collaborators, 2022). Drastic sociocultural shifts

(e.g. appearance norms, school environment, first access to social media) and changes to lifestyle (e.g. lack of physical activity in school, ability to purchase own food) that occur from early adolescence (Aceves-Martins et al., 2022; Kierans and Swords, 2016; Rounsefell et al., 2020), combined with individual genetic susceptibility likely contribute to the rise in the incidence of mental health disorders in adolescence (Baselmans et al., 2018).

Negative factors which contribute to mental health vulnerabilities in adolescence include childhood experiences, trauma, financial burden, social media and academic or career stress. In addition, adolescents show an increase in risk-taking and impulsivity behaviours compared to adults (Pavković et al., 2020; Reniers et al., 2016). More recently, research on dietary habits has highlighted a Western-style diet as an environmental stressor for adolescent mental health (Nicolas et al., 2020).

In developed countries in particular, overconsumption of a Western diet, a term used to describe the typical pattern of nutrition in Western societies characterised by ultra-processed foods rich in saturated fat and sugar ready for immediate consumption is becoming a major health problem (Gramza-Michałowska, 2020). In fact, the consumption of these ultra-processed foods has drastically increased worldwide due to their low cost, convenience, shelf stability, ease of consumption and high palatability, which has led to an increase in the prevalence of obesity and metabolic disturbances, as well as cognitive and emotional disorders (Kanoski and Davidson, 2011). Due to the high metabolic requirements of the brain, its function is strongly linked to peripheral metabolism, meaning that any metabolic malfunction can eventually lead to disruption of brain activity and reduced neuronal plasticity (Soch and Spencer, 2020). For example, metabolic dysfunctions such as type 2 diabetes have been associated with a Western dietary pattern (Schulze et al., 2005), and are often linked to cognitive and emotional issues (Marissal-Arvy and Moisan, 2022). Considering the heightened plasticity of the adolescent brain and its importance in brain development, any factors that perturb brain processes during adolescence could have negative outcomes.

Humans have complex food choices that are influenced by various factors such as environmental cues, cultural preferences, social attitudes, socioeconomic status, sex and genetics (Allafi et al., 2014; Chen and Antonelli, 2020; Grimm and Steinle, 2011; Manippa et al., 2017). Modelling a Western-style diet in rodents is typically done by feeding them a high-fat, or high-fat and high-sugar (cafeteria) diet. For example, a high-fat diet (HFD) consists of a diet that is high in saturated fats, such as butter or lard, and low in carbohydrates (Stott and Marino, 2020). A high-fat high-sugar (HFHS) diet provides sugar water in addition to food high in saturated fat (Moreno-Fernández et al., 2018). A cafeteria (CAF) diet mimics the diverse food choices and lack of healthy options found in a typical cafeteria setting, such as in a school or office building. A CAF diet consists of a variety of foods that are high in saturated fats, refined sugars, and processed foods, provided in addition to standard chow (Lalanza and Snoeren, 2021). Research in rodents using these diet types is essential to understand the mechanisms underlying diet-induced metabolic and neuropsychiatric disease which emerge during adolescence, and will be explored in this review article. It is well established that poor dietary habits are a potentially modifiable risk factor for mental disorders (Dash et al., 2016), as is a sedentary lifestyle (Huang et al., 2020). Unfortunately, increased use of electronic devices has led to an increase in sedentary lifestyle habits (Booth et al., 2012) and has been linked with increased BMI in adolescence (Shen et al., 2021), despite a plethora of evidence highlighting the beneficial effect of exercise on brain (Hillman et al., 2008) and metabolic functions (Seaborne and Sharples, 2020).

A growing body of evidence points to the fact that exercise has beneficial effects for brain health (Monda et al., 2017). In 2020, the World Health Organization (WHO) released global guidelines on physical activity for children and adolescents (Chaput et al., 2020) after gathering evidence that higher levels of physical activity as well as different types of exercise (aerobic or strengthening activities) are correlated with improved health outcomes (World Health Organisation, 2020). In humans, exercise has been shown to change the activity of several metabolic pathways (*e.g. glycolysis, lipolysis, amino-acid catabolism, oxidative stress*) (Lewis et al., 2010); more than 200 serum metabolites were

significatively changed by exercise (Nieman et al., 2013). For example, a study carried out in young female athletes (15-18 years) showed that one month of exercise was able to reduce the blood level of total cholesterol and increased the beneficial high-density lipoprotein (HDL) cholesterol (Hanai et al., 1999). Interestingly, humans and rats present the same metabolic signature in plasma after exercise (Goutianos et al., 2015), which makes rodents a good translational tool for studying the physiological response to exercise.

Diet and exercise are potent modulators of the composition and function of the gut microbiota and accumulating research supports the role of the gut microbiota in regulating the effects of diet and exercise on brain health (Donoso et al., 2022; Gubert et al., 2020). High-fat and high-sugar diets have been associated with an altered gut microbiota (Agus et al., 2016), while physical exercise has been shown to promote the growth of beneficial microbial species and enrich the diversity of gut microbiota (Monda et al., 2017). The gut microbiota influences brain function through the production of various gut microbial metabolites, such as short-chain fatty acids (SCFAs) and neurotransmitters (Parker et al., 2020). Interestingly, there is emerging evidence that changes in the gut microbiota may increase the risk or severity of depression and other psychiatric disorders in adolescents experiencing stress (Soltysova et al., 2022). While it is currently underexplored how the combination of a Western diet and lack of exercise might increase metabolic dysregulation and promote an unhealthy composition of gut microbiota, which may subsequently provoke mental health disorders, the evidence confirms that the independent impact of these lifestyle factors adversely affect mental health (Martínez Leo and Segura Campos, 2020; O'Neil et al., 2014). Indeed, a recent study in male and female Brazilian adolescents has indicated an association between processed food consumption and symptoms of poor mental health (Mesas et al., 2022).

Understanding the interactions between diet and exercise on metabolic health, gut microbiota composition, stress susceptibility and mental health in adolescence may guide research on the potential for lifestyle factor-based intervention to improve mental health. Focussing on preclinical

128 studies, we discuss the role of stress and lifestyle factors on mental health in adolescence. We examine
129 current evidence providing insight into the metabolic changes that occur during adolescence in
130 response to diet and exercise that may underlie mental health problems. Finally, we explore how the
131 gut microbiota and related metabolites are affected by these lifestyle factors, and their potential
132 impact on adolescent mental health (Figure 1).

2. Adolescent mental health

2.1 Mental health disorders and stress susceptibility in adolescence

Approximately 14% of adolescents suffer from mental health illness, with mood and behavioural disorders observed most frequently (World Health Organisation, 2021). Depending on age, anxiety disorders occur in 3.6-4.6% of 10-19 year-olds, while depression is prevalent in 1.1-2.8% (World Health Organisation, 2021). In addition, 2.4-3.6% of adolescents experience behavioural disorders such as attention deficit hyperactivity disorder (ADHD) and conduct disorder (World Health Organisation, 2021). Other mental health conditions that typically develop during adolescence include eating disorders and psychosis. Mental health disorders heavily impact academic performance and can lead to risk-taking, substance-seeking and criminal behaviours, further exacerbating mental health problems. In severe cases, mood disorders can lead to suicide, which is one of the leading causes of death among 15-19 year-olds (World Health Organisation, 2021). Importantly, first onset of mental health disorders predominantly occurs in adolescence, highlighting the need for early intervention (Kessler et al., 2005). Furthermore, there are sex differences in the prevalence of specific mental health disorders; for example, women are more likely to suffer from depression than men, a difference which first emerges during adolescence (Blakemore, 2019). Conversely, adolescent boys are much more likely to be diagnosed with ADHD than adolescent girls (Ramtekkar et al., 2010).

The cause of these disorders is not yet fully understood, but susceptibility to stress is an important risk factor for the development of mental health disorders. Indeed, the adolescent period is typically associated with a variety of chronic stressors including bullying, academic pressure and socioeconomic adversity (World Health Organisation, 2021). The stress response is regulated by a complex neuroendocrine system, the hypothalamic-pituitary-adrenal (HPA) axis (Joseph and Whirledge, 2017). Exposure to stress causes activation of the HPA axis, which leads to the release of the glucocorticoid cortisol in humans or corticosterone in rodents (Hueston et al., 2017; Raff, 2016). In humans, elevated

concentrations of cortisol are associated with a variety of mental health disorders, such as depression, bipolar disorder and psychosis (Dziurkowska and Wesolowski, 2021).

Maturation of the HPA axis takes place during adolescence, which is associated with high activation and expression of the hippocampal glucocorticoid receptor (GR), therefore making adolescents more sensitive to the stressors they experience and thus more vulnerable to the development of mental health disorders (Pryce, 2008; Roberts and Lopez-Duran, 2019; Romeo, 2013). Indeed, dysregulation of the HPA axis has been associated with depression, anxiety and schizophrenia in adolescents (Clemens et al., 2020; Guerry and Hastings, 2011; Mittal et al., 2007).

Animal studies have demonstrated that dysfunction of the HPA axis impacts hippocampal function. Sustained elevation of corticosterone, through injection or surgical implantation of corticosterone-releasing pellets, has been shown to cause hippocampal neuronal atrophy (Watanabe et al., 1992), and decreased neurogenesis in the hippocampus of adult rats (Brummelte and Galea, 2010; Diniz et al., 2013). Conversely, adrenalectomy-induced low concentrations of corticosterone in middle-aged and old rats improved hippocampal proliferation, cell survival and cognitive performance (Montaron et al., 2006). Hippocampal neurogenesis is necessary for pattern separation and cognitive flexibility (Kempermann, 2022); impairments in these behaviours may contribute to aspects of adolescent mental health disorders including depression, anxiety, bipolar disorder and autism (Bernstein and McNally, 2018; Dickstein et al., 2016; Hollocks et al., 2022). Importantly, hippocampal neurogenesis, especially in the ventral region of the hippocampus, plays an important role in stress susceptibility (Levone et al., 2015). Research in mice has shown that inhibition of ventral hippocampal neurogenesis increases susceptibility to stress (Anacker et al., 2018), and it has been suggested that disruptions to the ventral hippocampus contribute to development of mental health disorders (Gomes-Leal, 2021). In addition, chronic stress has been shown to cause hippocampal GR downregulation in male, and upregulation in female adult rats (Kitraki et al., 2004). Importantly, adequate GR expression is crucial for antidepressants to enact neurogenic effects, and provide a potential mechanism underlying

improvements in mental health (Anacker et al., 2011). The evidence for this mostly comes from studies in adult animals, with not much known about the process in the adolescent brain, even though the HPA axis undergoes maturation during this time. However, research suggests that lifestyle factors such as diet and exercise alter the susceptibility to stress in adolescents and young adults, which may negatively impact upon hippocampal neurogenesis and other cellular processes underlying mental health function (Herbert et al., 2020; Kalyan-Masih et al., 2016).

2.2 Changes in HPA axis activation in response to exercise and Western-style diets

Adolescent-initiated Western-style diets have been shown to increase adolescent and adult corticosterone concentrations in rodents (Boitard et al., 2015; Boukouvalas et al., 2008; Harrell et al., 2018, 2015) while it has been shown that long-term exercise can reverse negative effects of physiological stressors on corticosterone concentration (Rahimi et al., 2020), even though acutely, higher-intensity exercise increases corticosterone (Budde et al., 2015). While some evidence in adolescent rodents suggests that exercise can prevent high-fat diet-induced alterations in corticosterone, to date there is no clear consensus on this. In a recent study, male adolescent mice were fed a HFHS diet for 12 weeks, with or without treadmill exercise intervention. Faecal corticosterone was increased by HFHS compared to standard chow, which was prevented by treadmill exercise (Aubin et al., 2022). Furthermore, adult-initiated HFD blunted an acute exercise challenge-induced (i.e. trained to exhaustion) increase in corticosterone, which was prevented by chronic treadmill exercise initiated during adolescence (Huston et al., 1975). Specifically, while corticosterone was decreased in sedentary HFD-fed animals after the exercise challenge, compared to standard chow-fed controls, it was increased in exercised HFD-fed animals, likely indicating an interaction between diet and exercise (Huston et al., 1975). In support, a study in humans reported that a yearlong weight loss intervention with healthy diet and exercise reduced baseline cortisol concentrations in

overweight/obese children and adolescents (Karampatsou et al., 2021), although it cannot be determined whether this change is driven by diet or exercise.

In contrast however, some studies do not report a rescuing effect of exercise on corticosterone concentrations. For example, in male adolescent mice, 12 weeks of a HFD increased plasma corticosterone concentrations, compared to standard chow, but treadmill exercise concurrent with HFD did not mitigate this increase (Dassonvalle et al., 2020). Similarly, three weeks of voluntary exercise during adolescence decreased adult circulating corticosterone in standard chow-fed, but not Western diet-fed male mice. However, anxiety-like behaviour was reduced by exercise regardless of diet (Table 1) (Cadney et al., 2021). Still, others report no effects of either HFD or swimming exercise, with intervention durations of 1-2 months, on corticosterone concentrations in adolescent rats (Kibenge and Chan, 2002; Perše et al., 2012).

Evidently, there is no clear pattern of diet-exercise interactions on glucocorticoid concentrations emerging from the available literature. While the length of intervention and type of diet or exercise may certainly play a role, the time at which corticosterone, which fluctuates naturally throughout the day, was measured may also influence the results that have been reported (Gibson and Krieger, 1981). Corticosterone is often only measured once at the end of a rodent experiment, and the time of sampling is usually not reported, making it difficult to compare between studies. Additionally, the timing of sampling after cessation of exercise is important as corticosterone can initially increase after exercise, even though it may be subsequently reduced (Wang et al., 2021). It would be informative for future studies to include the effects of diet and exercise on the corticosterone response to a stressor (e.g. forced swim) as a measure of HPA axis response to stress (Solich et al., 2008). This approach has not been investigated to any great extent in adolescence. However, one study in male rats showed that adult baseline elevations of corticosterone concentrations, due to prolonged maternal separation stress, were not observed in animals that had undergone either a CAF diet or voluntary exercise intervention during adolescence. In addition, a maternal separation stress-induced decrease in adult

antidepressant-like behaviour and increase in adult anxiety-like behaviours was rescued by both interventions independently and in combination (Table 1), thus suggesting that a CAF diet and/or exercise in adolescence can reverse the deleterious effects of maternal separation stress on HPA axis function and behaviour in adulthood (Maniam and Morris, 2010).

Glucocorticoid receptor (GR) expression mediates the effects of altered corticosterone concentrations both peripherally and centrally. However, little research has been done investigating diet-exercise interactions on GR expression in adolescence. In male rats, a 6-week intervention of either HFD or exercise started during adolescence reversed a maternal separation-induced decrease in adult hippocampal GR expression (Maniam and Morris, 2010). However, when administered in combination, HFD and exercise did not provide this benefit (Maniam and Morris, 2010). On the other hand, two recent studies demonstrated that a 12-week HFHS or HFD intervention in adolescent male mice increased hepatic GR expression and hepatic GR hypersensitivity, which play a role in metabolic syndrome; this was mitigated by concurrent treadmill exercise (Aubin et al., 2022; Bose et al., 2016; Dassonvalle et al., 2020). Additionally, an 11-week HFHS intervention in male adult mice decreased epididymal white adipose tissue GR expression, which was prevented by adolescence-initiated exercise (Eller et al., 2020). Similarly, in adolescent male hamsters fed a high-fructose diet, exercise increased GR expression in perirenal adipose tissue (Campbell et al., 2009). Importantly, GR expression in adipose tissue plays a role in adequate functioning of negative feedback in the HPA axis, thereby contributing to stress resilience (de Kloet et al., 2015). Overall, evidence indicates that in rodents, adolescent-initiated exercise can mitigate the negative effects of adolescent Western-style diets on peripheral GR expression later in adulthood, and therefore has the potential to alleviate some aspects of HPA axis dysfunction.

It is important to note that the studies described above were performed in male animals, with the exception of one where sex was unspecified. While there have been some studies investigating sex-effects in the context of Western diet (e.g. Underwood and Thompson, 2016), the literature regarding

sex differences in diet-exercise interactions on corticosterone concentrations and GR expression is lacking. This is surprising, given sex differences in the prevalence of stress related psychiatric disorders and that research has indicated that circulating corticosterone concentrations are elevated in adult females compared to males, both at baseline and following a stressor, while GR expression is lower (Bangasser, 2013; de Romero et al., 2013; Kitay, 1961).

3. Changes in metabolism during adolescence in the context of mental health disorders

3.1 Metabolic syndrome during adolescence

Metabolic syndrome (MetS) is an important risk factor for cardiovascular disorders and type 2 diabetes; it is characterized by visceral adiposity, hypertension, glucose intolerance, dyslipidaemia and decreased HDL cholesterol (Al-Hamad and Raman, 2017). A variety of factors contribute to the development of MetS, including poor dietary habits and sedentary behaviour (Al-Hamad and Raman, 2017). Its exact prevalence is unclear; however, it is estimated that depending on the country, between 3.9-7.0% of adolescents suffer from MetS (Noubiap et al., 2022). Indeed, adolescence is a critical time window sensitive to metabolic stress due to several factors. Accelerated growth and physical maturation during adolescence is associated with an increase in energy intake and requires adequate nutrition. As food intake increases to meet these requirements, sedentary adolescents become more likely to develop obesity, a common MetS component (Das et al., 2017). In addition, hormonal imbalances like polycystic ovarian syndrome, which may first develop in females during adolescence, pose a risk for MetS (Al-Hamad and Raman, 2017). Approximately 6-18% of adolescent girls suffer from polycystic ovarian syndrome (Peña et al., 2020).

Importantly, MetS is associated with decreased cognitive performance (for a review on this topic, see Yates et al., 2012) as well as mental health disorders such as depression, anxiety and personality disorders (Penninx and Lange, 2018). In adolescents and young adults diagnosed with bipolar disorder, MetS was shown to be twice as common as in the average population, especially associating with depressive symptomatology (Li et al., 2019). Furthermore, it has been demonstrated in humans that adolescent MetS correlates with decreased cognitive function and reduced hippocampal volume, a key hallmark of mental health disorders (Peyton et al., 2021; Yau et al., 2012).

A primary component of MetS is insulin resistance, which leads to elevated glucose and eventually type 2 diabetes (Al-Hamad and Raman, 2017). In a healthy state, insulin regulates blood glucose concentrations and facilitates release of growth hormones. However, increased secretion of insulin

due to extended overconsumption of energy may cause cellular resistance to insulin (Wilcox, 2005). Interestingly, while insulin plays a key role in brain development and can stimulate neurogenesis, prolonged increase of insulin may negatively impact on neuronal stem cells (Spinelli et al., 2019). Furthermore, insulin resistance in rodents has been associated with decreased performance in behavioural tests associated with hippocampal neurogenesis, such as novel object recognition, and spatial memory in the Morris Water Maze and Y-maze (Spinelli et al., 2019). Similarly, in human adolescents it has been shown that insulin resistance correlated with diminished hippocampal volume, as well as an increase in depressive symptoms (Singh et al., 2019).

3.2 Changes to metabolism in response to exercise and Western diet

Glucose & insulin tolerance

The negative impacts of a high-fat diet on glucose and insulin tolerance are well-established (Small et al., 2018). In adolescent rats, a HFHS diet induces hyperinsulinemia and insulin resistance (Marwitz et al., 2015). These metabolic alterations are correlated with a reduction in hippocampal neurogenesis and increased neuroinflammation in rodents, and lead to behavioural impairments in hippocampus-dependent processes (Molteni et al., 2002). For example, adolescent rats fed a diet supplemented with sugar exhibit a diminished capacity for hippocampal neurogenesis-associated pattern separation and hippocampal-dependent place recognition memory (Reichelt et al., 2016).

On the other hand, research has indicated beneficial effects of exercise on insulin sensitivity and glucose tolerance (Borghouts and Keizer, 2000). However, there are limited studies investigating the effects of these lifestyle factors in combination, in the context of adolescence. For example, a 10-week intervention with moderate treadmill exercise in adolescent male rats showed attenuation of a HFD-induced increase in fasting plasma insulin and insulin resistance (Gomes et al., 2013). Similar effects of swimming exercise (8 weeks) on insulin resistance were observed in HFD-fed adolescent mice (Qi et al., 2020). Moreover, in male rats, 12 weeks of treadmill exercise during adulthood rescued the

311 negative effects of adolescent-initiated HFD on glucose tolerance and insulin resistance (Machado et
312 al., 2014). In genetically obese (BFMI860) adolescent mice, a significant interaction between HFD and
313 voluntary running exercise on fasting insulin concentrations has been shown; both adolescent and
314 adult-initiated exercise reduced adolescent HFD-induced increases in insulin, and reduced insulin
315 concentrations in standard-chow fed genetically obese animals (Wagener et al., 2012). Furthermore,
316 the intensity of exercise may be important for its beneficial effects on insulin resistance and glucose
317 tolerance. For example, in male adolescent mice fed a HFD, high intensity interval training (HIIT) more
318 potently reduced fasting insulin and glucose, as well as insulin resistance, than endurance exercise
319 (Wang et al., 2017).

320 Conversely, in male adolescent rats, exercise has been shown to reduce glucose in lean, but not
321 genetically obese animals (Kibenge and Chan, 2002). Furthermore, in male mice, the negative effects
322 of a 19-week HFD intervention started during adolescence on fasting glucose and glucose tolerance
323 could not be reversed by a subsequent 13-week voluntary running exercise intervention with
324 continued HFD access (Griffin et al., 2020). It is possible that ceasing intake of a HFD is important for
325 the beneficial effects of exercise, which has been investigated by Palmer *et al*. However, in their study,
326 4 weeks of exercise during adulthood reduced fasting glucose in male mice fed a HFD from
327 adolescence, which was not aided by cessation of a HFD (Palmer et al., 2012).

328 Little is known about the effects of Western diet and exercise on glucose tolerance and insulin
329 resistance in adolescent females. However, unlike investigation of these metabolic factors in males,
330 research in females has included behavioural testing, thus providing better insight into the
331 relationship between metabolism and mental health. A 2016 study in female rats indicated that while
332 adolescent CAF diet increased adult plasma glucose and insulin as well as insulin resistance, neither
333 low nor high-intensity treadmill exercise could rescue these effects (Cigarroa et al., 2016).
334 Nevertheless, adolescent treadmill exercise partially restored CAF-induced adult impairments in two-
335 way active avoidance learning, which is a measure of stress-coping behaviour (Table 1) (Cigarroa et

al., 2016). In early adulthood, 6 weeks of voluntary running exercise improved fasting insulin in HFD-fed male but not female rats. While insulin tolerance was more robustly improved by exercise in males than in females, exercise improved hippocampal-dependent learning behaviour in the Barnes Maze in both sexes (Table 1) (Yang et al., 2020), suggesting that at least in females, this behaviour may be affected by other peripheral alterations. It is not yet clear what might cause these sex differences, highlighting the need for inclusion of females in the investigation of this topic, particularly during adolescence.

Other metabolic factors involved in glucose and insulin tolerance include FGF21, IGF1, C-peptide and irisin, all of which have been associated with (symptoms of) mental health disorders such as depression and schizophrenia (Mason et al., 2022; Okamoto et al., 2021; Sousa et al., 2021; Wang et al., 2021). *In vitro* as well as *in vivo* rodent studies have shown that FGF-21, IGF1 and irisin increase hippocampal neurogenesis (Nieto-Estévez et al., 2016; Qi et al., 2022; Wang et al., 2018). Moreover, in stressed adult male but not female mice, a hippocampal injection of irisin improved anxiety-like behaviour and novel object recognition memory (Farshbaf et al., 2020). One week of daily subcutaneous IGF1 injections in new-born rats similarly reduced anxiety-like behaviour (Baldini et al., 2013). In addition, 3 weeks of daily subcutaneous FGF21 injections in adolescent mice has been shown to rescue HFD-induced cognitive impairment and anxiety-like behaviour (Wang et al., 2018). Despite their importance for mental health, only a few studies have investigated these metabolic factors in adolescence within the context of diet-exercise interactions. For example, in overweight children and adolescents, diet and exercise for weight loss increased blood concentrations of IGF1 while decreasing irisin in the blood, but it is unclear whether this was caused by diet or exercise. Blood FGF-21 concentrations were unaffected by the intervention (Karampatsou et al., 2021). However, research has shown that exercise increased serum concentrations of irisin in adolescent humans, and indeed irisin was negatively associated with poor metabolic health (Morelli et al., 2020). Surprisingly, adolescent-initiated HFD increased, rather than decreased, serum concentrations of IGF1 in male mice, regardless of exercise (Griffin et al., 2020).

Although most studies did not include behavioural measures, the current literature suggests that at least in male adolescent rodents, exercise improves both glucose and insulin measures in HFD-fed but not standard chow-fed animals, indicating that exercise can rescue the negative effects of a HFD diet but does not provide additional benefits in the presence of a normal diet. Considering the adverse mental health effects of insulin resistance and glucose intolerance, these findings indicate that in rodents, exercise is likely to alleviate Western-style diet-induced markers of MetS, thereby possibly improving adolescent mental health. However, it is important to consider that these findings may not be directly translatable to humans. For example, in young adults, a two-week dietary intervention high in saturated fat did not alter insulin resistance or glucose tolerance, and was not affected by exercise (Ortega et al., 2013), although the intervention was shorter than typically used in rodent studies. While dietary interventions are more easily applied in animal models, outcomes should be confirmed in human studies. Moreover, additional factors contributing to healthy metabolism such as FGF21, IGF1, C-peptide and irisin should be further investigated in the context of diet and exercise.

Hormones regulating appetite

Leptin and adiponectin play important roles in the regulation of food intake and energy homeostasis; while increased concentrations of leptin lead to inhibition of food consumption, an increase in adiponectin has the opposite effect (Laursen et al., 2017). Indeed, the ratio of leptin to adiponectin (LAR) is a valuable marker of MetS (Suárez-García et al., 2017). Alterations in these hormones as well as the LAR have been associated with mental health disorders such as depression and schizophrenia (Wędrychowicz, 2014; Xu et al., 2018; Zeman et al., 2009; Zou et al., 2019). Research in adult male rats has shown that leptin has antidepressant-like behavioural effects when infused directly into the hippocampus (Lu et al., 2006). Furthermore, it is interesting to note that increased systemic concentrations of leptin following intraperitoneal injection have been shown to stimulate hippocampal neurogenesis adult mice (Garza et al., 2008), although plasma leptin concentrations are not necessarily correlated with hippocampal leptin. For example, in adult mice, exercise has been

388 shown to increase hippocampal, but not plasma leptin concentrations (Yook et al., 2019). Moreover,
389 chronic systemic elevation of leptin due to obesity can lead to leptin resistance, potentially causing
390 decreased leptin penetration of the blood-brain barrier, which has been observed in both rodents and
391 humans (Gruzdeva et al., 2019; Izquierdo et al., 2019). Similarly, in adult male adiponectin knockout
392 mouse models, adiponectin deficiency has been shown to reduce hippocampal neurogenesis, and it
393 has been demonstrated that adiponectin is necessary for exercise-mediated benefits on hippocampal
394 neurogenesis (Yau et al., 2018; Zhang et al., 2016). Moreover, intravenous administration of
395 adiponectin in adolescent male mice increases antidepressant-like behaviour (Nicolas et al., 2015).
396 Treadmill exercise during adulthood decreased circulating leptin in male rats fed a HFD from
397 adolescence (Lambert et al., 2018). Similarly, adolescent-initiated exercise greatly reduced serum
398 leptin concentrations in male mice fed a modern Japanese diet (i.e. high in fat, and low in fermented
399 foods) (Asano et al., 2019). Conversely, Griffin *et al.* demonstrated that while a HFD increased serum
400 leptin in adolescent male mice, this was not reversed by 12 weeks of voluntary exercise (Griffin et al.,
401 2020). In female adolescent rats, the LAR was increased by a CAF diet, and was reduced by high but
402 not low intensity running exercise (Suárez-García et al., 2017), suggesting that intensity of exercise
403 may be important for metabolic benefits. Equally, in female rats, adolescent CAF diet increased adult
404 plasma leptin concentrations, which was decreased by concurrent high-intensity but not low-intensity
405 treadmill exercise (Cigarroa et al., 2016). However, both low and high intensities of treadmill exercise
406 partially restored CAF-induced impairments in adult two-way active avoidance learning, a measure of
407 stress-coping behaviour (Table 1) (Cigarroa et al., 2016). In adult mice, exercise has been shown to
408 prevent a CAF diet-induced decrease in serum adiponectin concentrations (Higa et al., 2014), but thus
409 far there is not much indication of effects of lifestyle factors on adiponectin in adolescence (Asano et
410 al., 2019; Griffin et al., 2020; Liu et al., 2015). However, one study has indicated that a HIIT intervention
411 in adolescent male mice fed a HFD increased serum adiponectin, compared to HFD-fed animals
412 exposed to moderate-intensity exercise (Wang et al., 2017). Serum adiponectin was similarly

413 increased by a weight loss intervention using healthy diet and exercise, in overweight children and
414 adolescents (Karampatsou et al., 2021).

4. Changes in gut microbiota and microbial metabolites during adolescence in the context of mental health disorders

The gut microbiota, i.e. the microorganisms populating the gastrointestinal tract, has been shown to play a role in mental health (Donoso et al., 2022). During adolescence, the gut microbiota diversifies and sees a shift in overall composition (Ronan et al., 2021). Indeed, gut microbiota alterations during adolescence are associated with mental health and neurodevelopmental disorders such as autism (Vuong and Hsiao, 2017) and depression (Wingfield et al., 2021). Moreover, gut dysbiosis, which is an imbalance in the gut microbiota, has been associated with the development of neurological disorders such as Alzheimer's and Parkinson's disease later in life (Yahfoufi et al., 2020). Changes in the gut microbiota can affect the brain through several routes, which have been extensively reviewed elsewhere, most notably by Cryan et al., 2019. Specifically, these mechanisms include communication through the vagus nerve (Fülling et al., 2019), activation of the immune system (Rutsch et al., 2020), modulation of neurotransmitters (Strandwitz, 2018) and hormones (de Weerth, 2017), and secretion of microbial metabolites (Krautkramer et al., 2021) into the systemic circulation. Notably, microbial metabolites are small compounds produced by microorganisms during their metabolism, which play a crucial role in maintaining host organism homeostasis (Krautkramer et al., 2021). An imbalanced gut microbiota can lead to alterations in the production of some of these microbial metabolites, which could contribute to the development of mental health disorders such as depression (Capuco et al., 2020). For example, dysbiosis can lead to a decrease in the production of beneficial microbial metabolites such as short-chain fatty acids (SCFAs), particularly acetate, butyrate and propionate (for review, see O'Riordan et al., 2022). Because SCFA production is regulated by dietary intervention and exercise, here we focus on their potential effects on mental health disorders. While there is a growing number of publications investigating how SCFAs impacts brain health, there are limited reports on their effects on the adolescent brain, nor is there any evidence of the impact of lifestyle factors such as diet and exercise during adolescence on SCFAs. Thus, we will examine the evidence on the

regulation of SCFAs by diet and exercise during adulthood, and attempt to place it in the context of mental health during adolescence.

4.1 Changes in gut microbiota composition in response to diet during adolescence

Diet is one of the lifestyle factors that is known to have a significant influence on gut microbiota composition and function. Different types of foods can promote the expansion of specific bacterial species. Clinical research showed that a diet high in plant-based fibre promotes the growth of beneficial bacteria such as *Bifidobacteria* and *Lactobacilli* (Allen et al., 2016), while a diet high in saturated fats, such as a Western-style diet, promotes the growth of bacteria such as Bacillota (previously known as Firmicutes) which is known to be increased in obesity and inflammatory bowel disease (Stojanov et al., 2020). Pre-clinical studies offer the possibility of a deeper investigation of the links between diet and the gut microbiota with a focus on particular time windows. For example, adolescent female rats fed a CAF diet showed a shift in their gut microbiota composition; indeed, 27 operational taxonomic units (OTUs) were depleted and 28 OTUs were enriched in the CAF diet group when compared to the control group (Kendig et al., 2022). Similarly, an intermittent HFHS diet (2 hours access per day) in adolescent male rats affected the relative abundance of specific taxa, such as inducing increased level of bacteria from the Bacillota and Actinomycetota (previously known as Actinobacteria) phyla when compared to the control group (Reichelt et al., 2020). Importantly, the gut microbiota changes induced by poor dietary habits have long lasting effects. In male mice fed a CAF diet during adolescence (P28-P49) and then switched back to normal chow, the abundance of members of the families *Ruminococcaceae, Lachnospiraceae, Erysipelorichaceae, Coriobacteriaceae* and *Alcaligenaceae* were changed when compared to standard chow-fed animals at P90 (Fülling et al., 2020). A similar experiment in female rats fed a CAF diet between P26-P66 and then switched back to normal chow reported changes in microbiota composition at P106 (Tsan et al., 2022). Interestingly, in some of these studies, the gut microbiota composition change was concomitant with behavioural

impairment. Intermittent HFHS diet impaired social behaviours (social novelty), and object recognition memory in adolescent male rats (Reichelt et al., 2020). The female rats fed a CAF diet only during the adolescent period presented with decreased episodic memory 6 weeks after the switch back to standard chow (Tsan et al., 2022). These data suggest that the adolescence period is critical for diet-induced changes in gut microbiota composition, and poor dietary habits can have long lasting effect on social and cognitive functions in rodents. While there is limited evidence on the regulation of SCFAs by diet during adolescence, it has been shown in adult humans that the consumption of a balanced diet (Mediterranean diet) leads to an increased faecal SCFA concentration (De Filippis et al., 2016). In adult male rats, HFD administration decreased caecal levels of SCFAs (Sulistyowati et al., 2022) and supplementing a HFD diet with butyrate could restore HFD-induced spatial memory impairment observed in the Morris water maze in adult male mice (Arnoldussen et al., 2017), thus suggesting that SCFA levels are dependent on diet and that they may have a protective effect against diet-induced cognitive impairment at least in adulthood.

4.2 Changes in gut microbiota composition in response to exercise during adolescence

Regular exercise has been shown to positively impact the gut microbiota. Exercise has been found to increase the diversity of the gut microbiota, which is associated with better overall health (Mitchell et al., 2019; Monda et al., 2017). One study has shown that physically active adolescents have a more diverse gut microbiota and better immune function when compared to sedentary ones (Xu et al., 2022). In young adults, low physical activity was associated with differential abundance of several microbial taxa, such as decreased *Paraprevotellaceae*, *Lachnospiraceae* and *Lachnospira,* as well as increased *Enterobacteriaceae* and *Enterobacteriales* (Whisner et al., 2018). Interestingly, a decrease in *Lachnospiraceae* and *Lachnospira*, and an increase in *Enterobacteriaceae* have been associated with depression (Andrioaie et al., 2022). In pre-clinical research, only one study has investigated the effect of adolescent exercise on gut microbial composition. Mika and colleagues showed that adolescent-

initiated (P24) exercise increased the relative abundance of Bacteroidota (previously known as Bacteroidetes) and decreased Bacillota in rats (Mika et al., 2015). To date, it is the only pre-clinical investigation of the interaction between gut microbiota and exercise in adolescence. However, from a behavioural point of view, studies in rats have shown that exercise in adolescence produces more robust effect on hippocampal neurogenesis and associated behaviour (pattern separation) than exercise initiated in adulthood (O'Leary et al., 2019), further highlighting the importance of this time window for lifestyle interventions. Exercise can also modify faecal SCFA levels. A cross-sectional study investigating gut microbiota changes in young adult rugby athletes showed that the faecal concentration of acetate, propionate, and butyrate were significantly higher in the athlete compared to the control group (Barton et al., 2018). However, it is important to note that the effect of exercise may not persist over time when the intervention is performed in adulthood. A study from Allen *et al.* reported that a 6-week exercise intervention in healthy sedentary adults increased faecal SCFA concentrations, but these changes were not observable after a washout period of 6 weeks (Allen et al., 2018).

4.3 Changes in gut microbiota composition in response to diet and exercise during adolescence

It is important to note here that while the effects of diet and exercise on the microbiota-gut-brain axis have been characterised individually, there is little to be found in the current literature regarding the interactions between diet and exercise on the gut microbiota in adolescence. In male and female adolescent mice, exercise has been shown to rescue a HFD-induced decrease in microbial community richness (Ortega-Santos et al., 2020). However, a combination of HFD and exercise yields a gut microbiota that is different from controls, as indicated by beta diversity (Evans et al., 2014; Lai et al., 2018; Ortega-Santos et al., 2020). For example, a study by Evans *et al*. reported that 13 weeks of HFD combined with exercise started at adolescence altered the gut microbiota compared to standard control-fed sedentary mice. In addition, they reported an interaction between HFD and exercise,

whereby the relative abundance of Actinomycetota was decreased by exercise in the standard chow-fed group, but not in the HFD group as it was already low (Evans et al., 2014). Interestingly, an increased abundance of Actinomycetota has been found in adult individuals with major depressive disorder (MDD), while a decreased abundance has been observed in individuals suffering from post-traumatic stress disorder (Halverson and Alagiakrishnan, 2020). On the other hand, it has been suggested that the beneficial effects of exercise may be lost when an unhealthy diet is consumed; an 8-week exercise intervention in adolescent male mice fed a HFD did not revert their overall gut microbiota composition to one similar to controls. Furthermore, the study showed that exercise yielded a much larger increase of the genus *Vagococcus,* which may have anti-obesogenic properties, in the standard chow-fed than in the HFD-fed animals (Ribeiro et al., 2019). Indeed, these data indicate that the advantageous effects of exercise on the gut microbiota, such as increased alpha diversity and abundance of mutualistic bacteria, are only attained when the host consumes a healthy diet.

It has been reported that in male adolescent mice, exercise rescues a HFD-induced increase in Bacillota:Bacteroidota ratio (Asano et al., 2019; McCabe et al., 2019). Interestingly, a decrease, rather than increase, in Bacillota has been associated with depression in adults, suggesting that the effects of exercise on this ratio might not actually be beneficial (Huang et al., 2018). However, the meaningfulness of the Bacillota:Bacteroidota ratio as a marker of health is still in question (Magne et al., 2020). It is interesting to note that most of the studies investigating the effect of exercise use voluntary exercise, where the rodent has access to a running wheel any time of the day. The use of treadmill exercise, where exercise occurs in shorted periods at defined times and durations, may be more translatable to human physical activity. Indeed, one study showed that a long term treadmill intervention (12 m/min, 45 min/day, 5 days/week for 12 week) could rescue gut microbial diversity as well as intestinal barrier integrity in HFD-fed adolescent male mice (Wang et al., 2022). These findings imply that it is still possible for exercise to exert its effects on the gut microbiota regardless of diet.

While there have been a few studies investigating interaction between exercise and diet on gut microbiota in rodents, there is a lack of research investigating the effects of interactions between these factors on behavioural outcomes. However, there is some evidence that exercise interacts with diet to produce behavioural effects. In a study by Klein *et al.*, exercise was able to prevent the HFD-induced impairment of cognitive flexibility tested in the Morris Water Maze when the exercise intervention was initiated at the same time as a HFD in adolescent male mice (Table 1) (Klein et al., 2016). Similarly in rats, a treadmill exercise intervention could partially recover a CAF diet-induced deficit in stress-coping strategies observed in the shuttle box active avoidance paradigm in female adolescents (Table 1) (Cigarroa et al., 2016). Another study showed that the consequences of adolescent administration of a HFD on anxiety-like and stress-coping behaviour was reversed by forced treadmill exercise when introduced 8 weeks after the start of HFD administration and with maintenance of HFD during the exercise intervention. Specifically, male mice that were exercising showed decreased anxiety-like behaviour in the open field test (increased distance and time in the centre) and decreased despair-like behaviour in the forced swim test (decreased immobility time) (Liu et al., 2014). Similarly, a treadmill exercise intervention that started in adulthood, after a 13-week HFD administration initiated in adolescence, could reverse the HFD-induced deficit in spatial learning in the Morris Water Maze in male rats (Table 1) (Woo et al., 2013). Given the impact of a HFD on the gut microbiota, it is not unlikely that one of the factors responsible for these behavioural effects is the gut microbiota, although this was not assessed in these different studies. Therefore, there is a need for more studies investigating the interplay between exercise, diet, and gut microbiota on behaviour, in order to gain a more comprehensive understanding of their combined effects on mental health.

As adolescence is a period of high microbiota plasticity, it is likely that the changes that occur during this period are sufficient to establish the foundation for either a healthy or unhealthy microbiota later in life. SCFAs have been associated with many different host physiological processes including gut function (Parada Venegas et al., 2019), regulation of blood-pressure (Huart et al., 2019), and immune system regulation (Corrêa-Oliveira et al., 2016). In addition, SCFAs can cross the blood-brain barrier

and directly influence brain homeostasis (Frost et al., 2014) or microglial maturation (Erny et al., 2021). In rodents, SCFAs like butyrate, propionate, and acetate, produced by the gut microbiota, have been shown to have anti-inflammatory effects (Shippy et al., 2020) and promote hippocampal neurogenesis (Marrocco et al., 2022).

In the context of adolescence and lifestyle factors, drastic alterations in SCFA levels may have consequences for mental health. SCFAs can influence the release of metabolic hormones, such as leptin which as described earlier is associated with mental health disorders. SCFAs regulate the production of leptin, but the specific mechanisms are not well understood (Byrne et al., 2015). Some studies carried out in murine adipocytes have found that acetate and propionate increased leptin secretion (Xiong et al., 2004), while butyrate does not (Zaibi et al., 2010). SCFAs have also been reported to regulate neurotransmitters. It has been shown that butyrate induces *in vitro* expression of tyrosine hydroxylase (Shah et al., 2006), which is the limiting enzyme for catecholamine biosynthesis. While still debated, hypo- or hyperactivity of dopamine in the adolescent brain has been associated with ADHD (Nikolaus et al., 2022). In addition, butyrate and propionate have been shown to regulate both colon and serum levels of serotonin in adult mice (Yano et al., 2015). Serotonin is involved in brain network and maturation of neuronal functions (Lesch and Waider, 2012). Any modifications in dopamine and serotonin levels during adolescence due to alterations in SCFAs could therefore contribute to the development of mental health disorders, such as depression (Krishnan and Nestler, 2008). Interestingly, a study performed in young adults (~22 years old) showed that the severity of the depressive state was positively correlated with faecal acetate but negatively correlated with both butyrate and propionate levels (Müller et al., 2021).

Finally, SCFAs can modulate the immune system. In the periphery, SCFAs have been implicated in intestinal immune regulation. For example, butyrate can reduce colitis symptoms by regulating the differentiation of regulatory T cells in mice (Furusawa et al., 2013). SCFAs help to reduce systemic inflammation by maintaining intestinal barrier integrity (Wells et al., 2017), which indirectly

590 contributes to reduced neuroinflammation in the brain. SCFAs also directly influence
591 neuroinflammation by affecting microglia cell morphology and function; acetate has been shown to
592 inhibit the transformation of microglia into a pro-inflammatory phenotype (Liu et al., 2020), while
593 propionate can maintain the blood-brain-barrier and reduce its permeability (Hoyles et al., 2018).
594 Thus, robust changes in SCFA levels could lead to chronic peripheral inflammation, blood-brain barrier
595 leakage and subsequent neuroinflammation. There are very few studies investigating how
596 neuroinflammation permanently alters the adolescent brain; however, microglial cells are critically
597 involved because of their dual role in neuroinflammatory response and synaptic pruning, which is
598 essential during adolescence (Germann et al., 2021). Critically, chronic neuroinflammation can elicit
599 mental disorders such as depression and anxiety (Skaper et al., 2014).

600 Clearly, a consensus has yet to be reached on the combined effects of diet and exercise on the gut
601 microbiota and related metabolites. In particular, more research is needed to understand whether
602 these lifestyle factors interact with one another to modify the gut microbiota and metabolites during
603 adolescence. Furthermore, the current body of literature mainly describes effects of a HFD.
604 Meanwhile, interactions of exercise with a CAF diet, which more closely mimics human diet, on gut
605 microbiota in adolescence have been under-investigated. Although there is no work investigating the
606 interaction between diet, exercise and microbial metabolites, one study reports the interaction
607 between CAF diet and treadmill exercise on the serum metabolome of female adult rats. The authors
608 found that 8 weeks of treadmill exercise combined with a CAF diet could not reverse the negative
609 impact of the CAF diet on serum metabolome (Suárez-García et al., 2017). Among the metabolites
610 assessed, glycocholic acid and hydroxylated bile acid, two bile acids, were significantly decreased by
611 the diet and not rescued by exercise. Interestingly, bile acids production is regulated by the gut
612 microbiota (Cai et al., 2022). On the other hand, Ortega-Santos and colleagues found that exercise
613 rescued a HFD-induced decrease in faecal bile acids in female, but not male adolescent mice (Ortega-
614 Santos et al., 2020). Such studies highlight the need to fully understand the ways in which Western-

615 style diets may interact with exercise on the adolescent gut microbiota, and underscore the
616 importance of increasing female representation in future research.

5. Discussion

This review has provided an overview of the current knowledge on interactions between Western diet and exercise in adolescence on peripheral systems that play a role in behaviour and mental health (Figure 1). There is preclinical evidence to suggest that during this life stage, exercise can reverse the negative effects of a Western-style diet on insulin resistance, thus improving metabolic status. Similarly, exercise has repeatedly been shown to mitigate negative effects of Western-style diets on peripheral GR expression, which is important for proper HPA axis function. It is not yet clear whether this is also the case for other peripheral measures such as corticosterone and the gut microbiota, thus highlighting the need for additional research on these topics. While there is a lack of knowledge on the implications of interactions between adolescent exercise and Western-style diets on animal behaviour, it seems that exercise has a clear potential to improve adolescent mental health by partially restoring metabolic and HPA axis function.

There is outstanding research that should be addressed in future studies. First, the CAF diet is underrepresented in the existing literature; indeed, as it is more translational than HF or HFHS diets, use of the CAF diet should be expanded in the investigation of diet-exercise interactions. In addition, while the research reviewed here focuses on diet and exercise interventions initiated during adolescence, the vast majority of studies investigate outcomes during adulthood only. Consequently, the exact effects of these interventions on stress susceptibility, metabolism and the gut microbiota during the actual adolescent period are still unknown. Lastly, there is a striking shortage of female representation in the research on interactions of diet and exercise. Because of clear evidence of sex differences in hippocampal neurogenesis and related behaviours, as well as increased prevalence of depression in females and ADHD in males (Blakemore, 2019; Ramtekkar et al., 2010; Yagi and Galea, 2019), further investigation of sex differences in diet-exercise interactions on peripheral outcomes and behaviour is incredibly important.

6. Conclusion

Western-style diets have deleterious effects on stress susceptibility, metabolism, and the gut microbiota, leading to adverse mental health outcomes such as depressive/anxiety-like and poor stress-coping behaviours. At the same time, there is reasonable indication from preclinical research that exercise interventions partially restore peripheral homeostasis. Although investigation of the effects of such changes on behaviour is lacking, these findings suggest a potential for exercise to improve adolescent mental health, especially considering that exercise interventions are highly translatable to humans. While it may not be entirely possible to outrun a bad diet, the emerging evidence suggests that exercise in the context of a Western-style diet is critical for adolescent mental health, metabolites and microbes.

Declaration of Competing Interest

None

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Figure captions

Figure 1: Overview of interactions between exercise and Western-style diet in adolescent rodents, showing peripheral and hippocampal effects as well as potential consequences for behaviour and mental health. GR: glucocorticoid receptor.

Table captions

Table 1: Summary of studies investigating behavioural outcomes in the context of exercise-Western diet interactions. SC: standard chow; HFHS: high-fat/high-sugar; HFD: high-fat diet; CAF: cafeteria.