British Journal of Nutrition (2021), 126, 1771–1787 doi:10.1017/S0007114521000659

Dietary and metabolic risk of neuropsychiatric disorders: insights from animal models

Yinji Liang[1], Lili Zou[2], Yaling Tian[2], Shuang Zhou[1], Xinhe Chen[3] and Chenli Lin[2]*

[1]*School of Nursing, Jinan University, No. 601 Huangpu Avenue West, Guangzhou, Guangdong 510632, People's Republic of China*

[2]*School of Medicine, Jinan University, No. 601 Huangpu Avenue West, Guangzhou, Guangdong 510632, People's Republic of China*

[3]*School of Stomatology, Jinan University, No. 601 Huangpu Avenue West, Guangzhou, Guangdong 510632, People's Republic of China*

(Submitted 29 July 2020 – Final revision received 3 February 2021 – Accepted 15 February 2021 – First published online 23 February 2021)

Abstract

Neuropsychiatric disorders are major causes of the global burden of diseases, frequently co-occurring with multiple co-morbidities, especially obesity, type 2 diabetes mellitus, non-alcoholic fatty liver disease and its various risk factors in the metabolic syndrome. While the determining factors of neuropsychiatric disorders are complex, recent studies have shown that there is a strong link between diet, metabolic state and neuropsychiatric disorders, including anxiety and depression. There is no doubt that rodent models are of great value for preclinical research. Therefore, this article focuses on a rodent model of chronic consumption of high-fat diet (HFD), and/or the addition of a certain amount of cholesterol or sugar, meanwhile, summarising the pattern of diet that induces anxiety/depressive-like behaviour and the underlying mechanism. We highlight how dietary and metabolic risk influence neuropsychiatric behaviour in animals. Changes in dietary patterns, especially HFD, can induce anxiety- or depression-like behaviours, which may vary by diet exposure period, sex, age, species and genetic background of the animals used. Furthermore, dietary patterns significantly aggravate anxiety/depression-like behaviour in animal models of neuropsychiatric disorders. The mechanisms by which diet induces anxiety/depressive-like behaviour may involve neuroinflammation, neurotransmitters/neuromodulators, neurotrophins and the gut–brain axis. Future research should be focused on elucidating the mechanism and identifying the contribution of diet and diet-induced metabolic risk to neuropsychiatric disorders, which can form the basis for future clinical dietary intervention strategies for neuropsychiatric disorders.

Key words: **Diet: Neuropsychiatric disorders: Depression: Metabolic risk: Animal model**

Highlights

- A high-fat diet and/or the addition of a certain amount of cholesterol or sugar induces neuropsychiatric disorders in rats and mice.
- A high-fat diet and/or the addition of a certain amount of cholesterol or sugar exacerbates the neuropsychiatric disorders observed in animal models of depression.
- The mechanisms by which diet induces anxiety/depressive-like behaviour may involve neuroinflammation, neurotransmitters/neuromodulators, neurotrophins and the gut–brain axis.
- Future research should be focused on identifying the contribution of diet and diet-induced metabolic risk to neuropsychiatric disorders, which can serve as the basis for future clinical dietary intervention strategies for neuropsychiatric disorders.

The massive but largely unrecognised burdens of neuropsychiatric disorders are obvious throughout the world, while the most common neuropsychiatric disorders are anxiety and depression disorders. Globally, an estimated 4·4 % of the global population suffers from depression and 3·6 % from anxiety[1,2]. In most countries, the lifetime incidence of depression is 8–12 %[3]. Similarly, anxiety is a serious neuropsychiatric disorder that often coexists with other neuropsychiatric disorders, especially major depressive disorder[4]. In Europe, Africa, Asia and the USA, the lifetime incidence of anxiety is between 9 and 29 %[5,6].

Abbreviations: BDNF, brain-derived neurotrophic factor; cAMP, 3′,5′-cyclic AMP; CSDS, chronic social defeat stress; CUMS, chronic unpredictable mild stress; HFD, high-fat diet; 5-HT, 5-hydroxytryptamine; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

* **Corresponding author:** Chenli Lin, email igene@foxmail.com

Shockingly, suicide has been linked to neuropsychiatric disorders and is now the third leading cause of death among young people in Western countries[7]. Unfortunately, we still know very little about anxiety and depression, and a large proportion of patients are treated with drugs targeting the central nervous system that have poor therapeutic effects and serious side effects[8].

Currently, chronic metabolic diseases such as obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), atherosclerosis and the metabolic syndrome are also major health problems. In 2016, more than 1·9 billion adults were overweight and more than 650 million adults were obese, representing 39 and 13 % of the world's adult population, respectively[9]. T2DM worldwide has increased from 108 million in 1980 to 422 million in 2014[10] and is largely the result of overweight and sedentary lifestyles. In addition, NAFLD is closely related to diabetes and obesity and affects one-quarter of the world's population[11]. However, there is still a lack of effective medications for NAFLD[12]. Although genetics plays a role in regulating the metabolic responses of body weight, lipids and glucose to food intake in humans and animals, genetics cannot account for the climb in metabolic diseases worldwide in a short time, which may result from individual differences in genetic susceptibility to dietary factors. Diets rich in fat, cholesterol and/or sugar can cause a series of metabolic diseases in humans and animals[13–16].

Individual metabolic status is highly correlated with diet. Diets rich in fat not only induce metabolic disorders in humans and animals but also induce chronic metabolic diseases. Recent studies have shown that individuals with anxiety or depression frequently co-occur with multiple co-morbidities, especially obesity, T2DM, NAFLD and its various risk factors in the metabolic syndrome[17,18]. Obese individuals have a higher risk of depression and anxiety, and diet is a risk factor for the development of depression[19]. Clinically, one in four patients with T2DM has significant depression. Depression not only increases the risk of developing T2DM but also increases the risk of hyperglycaemia, insulin resistance and microvascular and macrovascular complications[20,21]. Two studies recently found that depression is independently associated with NAFLD in adults[22], and the association is stronger after adjusting for covariates such as age, sex and insulin resistance[23]. Therefore, diet is a risk factor for anxiety and depression in addition to altered metabolic status[24]. Recent studies have shown that there are clear links between diet and vulnerability to or protection from neuropsychiatric disorders, including anxiety and depression, but the mechanisms are not yet understood[25]. In fact, some patients with anxiety and depression have metabolic diseases and the therapeutic effect of drugs targeting the central nervous system is not as satisfactory[20]. Furthermore, an estimated 50 % of patients with depression is inadequately treated by available interventions. This condition can be called treatment-resistant depression, which is associated with a variety of factors, including metabolic risks of CVD and past depressive episodes[26]. At the same time, some scholars have pointed out that immune-metabolic depression is a subtype of chronic depression[27–29]. If depression is combined with the metabolic syndrome, depressive symptoms can worsen and the risk of depression recurrence increases nearly 3-fold. Thus, metabolic disorders are important risk factors for depression[28]. While the determining factors of neuropsychiatric disorders are complex, preclinical and clinical studies have shown that there is a strong link between diet, metabolic state and neuropsychiatric disorders, including anxiety and depression[30–32]. Undoubtedly, rodent models have become an important tool for understanding preclinical research on anxiety and depression[33]. With the widespread use of transgenic animals, a great deal of research has focused on transgenic animal models of neuropsychiatric disorders such as anxiety and depression[34]. Although transgenic animals have greatly aided our understanding of the interactions between genes and neuropsychiatric disorders, relatively little attention has been given to dietary risk factors in animal models[35,36]. In fact, exposure to a high-fat diet (HFD) and/or adding a certain amount of cholesterol or sugar to the diet of rats or mice induces metabolic disorders that can lead to some of the hallmark symptoms of depression, including anxiety, anhedonia and despair, and exacerbate neuropsychiatric disorders observed in animal models of depression. Diet and its associated metabolic disorders have important implications for the development of neuropsychiatric disorders in rodent models. Therefore, this article focuses on a rodent model of chronic consumption of HFD, and/or the addition of a certain amount of cholesterol or sugar, meanwhile, summarising the pattern of diet that induces anxiety/depressive-like behaviour and explores the mechanisms that have been proposed for neuropsychiatric disorders induced by dietary patterns, especially a diet rich in fat.

Behavioural assessment of animal models

Testing for anxiety-like behaviours

In an attempt to model human pathological anxiety in rodents, a wide range of behavioural testing paradigms have been developed. The social interaction test was the first ethologically based anxiety model that used natural behaviour as a dependent variable[37]. Once a social partner is present, the latency and time spent with the partner are measured and the ratio of the time spent in the zone with and without the social partner is used as an indicator of anxiety. The open field test is a common measure of exploratory behaviour and general activity in rodents, where both the quality and quantity of the activity can be measured[38]. Some outcomes, particularly defecation, centre time and activity within the first 5 min, likely gauge some aspects of emotionality, including anxiety. The elevated plus maze is a widely used behavioural assay for rodents, and it has been validated to define brain regions and mechanisms underlying anxiety-related behaviour[39]. A decrease in open arm activity (duration and/or entries) in which rodents are exposed to the plus maze for 5 min reflects anxiety behaviour. The light/dark transition test is a characteristic method used in the assessment of anxiety: the apparatus consists of a simple chamber divided into dark and light compartments. Rodents are allowed to move freely between the two chambers[40]. The number of entries into the bright chamber, the duration of time spent there and the related exploratory behaviours, detected via a video tracking system, are reliable parameters for assessing anxiolytic effects.

Testing for depressive-like behaviours

The clinical diagnosis of depression requires the presence of several 'core' symptoms (depressed mood, decreased pleasure), and these signs can be followed with behavioural assessments in different animal models of depressive states. The forced swim test is the most widely used tool for assessing anti-depressant activity preclinically[41]. Investigators measure the amount of time between when the animal is placed in an inescapable cylinder of water and the onset of immobility. Rodent models of depression exhibit a decrease in the time spent trying to escape. The tail suspension test is a reliable test procedure for antidepressants in which a mouse is suspended by the tail from a lever, and the movements of the animal are recorded[42]. During this test, typically 6 min in duration, the resulting escape-oriented behaviours are quantified. The sucrose preference test is a reward-based test used as an indicator of anhedonia[43]. Anhedonia, or the decreased ability to experience pleasure, represents one of the core symptoms of depression. In general, this test measures the amount of a sweet-tasting solution that the animal ingests across a fixed period. The reduced preference for sweet solution in the sucrose preference test represents anhedonia.

High-fat diet-induced neuropsychiatric disorders

Diets rich in fat not only induce metabolic disorders in humans but also cause animal metabolic disorders. In animal models, as in humans, metabolic disorders can be assessed by criteria based on metabolic abnormalities in body weight, blood glucose, insulin levels, TAG, total cholesterol, LDL-cholesterol and HDL-cholesterol levels[44,45]. A growing body of research in humans and in animals has found that HFD not only causes these metabolic phenotypes but can also induce or increase the risk of neuropsychiatric disorders. In recent years, research on diet-induced neuropsychiatric disorders in animal models has increased dramatically. This section focuses on dietary patterns and summarises the literature of the past 10 years to explore the mechanisms that have been proposed for neuropsychiatric disorders induced by diets rich in fat and the possibility of reversing diet-induced neuropsychiatric disorders in animal models.

Dietary fat content

In a previous review, low-, medium- and high-fat diets were defined as <20, 20–35 and >35 % of total energy, respectively[35]. Currently, feeding a HFD leads to metabolic disorders and cognitive and neuropsychiatric disorders compared with feeding a low-fat diet in a rodent model. Chudasama & Bhatt's research team[46] first fed male Sprague–Dawley rats a HFD containing 60·29 % kcal fat, 17·85 % kcal carbohydrate and 20·15 % kcal protein for 5 weeks. The results showed for the first time that the body weight and systolic blood pressure of the rats increased significantly, and the immobility time in the 5-min forced swim test, reflecting depression-like behaviour, increased meaningfully. On the other hand, the immobility time in the 6-min tail suspension test, which reflects anxiety-like behaviour, also increased significantly. Then, the number of obese rats that passed the 5-min open field test, which reflects anxiety-like behaviour (an indicator that indirectly reflects immobility time), was also significantly reduced. These results suggest that a HFD and its related metabolic characteristics are positively correlated with depression and anxiety. In the literature included in this study (Table 1), most of the animal model studies on anxiety- and depression-like behaviour induced by HFD used 45 % of energy from fat[47–53], even up to 60 % or higher of the energy from fat[46,54–70]. The control diet is generally below 20 % of energy from fat. However, there are several studies[71,72] that use male C57BL/6 mice and fed a medium-fat diet (23·7 % kcal fat) compared with a control low-fat diet (13·3 % kcal fat) for 3–6 weeks. The mice in the medium-fat diet group showed significant weight gain and decreased glucose tolerance. Because most neurobehavioural performance tests, including the open field test, tail suspension test, forced swim test and sucrose preference test, were abnormal, these results suggest that the medium-fat diet can also induce depression-like behaviour. In fact, several studies have used a HFD and/or adding a certain amount of cholesterol or sugar to intervene in rodents and observed the effects of high cholesterol on anxiety/depression-like behaviour. A fat-rich diet (>20 %) and adding 0·2–2·5 % cholesterol can induce anxiety/depressive behaviour in male mice and rats[73–77]. A low-fat diet with 0·2–10 % cholesterol[78–80] can also induce anxiety/depressive behaviour in female mice but no anxiety/depressive behaviour in male rats[77]. There are sex differences in the role of cholesterol in the diet in anxiety and depression, and its detailed mechanism needs to be further studied. The high-sugar diet is associated with an increased consumption of simple sugars, typically in the form of sucrose- or fructose-derived sweeteners. Several studies[81–89] have used a high-sugar diet (or 'high-sugar and high-fat' or 'Western diet') to intervene in rodents and observed the effects of anxiety/depression-like behaviour (also shown in Table 1). There is a study that has particularly attracted attention; male BALBc mice (an inbred immune-deficient mouse) were fed a high-sugar diet (60 % sugar) for 9 weeks, with a significant increase in body weight and total cholesterol, and the mice showed anxiety-like behaviour abnormalities. Importantly, the authors showed that fat and sucrose affect behaviour differently and sometimes oppositely, and thus, the proportion of fat and sugar in the diet should be given more attention when designing behavioural studies[90]. These effects of the HFD inducing neuropsychiatric behaviour are often attributed to the high dietary content of fat. Therefore, the fat content of HFD may be the major cause of anxiety and depression-like behaviour[91].

Diet exposure period

Most of the included studies used medium- and long-term HFD to induce neuropsychiatric disorders, most commonly at 8–32 weeks. In some studies, male Wistar rats or mice were fed a HFD (60 % kcal from fat) for 8 weeks[55,66] or a HFD (45 % kcal from fat) and HSD (10 % sugar water) for 8 weeks[89]. They found that a HFD led to metabolic disorders and triggered similar anxiety- and depressive-like phenotypes, such as decreased social interaction. This strongly suggests that a HFD can lead to anhedonia. Furthermore, female C57BL/6 mice were fed a HFD (60 % kcal from fat) for 32 weeks, and body weight, fasting blood glucose and oral glucose tolerance tests increased significantly in HFD-induced mice. The error time in the Y-maze test was significantly higher than that in the control group, and the sucrose consumption rate in the sucrose preference test was significantly reduced. A long-term HFD

Table 1 Most commonly used high-fat diets to induce anxiety/depressive-like behaviour in rodent models

References	Species, strain, sex, age	Intervention diet	Control diet	Duration (weeks)	Metabolic state	Metabolic abnormalities	Anxiety-like behaviours	Depressive-like behaviour
Agusti *et al.*[54]	6–8 weeks old, male C57BL/6 mice	60·3 % kcal fat 18·4 % kcal protein 21·3 % kcal carbohydrate	12·4 % kcal fat 18·8 % kcal protein 68·8 % kcal carbohydrate	14	Obesity	Weight↑* TC, TAG↑* Glucose↑* Insulin↑*	LDT* OFT*	SPT* FST*
Almeida-Suhett *et al.*[63]	5 weeks old, male C57BL/6 mice	60·3 % kcal fat 18·4 % kcal protein 21·3 % kcal carbohydrate	18 % kcal fat 24 % kcal protein 18 % kcal carbohydrate	18	Obesity	Weight↑* Glucose↑* Insulin↑*	OFT* EZM*	FST*
Aslani *et al.*[47]	3 weeks old, male Wistar Han Rats	45 % kcal fat 20 % kcal protein 35 % kcal carbohydrates	3 % kcal fat 18·5 % kcal protein 53·5 % kcal carbohydrate	19	Obesity	Weight↑* Glucose↑* Insulin↑*	EPM*	FST*
Bridgewater *et al.*[64]	6 weeks old, male and female C57BL/6 mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate	12	Obesity	Weight↑*	OFT* EPM*	–
Bruce-Keller *et al.*[65]	8 weeks old, male C57BL/6J mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	13·5 % kcal fat 28·5 % kcal protein 58 % kcal carbohydrate	10	obesity	Glucose↑* Insulin↑*	OFT* EPM*	–
Chudasama *et al.*[46]	Male SD rats	60·29 % kcal fat 20·15 % kcal protein 17·85 % kcal carbohydrate	9·12 % kcal fat 22·1 % kcal protein 58·92 % kcal carbohydrate	5	Obesity	Weight↑*	OFT*	FST* TST*
Del Rio *et al.*[92]	5 weeks old, male C57BL/6 mice	45 % kcal fat 20 % kcal protein 35 % kcal carbohydrate	18 % kcal fat 24 % kcal protein 58 % kcal carbohydrate	8	Obesity	Weight↑*	OFT* EPM*	–
Del Rosario *et al.*[93]	4 weeks old, male CD-1 genetic background mice	45 % kcal fat	10 % kcal fat	8	Obesity	Weight↑*	OFT* HBT*	FST*
Ganji *et al.*[48]	2–2·5 months old, male Wistar rats	45 % kcal fat	10 % kcal fat	12	Obesity	Weight↑* Insulin↑*	EPM*	–
de Noronha *et al.*[53]	Male Wistar rats	45 % kcal fat 20 % kcal protein 35 % kcal carbohydrate	11 % kcal fat	9	obesity	Weight↑*	ETM*	–
Wu *et al.*[71]	5–6 weeks old, male C57BL/6 mice	23·7 % fat 23·0 % protein 53·3 % carbohydrate	13·3 % saturated fat 26·2 % protein 60·5 % carbohydrate	3–6	Obesity	Weight↑* Glucose↑*	OFT*	FST* TST*
Hassan *et al.*[66]	8 weeks old, male C57BL/6 mice	60 % kcal fat 16 % kcal protein 24 % kcal carbohydrate	12 % kcal fat 23 % kcal protein 65 % kcal carbohydrate	8	Obesity	Weight↑*	–	SPT* SIT* HCl*
Karth *et al.*[94]	2–4 months old, male homozygous WT or KI animals from the Tph2R439H mice	39·7 % kcal fat 18·8 % kcal protein 41·4 % kcal carbohydrate	9 % kcal fat 19 % kcal protein 72 % kcal carbohydrate	22	Obesity	Weight↑*	OFT*	FST*
Kurhe *et al.*[95]	Male Swiss albino mice	58 % kcal fat 25 % kcal protein 17 % kcal carbohydrate	12 % kcal fat	14	Obesity	Weight↑*	–	SPT* FST*
Kurhe *et al.*[96]	Male Swiss albino mice	58 % kcal fat 25 % kcal protein 17 % kcal carbohydrate	12 % kcal fat	14	Obesity	Weight↑*	LDT* HBT*	SPT* FST*
Kurhe *et al.*[97]	Male Swiss albino mice	58 % kcal fat 25 % kcal protein 17 % kcal carbohydrate	12 % kcal fat	14	Obesity	Weight↑* Glucose↑* Insulin↑*	EPM*	SPT* FST*

Table 1 (*Continued*)

References	Species, strain, sex, age	Intervention diet	Control diet	Duration (weeks)	Metabolic state	Metabolic abnormalities	Anxiety-like behaviours	Depressive-like behaviour
Kurhe *et al.*[98]	Male Swiss albino mice	58 % kcal fat 25 % kcal protein 17 % kcal carbohydrate	12 % kcal fat	14	Obesity	Weight↑* Glucose↑* Insulin↑*	LDT* HBT*	SPT* FST*
Xu *et al.*[99]	Male C57BL/6 mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate	12	Obesity	Weight↑* Glucose↑*	EPM* OFT* LDT*	–
Nakajima *et al.*[91]	8 weeks old, male Swiss albino mice	300 g/kg fat 200 g/kg protein 399·5 g/kg carbohydrate	70 g/kg fat 200 g/kg protein 629·5 g/kg carbohydrate	8	Obesity	Weight↑* TG↑ Insulin↑*	OFT*	SIT*
Ogrodnik *et al.*[67]	8 months old, male C57BL/6J mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	13·1 % kcal fat 24·5 % kcal protein 62·3 % kcal carbohydrate	8	Obesity	Weight↑*	OFT* EPM*	–
Park *et al.*[68]	4 weeks old, male C57BL/6 mice	60 % kcal fat	–	20	Obesity	Weight↑*	EPM*	TST*
Sharma *et al.*[100]	8 weeks old, male C57BL/6 mice	58 % kcal fat 16·4 % kcal protein 25·5 % kcal carbohydrate	10·5 % kcal fat 16·4 % kcal protein 73·1 % kcal carbohydrate	12	Obesity	Weight↑*	OFT* EPM*	FST*
Suárez *et al.*[101]	6–7 weeks old, male ati-CB1-WT or KO mice	60 % kcal fat 17 % kcal protein 23 % kcal carbohydrate	11 % kcal fat 36 % kcal protein 53 % kcal carbohydrate	26	Obesity	Weight↑* Glucose↑* Insulin↑*	–	FST*
Tomiga *et al.*[102]	4–5 weeks old, male C57BL/6 mice	57 % kcal fat 20 % kcal protein 23 % kcal carbohydrate	14 % kcal fat 25 % kcal protein 62 % kcal carbohydrate	12	Obesity	Weight↑*	EPM*	–
Tomiga *et al.*[103]	5 weeks old, male C57BL/6 mice	57 % kcal fat 20 % kcal protein 23 % kcal carbohydrate	14 % kcal fat 25 % kcal protein 62 % kcal carbohydrate	12	Obesity	Weight↑*	EPM*	–
Vagena *et al.*[69]	WT C57BL/6J mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	13·1 % kcal fat 24·5 % kcal protein 62·3 % kcal carbohydrate	3 or 8	Obesity	Weight↑*	–	TST* FST*
Gainey *et al.*[62]	3–4 weeks old, male C57BL/6J mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate	3	Obesity	Weight↑*	EZM* OFT*	–
Yamada *et al.*[70]	6 weeks old, male C57BL/6J mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	12·6 % kcal fat	16	Obesity	Weight↑* TC↑ Glucose↑* Insulin↑*	–	FST* SPT*
Yang *et al.*[55]	9 weeks old, male Wistar rats	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	8 % kcal fat	8	Obesity	Weight↑*	OFT* EPM*	SPT*
Sweeney *et al.*[56]	Male and female, C57BL/6J mice	61·6 % kcal fat 18·1 % kcal protein 20·3 % kcal carbohydrate	16·7 % kcal fat 26·8 % kcal protein 56·4 % kcal carbohydrate	5	Obesity	–	OFT* EPM*	–
Sweeney *et al.*[56]	Male and female, C57BL/6J mice	61·6 % kcal fat 18·1 % kcal protein 20·3 % kcal carbohydrate	16·7 % kcal fat 26·8 % kcal protein 56·4 % kcal carbohydrate	15	Obesity	Weight↑* Glucose↑*	OFT* EPM*	–
Wu *et al.*[57]	8 weeks old, female C57BL/6 mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate	32	Obesity/diabetes	Weight↑* TC↑*, TAG↑ HDL-cholesterol↑* AST↑, ALT↑ Glucose↑* Insulin↓	–	SPT*

Table 1 (*Continued*)

References	Species, strain, sex, age	Intervention diet	Control diet	Duration (weeks)	Metabolic state	Metabolic abnormalities	Anxiety-like behaviours	Depressive-like behaviour
Pan *et al.*[72]	5–6 weeks old, male C57BL/6 mice	23·7 % kcal fat 23·0 % kcal protein 53·3 % kcal carbohydrate	13·3 % kcal fat 26·2 % kcal protein 60·5 % kcal carbohydrate	6	Obesity/hyperlipidaemia	Weight↑* TC, TAG ↑* Glucose↑* Insulin↑*	OFT*	FST* TST* SPT*
Alonso-Caraballo *et al.*[58]	65–70 d, male and female SD rats (obesity-prone)	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	13·5 % kcal fat 28·5 % kcal protein 58 % kcal carbohydrate	4 or 8	Obesity	Weight ↑* Insulin↑*	OFT * EPM*	–
Dutheil *et al.*[59]	Male SD rats	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate	16	T2DM	Weight↑* Glucose↑* Insulin↑*	OFT* ORT* NSFT*	SPT*
Zemdegs *et al.*[51]	7 weeks old, male C57BL/6 mice	45 % kcal fat 20 % kcal protein 35 % kcal carbohydrate	3·1 % kcal fat 26·2 % kcal protein 60 % kcal carbohydrate	16	T2DM	Weight↑* Glucose↑* Insulin↑*	OFT* NSFT*	–
Kaczmarczyk *et al.*[104]	3 weeks old, male C57BL/6J mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate	1–3	Weight gain/ pre-diabetes	Weight↑* Insulin↑*	ORT* EZM*	FST*
Tsai *et al.*[60]	8 weeks old, male C57BL/6 mice	61·6 % kcal fat 18·1 % kcal protein 20·3 % kcal carbohydrate	13·5 % kcal fat 27·6 % kcal protein 58·9 % kcal carbohydrate	12	Metabolic disruption	Weight↑* HDL-cholesterol, LDL-cholesterol↑* Glucose↑* Insulin↑*	ORT* OFT*	SPT* FST*
Abildgaard *et al.*[105]	4 weeks old, male SD rats	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	11 % kcal fat 23 % kcal protein 66 % kcal carbohydrate	10	–	Glucose↑* Insulin↑*	OFT*	–
Feng *et al.*[106]	5 weeks old, C57BL/6 mice	59 % kcal fat 15 % kcal protein 26 % kcal carbohydrate	16 % kcal fat 21 % kcal protein 63 % kcal carbohydrate	18	–	Weight↑* Glucose↑*	OFT* NSFT*	–
Liu *et al.*[49]	5–6 weeks old, male C57BL/6 mice	45 % kcal fat 20 % kcal protein 35 % kcal carbohydrate	10 % kcal fat 30 % kcal protein 60 % kcal carbohydrate	8	Insulin-resistant	Glucose↑* Insulin↑*	OFT*	–
Zemdegs *et al.*[52]	5–7 weeks old, male C57BL/6J mice	45 % kcal fat 20 % kcal protein 35 % kcal carbohydrate	3 % kcal fat 26 % kcal proteins 60 % kcal carbohydrate	16	Insulin-resistant	Weight↑* Glucose↑* Insulin↑*	EPM* NSFT*	–
Marion Soto *et al.*[84]	6 weeks old, male, C57BL/6 mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	22 % kcal fat 23 % kcal protein 55 % kcal carbohydrate	6	Obesity and diabetes	Weight↑* Glucose↑*	LDT* NSFT* OFT*	–
Batschauer *et al.*[85]	8–10 weeks old, male, Wistar rats	19 g fat 13 g protein 40 g carbohydrate	4 g fat 22 g protein 48 g carbohydrate	6	Obesity	Weight↑* Glucose↑* TC↑, TAG↑* TGL↑*	EPM*	–
André *et al.*[86]	3 weeks old, male, C57BL/6 mice	49 % kcal fat	9·3 % kcal fat	9 or 18	Obesity	Weight↑* Glucose↓ Insulin↑	EPM Y-maze*	TST FST
Peris-Sampedro *et al.*[87]	7 weeks old, male, SD rats	100 % fat (and/or the addition of 9 % sucrose or glucose solution)	12 % kcal fat 22 % kcal protein 66 % kcal carbohydrate	3	Obesity	Weight↑ Insulin↑	OFT* EPM*	–

Table 1 (*Continued*)

References	Species, strain, sex, age	Intervention diet	Control diet	Duration (weeks)	Metabolic state	Metabolic abnormalities	Anxiety-like behaviours	Depressive-like behaviour
Ji *et al.*[88]	6 weeks old, male, C57BL/6 mice	60 % kcal fat 8·9 % sucrose	10 % kcal fat	3	Obesity	Weight↑*	OFT* EPM*	
Xu *et al.*[83]	4 weeks old, male SD rats	23·53 % fat 66·14 % sugar 10·33 % protein	12·05 % fat 63·02 % sugar 24·93 % protein	90 d	–	Weight↑*	EPM* OFT*	–
Gancheva *et al.*[89]	6 weeks old, male Wistar rats	38 % kcal fat 20 % kcal fructose (high-sucrose diet) 10 % fructose solution	10 % kcal fat 29 % kcal protein 61 % kcal carbohydrate	8	Metabolic syndrome	Weight↑ TC, TAG↑* HDL-cholesterol↑ Insulin↓	OFT*	FST*
Rebolledo-Solleiro *et al.*[81]	8 weeks old, male, Wistar rats	13·5 % fat 28·5 % protein 58 % carbohydrate 20 % (w/v) sucrose solution	13·5 % fat 28·5 % protein 58 % carbohydrate	24	Metabolic syndrome	Weight↑* TAG ↑* Glucose↑* Insulin↑*	OFT* SPBT*	–
Choudhary *et al.*[82]	3 months old, male C57BL/6 mice	20 % sucrose solution	–	12	Alzheimer's disease	Weight↑* Glucose↑* Insulin↑*	–	FST*
Jørgensen *et al.*[90]	7 weeks old, male BALB/c mice	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate 60 % sugar	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate	9	–	Weight↑* TC↑	OFT*	–
Magdy *et al.*[74]	Male Wistar rats	72·8 % ordinary chow 25 % fat 2 % cholesterol	Ordinary chow	12	NAFLD	Weight↑* TC, TAG↑* HDL-cholesterol↓*, LDL-cholesterol↑* AST, ALT↑* Glucose↑* Insulin↑*	OFT* SIT*	FST*
Higarza *et al.*[75]	8 weeks old, male SD rats	65 % kcal fat 2 % kcal cholesterol	13 % kcal fat	14	NAFLD	Weight↑* TC↑*, TAG↑* HDL-cholesterol↓*, LDL-cholesterol↑* AST, ALT↑* Glucose↑*	SIT*	FST* SPT*
Khedr *et al.*[76]	Male Wistar rats	72·8 % ordinary chow 25 % fat 2 % cholesterol	Ordinary chow	12	–	Weight↑* TC↑*, TAG↑* HDL-cholesterol↓*, LDL-cholesterol↑* Glucose↑* Insulin↑*	OFT*	SIT* FST*

British Journal of Nutrition

Table 1 (*Continued*)

References	Species, strain, sex, age	Intervention diet	Control diet	Duration (weeks)	Metabolic state	Metabolic abnormalities	Anxiety-like behaviours	Depressive-like behaviour
Hu *et al.*[77]	2–3 months old, male SD rats	65·2 % regular diet 20 % fat 2 % carbohydrate 2·5 % cholesterol	5·0 % fat 20·0 % protein 75 % carbohydrate	9	Obesity	Weight↑* TC, TAG ↑* HDL-cholesterol↓*, LDL-cholesterol↑*	–	SPT*
Metwally *et al.*[80]	6 weeks old, female Wistar rats	6·85 % fat 17·48 % protein 52·99 % carbohydrate 10 % cholesterol	6·85 % fat 17·48 % protein 62·99 % carbohydrate	8	Obesity	Weight↑* TC, TAG ↑* Glucose↑* Insulin↑*	OFT* ORT* LDT*	FST*

–, Not reported; ↑, increase *v.* control diet; TC, total cholesterol; LDT, Light and dark test; OFT, open field test; SPT, sucrose preference test; FST, forced swim test; EZM, elevated zero maze; EPM, elevated plus-maze; WT, wild-type; KI, knock-in; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T2DM, type 2 diabetes mellitus; ORT, object recognition test; NSFT, novelty suppressed feeding test; NAFLD, non-alcoholic fatty liver disease; SD, Sprague–Dawley; SPBT, Shock-probe/burying test; ETM, elevated T-Maze; TST, tail suspension test; SLA, spontaneous locomotor activity score; SIT, social interaction test; HBT, hole-board test.
*$P < 0.05$ was considered significant.

not only leads to depression-like behaviour but also affects spatial memory damage[57]. In addition, whether short-term (1–4 weeks) high-fat feeding induces anxiety-like and depression-like behaviour remains controversial. Several studies involving short-term feeding of rodent models with a HFD (60 % kcal from fat) for 1–4 weeks have found that anxiety- and depression-like behaviour is significantly changed[58,62,69,71,104]. However, evidence from rodent models suggests that the consumption of a HFD for 3 weeks can have anti-depressant and anxiolytic effects[107]. Sweeney's study[56] sought to determine whether the duration of exposure to a HFD (60 % kcal from fat) had a significant effect on anxiety-related behaviour. Their results showed that HFD feeding had a time-dependent biphasic effect on anxiety-related behaviours, and the level of weight gain and the degree of decreased glucose tolerance were positively correlated with the severity of anxiety. Anxiety-like behaviour was reduced in mice fed a short-term HFD (60 % kcal from fat) for 5 weeks. Interestingly, after 15 weeks of HFD feeding, mice exhibiting metabolic symptoms of obesity (significant weight gain and reduced glucose tolerance) showed an increase in anxious behaviour. Taken together, these findings suggest that metabolic abnormalities, such as weight fluctuations, glucose tolerance and blood lipids, promote anxiety-related behaviour in animals fed a HFD and that the feeding duration is likely to affect the progression of this relationship. It is certain that, in particular, long-term HFD (over 8 weeks) and their induced metabolic disorders may produce persistent depressive/anxiety behaviours.

Species and genetic background

Similar to other animal models of disease, Sprague–Dawley rats, Wistar rats and C57BL/6 mice are currently used to observe metabolic abnormalities and neuropsychiatric disorders induced by a HFD. Wistar Han rats[47], Long Evans Rattus rats[108] and Swiss albino mice[91,95–97] have also been used. In addition, several studies using rodents with specific genetic backgrounds have produced interesting results. In a recent study[58], two types of obesity-prone and obesity-resistant Sprague–Dawley rats were selected. After feeding a HFD for 8 weeks, the weight and insulin level increased significantly and anxiety-like behaviours were enhanced in obese-susceptible rats. However, anxiety-like behaviour remained unaffected in obesity-resistant rats, despite a significant increase in weight and insulin levels. Therefore, obesity-prone mice may be one of the appropriate models to explore the mechanism of HFD-induced anxiety-like behaviour. The tryptophan hydroxylase 2 R439H knock-in mouse line harbours a partial loss-of-function mutation in the brain 5-hydroxytryptamine (5-HT) synthesis enzyme tryptophan hydroxylase 2[109]. Homozygous knock-in animals from this line have 60–80 % less brain 5-HT than their homozygous wild-type littermates[109,110]. Tryptophan hydroxylase 2 R439H knock-in mice with brain 5-HT deficiency were fed a HFD (39·7 % kcal from fat) for 22 weeks, and it was shown that a HFD could increase body weight and anxiety-like behaviour and decrease the depression-like behaviour of wild-type mice. However, in tryptophan hydroxylase 2 R439H knock-in mice with brain 5-HT deficiency, HFD intervention did not significantly affect weight, anxiety-like behaviour or depression-like behaviour. This preliminary study suggests that 5-HT deficiency in the brain has a

significant effect on HFD-induced behaviour and the molecular response[94]. Suarez's study[101] used transgenic mice to assess the effects of cannabinoid type 1 receptor knockout on behavioural and molecular changes induced by a HFD (60 % kcal from fat) after long-term feeding for 26 weeks. The results showed that a HFD could significantly increase depression-like behaviour in wild-type mice but not in cannabinoid type 1 receptor knockout mice.

In 2012, Del Rosario *et al.*[93] used male mice with close homology to human genes and a CD-1 genetic background to conduct research. Fed a HFD (45 % kcal from fat) for 8 weeks, body weight was significantly increased by 14 %, the anxiety level increased significantly and the depression-like behaviour was reduced significantly, which implied that the HFD had an anti-depressant effect on the mice. Interestingly, the study found that the effects of a HFD on anxiety- and depression-like behaviour in male mice with a CD-1 genetic background were inconsistent. To date, most of the included studies have used mouse models and a few have used rat models. Careful consideration of the baseline traits of the strain in both rats and mice should be considered before experimentation[111], although there is no systematic literature to study the advantages and disadvantages of various rodent models induced by HFD. More importantly, several studies using rodents with specific genetic backgrounds have yielded some interesting results, and they may represent appropriate models to explore the mechanism of HFD-induced mood disorders. Furthermore, non-human primates have been used to model mood disorders for several decades. The success of this paradigm is related to the fact that there are comparable cognitive skills, brain morphology and social complexity in adult monkeys and humans[112]. Therefore, in addition to rodent models, this field could benefit from additional studies of non-human primate models.

Sex and age

Although depression is more common in women than men (almost 2:1), the vast majority of preclinical studies have been conducted in male animals[113]. Only a limited number of studies have been conducted in female rodent models. There is little evidence supporting sex differences in mood disorders induced by a HFD. C57BL/6 mice were fed a HFD (60 % kcal from fat) for 12 weeks. Both male and female mice gained significantly more weight, but only males showed an increase in anxiety-like behaviour, not females[64]. In another study[56], after feeding mice a HFD (60 % kcal from fat) for 15 weeks, anxiety-like behaviour and body weight increased and glucose tolerance decreased in both female and male C57BL/6J mice. HFD (59 % kcal from fat) exposure for 18 weeks led to glucose intolerance, anxiety/depression-like behaviour and neuroinflammation in male mice, with similar but non-significant trends in females[106]. Wu *et al.* [57] also fed C57BL/6 female mice a HFD (60 % kcal from fat) and showed depression-like behaviour 32 weeks later. Therefore, there are significant sex differences in anxiety-like behaviours induced by a HFD, and male mice seem to be more sensitive to the anxiety-inducing effects of a HFD than female mice[64]. The importance of sex as a biological variable must be emphasised in future similar studies.

Although almost all studies adopt 4- to 8-week-old adult rodents, it is important to point out that a research group[67] used 32-week-old elderly male C57BL/6J mice fed a HFD (60 % kcal fat) for 8 weeks and found that obesity results in the accumulation of senescent glial cells in proximity to the lateral ventricle, a region in which adult neurogenesis occurs. Furthermore, senescent glial cells exhibit excessive fat deposits, a phenotype termed 'accumulation of lipids in senescence.' Clearing senescent cells from high-fat-fed or leptin receptor-deficient obese mice restored neurogenesis and alleviated anxiety-related behaviour. Current animal literature supports the programming effect of maternal nutrition (Western style diet) on negative-valence behaviours (including depression and anxiety) of offspring[114,115]. The next stage is not only to study the relationship between diet and neuropsychiatric disorders in adult mice but also to consider related research in offspring and elderly mice. Because of different ages, the pathogenesis may be different.

Mechanisms of high-fat diet-induced neuropsychiatric disorders

In this section, the discussed mechanisms include elevated neuroinflammation, changes in neurotransmitters/neuromodulators (e.g. 5-HT, glutamic acid, neuronal nitric oxide synthase and 3′,5′-cyclic AMP (cAMP)), neurotrophins (e.g. brain-derived neurotrophic factor (BDNF)) and the gut–brain axis (e.g. microbiota, metabolites), which may be involved in the pathogenesis of diet-induced neuropsychiatric disorders.

Neuroinflammation. A number of studies support the idea that HFD-induced neuropsychiatric disorders may be related to inflammatory responses in the brain[59,63,65,73,101,106], referred to as neuroinflammation, and to peripheral inflammatory responses[61,73]. Two animal models examining short-term HFD-induced depression-like behaviour noted increased serum inflammatory factors, including IL-6, IL-1β, TNFα and IL-6[61,104]. Furthermore, a long-term HFD significantly increased the expression of pro-inflammatory cytokines (TNFα, IL-1β, IL-6, IL-2 and IL-17A) in the hippocampus, amygdala and prelimbic cortex[63,73,106] and down-regulated the expression of anti-inflammatory cytokines (IL-10 and IL-4) in the hippocampus[73]. Increased anxiety-like behaviour was positively correlated with high expression of IL-1β in the amygdala[59,63,101]. Four-month HFD feeding leads to anxiety and anhedonic behaviour associated with TLR expression and pro-inflammatory cytokine production (IL-6, IL-1β and TNFα)[59]. Another experiment found that adipocyte-specific cannabinoid type 1 receptor influences obesity-related depression-like behaviour concomitantly with neuroinflammation in the hippocampus and hypothalamus[101]. In addition, obesity drives senescence in glial cells in the lateral ventricle of mouse brains, and clearing senescent cells from HFD-fed or leptin receptor-deficient obese mice restores neurogenesis and alleviates anxiety-related behaviour[67].

Neurotransmitters/neuromodulators. As a monoamine neurotransmitter, serotonin, also named 5-HT, is widely involved in the mediation of various life activities in the central and peripheral regions and its regulatory effect is related to the diversity of receptor subtypes[116]. As an ion-gated channel

receptor, the 5-HT receptor is widely expressed in the hippocampus, amygdala and posterior polar region[117]. In recent years, research on improving neuropsychiatric disorders induced by HFD has focused on 5-HT and its receptors[118]. A number of preclinical studies have shown that a HFD regulates the metabolism of 5-HT in the brain and in the periphery and that 5-HT receptor antagonists may have anti-depressant and anti-anxiety effects[119]. First, several studies have demonstrated that a HFD regulates peripheral 5-HT metabolism. Male C57BL/6 mice were fed a HFD for 4 weeks, which significantly increased circulating 5-HT levels[72]. Female adult C57BL/6 mice were fed a HFD for 10 months, which led to decreased serum 5-HT and induced depression[57]. An untargeted plasma metabolomic analysis showed that a HFD that induces depressive-like behaviour could affect peripheral tryptophan metabolites (kynurenine pathway)[105]. Several studies have focused on how a HFD regulates 5-HT metabolism in the brain. Male C57BL/6 mice were fed a HFD for 14 weeks, which caused hippocampal neuron loss and decreased the gene expression of BDNF, 5-HT1A, 5-HTT and IDO2[73]. Three studies from Kurhe's team[95–97] confirmed that a HFD decreased the concentrations of cAMP, BDNF and 5-HT in the hippocampus, leading to anxiety and depression. Additionally, depressive- and anxiety-like behaviours increased in HFD-induced obese mice, the number of 5-HT- and TPH-positive cells decreased, and 5-HT1A and 5-HTTP protein expression decreased in the dorsal raphe[68]. Finally, two recent studies by Zemdegs' team[51,52] systematically demonstrated the mechanism of HFD-induced anxiety and depression-like behaviour. The increased body weight, hyperglycaemia, impaired glucose tolerance and insulin resistance accompanied by elevated circulating levels of branched-chain amino acids in response to HFD were correlated with anxiogenic-like/depressive-like symptoms. Moreover, this phenotype was associated with decreased extracellular 5-HT levels in the hippocampus, which may result from increased sensitivity of the dorsal raphe 5-HT1AR.

Glutamic acid is considered to be the most abundant neurotransmitter in the brain, and its excitability plays a crucial role in brain structure and function. The two studies found that a decrease in hippocampal glutamate transporters may play a critical role in the pathogenesis of metabolic disorder-related depression. On the one hand, a HFD disturbs the function of hippocampal astrocytic neuroplasticity-related protein, GLAST, glutamate transporter 1 and connexin-43 and induces depression-like behaviours in mice[60]. On the other hand, high-lard/high-sucrose diets induced anxiety-like behaviour and an increase in glutamate transporters and a decrease in glutamate receptor mRNA expression in the prefrontal cortex[91]. Neuronal nitric oxide synthase is a key regulator of emotional behaviour. Some experiments[62,102,103] found that anxiety caused by a HFD was associated with increased levels of neuronal nitric oxide synthase in the hippocampus and cerebral cortex. The content of glutathione in the blood is used as a biomarker to reflect the redox state of mice[120]. A HFD led to a more than 60 % reduction in total glutathione levels in the blood, which may have contributed to the increased anxiety levels in the mice[102]. Consumption of a HFD selectively induced the accumulation of palmitic acid in the hypothalamus, suppressed the cAMP/protein kinase A signalling pathway and increased the concentration of free fatty acid receptor 1. Deficiency of phosphodiesterase 4A, an enzyme that degrades cAMP and modulates stimulatory regulative G protein (Gs)-coupled receptor signalling, protected animals from either a genetic- or dietary-induced depression phenotype[69].

Neurotrophin. BDNF, one of the major neurotrophic factors, plays an important role in the maintenance and survival of neurons and in synaptic plasticity. Several lines of evidence suggest that the expression of BDNF is decreased in depressed models. BDNF concentrations in the hippocampus were significantly lower in diet-induced obese mice, and leptin administration significantly increased hippocampal BDNF concentrations in CD mice[70]. HFD rapidly impacts dopamine metabolism in the brain, appearing to trigger anxiety-like behaviours and learning/memory impairments prior to the onset of weight gain and/or pre-diabetes. Examination of the mouse cortex, hippocampus and hypothalamus for dopamine and its metabolites demonstrated increased homovanillic acid concentrations in the hippocampus and cortex that were associated with decreased cortical BDNF gene expression[104].

Gut–brain axis. Research into the role of the microbiota in modulating brain function has rapidly increased over the past 10 years. Increasing clinical and preclinical evidence implicates the microbiome as a possible key susceptibility factor for neurological disorders[25,121,122]. In fact, HFD consumption generally leads to a decrease in Bacteroidetes and an increase in Firmicutes. These alterations have been associated with obesity and the subsequent development of chronic diseases[123]. First, a HFD damages markers of intestinal barrier function and increases circulating endotoxin levels. The evaluation of brain homogenates revealed that the HFD-shaped microbiota increased neuroinflammation and disrupted cerebrovascular homoeostasis[65]. Second, prolonged HFD-induced depression-like behaviour in mice was associated with significant changes in IM, brain metabolome, the NPY system and DPP-4 activity[66]. Finally, a HFD increased the concentration of plasma leptin and faecal corticosterone and significantly decreased the relative expression of the leptin receptor OB-R in the hippocampus and small intestine. On the other hand, dopamine and noradrenaline levels in the small intestine and adrenaline levels in the hypothalamus were reduced. More importantly, the concentration of 5-HT in the hippocampus of mice was significantly reduced, and the relative expression of TLR2 in the small intestine and hippocampus was significantly increased, leading to the occurrence of anxiety and depression[54]. Intervention with Bifidobacterium pseudocatenulatum CECT 7765 for 14 weeks can adjust the endocrine and gut–brain axis and plays a role in obesity co-morbid with depressive behaviour. Diet is perhaps one of the greatest factors influencing microbiota composition[124]. Where research has shown that there are clear links between diet and neuropsychiatric disorders, assessing what role, if any, the microbiome has in terms of causality will be important[25]. The effects of both dietary components and microbial-generated metabolites on host physiology and health are gaining attention, which will be important for moving therapeutic approaches forward.

Diet exacerbates neuropsychiatric disorders observed in animal models of depression

Finally, some literature supports that not only does diet induce or increase the risk of anxiety and depression-like behaviour, but, more importantly, it may also aggravate anxiety- and depression-like behaviour in rodent models of neuropsychiatric disorders (Table 2).

Chronic social defeat stress paradigm-induced depression model

The chronic social defeat stress (CSDS) paradigm induces depression by repeatedly exposing naïve mice to aggressor mice. After 7–15 d in this emotionally stressful environment, mice display robust depressive phenotypes, which are characteristic of human symptoms[125]. Male C57BL6/J mice (8–10 weeks old) were subjected to CSDS for 10 d and then fed a HFD (42 % kcal from fat) for 30 d. Mice subjected to CSDS and then fed a HFD for 30 d display significantly severe depression-related behaviour (greater social avoidance than mice receiving regular chow) accompanied by redistribution of body fat and increased serum leptin levels[126]. Male Wistar rats (21 d old) were subjected to social isolation during the prepubertal period for 7 d and then fed a HFD (42 % kcal from fat) for 70 d. They found that both social isolation and HFD induced depressive-like behaviour. These findings showed that brief social isolation and chronic HFD during a sensitive developmental period cause depressive-like behaviour in adulthood[127]. Eight-week-old male C57BL/6 mice were subjected to CSDS for 10 d and then fed a HFD (60 % kcal from fat) for 2 h or 24 h[128]. HFD intervention for 2 h increased the anxiety-like behaviour of the CSDS mice. However, HFD intervention for 24 h can reduce the anxiety of CSDS mice. It is suggested that a HFD may reduce the burden of stress and this benefit is probably related to the metabolism of cholesterol in the liver.

Chronic unpredictable mild stress-induced depression model

Chronic unpredictable mild stress (CUMS) is currently the most commonly used, reliable and effective rodent model of depression[129]. Experimental mice underwent CUMS exposure for approximately 14 consecutive days with exposure each day to at least one stressor that was randomly chosen from nine different stressors, and stressors were given in a random order to ensure unpredictability[130]. A HFD and/or the addition of a certain amount of cholesterol or sugar exacerbates the neuropsychiatric disorders observed in animal models of depression. Six-week-old female and male C57BL/6 mice were fed a HFD (60 % kcal from fat) for 12 weeks and then subjected to CUMS for 18 d. Male mice were more vulnerable to the anxiogenic effects of the HFD, and obese male mice showed decreased locomotion activity in response to stress, whereas obese female mice did not. These results revealed distinct sex differences in the impacts of obesity and stress on anxiety-like behaviours in mood disorders[64]. Male Wistar Han rats were fed a HFD (45 % kcal from fat) for 19 weeks and subjected to CUMS for 6 weeks. Specifically, animals fed a HFD displayed depressive- and anxious-like behaviours that were only present in the normal diet group upon exposure to CUMS. Of note, these mood impairments were not further aggravated when the HFD animals were exposed to CUMS, which suggests a ceiling effect[47]. Male Wistar rats were fed a HFD (60 % kcal from fat) for 8 weeks and repeatedly exposed to CUMS for 3 weeks. The rats exhibited the most severe depression-like and anxiety-like behaviour. Depressive- and anxiety-like behaviours as well as cognitive impairment were positively correlated with the highest weight, plasma leptin levels and LepRb protein and mRNA levels in the hippocampus and hypothalamus[55]. Several studies[74,76] used a diet containing 2 % cholesterol to feed rats for 8–12 weeks and exposed them to chronic restraint stress for 6–8 weeks. In addition to abnormal liver lipids, atherosclerosis and other metabolic disorders, with the high cholesterol intervention, the rats later developed depression-like behaviours, cognitive impairment and diminished object recognition memory as well. In addition, sitagliptin is recommended in the management of NASH, especially when associated with depression[74], and metformin, which is commonly used to treat hepatogenic diabetes, can ameliorate resistance to fluoxetine in depression[76].

Genetic animal model of depression

Flinders Sensitive Line rats were, through selective breeding techniques, bred to be more sensitive to the anticholinesterase diisopropyl fluorophosphate[131], and Flinders Sensitive Line rats have been widely described and highly validated as a genetic animal model of depression[132]. Abildgaard *et al.* used Flinders Sensitive Line rats fed with a HFD (60 % kcal from fat, mainly lard) for 10 weeks and subjected them to behavioural testing and metabolic assessment. They found that the HFD increased weight, insulin levels and fasting blood glucose levels. At the same time, HFD consumption led to exacerbation of the depressive-like behaviour of Flinders Sensitive Line rats in the forced swim test, which is a depression screening tool, and diminished social interaction as well[133].

Conclusions

The association between the development of metabolic disorders and chronic consumption of a HFD has been well demonstrated. Interestingly, emerging evidence indicates that HFD and metabolic risk are also associated with an increased risk of neuropsychiatric disorders, including anxiety and depression, in humans and in animals. A HFD and/or the addition of a certain amount of cholesterol or sugar can induce anxiety- or depression-like behaviours, which may vary based on the diet exposure period, sex, age, species and genetic background of the animals used. In addition, diet significantly aggravates anxiety- or depression-like behaviour in animal models of neuropsychiatric disorders. The effects of a HFD on anxiety are critically linked to the duration of HFD exposure. Prolonged exposure to a HFD promotes anxiety and depression in animals that are susceptible to HFD-induced metabolic disorders, and diets with a high fat percentage may accelerate the progression of this relationship in animal models of depression. In addition, there are significant sex differences in anxiety-like behaviours induced by a HFD and/or the addition of a certain amount of cholesterol or sugar. However, there have been a very limited number of studies

British Journal of Nutrition

Table 2 Diet exacerbates neuropsychiatric disorders observed in animal models of depression

References	Species, strain, sex, age	Intervention diet	Control diet	Duration (weeks)	Model	Metabolic abnormalities	Anxiety-like behaviours	Depressive-like behaviour
Chuang *et al.* [126]	8–10 weeks old, male C57/B16 mice	42 % kcal fat	4 % kcal fat	30 d	Chronic social defeat stress (40 d)	Weight↑*	EPM*	FST* SPT*
Bridgewater *et al.* [64]	6 weeks old, male and female C57BL/6 mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate	12	Chronic unpredictable mild stress (18 d)	Weight↑*	OFT* EPM*	–
Otsuka *et al.* [128]	8 weeks old, male C57BL/6 mice	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	Normal chow diet	24 h	Social-defeat stress (10 d)	Weight↑*	SIT*	–
Arcego *et al.* [127]	21 d old, male Wistar rats	42 % kcal fat 28 % kcal protein 25 % kcal carbohydrate	4 % fat 22 % kcal protein 50 % kcal carbohydrate	10	Social isolated animals	Weight↑*	–	FST* SPT*
Aslani *et al.* [47]	3 weeks old, male Wistar Han Rats	45 % kcal fat 20 % kcal protein 35 % kcal carbohydrate	3 % kcal fat 18·5 % kcal protein 53·5 % kcal carbohydrate	19	Chronic unpredictable mild stress (6 weeks)	Weight↑* Glucose↑* Insulin↑*	EPM*	FST*
Yang *et al.* [55]	9 weeks old, male Wistar rats	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	8 % kcal fat	8	Chronic unpredictable mild stress (3 weeks)	Weight↑*	OFT* EPM*	SPT*
Magdy *et al.*[74]	Male Wistar rats	72·8 % ordinary chow 25 % fat 2 % cholesterol	Standard chow diet	12	Chronic restraint stress (6 weeks)	Weight↑* TC, TG↑* HDL-C↓*, LDL-C↑* AST, ALT↑* Glucose↑* Insulin↑*	OFT* SIT*	FST*
Abildgaard *et al.* [133]	44 d old, male Flinders line rats	60 % kcal fat 20 % kcal protein 20 % kcal carbohydrate	10 % kcal fat 20 % kcal protein 70 % kcal carbohydrate	10	A genetic animal model of depression	Weight↑* Glucose↑* Insulin↑*	EPM*	FST*
Khedr *et al.* [76]	male Wistar rats	72·8 % ordinary chow 25 % fat 2 % cholesterol	Ordinary chow	12	Chronic restraint stress (6 weeks)	Weight↑* TC↑*, TAG↑* HDL-cholesterol↓*, LDL-cholesterol↑* Glucose↑* Insulin↑*	OFT*	SIT* FST*

–, Not reported; ↑, increase *v.* control diet; EPM, elevated plus-maze; OFT, open field test; ORT, object recognition test; LDT, light and dark test; FST, forced swim test; TST, tail suspension test; SLA, spontaneous locomotor activity score; SIT, social interaction test; SPT, sucrose preference test; TC, total cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
*$P < 0{\cdot}05$ was considered significant.

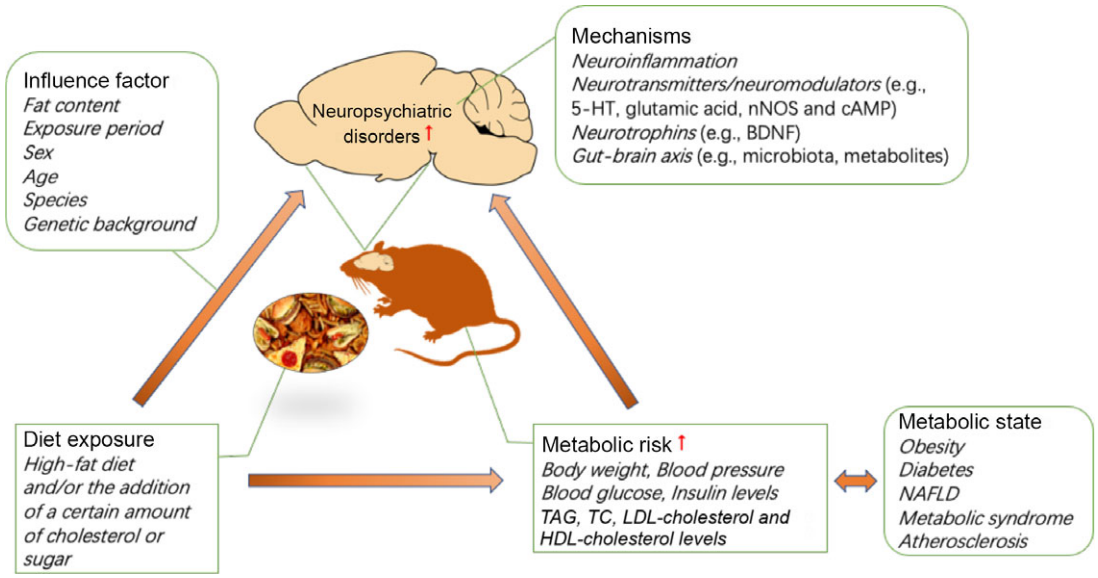

Fig. 1. Impact of diet and metabolic risk on neuropsychiatric disorders. BDNF, brain-derived neurotrophic factor; cAMP, 3′,5′-cyclic AMP; HFD, high-fat diet; 5-HT, 5-hydroxytryptamine; NAFLD, non-alcoholic fatty liver disease; nNOS, neuronal nitric oxide synthase; TC, total cholesterol.

involving female mice, and the direction of the sex differences in any individual behavioural test has not been well described. Future studies should investigate the extensive contributions of sex to neurobehavioural outcomes. It is not clear how diet affects anxiety- and depression-related behaviours, while the strong foundation of the literature supports continued investigation of the mechanisms of diet-induced neuropsychiatric behaviour. In addition to diet, metabolic conditions can increase the risk of neuropsychiatric diseases. Individual metabolic status are highly correlated with diet, so it is difficult to distinguish their contribution to individual neuropsychiatric disorders. Currently, epidemiological studies are complicated by individual differences in diet and nutrition, but the dietary pattern and exposure period can be precisely controlled in animal models. To date, most studies have used rodent models, yielding some interesting results. The mechanisms by which diet induces anxiety/depressive-like behaviour may involve neuroinflammation, neurotransmitters/neuromodulators (e.g. 5-HT, glutamic acid, neuronal nitric oxide synthase and cAMP), neurotrophins (e.g. BDNF) and the gut–brain axis (e.g. microbiota, metabolites) (see Fig. 1). Further studies are needed to determine the cellular and neural circuit mechanisms governing the complex relationship between diet, metabolic state and neuropsychiatric behaviour. Furthermore, non-human primates have been used to model mood disorders for several decades. The success of this paradigm is related to the comparable cognitive skills, brain morphology and social complexity between adult monkeys and humans[112]. Therefore, in addition to rodent models, this field could benefit from additional studies of non-human primate models. Altogether, the presented literature has provided reliable evidence for the association between diet and neuropsychiatric disorders, and future research should be focused on elucidating the mechanism and identifying the contribution of diet and diet-induced metabolic risk to neuropsychiatric disorders, which can form the basis for future clinical dietary intervention strategies for neuropsychiatric disorders.

Acknowledgements

This work was supported in part by the Traditional Chinese Medicine Bureau of Guangdong in China (no. 20161065 and 20201075), the National Health and Family Planning Commission of Guangdong in China (no. A2016583, A2017228, A2017140, A2020137 and A2021374), the Natural Science Foundation of Guangdong in China (no. 2016A030313824), the Undergraduate Training Programs for Innovation and Entrepreneurship of Jinan University in China (no. CX20157 and CX20145), the 'Challenge Cup' Undergraduate Academic Science and Technology Curriculum of Jinan University in China (no. 19113028), the 22nd Batch of Teaching Reform Research Projects of Jinan University (JG2020080) and Teaching Quality and Teaching Reform Project of Undergraduate University of Guangdong in China (2017 and 2020).

Y. L. and C. L. designed the study; L. Z. and Y. T. analysed data; S. Z. and X. C. edited for English; Y. L. wrote the manuscript, and C. L. revised the manuscript. All the authors read and approved the manuscript.

The authors declare that there are no conflicts of interest.

References

1. Vos T, Allen C, Arora M, *et al.* (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **389**, 1545–1602. https://doi.org/10.1016/S0140–6736(16)31678–6.
2. Murray CJL & Lopez AD (1997) Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* **349**, 1498–1504. https://doi.org/10.1016/S0140–6736(96)07492–2.
3. Andrade L, Caraveo-Anduaga JJ, Berglund P, *et al.* (2003) The epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) surveys. *Int J Methods Psychiatr Res* **12**, 3–21. https://doi.org/10.1002/mpr.138.

4. Craske MG & Stein MB (2016) Anxiety. *Lancet* **388**, 3048–3059.
5. Simpson HB, Neria Y, Lewis-Fernández R, *et al.* (2010) *Anxiety Disorders: Theory, Research, and Clinical Perspectives*. United Kingdom: Cambridge University Press.
6. Kessler RC, Berglund P, Demler O, *et al.* (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* **62**, 593–602.
7. Mullins N, Bigdeli TB, Børglum AD, *et al.* (2019) GWAS of suicide attempt in psychiatric disorders and association with major depression polygenic risk scores. *Am J Psychiatry* **176**, 651–660. https://doi.org/10.1176/appi.ajp.2019.18080957.
8. Wong CH, Siah KW & Lo AW (2019) Estimation of clinical trial success rates and related parameters. *Biostatistics* **20**, 366. https://doi.org/10.1093/biostatistics/kxx069.
9. Blüher M (2019) Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol* **15**, 288–298.
10. Sarwar N, Gao P, Kondapally Seshasai SR, *et al.* (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* **376**, 958. https://doi.org/10.1016/S0140–6736(10)60484–9.
11. Younossi Z, Anstee QM, Marietti M, *et al.* (2018) Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention . *Nat Rev Gastroenterol Hepatol* **15**, 11–20.
12. Eslam M, Sanyal AJ, George J, *et al.* (2020) MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* **158**, 1999–2014. https://doi.org/10.1053/j.gastro.2019.11.312.
13. Zheng Y, Ley SH & Hu FB (2018) Global aetiology and epidemiology of type 2 diabetes mellitus and its complications . *Nat Rev Endocrinol* **14**, 88-98.
14. Eslamparast T, Tandon P & Raman M (2017) Dietary composition independent of weight loss in the management of non-alcoholic fatty liver disease. *Nutrients* **9**, 800.
15. Wong SK, Chin KY, Suhaimi FH, *et al.* (2016) Animal models of metabolic syndrome: a review. *Nutr Metab* **13**, 65.
16. Santhekadur PK, Kumar DP & Sanyal AJ (2018) Preclinical models of non-alcoholic fatty liver disease. *J Hepatol* **68**, 230–237.
17. Roy T & Lloyd CE (2012) Epidemiology of depression and diabetes: a systematic review. *J Affect Disord* **142**, S8–21. https://doi.org/10.1016/S0165–0327(12)70004–6.
18. Schmitz N, Deschênes SS, Burns RJ, *et al.* (2016) Depression and risk of type 2 diabetes: the potential role of metabolic factors. *Mol Psychiatry* **21**, 1726–1732. https://doi.org/10.1038/mp.2016.7.
19. Jebeile H, Gow ML, Baur LA, *et al.* (2019) Association of pediatric obesity treatment, including a dietary component, with change in depression and anxiety: a systematic review and meta-analysis. *JAMA Pediatr* **173**, e192841. https://doi.org/10.1001/jamapediatrics.2019.2841.
20. Semenkovich K, Brown ME, Svrakic DM, *et al.* (2015) Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. *Drugs* **75**, 577–587. https://doi.org/10.1007/s40265–015–0347–4.
21. Vancampfort D, Correll CU, Galling B, *et al.* (2016) Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry* **15**, 166–174. https://doi.org/10.1002/wps.20309.
22. Kim D, Yoo ER, Li AA, *et al.* (2019) Depression is associated with non-alcoholic fatty liver disease among adults in the United States. *Aliment Pharmacol Ther* **50**, 590–598.
23. Jung JY, Park SK, Oh C-M, *et al.* (2019) Non-alcoholic fatty liver disease and its association with depression in Korean general population. *J Korean Med Sci* **34**, e199.
24. Adan RAH, van der Beek EM, Buitelaar JK, *et al.* (2019) Nutritional psychiatry: towards improving mental health by what you eat. *Eur Neuropsychopharmacol* **29**, 1321–1332.
25. Cryan JF, O'Riordan KJ, Sandhu K, *et al.* (2020) The gut microbiome in neurological disorders. *Lancet Neurol* **19**, 179–194.
26. Akil H, Gordon J, Hen R, *et al.* (2018) Treatment resistant depression: a multi-scale, systems biology approach. *Neurosci Biobehav Rev* **84**, 272–288.
27. Vogelzangs N, Beekman ATF, Boelhouwer IG, *et al.* (2011) Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. *J Clin Psychiatry* **72**, 598–604. https://doi.org/10.4088/JCP.10m06559.
28. Leite F, Leite Â, Rasini E, *et al.* (2018) Dopaminergic pathways in obesity-associated immuno-metabolic depression. *Psychol Med* **48**, 2273–2275.
29. Lamers F, Milaneschi Y & Penninx B (2019) Immune-metabolic depression: evidence for a subtype of depression. *Eur Neuropsychopharmacol* **29**, S2.
30. Oliver G & Wardle J (1999) Perceived effects of stress on food choice. *Physiol Behav* **66**, 511-515. https://doi.org/10.1016/S0031–9384(98)00322–9.
31. Leigh Gibson E (2006) Emotional influences on food choice: sensory, physiological and psychological pathways. *Physiol Behav* **89**, 53–61. https://doi.org/10.1016/j.physbeh.2006.01.024.
32. Dallman MF (2010) Stress-induced obesity and the emotional nervous system. *Trends Endocrinol Metab* **21**, 159–165.
33. Gururajan A, Reif A, Cryan JF, *et al.* (2019) The future of rodent models in depression research. *Nat Rev Neurosci* **20**, 686–701.
34. Cryan JF & Holmes A (2005) Model organisms: the ascent of mouse: advances in modelling human depression and anxiety. *Nat Rev Drug Discov* **4**, 775–790.
35. Hintze KJ, Benninghoff AD, Cho CE, *et al.* (2018) Modeling the western diet for preclinical investigations. *Adv Nutr* **9**, 263–271.
36. Hollander JA, Cory-Slechta DA, Jacka FN, *et al.* (2020) Beyond the looking glass: recent advances in understanding the impact of environmental exposures on neuropsychiatric disease. *Neuropsychopharmacology* **45**, 1086–1096.
37. File SE & Seth P (2003) A review of 25 years of the social interaction test. *Eur J Pharmacol* **463**, 35–53.
38. Fernandez F, Misilmeri MA, Felger JC, *et al.* (2004) Nociceptin/orphanin FQ increases anxiety-related behavior and circulating levels of corticosterone during neophobic tests of anxiety. *Neuropsychopharmacology* **29**, 59–71. https://doi.org/10.1038/sj.npp.1300308.
39. Walf AA & Frye CA (2007) The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. *Nat Protoc* **2**, 322–328. https://doi.org/10.1038/nprot.2007.44.
40. Takao K & Miyakawa T (2006) Light/dark transition test for mice. *J Vis Exp* 104. https://doi.org/10.3791/104.
41. Petit-Demouliere B, Chenu F & Bourin M (2005) Forced swimming test in mice: a review of antidepressant activity. *Psychopharmacology (Berl)* **177**, 245–255.
42. Steru L, Chermat R, Thierry B, *et al.* (1985) The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology (Berl)* **85**, 367–370. https://doi.org/10.1007/BF00428203.
43. Eagle A, Mazei-Robison M & Robison A (2016) Sucrose preference test to measure stress-induced anhedonia. *Bio-Protocol* 1822. https://doi.org/10.21769/bioprotoc.1822.

44. Hariri N & Thibault L (2010) High-fat diet-induced obesity in animal models. *Nutr Res Rev* **23**, 270–299. https://doi.org/10.1017/S0954422410000168.
45. Willebrords J, Pereira IVA, Maes M, *et al.* (2015) Strategies, models and biomarkers in experimental non-alcoholic fatty liver disease research. *Prog Lipid Res* **59**, 106–125.
46. Chudasama HP & Bhatt PA (2009) Evaluation of anti-obesity activity of duloxetine in comparison with sibutramine along with its anti-depressant activity: an experimental study in obese rats. *Can J Physiol Pharmacol* **87**, 900–907.
47. Aslani S, Vieira N, Marques F, *et al.* (2015) The effect of high-fat diet on rat's mood, feeding behavior and response to stress. *Transl Psychiatry* **5**, e684.
48. Ganji A, Salehi I, Sarihi A, *et al.* (2017) Effects of Hypericum Scabrum extract on anxiety and oxidative stress biomarkers in rats fed a long-term high-fat diet. *Metab Brain Dis* **32**, 503–511.
49. Liu W, Wang Y, Li H, *et al.* (2016) The role of nitric oxide in the antidepressant actions of 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside in insulin-resistant mice. *Psychosom Med* **78**, 102–112.
50. Liu W, Zhai X, Li H, *et al.* (2014) Depression-like behaviors in mice subjected to co-treatment of high-fat diet and corticosterone are ameliorated by AICAR and exercise. *J Affect Disord* **156**, 171–177.
51. Zemdegs J, Quesseveur G, Jarriault D, *et al.* (2016) High-fat diet-induced metabolic disorders impairs 5-HT function and anxiety-like behavior in mice. *Br J Pharmacol* **173**, 2095–2110.
52. Zemdegs J, Martin H, Pintana H, *et al.* (2019) Metformin promotes anxiolytic and antidepressant-like responses in insulin-resistant mice by decreasing circulating branched-chain amino acids. *J Neurosci* **39**, 5935–5948.
53. de Noronha SR, Campos GV, Abreu AR, *et al.* (2017) High fat diet induced-obesity facilitates anxiety-like behaviors due to GABAergic impairment within the dorsomedial hypothalamus in rats. *Behav Brain Res* **316**, 38–46. https://doi.org/10.1016/j.bbr.2016.08.042.
54. Agusti A, Moya-Pérez A, Campillo I, *et al.* (2018) Bifidobacterium pseudocatenulatum CECT 7765 ameliorates neuroendocrine alterations associated with an exaggerated stress response and anhedonia in obese mice. *Mol Neurobiol* **55**, 5337–5352.
55. Yang JL, Liu DX, Jiang H, *et al.* (2016) The effects of high-fat-diet combined with chronic unpredictable mild stress on depression-like behavior and Leptin/LepRb in male rats. *Sci Rep* **6**, 35239.
56. Sweeney P, O'Hara K, Xu Z, *et al.* (2017) HFD-induced energy states-dependent bidirectional control of anxiety levels in mice. *Int J Obes (Lond)* **41**, 1237–1245.
57. Wu F, Guo X, Zhang M, *et al.* (2019) An Akkermansia muciniphila subtype alleviates high-fat diet-induced metabolic disorders and inhibits the neurodegenerative process in mice. *Anaerobe* **61**, 102138.
58. Alonso-Caraballo Y, Hodgson KJ, Morgan SA, *et al.* (2019) Enhanced anxiety-like behavior emerges with weight gain in male and female obesity-susceptible rats. *Behav Brain Res* **360**, 81–93.
59. Dutheil S, Ota KT, Wohleb ES, *et al.* (2016) High-fat diet induced anxiety and anhedonia: impact on brain homeostasis and inflammation. *Neuropsychopharmacology* **41**, 1874–1887.
60. Tsai S-F, Wu H-T, Chen P-C, *et al.* (2018) High-fat diet suppresses the astrocytic process arborization and downregulates the glial glutamate transporters in the hippocampus of mice. *Brain Res* **1700**, 66–77.
61. Huang Y, Zhang W, Ding Z, *et al.* (2019) FoxO1 inhibitor AS1842856 prevents the depression-like behaviors induced by chronic high-fat diet in mice. *Chin J Drug Depend* **28**, 426–431.
62. Gainey SJ, Kwakwa KA, Bray JK, *et al.* (2016) Short-term high-fat diet (HFD) induced anxiety-like behaviors and cognitive impairment are improved with treatment by glyburide. *Front Behav Neurosci* **10**, 156. https://doi.org/10.3389/fnbeh.2016.00156.
63. Almeida-Suhett CP, Graham A, Chen Y, *et al.* (2017) Behavioral changes in male mice fed a high-fat diet are associated with IL-1β expression in specific brain regions. *Physiol Behav* **169**, 130–140.
64. Bridgewater LC, Zhang C, Wu Y, *et al.* (2017) Gender-based differences in host behavior and gut microbiota composition in response to high fat diet and stress in a mouse model. *Sci Rep* **7**, 10776.
65. Bruce-Keller AJ, Salbaum JM, Luo M, *et al.* (2015) Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. *Biol Psychiatry* **77**, 607–615.
66. Hassan AM, Mancano G, Kashofer K, *et al.* (2019) High-fat diet induces depression-like behaviour in mice associated with changes in microbiome, Neuropeptide Y, and brain metabolome. *Nutr Neurosci* **22**, 877–893.
67. Ogrodnik M, Zhu Y, Langhi LGP, *et al.* (2019) Obesity-induced cellular senescence drives anxiety and impairs neurogenesis. *Cell Metab* **29**, 1061–1077.e8.
68. Park H-S, Lee J-M, Cho H-S, *et al.* (2017) Physical exercise ameliorates mood disorder-like behavior on high fat diet-induced obesity in mice. *Psychiatry Res* **250**, 71–77.
69. Vagena E, Ryu JK, Baeza-Raja B, *et al.* (2019) A high-fat diet promotes depression-like behavior in mice by suppressing hypothalamic PKA signaling. *Transl Psychiatry* **9**, 141.
70. Yamada N, Katsuura G, Ochi Y, *et al.* (2011) Impaired CNS leptin action is implicated in depression associated with obesity. *Endocrinology* **152**, 2634–2643.
71. Wu H, Liu Q, Kalavagunta PK, *et al.* (2018) Normal diet Vs High fat diet – a comparative study: behavioral and neuroimmunological changes in adolescent male mice. *Metab Brain Dis* **33**, 177–190.
72. Pan Q, Liu Q, Wan R, *et al.* (2019) Selective inhibition of intestinal 5-HT improves neurobehavioral abnormalities caused by high-fat diet mice. *Metab Brain Dis* **34**, 747–761.
73. Wu H, Lv W, Pan Q, *et al.* (2019) Simvastatin therapy in adolescent mice attenuates HFD-induced depression-like behavior by reducing hippocampal neuroinflammation. *J Affect Disord* **243**, 83–95.
74. Magdy YM, El-Kharashi OA, Nabih ES, *et al.* (2017) Potential involvement of JNK1 repression in the hepatic effect of sitagliptin and metformin in rats subjected to high fat diet and chronic mild distress. *Biomed Pharmacother* **85**, 225–238.
75. Higarza SG, Arboleya S, Gueimonde M, *et al.* (2019) Neurobehavioral dysfunction in nonalcoholic steatohepatitis is associated with hyperammonemia, gut dysbiosis, and metabolic and functional brain regional deficits. *Plos One* **14**, e0223019.
76. Khedr SA, Elmelgy AA, El-Kharashi OA, *et al.* (2018) Metformin potentiates cognitive and antidepressant effects of fluoxetine in rats exposed to chronic restraint stress and high fat diet: potential involvement of hippocampal c-Jun repression. *Naunyn Schmiedebergs Arch Pharmacol* **391**, 407–422.
77. Hu H, Xu Y, Liu C, *et al.* (2014) Changes in behavior and in brain glucose metabolism in rats after nine weeks on a high fat diet: a randomized controlled trial. *Shanghai Arch Psychiatry* **26**, 129–137.

British Journal of Nutrition

78. Strekalova T, Evans M, Costa-Nunes J, *et al.* (2015) Tlr4 upregulation in the brain accompanies depression- and anxiety-like behaviors induced by a high-cholesterol diet. *Brain Behav Immun* **48**, 42–47.
79. Strekalova T, Costa-Nunes JP, Veniaminova E, *et al.* (2016) Insulin receptor sensitizer, dicholine succinate, prevents both Toll-like receptor 4 (TLR4) upregulation and affective changes induced by a high-cholesterol diet in mice. *J Affect Disord* **196**, 109–116.
80. Metwally FM, Rashad H & Mahmoud AA (2019) Morus alba L. Diminishes visceral adiposity, insulin resistance, behavioral alterations via regulation of gene expression of leptin, resistin and adiponectin in rats fed a high-cholesterol diet. *Physiol Behav* **201**, 1–11.
81. Rebolledo-Solleiro D, Roldán-Roldán G, Díaz D, *et al.* (2017) Increased anxiety-like behavior is associated with the metabolic syndrome in non-stressed rats. *PLOS ONE* **12**, e0176554.
82. Choudhary P, Pacholko AG, Palaschuk J, *et al.* (2018) The locus coeruleus neurotoxin, DSP4, and/or a high sugar diet induce behavioral and biochemical alterations in wild-type mice consistent with Alzheimers related pathology. *Metab Brain Dis* **33**, 1563–1571.
83. Xu W, Yu J, Jiang Z, *et al.* (2019) The impact of subchronic low-dose exposure to nonylphenol on depression-like behaviors in high-sucrose and high-fat diet induced rats. *Toxicology* **414**, 27–34.
84. Soto M, Herzog C, Pacheco JA, *et al.* (2018) Gut microbiota modulate neurobehavior through changes in brain insulin sensitivity and metabolism. *Mol Psychiatry* **23**, 2287–2301.
85. Batschauer T, Cordeiro JM, Simas BB, *et al.* (2020) Behavioral, cardiovascular and endocrine alterations induced by chronic stress in rats fed a high-fat diet. *Physiol Behav* **223**, 113013. https://doi.org/10.1016/j.physbeh.2020.113013.
86. André C, Dinel A, Ferreira G, *et al.* (2014) Diet-induced obesity progressively alters cognition, anxiety-like behavior and lipopolysaccharide-induced depressive-like behavior: focus on brain indoleamine 2,3-dioxygenase activation. *Brain Behav Immun* **41**, 10–21.
87. Peris-Sampedro F, Mounib M, Schéle E, *et al.* (2019) Impact of free-choice diets high in fat and different sugars on metabolic outcome and anxiety-like behavior in rats. *Obesity (Silver Spring)* **27**, 409–419.
88. Ji S, Wang L & Li L (2019) Effect of metformin on short-term high-fat diet-induced weight gain and anxiety-like behavior and the gut microbiota. *Front Endocrinol (Lausanne)* **10**, 704.
89. Gancheva S, Galunska B & Zhelyazkova-Savova M (2017) Diets rich in saturated fat and fructose induce anxiety and depression-like behaviours in the rat: is there a role for lipid peroxidation? *Int J Exp Pathol* **98**, 296–306.
90. Pyndt Jørgensen B, Hansen JT, Krych L, *et al.* (2014) A possible link between food and mood: dietary impact on gut microbiota and behavior in BALB/c mice. *PLOS ONE* **9**, e103398.
91. Nakajima S, Fukasawa K, Gotoh M, *et al.* (2019) Saturated fatty acid is a principal cause of anxiety-like behavior in diet-induced obese rats in relation to serum lysophosphatidyl choline level. *Int J Obes (Lond)* **44**, 727–738. https://doi.org/10.1038/s41366–019–0468-z.
92. Del Rio D, Morales L, Ruiz-Gayo M, *et al.* (2016) Effect of high-fat diets on mood and learning performance in adolescent mice. *Behav Brain Res* **311**, 167–172.
93. Del Rosario A, McDermott MM & Panee J (2012) Effects of a high-fat diet and bamboo extract supplement on anxiety- and depression-like neurobehaviours in mice. *Br J Nutr* **108**, 1143–1149.
94. Karth MM, Baugher BJ, Daly N, *et al.* (2019) Brain 5-HT deficiency prevents antidepressant-like effects of high-fat-diet and blocks high-fat-diet-induced GSK3$β$ phosphorylation in the hippocampus. *Front Mol Neurosci* **12**, 298.
95. Kurhe Y & Mahesh R (2017) Ondansetron ameliorates depression associated with obesity in high-fat diet fed experimental mice: an investigation-based on the behavioral, biochemical, and molecular approach. *Indian J Pharmacol* **49**, 290–296.
96. Kurhe Y, Mahesh R & Devadoss T (2015) QCM-4, a 5-HT3 receptor antagonist ameliorates plasma HPA axis hyperactivity, leptin resistance and brain oxidative stress in depression and anxiety-like behavior in obese mice. *Biochem Biophys Res Commun* **456**, 74–79.
97. Kurhe Y, Mahesh R & Devadoss T (2017) Novel 5-HT3 receptor antagonist QCM-4 attenuates depressive-like phenotype associated with obesity in high-fat-diet-fed mice. *Psychopharmacology (Berl)* **234**, 1165–1179.
98. Kurhe Y & Mahesh R (2015) Ondansetron attenuates comorbid depression and anxiety associated with obesity by inhibiting the biochemical alterations and improving serotonergic neurotransmission. *Pharmacol Biochem Behav* **136**, 107–116.
99. Xu L, Xu S & Lin L (2018) High-fat diet mediates anxiolytic-like behaviors in a time-dependent manner through the regulation of SIRT1 in the brain. *Neuroscience* **372**, 237–245.
100. Sharma S & Fulton S (2013) Diet-induced obesity promotes depressive-like behaviour that is associated with neural adaptations in brain reward circuitry. *Int J Obes (Lond)* **37**, 382–389.
101. Suárez J, Rivera P, Aparisi Rey A, *et al.* (2019) Adipocyte cannabinoid CB1 receptor deficiency alleviates high fat diet-induced memory deficit, depressive-like behavior, neuroinflammation and impairment in adult neurogenesis. *Psychoneuroendocrinology* **110**, 104418.
102. Tomiga Y, Yoshimura S, Ito A, *et al.* (2017) Exercise training rescues high fat diet-induced neuronal nitric oxide synthase expression in the hippocampus and cerebral cortex of mice. *Nitric oxide Biol Chem* **66**, 71–77.
103. Tomiga Y, Yoshimura S, Ra S-G, *et al.* (2019) Anxiety-like behaviors and hippocampal nNOS in response to diet-induced obesity combined with exercise. *J Physiol Sci* **69**, 711–722.
104. Kaczmarczyk MM, Machaj AS, Chiu GS, *et al.* (2013) Methylphenidate prevents high-fat diet (HFD)-induced learning/memory impairment in juvenile mice. *Psychoneuroendocrinology* **38**, 1553–1564.
105. Abildgaard A, Elfving B, Hokland M, *et al.* (2017) Probiotic treatment reduces depressive-like behaviour in rats independently of diet. *Psychoneuroendocrinology* **79**, 40–48.
106. Feng M, Crowley NA, Patel A, *et al.* (2019) Reversal of a treatment-resistant, depression-related brain state with the Kv7 channel opener retigabine. *Neuroscience* **406**, 109–125.
107. Finger BC, Dinan TG & Cryan JF (2011) High-fat diet selectively protects against the effects of chronic social stress in the mouse. *Neuroscience* **192**, 351–360. https://doi.org/10.1016/j.neuroscience.2011.06.072.
108. Blaisdell AP, Lau YLM, Telminova E, *et al.* (2014) Food quality and motivation: a refined low-fat diet induces obesity and impairs performance on a progressive ratio schedule of instrumental lever pressing in rats. *Physiol Behav* **128**, 220–225.
109. Beaulieu JM, Zhang X, Rodriguiz RM, *et al.* (2008) Role of GSK3β in behavioral abnormalities induced by serotonin deficiency. *Proc Natl Acad Sci USA* **105**, 1333–1338. https://doi.org/10.1073/pnas.0711496105.
110. Jacobsen JPR, Siesser WB, Sachs BD, *et al.* (2012) Deficient serotonin neurotransmission and depression-like serotonin biomarker alterations in tryptophan hydroxylase 2 (Tph2)

British Journal of Nutrition

loss-of-function mice. *Mol Psychiatry* **17**, 694–704. https://doi.org/10.1038/mp.2011.50.
111. Jacobson LH & Cryan JF (2007) Feeling strained? Influence of genetic background on depression-related behavior in mice: a review. *Behav. Genet* **37**, 171–213.
112. Nelson EE & Winslow JT (2009) Non-human primates: model animals for developmental psychopathology. *Neuropsychopharmacology* **34**, 90–105.
113. Salk RH, Hyde JS & Abramson LY (2017) Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms. *Psychol Bull* **143**, 783–822. https://doi.org/10.1037/bul0000102.
114. Baker KD, Loughman A, Spencer SJ, *et al.* (2017) The impact of obesity and hypercaloric diet consumption on anxiety and emotional behavior across the lifespan. *Neurosci Biobehav Rev* **83**, 173–182.
115. Sullivan EL, Nousen EK & Chamlou KA (2014) Maternal high fat diet consumption during the perinatal period programs offspring behavior. *Physiol Behav* **123**, 236–242.
116. Hoyer D, Hannon JP & Martin GR (2002) Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav* **71**, 533–554.
117. Enge S, Fleischhauer M, Gärtner A, *et al.* (2016) Brain-derived neurotrophic factor (Val66Met) and serotonin transporter (5-HTTLPR) polymorphisms modulate plasticity in inhibitory control performance over time but independent of inhibitory control training. *Front Hum Neurosci* **71**, 533–554. https://doi.org/10.3389/fncel.2016.00370.
118. Sumaya IC, Bailey D & Catlett SL (2016) Differential effects of a short-term high-fat diet in an animal model of depression in rats treated with the 5-HT3 receptor antagonist, ondansetron, the 5-HT3 receptor agonist, 2-methyl-5-HT, and the SSRI, fluoxetine. *Pharmacol Biochem Behav* **144**, 78–84. https://doi.org/10.1016/j.pbb.2016.03.005.
119. Fakhfouri G, Rahimian R, Dyhrfjeld-Johnsen J, *et al.* (2019) 5-HT3 receptor antagonists in neurologic and neuropsychiatric disorders: the iceberg still lies beneath the surface. *Pharmacol Rev* **71**, 383–412. https://doi.org/10.1124/pr.118.015487.
120. Masood A, Nadeem A, Mustafa SJ, *et al.* (2008) Reversal of oxidative stress-induced anxiety by inhibition of phosphodiesterase-2 in mice. *J Pharmacol Exp Ther* **326**, 369–379. https://doi.org/10.1124/jpet.108.137208.
121. Valles-Colomer M, Falony G, Darzi Y, *et al.* (2019) The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat Microbiol* **4**, 623–632. https://doi.org/10.1038/s41564–018–0337-x.
122. Sherwin E, Dinan TG & Cryan JF (2018) Recent developments in understanding the role of the gut microbiota in brain health and disease. *Ann NY Acad Sci* **1420**, 5–25.
123. Murphy EA, Velazquez KT, Herbert KM (2015) Influence of high-fat diet on gut microbiota: a driving force for chronic disease risk. *Curr Opin Clin Nutr Metab Care* **18**, 515–520.
124. Sandhu KV, Sherwin E, Schellekens H, *et al.* (2017) Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry. *Transl Res* **179**, 223–244.
125. Allen NB & Badcock PBT (2003) The social risk hypothesis of depressed mood: evolutionary, psychosocial, and neurobiological perspectives. *Psychol Bull.*
126. Chuang J-C, Krishnan V, Yu HG, *et al.* (2010) A beta3-adrenergic-leptin-melanocortin circuit regulates behavioral and metabolic changes induced by chronic stress. *Biol Psychiatry* **67**, 1075–1082.
127. Arcego DM, Toniazzo AP, Krolow R, *et al.* (2018) Impact of high-fat diet and early stress on depressive-like behavior and hippocampal plasticity in adult male rats. *Mol Neurobiol* **55**, 2740–2753.
128. Otsuka A, Shiuchi T, Chikahisa S, *et al.* (2019) Sufficient intake of high-fat food attenuates stress-induced social avoidance behavior. *Life Sci* **219**, 219–230.
129. Willner P, Towell A, Sampson D, *et al.* (1987) Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. *Psychopharmacology (Berl)* **93**, 358–364. https://doi.org/10.1007/BF00187257.
130. Willner P (1997) Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. *Psychopharmacology (Berl)* **134**, 319–329.
131. Overstreet DH & Russell RW (1982) Selective breeding for diisopropyl fluorophosphate-sensitivity: behavioural effects of cholinergic agonists and antagonists. *Psychopharmacology (Berl)* **78**, 150–155. https://doi.org/10.1007/BF00432254.
132. Overstreet DH, Friedman E, Mathé AA, *et al.* (2005) The flinders sensitive line rat: a selectively bred putative animal model of depression. *Neurosci Biobehav Rev* **29**, 739–759.
133. Abildgaard A, Solskov L, Volke V, *et al.* (2011) A high-fat diet exacerbates depressive-like behavior in the Flinders Sensitive Line (FSL) rat, a genetic model of depression. *Psychoneuroendocrinology* **36**, 623–633.