REVIEW

Obesity, Cardiovascular and Neurodegenerative Diseases: Potential Common Mechanisms

Jaroslav KUNEŠ[1,2], Silvie HOJNÁ[1], Lucia MRÁZIKOVÁ[2], Augusto MONTEZANO[3], Rhian M. TOUYZ[3,4], Lenka MALETÍNSKÁ[2]

[1]Institute of Physiology Czech Academy of Sciences, Prague, Czech Republic, [2]Institute of Organic Chemistry and Biochemistry Czech Academy of Sciences, Prague, Czech Republic, [3]Research Institute of the McGill University Health Centre, Montreal, Canada, [4]Department of Medicine and Department of Family Medicine, McGill University, Montreal, Canada

Summary

The worldwide increase in the incidence of obesity and cardiovascular and neurodegenerative diseases, e.g. Alzheimer's disease, is related to many factors, including an unhealthy lifestyle and aging populations. However, the interconnection between these diseases is not entirely clear, and it is unknown whether common mechanisms underlie these conditions. Moreover, there are currently no fully effective therapies for obesity and neurodegeneration. While there has been extensive research in preclinical models addressing these issues, the experimental findings have not been translated to the clinic. Another challenge relates to the time of onset of individual diseases, which may not be easily identified, since there are no specific indicators or biomarkers that define disease onset. Hence knowing when to commence preventive treatment is unclear. This is especially pertinent in neurodegenerative diseases, where the onset of the disease may be subtle and occur decades before the signs and symptoms manifest. In metabolic and cardiovascular disorders, the risk may occur in-utero, in line with the concept of fetal programming. This review provides a brief overview of the link between obesity, cardiovascular and neurodegenerative diseases and discusses potential common mechanisms including the role of the gut microbiome.

Corresponding authors

Jaroslav Kuneš, Institute of Physiology AS CR. Vídeňská 1083, Prague 4, CS-14220. Czech Republic. E-mail: kunes@biomed.cas.cz; Rhian M. Touyz, Research Institute of McGill University Health Centre (RI-MUHC), 1001, boul. Décarie, ES1.5066.6, Québec, Canada HYA 3/1. E-mail: rhian.touyz@mcgill.ca

Introduction

The current lifestyle patterns clearly contribute to the worldwide increase in the incidence of obesity, cardiovascular diseases (CVD) and neurodegenerative disorders, including Alzheimer's disease (AD). Increasing aging is one of the main causes of the growing incidence of AD. Despite intensive research in the field of obesity and neurodegeneration, there are still no effective disease-specific therapies. Reasons for this are multifactorial, including lack of understanding of underlying mechanisms of disease, sub-optimal targeting of potential mediators of disease and lack of pre-clinical models that recapitulate disease in patients [1]. Moreover, the developmental window during which the pathological process leading to the respective disease occurs, remains still-defined.

Although it has been suggested that there is a direct relationship between obesity and CVD as well as obesity and neurodegenerative disorders, the exact mechanisms linking these pathologies are elusive.

Clarification of direct relationships is important when looking for an appropriate therapy; however, this is not simple due to multiple interacting factors. In addition, there is inconsistency in the literature. Nakajima *et al.* [2] showed that in individuals with obesity, alterations of cardiac performance with left ventricular enlargement and wall thickening depend not only on excess body weight (BW) but also on the duration of obesity. Several other studies showed similar results suggesting that the risk of all-cause mortality increased in relation to the number of years that an individual is obese, and this is independent of current body mass index (BMI) [3]. However, other findings based on data from the Framingham Heart Study [4] showed a positive association between obesity and the incidence of hypertension in women. This association disappeared when the increased risk of incidence was adjusted for current BMI, suggesting that the mechanism by which obesity may influence blood pressure (BP) elevation is more immediate and that long-term exposure to increased BW does not worsen the development of hypertension beyond the level of the BMI attained [4].

One of the potential mechanisms whereby obesity may increase the risk of neurodegenerative diseases is a change in cerebral blood perfusion. This perfusion is regulated by functional and structural changes in the cerebral vasculature. Functional changes in vasoconstriction and vasodilation influence myogenic tone, while structural changes involve vascular remodeling in cerebral vessels. Disorders of cerebral vessels could play a significant role in the brain, leading to minor and/or massive cerebral bleeding. Changes in the mechanical and architectural properties of the cerebral vasculature, specifically internal remodeling of larger cerebral arteries, are common findings in hypertensive populations [5]. Moreover, it was demonstrated that cerebral arterioles change their properties during aging [6]. These changes are characterized as reduced distensibility and atrophy. The reduced distensibility means that cerebral vessels may not dilate effectively, predisposing them to cerebral ischemia and infarction during aging.

Cerebral small vessel disease (cSVD), a common risk factor for cognitive impairment [7], includes lacunes, cerebral microbleeds, and perivascular spaces as pathological changes in the brain [8]. The clinical manifestations of cSVD present a variety of pathologies, including stroke, changes from mild to progressive cognitive decline and dementia. [9]. Kim

et al. [10] suggested that obesity affects cerebral small vessels through arteriosclerotic vasculopathy. Based on their findings, they postulated that obesity is associated with subclinical and bleeding-prone cerebrovascular disease in the elderly.

This comprehensive review focuses on current knowledge linking obesity, CVD and neurodegenerative disorders, including Alzheimer's disease. The possibility that there are common mechanisms that underlie these conditions is discussed and we provide an update on the potential role of the gut microbiome in these pathologies.

Risk factors in cardiovascular and cerebrovascular diseases
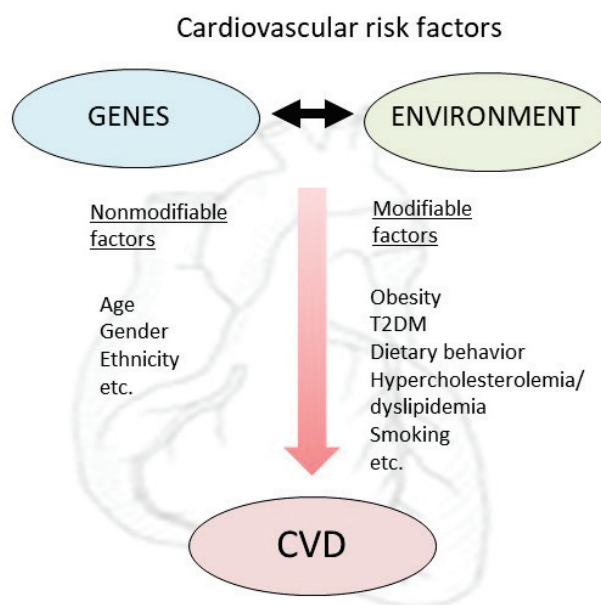
Fig. 1. The scheme showing risk factors for CVD.

Risk factors for CVD include those that are modifiable and those that are nonmodifiable (Fig. 1). Age is an important and potent nonmodifiable risk factor because mortality from CVD gradually increases with age [11]. Another uncontrolled risk factor for CVD is gender. Men have a higher risk of CVD than women. However, in the age group of 65 and older, women who have a myocardial infarction are twice as likely to die as men. In contrast, men under the age of 65 have a much higher risk of experiencing a heart attack. Individuals with a family history of CVD are more likely to develop CVD. This is related to the genetic nature of CVD [12]. Epidemiological studies suggest that polymorphisms of several genes, such as endothelial nitric oxide (NO) synthase [13], angiotensin converting enzyme [14],

angiotensin II type 1 receptor [15] and paraoxonase gene [16,17], increase the risk of coronary artery disease (CAD). However, other genes contributing to the genetic predisposition of these conditions remain to be identified. Another risk factor is ethnicity. For example, Afro-Americans are prone to severe hypertension and obesity and have an increased incidence of CVD compared to Caucasians [18].

There are numerous risk factors that predispose to CVD that can be prevented or controlled. These modifiable risk factors include type 2 diabetes mellitus (T2DM), dietary behavior, hypercholesterolemia/ dyslipidemia, cigarette smoking and obesity. Obesity is an important determinant of CVD. Overweight or individuals with obesity have significantly increased morbidity and mortality related to almost all common CVD [19]. Although the pathogenesis of cardiomyopathy is multifactorial, diabetic dyslipidemia and intramyocardial lipid accumulation are the key pathological features, triggering cellular signaling and modifications of proteins and lipids *via* the generation of toxic metabolic intermediates [19]. There is also a very strong association between cigarette smoking and CVD [20]. However, there are only a few discrepant data regarding the gender differences and the impact of smoking on CVD [21]. Considering the International Survey of Acute Coronary Syndrome in Transitional Countries, Manfrini *et al.* [22] demonstrated that women who were current smokers had a much greater risk of acute coronary syndrome with obstructive CAD than men. Moreover, hyperchole-sterolemia and hypertension increased the risk of obstructive CAD in both genders, although a higher prevalence was seen in women later on [22]. It was suggested that endothelial dysfunction and damage are the main reasons why smoking is a risk factor for CVD [23]. During this process, proatherogenic lipids are increased and oxidized in parallel to a decrease in high-density lipoprotein, induction of inflammation, and the shift toward a procoagulant state in the circulation. The data also clearly showed that secondhand smoking can trigger life-threatening conditions (including in children) [23].

Unhealthy diet as an important risk factor

An unhealthy diet is considered an important risk factor for CVD [24]. While the relationship between serum cholesterol and CVD risk is well established, the association between dietary fat intake and CVD prevention is still debated [25]. However, dietary fat is not the only dietary component that is "bad". Dietary protein has also been suggested to be important especially the association of maternal protein intake during pregnancy in humans with increased risk of metabolic diseases and CVD for offspring [26] (for more details see below). A more controversial issue relates to the impact of sugar consumption on human health [27]. Excess intake of sugar, especially fructose rather than glucose, can promote the development of CVD and T2DM. However, the effect of increased sugar intake on human health is controversial. Several authors have shown that the consumption of sweetened beverages plays an important role in the epidemic of obesity and CVD [28-32]. On the other hand, minimal harmful effect of higher sugar intake on metabolic parameters was also demonstrated [33]. Evidence that the consumption of sweetened beverages can increase the risk of metabolic syndrome is supported by experimental data [34,35].

Chronic hyperglycemia and underlying T2DM are important risk factors for CVD. Epidemiologic evidence revealed that persistence of higher serum glucose levels, even within the sub-diabetic range, leads to higher levels of glycated hemoglobin, which increases the risk of CVD. Reduced levels of glycated hemoglobin seem to be associated with beneficial effects on CVD [36]. Hyperglycemia in pregnancy can predispose to ill effects in the offspring. This "metabolic memory" [37], leads to pathological disturbances in glucose metabolism, insulin and energy balance of the offspring. Molecular mechanisms that may play a role include cellular stress and activation of pro-inflammatory pathways, oxidative stress and cardiovascular complications [37].

As recommended by the World Health Organization the daily amount of dietary salt should be 5 g/day [38], however, the practice is different and is usually higher than 10 g/day in many populations [39]. Recently it has been shown that consumption of chronic high-salt diet is associated not only with CVD but also with several metabolic disorders including obesity, type 2 diabetes and metabolic syndrome in both rodents and human [40-43]. In spite of the fact that high salt intake could predict the development of obesity and insulin resistance [42], the mechanism is not clear. Lanaspa *et al.* [42] demonstrated that high-salt diet in mice activated fructose production in the liver leading to leptin resistance. Moreover, in Sprague-Dawley rats, a high-salt diet leads to increase of insulin resistance in isolated muscle and liver [43]. It is clear that reduction of dietary salt intake is recommended in guidelines for CVD,

T2DM etc. [44].

Unhealthy diets cause systematic inflammation [45]. The Dietary Inflammatory Index (DII®) was established by Hariharan *et al.* [45] to characterize the inflammatory potential of the diet. An association between DII and cardiometabolic risk factors was studied among 31 684 Brazilian adolescents [46]. It was demonstrated that the effect of pro-inflammatory diet is gender dependent, showing for example that pro-inflammatory diet was positively associated with high HOMA-IR among girls and high total cholesterol among boys [46].

Risk factors of cerebrovascular diseases

The cerebral microcirculation is critically involved in the regulation and function of neurons; thus, any impairment of this circulation may be dangerous for their function. Aging plays a major role in cerebral microcirculation impairment and thus is important for age-related cognitive changes [47,48]. Moreover, other factors, such as obesity, diabetes, hypertension, vitamin B_{12}/folate deficiency, etc., trigger neuroinflammation and oxidative stress, which promote cerebral hypoperfusion and glucose hypometabolism [47]. Cerebral hypoperfusion leads to amyloid-β deposition, cerebral amyloid angiopathy and blood-brain barrier disruption. Interestingly, these changes seem to precede cognitive/memory decline (including AD-like pathology), suggesting how important it is to know a precise developmental window(s) important for therapeutic strategies, including pharmacotherapy and changes in lifestyle [47].

Vascular cognitive impairment (VCI) is associated with numerous cerebral vascular pathologies resulting in vascular dementia [49], the second most common cause of dementia after AD. Patients with VCI characteristically have problems with memory, planning, and organization and often suffer from apathy, anxiety and depression. Risk markers for VCI are the same as traditional risk factors for stroke, and these risks may include but are not limited to atrial fibrillation, hypertension, T2DM, and hypercholesterolemia. Carotid intima-media thickness and arterial stiffness are emerging as markers of arterial aging and may also serve as risk markers for VCI [50]. Although it is still accepted that AD is caused primarily by amyloid beta plaques, neurofibrillary pathology, decreased synaptic plasticity and reduced neurogenesis, postmortem studies have shown that cSVD pathology incorporating small cortical and subcortical infarcts, microinfarcts, perivascular spacing and white matter attenuation is commonly found in sporadic as well as in familial AD [51].

Hypertension is a major modifiable risk factor for cerebral vascular disorders, including cSVD. Because pathological changes in BP tend to be directly associated with pathological changes in the brain leading to cognitive decline, one might assume that consistent BP control could lead to optimal brain perfusion and thus eliminate AD and vascular dementia [52]. It is not the purpose of this review to describe in detail the structure of the vascular supply to the brain (for review see [52]); however, it is clear that cerebral capillaries are the primary target of chronic BP elevation. Increased vasoconstriction associated with reduction of the lumen diameter leads to an increase in overall peripheral resistance. Loss of cerebral capillary elasticity due to degeneration of elastin fibers and collagen deposition completely alters the properties of the capillary bed of the brain. In addition, oxidative stress and inflammatory processes, in which pro-inflammatory cytokines like tumor necrosis factor alpha (TNFα) play a crucial role, lead to vascular calcification.

Age-dependent changes

Obesity is the result of an imbalance between energy intake and expenditure. In addition to environmental factors and epigenetic changes, genetic predisposition plays an important role. Obesity in the human population does not have a precise developmental window because obesity is found in children, teenagers and the adult population. According to the Barker theory, some metabolic and cardiovascular diseases may even have a fetal and infantile onset [53]. Prenatal nutritional risk factors may interact with postnatal ones, resulting in mutual strengthening or weakening. For example, rapid weight gain in the first months of life is associated with metabolic syndrome and late-onset obesity, and the combination of low birth weight and rapid weight gain in the first months of life is strongly associated with metabolic syndrome in adulthood [54]. Systemic reviews have shown that a rapid increase in BW in infancy and childhood is a possible determinant of being overweight and obesity later in life [55]. Moreover, interesting information exist about the relation between obesity and metabolic changes in prepubertal children. Barbosa *et al.* [56] divided a cohort of 64 children into healthy lean, healthy obese and unhealthy obese groups and found that fasting insulin levels were the highest in unhealthy obese

children, although all groups presented normal fasting glycemia. Normoglycemia in all groups depends on insulin resistance level driven by circulating insulin being the highest is in unhealthy obese group which maintains their euglycemia [57]. This is in agreement with the notion that insulin resistance may precede, by years, altered circulating glucose levels [58].

Pregnancy and the developmental window during fetal growth are vulnerable periods that can impact health of offspring later in life [59]. An unhealthy diet during pregnancy can influence development of metabolic disorders, such as glucose homeostasis and insulin sensitivity, in the adult offspring [26,60,61]. Malnutrition, including obesity, during pregnancy influences the fetal epigenome and metabolic programming, which predispose to CVD, obesity, and diabetes mellitus [62]. The influence of perinatal diet on cerebrovascular disease is unclear.

The transition from childhood to adolescence is an important phase of development with rapid growth and hormonal and psychological changes. In recent decades, the incidence of overweight and obesity has increased among adolescents [63]. Using a meta-analysis of 49,220 individuals from 63 studies, Friedeman *et al.* [64] showed worsening of cardiovascular risk factors in overweight and obese individuals. While lifestyle modifications are essential during these developmental periods to reduce obesity, pharmacological intervention may also be necessary. Currently, liraglutide (a glucagon-like peptide-1 (GLP-1) analog) has been authorized for the treatment of obesity in adolescents [63]. A randomized, double-blind trial of liraglutide for adolescents with obesity demonstrated that liraglutide together with lifestyle changes led to a significantly greater reduction in the BMI compared to placebo plus lifestyle therapy [65].

Obesity-related cerebrovascular disease

The relationship between obesity and pathological changes in the brain that lead to memory impairment and neurodegenerative disorders is an area of active study [66]. However, mechanisms linking these pathologies are elusive. Insulin resistance appears to be an important factor connecting obesity with cognitive functions [67]. This is supported by the fact that alterations in insulin concentration and insulin receptor function in the brain have been described in AD, and AD is also called "type 3 diabetes" [68]. Studies on different

animal models confirmed the observations in humans that insulin resistance developed by consuming a high-fat (HF) diet increases amyloid-β (Abeta) production and plaque deposition in the brains of transgenic Tg2576 mice [69] and triple transgenic (3xTg-AD) mice [70]. Another possible mechanism is the presence of oxidative stress caused by inflammation [71]. It was demonstrated that proinflammatory cytokines that are able to cross the blood brain barrier (BBB) can affect neuronal processes [72]. Moreover, several studies have demonstrated that peripheral inflammation is able to alter the integrity of the BBB by damaging the tight junctions of microvascular endothelial cells of the BBB [73]. The major components of tight junctions are the proteins claudin, which seems to regulate permeability, and ocludin, which forms the backbone of tight junction strands and seem to be a sensitive indicator of structural changes in the BBB [74]. Thus, these obesity-mediated inflammatory changes can lead to neuroinflammation, followed by subsequent damage to the central nervous system by oxidative stress, which may alter synaptic plasticity, affect the development of neuronal synaptic activity and function and lead to neuronal death [75].

Vascular remodeling and perivascular adipose tissue

Obesity is characterized by fat deposition in adipose tissue (AT), especially in the subcutaneous and visceral areas. However, AT is not only a depot of energy but also an important endocrine organ. In addition to these main fat depots, there are other important fat deposits in the body. These include epicardial, pericardial and perivascular AT, which can play an important role in the development and progression of CVD [76]. Interestingly, the measurement of the size of epicardial AT serves as a powerful potential diagnostic tool in assessing cardiovascular and metabolic risk. Measurement of epicardial AT using transthoracic echocardiography is cost-effective, more convenient, accurate and reproducible [77], suggesting that increased epicardial AT is a risk factor for metabolic syndrome and is associated with T2DM, insulin resistance and liver steatosis. In this review, we will focus only on the function of perivascular AT (PVAT).

PVAT is a highly dynamic and metabolically active tissue surrounding a vascular bed, with the exception of neural, retinal and pulmonary vasculature [78]. The composition of PVAT, with regard to white AT

(WAT) or brown AT (BAT), depends on the location. The PVAT surrounding the aorta varies by location and is thought to influence the distribution of atherosclerosis [79]. In rodents, PVAT surrounding the thoracic aorta comprises BAT, whereas abdominal aortic PVAT in both humans and rodents is a mixture, mostly WAT and some BAT [80]. PVAT actively regulates blood vessel tone through PVAT-derived vasoactive factors, including both relaxing and contracting factors. In addition, PVAT contributes to atherosclerosis through paracrine secretion of a large number of bioactive factors, such as adipokines and cytokines [79]. It was demonstrated in male Sprague Dawley rats fed a HF diet that the function of "healthy" PVAT is abolished in diet-induced obesity through a mechanism involving increased local secretion of TNFα and reduced NO bioavailability [81]. When obesity was reduced by caloric restriction, PVAT function was improved, suggesting that PVAT dysfunction may be related to changes in inflammation and NO synthase activity [81]. It is easier to use fat isolated from experimental animals to study the properties of PVAT, but in humans, PVAT is studied from samples obtained by subcutaneous biopsy or from the PVAT surrounding the saphenous vein during cardiac bypass surgery. The challenges in isolating the saphenous vein and PVAT have been reviewed [77,78].

The effect of PVAT on vascular wall function is complex. The vasodilatory effect is mediated through several adipokines, such as adiponectin, leptin, and angiotensin 1-7 by activation of NO synthase in endothelial cells and finally by vasodilation of smooth muscle cells. In contrast, many vasoconstrictive agents, such as resistin, chemerin, and visfatin, act directly on vascular smooth muscle cells, but the exact mechanism is not fully understood [78]. However, no single factor has yet been identified as primarily responsible for the anticontractile effect of PVAT. Gao *et al.* [82] suggested that PVAT induces anticontractile effects through two distinct mechanisms, including endothelium-dependent relaxation and an endothelium-independent mechanism. One can ask the question, *"How is PVAT able to affect obesity-related hypertension?"* The answer is not simple. One possibility is that in addition to the release of vasodilators, PVAT surrounding renal arteries is able to release norepinephrine (NE). Renal PVAT, which is independent of renal sympathetic innervation, has a releasable pool of NE and thus sufficient potential to control BP through renal arterial function [83]. Nevertheless, other PVAT depots can also release NE. It

was suggested that even the thoracic aorta and superior mesenteric artery can do so and thus cause arterial contraction [84]. Thus, the balance between the vasodilatory and vasoconstrictive properties of PVAT plays a significant role in its function. Obesity can change the property of PVAT from the "healthy" to the "sick" stage, i.e., toward a higher production of the abovementioned vasoconstrictive substances, which could contribute to an increase in BP. It was reported that loss of "healthy" properties of PVAT positively correlated with increased BP in rodent models with diet-induced obesity [85]. The same was observed in obese patients after bariatric surgery [86]. The improvement in the anticontractile function of PVAT was accompanied by improvements in insulin sensitivity, serum glycemic indices, inflammatory cytokines, adipokine profile, and systolic BP together with increased PVAT adiponectin and NO bioavailability [86].

The original idea that PVAT induces effects only be serving as a mechanical support for the vascular bed does not hold true since PVAT releases various bioactive signaling molecules that regulate vascular tone [77, 78, 85]. The functional role of PVAT is unclear, but it depends on the type of vascular bed and the experimental species from which it is isolated [78]. A significant anticontractile effect in response to vasoconstrictors was demonstrated in various arteries, e.g., mesenteric resistance arteries, skeletal muscle arteries, thoracic aorta, etc. [87,88], and this effect is lost in obesity, probably as a consequence of the development of adipocyte hypertrophy, inflammation and oxidative stress [89]. Obesity, which enhances oxidative stress, worsens PVAT dysfunction and thus contributes to vascular damage [90].

Link between obesity, cardiovascular and neurodegenerative diseases

There is no doubt that obesity, cardiovascular and neurodegenerative diseases are interconnected. However, the onset and timeline of each disorder differs. The pathophysiological processes of neurodegenerative diseases (including AD) usually begin decades before symptom onset. Moreover, it is even more complicated in obesity because obesity can start at any age, from childhood to adulthood. Epidemiological and clinical studies have shown that obesity and metabolic disorders are important factors for the onset of AD [91]. This is supported by findings that treatment of metabolic diseases may protect against neurodegenerative diseases

[92]. The relationship between obesity and dementia is further supported by prospective cohort studies [91], which suggested that obesity in midlife increases the risk of incidence of dementia.

Aging is associated with an increase in the prevalence of cardiometabolic factors as well as with reduced total brain volume. Some brain areas are especially affected, including frontal and temporal lobes, and are prone to gray matter reduction [93]. White matter also shows age-related changes in small vessels [94]. Therefore, it is possible that obesity and its related metabolic complications may accelerate development of neurodegeneration [95].

As highlighted above, obesity is closely associated with CVD and neurodegenerative pathologies. Common factors in these disorders include inflammation, oxidative stress (increased bioavailability of reactive oxidative species (ROS)) and metabolic disturbances. Oxidative stress may be especially important because ROS stimulate many redox-sensitive signaling pathways that lead to inflammation, insulin resistance, and vascular damage. Oxidative stress is also responsible for the reduced bioavailability of the potent vasodilator nitric oxide (NO) leading to endothelial dysfunction. Recently, it has been shown that decreased NO production in obesity and associated insulin resistance may play a role in cognitive impairment and neurodegeneration [96].

The search for common biomarkers could also help to address the question whether there are similar mechanisms that underlie obesity, CVD and neurodegenerative disorders. Plasma metabolomic analysis revealed that insulin resistance in obese children is associated with two distinct metabolic pathways [97]. These involve amino acid metabolism and lipid metabolism and are different in obese children compared to non-obese ones. Other common molecular markers that can connect the described comorbidities include microRNAs (miRNA) [66]. Although the role of miRNAs has been demonstrated in obese phenotypes [98] and neurodegenerative diseases [99,100], there are only a few studies on the role of miRNAs in obesity-associated neurodegenerative disorders [66]. One of the miRNA families implicated in the development of neurodegenerative disorders and obesity is the miR-34 family [101]. This miRNAs family is overexpressed in the brain and could play an important role in AD pathologies. Because the expression of miR-34 family is also elevated in liver, this may be a molecular link between obesity and neurodegenerative disorders. This is

supported by the fact that more than 200 genes are targets of miR-34 family, classified by the association to either AD or metabolic syndrome and that are conserved among humans, mice and rats [101].

These diseases all have a polygenic basis, i.e. that several genes with a strong effect and certainly a number of genes with a small effect are involved in their development. In addition, interactions with environmental factors and epigenetic changes, which are dependent on the influence of the environment, are crucial. As a result, it is difficult to precisely define all the risk factors and common interactions that lead to obesity, CVD and neurodegenerative complications.

Neuroimaging methods, including magnetic resonance imaging (MRI) and positron emission tomography (PET), have been helpful to explore effects of therapies in experimental models of obesity, CVD and neurodegenerative disorders [102,103]. Because obesity is associated with structural, functional and chemical alterations in the brain, functional neuroimaging can be used in obesity research in pre-clinical models and in humans [104,105]. Data from functional magnetic resonance imaging (fMRI), PET and single-photon emission computed tomography (SPECT) have highlighted important relations between brain structure changes and/or abnormalities associated with eating behavior [106], insulin resistance, obesity and CVD risk [107]. Functional neuroimaging may help unravel neuronal mechanisms that contribute to obesity and CVD [108]. However, there are several limitations of fMRI, that need consideration in such studies [106]).

Role of the gut microbiome in the pathology of obesity, cardiovascular and neuro-degenerative diseases

Increasing evidence indicate that the gut microbiome may also play a role in the pathophysiology of obesity, CVD and neurodegenerative diseases (Fig. 2). Findings from the "Human Microbiome Project", started in 2008, have highlighted the effect of symbiotic microorganisms on health [109-111]. High fidelity phenotyping of the human microbiome (total of 4788 specimens) from 242 healthy adults showed large differences in the microbial population of the gut, skin and vagina suggesting that even in healthy subjects the microbiome is variable [109]. The field of obesity and the gut microbiome has grown exponentially as evidenced by the increasing number of papers published with 'obesity,

gut microbiome' (Pubmed) as keywords. In 2012 72 papers were published while the number in 2021 was over 1,000. Alterations in the gut microbiome have been associated with obesity through changes in metabolic pathways and eating behavior involving the gut-brain axis [111-114].
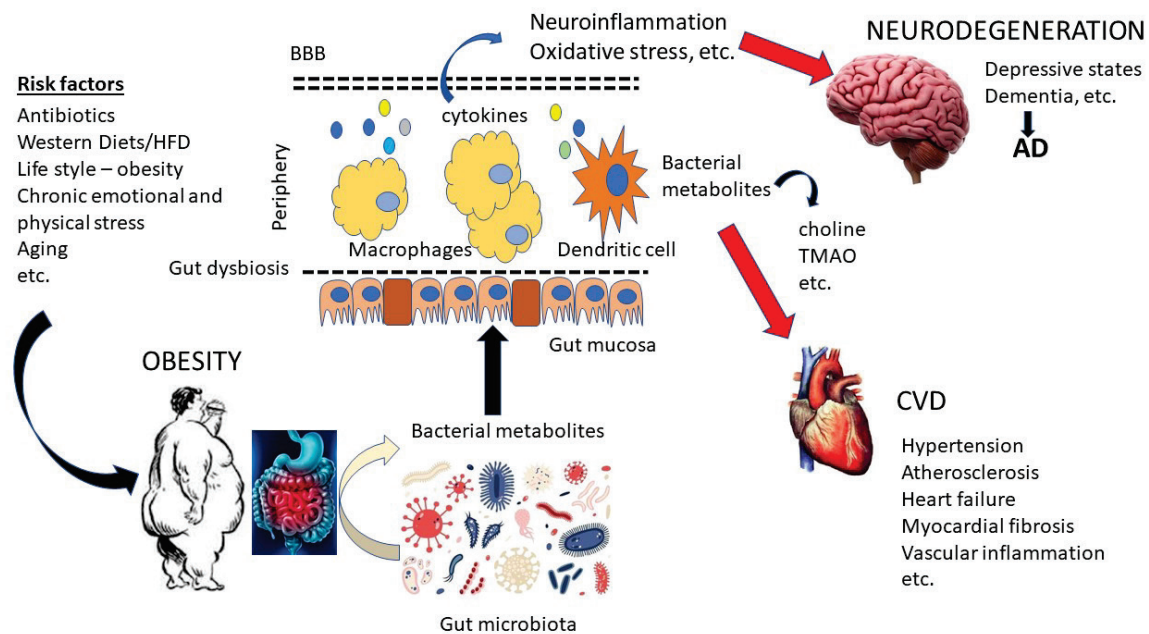
Fig. 2. The diagram showing the relationship among gut microbiota, obesity, CVD and neurodegenerative disease. It is clear that the gut microbiota reflect the state of the external environment and influence the development of individual pathologies through their metabolites.

Microbiota and obesity

Changes in the gut microbiota influence metabolic pathways associated with several metabolic diseases, including obesity, insulin resistance and T2DM (for review see [115-117]). Intestinal hyperpermeability is associated with dysbiosis, and the combination of these two circumstances can lead to an increase in the level of low-grade inflammation in obese patients. This is accompanied by an increase in pro-inflammatory cytokines [118, 119] and sub-clinical inflammation, which has been associated with obesity [120-122]. Studies in germ-free mice, which do not produce an inflammatory response, show that they are leaner than control animals even though they consume more calories [123]. Human studies have shown that fecal transmission from obese individuals transmits the obese phenotype [124]. The exact mechanisms still remain unclear, but it is clear that microbial metabolites can influence the central regulation of food intake [122,125] by modifying the secretion of intestinal peptides such as glucagon-like peptide (GLP)1 [125, 126]. Some probiotic strains have been shown to have 'anti-obesity effects' [122,127,128], such as *Bifidobacterium longum* APC 1472, which

modulates ghrelin signaling *in vitro*. Further evidence indicating a potential role for the microbiome in obesity relates to findings that vancomycin treatment casues a change in the gut microbiome, leading to obesity [129,130].

Microbiota and cardiovascular diseases

Although exact mechanisms remain unclear, there is growing evidence that the intestinal microflora is associated with a number of CVDs, including hypertension, heart failure, myocardial fibrosis, atherosclerosis, vascular inflammation, etc. [131, 132]. It was suggested in humans [133] that the sympathetic nervous system is important because the microbiome in the gut influences the parasympathetic and sympathetic nervous systems, which could in turn influences the cardiovascular system.

Various dietary substances, such as choline serve as exogenous precursors for intestinal bacteria. Choline, which is rich in Western diets, is converted to trimethylamine N-oxide (TMAO) by gut microbiota. TMAO in turn has been associated with atherosclerosis [134] through pro-inflammatory and pro-coagulant effects [135].

Studies in rats demonstrated a link between the gut microbiota and the severity of myocardial infarction [136, 137]. The use of broad-spectrum antibiotics was shown to affect levels of leptin and substances produced during aromatic amino acid catabolism, associated with reduced myocardial infarct size. In addition, administration of *Lactobacillus plantarum* to Dahl S rats was associated with significant reduction in infarct size and left ventricular function was improved after myocardial infarction. Another study in rats showed that administration of the *Lactobacillus rhamnosus* GR-1 attenuated left ventricular hypertrophy and heart failure after experimental myocardial infarction [138]. These observations may suggest that probiotics use, in the combination with standard medication, could offer additional benefits in patients with heart failure, leading to reduction of the severity of heart failure after myocardial infarction.

Microbiota and neurodegenerative diseases

The gut microbiome has also been implicated in various neurological disorders. Clinical studies showed that administration of a combination of probiotic cultures with multivitamins and minerals increases the level of glutathione (ROS scavenger), reduces insulin resistance, and improves depression in patients with depressive disorders. This appears to be independent of changes in plasma glucose levels [139]. Probiotics have been shown to be beneficial in improving inflammation in rheumatoid arthritis by reducing pro-inflammatory cytokines [140]. Neuroinflammation may also be ameliorated by probiotics [141]. Gut microbiota have a pivotal role in regulating multiple neurochemical pathways through the highly interconnected gut-brain axis. Modulation of this axis has been reported to affect the pathogenesis of AD. Communication between human gut microflora and brain has been described as the "second brain" and has been implicated in multiple metabolic and chronic disorders [142]. Specific microbiota implicated in obesity, CVD and neurodegenerative diseases are detailed in several publications [143-145].

Conclusions

Obesity, CVD and neurodegenerative disorders often co-exist and are common non-communicable age-related disorders. Growing evidence indicates that they are major causes of morbidity and mortality in both high income and low-middle income countries and that the prevalence of these conditions is increasing globally. Obesity is an important risk factor for CVD and together with cSVD, is a common risk factor for cognitive impairment and vascular dementia [146]. Epidemiological studies suggest that midlife CVD and/or symptoms of metabolic syndrome are associated with an increased risk of cognitive impairment and dementia later in life.

Although CVD, neurodegenerative disorders and obesity may exist separately, they are common co-morbidities and may have shared underlying mechanisms, such as inflammation, oxidative stress, impaired metabolism, sympathetic nervous system activation and the gut microbiome. While studies in preclinical models have helped to unravel some of the mechanisms, these still await confirmation in humans. Moreover, to truly study co-morbidities that are relevant in humans, experimental studies should focus on multi-disease models [147].

The lack of effective drugs for obesity and neurodegenerative diseases is a major clinical challenge. On the other hand, there are many effective drugs for CVD, which not only improve outcomes in patients with heart disease, but may also ameliorate cognitive decline and vascular dementia. Amongst the most important preventive measures for obesity, CVD and neurodegenerative disorders is lifestyle modification, including increased physical activity, healthy diet, reduced alcohol consumption and smoking cessation. Implementing these measures should be a priority in prevention and health care.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

Abbreviations

AD, Alzheimer´s disease; AT, adipose tissue; BAT, brown adipose tissue; BBB, blood brain barrier; BMI, body mass index; BP, blood pressure; BW, body weight; CAD, coronary artery disease; cSVD, cerebral small vessel disease; CVD, cardiovascular disease; DED, dietary energy density; HF diet, high fat diet; MHO, metabolically healthy obese; NE, norepinephrine; NO, nitric oxide; PVAT, perivascular adipose tissue; ROS, reactive oxidative species; T2DM, type 2 diabetes mellitus; TNFα, tumor necrosis factor alpha; TRP, transient receptor potential; VCI, vascular cognitive impairment; WAT, white adipose tissue.

References

1. Maletínská L, Popelová A, Železná B, Bencze M, Kuneš J. The impact of anorexigenic peptides in experimental models of Alzheimer's disease pathology. J Endocrinol. 2019;240(2):R47-r72. https://doi.org/10.1530/JOE-18-0532

2. Nakajima T, Fujioka S, Tokunaga K, Hirobe K, Matsuzawa Y, Tarui S. Noninvasive study of left ventricular performance in obese patients: influence of duration of obesity. Circulation. 1985;71:481-486. https://doi.org/10.1161/01.CIR.71.3.481

3. Reis JP, Loria CM, Lewis CE, Powell-Wiley TM, Wei GS, Carr JJ, *et al.* Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. JAMA. 2013;310:280-288. https://doi.org/10.1001/jama.2013.7833

4. Tanamas SK, Wong E, Backholer K, Abdullah A, Wolfe R, Barendregt J, *et al.* Duration of obesity and incident hypertension in adults from the Framingham Heart Study. J Hypertens. 2015;33:542-545; discussion 5. https://doi.org/10.1097/HJH.0000000000000441

5. Mulvany MJ, Baumbach GL, Aalkjaer C, Heagerty AM, Korsgaard N, Schiffrin EL, *et al.* Vascular remodeling. Hypertension. 1996;28:505-506.

6. Hajdu MA, Heistad DD, Siems JE, Baumbach GL. Effects of aging on mechanics and composition of cerebral arterioles in rats. Circ Res. 1990;66(6):1747-1754. https://doi.org/10.1161/01.RES.66.6.1747

7. Meissner A. Hypertension and the brain: a risk factor for more than heart disease. Cerebrovasc Dis. 2016;42(3-4):255-262. https://doi.org/10.1159/000446082

8. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al.* Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12:822-838. https://doi.org/10.1016/S1474-4422(13)70124-8

9. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. Lancet Neurol. 2019;18:684-696. https://doi.org/10.1016/S1474-4422(19)30079-1

10. Kim CK, Kwon HM, Lee SH, Kim BJ, Ryu WS, Kwon HT, *et al.* Association of obesity with cerebral microbleeds in neurologically asymptomatic elderly subjects. J Neurol. 2012;259:2599-2604. https://doi.org/10.1007/s00415-012-6546-y

11. Pucci G, Alcidi R, Tap L, Battista F, Mattace Raso F, Schillaci G. Sex- and gender-related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: A review of the literature. 2017. p. 34-42. https://doi.org/10.1016/j.phrs.2017.03.008

12. Whayne TF, Jr., Saha SP. Genetic Risk, Adherence to a Healthy Lifestyle, and Ischemic Heart Disease. Curr Cardiol Rep. 2019;21:1. https://doi.org/10.1007/s11886-019-1086-z

13. Yoshimura M, Yasue H, Nakayama M, Shimasaki Y, Ogawa H, Kugiyama K, *et al.* Genetic risk factors for coronary artery spasm: significance of endothelial nitric oxide synthase gene T-786-->C and missense Glu298Asp variants. J Investig Med. 2000;48:367-374.

14. Oike Y, Hata A, Ogata Y, Numata Y, Shido K, Kondo K. Angiotensin converting enzyme as a genetic risk factor for coronary artery spasm. Implication in the pathogenesis of myocardial infarction. J Clin Invest. 1995;96:2975-2579. https://doi.org/10.1172/JCI118369

15. Amant C, Hamon M, Bauters C, Richard F, Helbecque N, McFadden EP, *et al.* The angiotensin II type 1 receptor gene polymorphism is associated with coronary artery vasoconstriction. J Am Coll Cardiol. 1997;29:486-490. https://doi.org/10.1016/S0735-1097(96)00535-9

16. Ito T, Yasue H, Yoshimura M, Nakamura S, Nakayama M, Shimasaki Y, *et al.* Paraoxonase gene Gln192Arg (Q192R) polymorphism is associated with coronary artery spasm. Hum Genet. 2002;110:89-94. https://doi.org/10.1007/s00439-001-0654-6

17. Shokri Y, Variji A, Nosrati M, Khonakdar-Tarsi A, Kianmehr A, Kashi Z, *et al.* Importance of paraoxonase 1 (PON1) as an antioxidant and antiatherogenic enzyme in the cardiovascular complications of type 2 diabetes: Genotypic and phenotypic evaluation. Diabetes Res Clin Pract. 2020;161:108067. https://doi.org/10.1016/j.diabres.2020.108067

18. Sonel AF, Good CB, Mulgund J, Roe MT, Gibler WB, Smith SC, Jr., *et al.* Racial variations in treatment and outcomes of black and white patients with high-risk non-ST-elevation acute coronary syndromes: insights from CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines?). Circulation. 2005;111:1225-1232. https://doi.org/10.1161/01.CIR.0000157732.03358.64

19. Nakamura M, Sadoshima J. Cardiomyopathy in obesity, insulin resistance and diabetes. J Physiol. 2020;598:2977-2993. https://doi.org/10.1113/JP276747

20. Barua RS, Ambrose JA, Saha DC, Eales-Reynolds LJ. Smoking is associated with altered endothelial-derived fibrinolytic and antithrombotic factors: an in vitro demonstration. Circulation. 2002;106:905-908. https://doi.org/10.1161/01.CIR.0000029091.61707.6B

21. Bergami M, Scarpone M, Bugiardini R, Cenko E, Manfrini O. Sex beyond cardiovascular risk factors and clinical biomarkers of cardiovascular disease. Rev Cardiovasc Med. 2022;23:19. https://doi.org/10.31083/j.rcm2301019

22. Manfrini O, Yoon J, van der Schaar M, Kedev S, Vavlukis M, Stankovic G, *et al.* Sex differences in modifiable risk factors and severity of coronary artery disease. J Am Heart Assoc. 2020;9(19):e017235. https://doi.org/10.1161/JAHA.120.017235

23. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol. 2014;34:509-515. https://doi.org/10.1161/ATVBAHA.113.300156

24. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, *et al.* Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388(10046):761-775. https://doi.org/10.1016/S0140-6736(16)30506-2

25. Chareonrungrueangchai K, Wongkawinwoot K, Anothaisintawee T, Reutrakul S. Dietary factors and risks of cardiovascular diseases: an umbrella review. Nutrients. 2020;12. https://doi.org/10.3390/nu12041088

26. Allman BR, Andres A, Børsheim E. The Association of Maternal Protein Intake during Pregnancy in Humans with Maternal and Offspring Insulin Sensitivity Measures. Curr Dev Nutr. 2019;3:nzz055. https://doi.org/10.1093/cdn/nzz055

27. Stanhope KL. Sugar consumption, metabolic disease and obesity: The state of the controversy. Crit Rev Clin Lab Sci. 2016;53:52-67. https://doi.org/10.3109/10408363.2015.1084990

28. Bray GA. Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people. Adv Nutr. 2013;4:220-225. https://doi.org/10.3945/an.112.002816

29. Dwivedi AK, Dubey P, Reddy SY, Clegg DJ. Associations of Glycemic Index and Glycemic Load with Cardiovascular Disease: Updated Evidence from Meta-analysis and Cohort Studies. Curr Cardiol Rep. 2022;24(3):141-161. https://doi.org/10.1007/s11886-022-01635-2

30. Hu FB, Malik VS. Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. Physiol Behav. 2010;100:47-54. https://doi.org/10.1016/j.physbeh.2010.01.036

31. Li S, Cao M, Yang C, Zheng H, Zhu Y. Association of sugar-sweetened beverage intake with risk of metabolic syndrome among children and adolescents in urban China. Public Health Nutr. 2020;23:2770-2780. https://doi.org/10.1017/S1368980019003653

32. Mirrahimi A, de Souza RJ, Chiavaroli L, Sievenpiper JL, Beyene J, Hanley AJ, *et al.* Associations of glycemic index and load with coronary heart disease events: a systematic review and meta-analysis of prospective cohorts. J Am Heart Assoc. 2012;1:e000752. https://doi.org/10.1161/JAHA.112.000752

33. Kahn R, Sievenpiper JL. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes?: we have, but the pox on sugar is overwrought and overworked. Diabetes Care. 2014;37:957-962. https://doi.org/10.2337/dc13-2506

34. Benade J, Sher L, De Klerk S, Deshpande G, Bester D, Marnewick JL, et al. The Impact of Sugar-Sweetened Beverage Consumption on the Liver: A Proteomics-based Analysis. Antioxidants (Basel). 2020;9. https://doi.org/10.3390/antiox9070569

35. Souza Cruz EM, Bitencourt de Morais JM, Dalto da Rosa CV, da Silva Simões M, Comar JF, de Almeida Chuffa LG, et al. Long-term sucrose solution consumption causes metabolic alterations and affects hepatic oxidative stress in Wistar rats. Biol Open. 2020;9. https://doi.org/10.1242/bio.047282

36. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643-2653. https://doi.org/10.1056/NEJMoa052187

37. Giglio RV, Stoian AP, Haluzik M, Pafili K, Patti AM, Rizvi AA, et al. Novel molecular markers of cardiovascular disease risk in type 2 diabetes mellitus. Biochim Biophys Acta Mol Basis Dis. 2021;1867:166148. https://doi.org/10.1016/j.bbadis.2021.166148

38. Guidelines. WHO Guidelines Guideline: Sodium Intake for Adults and Children. Geneva: World Health Organization. Copyright © 2012, World Health Organization. 2012.

39. Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. Int J Epidemiol. 2009;38:791-813. https://doi.org/10.1093/ije/dyp139

40. Abdulai T, Runqi T, Mao Z, Oppong TB, Amponsem-Boateng C, Wang Y, et al. Preference for High Dietary Salt Intake Is Associated With Undiagnosed Type 2 Diabetes: The Henan Rural Cohort. Front Nutr. 2020;7:537049. https://doi.org/10.3389/fnut.2020.537049

41. Horikawa C, Yoshimura Y, Kamada C, Tanaka S, Tanaka S, Hanyu O, et al. Dietary Sodium Intake and Incidence of Diabetes Complications in Japanese Patients with Type 2 Diabetes: Analysis of the Japan Diabetes Complications Study (JDCS). J Clin Endocrinol Metab. 2014;99:3635-3643. https://doi.org/10.1210/jc.2013-4315

42. Lanaspa MA, Kuwabara M, Andres-Hernando A, Li N, Cicerchi C, Jensen T, et al. High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. Proc Natl Acad Sci U S A. 2018;115:3138-3143. https://doi.org/10.1073/pnas.1713837115

43. Ogihara T, Asano T, Ando K, Chiba Y, Sekine N, Sakoda H, et al. Insulin resistance with enhanced insulin signaling in high-salt diet-fed rats. Diabetes. 2001;50:573-583. https://doi.org/10.2337/diabetes.50.3.573

44. Ren J, Qin L, Li X, Zhao R, Wu Z, Ma Y. Effect of dietary sodium restriction on blood pressure in type 2 diabetes: A meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2021;31:1653-1661. https://doi.org/10.1016/j.numecd.2021.02.019

45. Hariharan R, Odjidja EN, Scott D, Shivappa N, Hébert JR, Hodge A, et al. The dietary inflammatory index, obesity, type 2 diabetes, and cardiovascular risk factors and diseases. Obes Rev. 2022;23:e13349. https://doi.org/10.1111/obr.13349

46. Todendi PF, Salla R, Shivappa N, Hebert JR, Ritter J, Cureau FV, Schaan BD. Association between dietary inflammatory index and cardiometabolic risk factors among Brazilian adolescents: results from a national cross-sectional study. Br J Nutr. 2022 Aug 28;128(4):744-752. https://doi.org/10.1017/S0007114521003767

47. Daulatzai MA. Cerebral hypoperfusion and glucose hypometabolism: Key pathophysiological modulators promote neurodegeneration, cognitive impairment, and Alzheimer's disease. J Neurosci Res. 2017;95:943-972. https://doi.org/10.1002/jnr.23777

48. Ighodaro ET, Abner EL, Fardo DW, Lin AL, Katsumata Y, Schmitt FA, et al. Risk factors and global cognitive status related to brain arteriolosclerosis in elderly individuals. J Cereb Blood Flow Metab. 2017;37:201-216. https://doi.org/10.1177/0271678X15621574

49. Gorelick PB, Counts SE, Nyenhuis D. Vascular cognitive impairment and dementia. Biochim Biophys Acta. 2016;1862:860-868. https://doi.org/10.1016/j.bbadis.2015.12.015

50. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, *et al.* Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2011;42:2672-2713. https://doi.org/10.1161/STR.0b013e3182299496

51. Kalaria RN, Sepulveda-Falla D. Cerebral small vessel disease in sporadic and familial Alzheimer disease. Am J Pathol. 2021;191:1888-1905. https://doi.org/10.1016/j.ajpath.2021.07.004

52. Iadecola C, Gottesman RF. Neurovascular and cognitive dysfunction in hypertension. Circ Res. 2019;124:1025-1044. https://doi.org/10.1161/CIRCRESAHA.118.313260

53. Barker DJ. The fetal and infant origins of adult disease. Bmj. 1990;301:1111. https://doi.org/10.1136/bmj.301.6761.1111

54. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. Bmj. 2000;320:967-971. https://doi.org/10.1136/bmj.320.7240.967

55. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life--a systematic review. Obes Rev. 2005;6:143-154. https://doi.org/10.1111/j.1467-789X.2005.00183.x

56. Barbosa P, Melnyk S, Bennuri SC, Delhey L, Reis A, Moura GR, *et al.* Redox imbalance and methylation disturbances in early childhood obesity. Oxid Med Cell Longev. 2021;2021:2207125. https://doi.org/10.1155/2021/2207125

57. Martyn JA, Kaneki M, Yasuhara S. Obesity-induced insulin resistance and hyperglycemia: etiologic factors and molecular mechanisms. Anesthesiology. 2008;109:137-148. https://doi.org/10.1097/ALN.0b013e3181799d45

58. Adeva-Andany MM, Funcasta-Calderón R, Fernández-Fernández C, Ameneiros-Rodríguez E, Domínguez-Montero A. Subclinical vascular disease in patients with diabetes is associated with insulin resistance. Diabetes Metab Syndr. 2019;13:2198-2206. https://doi.org/10.1016/j.dsx.2019.05.025

59. Zicha J, Kunes J. Ontogenetic aspects of hypertension development: analysis in the rat. Physiol Rev. 1999;79:1227-1282. https://doi.org/10.1152/physrev.1999.79.4.1227

60. Maslova E, Hansen S, Grunnet LG, Strøm M, Bjerregaard AA, Hjort L, *et al.* Maternal protein intake in pregnancy and offspring metabolic health at age 9-16 y: results from a Danish cohort of gestational diabetes mellitus pregnancies and controls. Am J Clin Nutr. 2017;106:623-636. https://doi.org/10.3945/ajcn.115.128637

61. Moreno-Fernandez J, Ochoa JJ, Lopez-Frias M, Diaz-Castro J. Impact of early nutrition, physical activity and sleep on the fetal programming of disease in the pregnancy: a narrative review. Nutrients. 2020;12. https://doi.org/10.3390/nu12123900

62. Zheng J, Xiao X, Zhang Q, Yu M. DNA methylation: the pivotal interaction between early-life nutrition and glucose metabolism in later life. Br J Nutr. 2014;112:1850-1857. https://doi.org/10.1017/S0007114514002827

63. Nicolucci A, Maffeis C. The adolescent with obesity: what perspectives for treatment? Ital J Pediatr. 2022;48:9. https://doi.org/10.1186/s13052-022-01205-w

64. Friedemann C, Heneghan C, Mahtani K, Thompson M, Perera R, Ward AM. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. Bmj. 2012;345:e4759. https://doi.org/10.1136/bmj.e4759

65. Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, *et al.* A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. N Engl J Med. 2020;382:2117-2128. https://doi.org/10.1056/NEJMoa1916038

66. Perdoncin M, Konrad A, Wyner JR, Lohana S, Pillai SS, Pereira DG, *et al.* A review of miRNAs as biomarkers and effect of dietary modulation in obesity associated cognitive decline and neurodegenerative disorders. Front Mol Neurosci. 2021;14:756499. https://doi.org/10.3389/fnmol.2021.756499

67. Terzo S, Amato A, Mulè F. From obesity to Alzheimer's disease through insulin resistance. J Diabetes Complications. 2021;35:108026. https://doi.org/10.1016/j.jdiacomp.2021.108026

68. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, *et al.* Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? J Alzheimers Dis. 2005;7:63-80. https://doi.org/10.3233/JAD-2005-7107

69. Ho L, Qin W, Pompl PN, Xiang Z, Wang J, Zhao Z, *et al.* Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. Faseb j. 2004;18:902-904. https://doi.org/10.1096/fj.03-0978fje

70. Julien C, Tremblay C, Phivilay A, Berthiaume L, Emond V, Julien P, *et al.* High-fat diet aggravates amyloid-beta and tau pathologies in the 3xTg-AD mouse model. Neurobiol Aging. 2010;31:1516-1531. https://doi.org/10.1016/j.neurobiolaging.2008.08.022

71. Verdile G, Keane KN, Cruzat VF, Medic S, Sabale M, Rowles J, *et al.* Inflammation and Oxidative Stress: The molecular connectivity between insulin resistance, obesity, and Alzheimer's disease. Mediators Inflamm. 2015;2015:105828. https://doi.org/10.1155/2015/105828

72. Kacířová M, Zmeškalová A, Kořínková L, Železná B, Kuneš J, Maletínská L. Inflammation: major denominator of obesity, Type 2 diabetes and Alzheimer's disease-like pathology? Clin Sci (Lond). 2020;134:547-570. https://doi.org/10.1042/CS20191313

73. Lucero J, Suwannasual U, Herbert LM, McDonald JD, Lund AK. The role of the lectin-like oxLDL receptor (LOX-1) in traffic-generated air pollution exposure-mediated alteration of the brain microvasculature in Apolipoprotein (Apo) E knockout mice. Inhal Toxicol. 2017;29:266-281. https://doi.org/10.1080/08958378.2017.1357774

74. Naik P, Fofaria N, Prasad S, Sajja RK, Weksler B, Couraud PO, *et al.* Oxidative and pro-inflammatory impact of regular and denicotinized cigarettes on blood brain barrier endothelial cells: is smoking reduced or nicotine-free products really safe? BMC Neurosci. 2014;15:51. https://doi.org/10.1186/1471-2202-15-51

75. Khan MSH, Hegde V. Obesity and Diabetes Mediated Chronic Inflammation: A Potential Biomarker in Alzheimer's Disease. J Pers Med. 2020;10. https://doi.org/10.3390/jpm10020042

76. Anthony SR, Guarnieri AR, Gozdiff A, Helsley RN, Phillip Owens A, Tranter M. Mechanisms linking adipose tissue inflammation to cardiac hypertrophy and fibrosis. Clin Sci (Lond). 2019;133:2329-2344. https://doi.org/10.1042/CS20190578

77. Xia N, Li H. The role of perivascular adipose tissue in obesity-induced vascular dysfunction. Br J Pharmacol. 2017;174(20):3425-3442. https://doi.org/10.1111/bph.13650, https://doi.org/10.1111/bph.13703

78. Saxton SN, Clark BJ, Withers SB, Eringa EC, Heagerty AM. Mechanistic Links Between Obesity, Diabetes, and Blood Pressure: Role of Perivascular Adipose Tissue. Physiol Rev. 2019;99:1701-1763. https://doi.org/10.1152/physrev.00034.2018

79. Hu H, Garcia-Barrio M, Jiang ZS, Chen YE, Chang L. Roles of Perivascular Adipose Tissue in Hypertension and Atherosclerosis. Antioxid Redox Signal. 2021;34:736-749. https://doi.org/10.1089/ars.2020.8103

80. Padilla J, Jenkins NT, Vieira-Potter VJ, Laughlin MH. Divergent phenotype of rat thoracic and abdominal perivascular adipose tissues. Am J Physiol Regul Integr Comp Physiol. 2013;304:R543-R552. https://doi.org/10.1152/ajpregu.00567.2012

81. Bussey CE, Withers SB, Aldous RG, Edwards G, Heagerty AM. Obesity-Related Perivascular Adipose Tissue Damage Is Reversed by Sustained Weight Loss in the Rat. Arterioscler Thromb Vasc Biol. 2016;36:1377-1385. https://doi.org/10.1161/ATVBAHA.116.307210

82. Gao YJ, Lu C, Su LY, Sharma AM, Lee RM. Modulation of vascular function by perivascular adipose tissue: the role of endothelium and hydrogen peroxide. Br J Pharmacol. 2007;151:323-331. https://doi.org/10.1038/sj.bjp.0707228

83. Restini CBA, Ismail A, Kumar RK, Burnett R, Garver H, Fink GD, *et al.* Renal perivascular adipose tissue: Form and function. Vascul Pharmacol. 2018;106:37-45. https://doi.org/10.1016/j.vph.2018.02.004

84. Ayala-Lopez N, Martini M, Jackson WF, Darios E, Burnett R, Seitz B, *et al.* Perivascular adipose tissue contains functional catecholamines. Pharmacol Res Perspect. 2014;2(3):e00041. https://doi.org/10.1002/prp2.41

85. Aghamohammadzadeh R, Unwin RD, Greenstein AS, Heagerty AM. Effects of Obesity on Perivascular Adipose Tissue Vasorelaxant Function: Nitric Oxide, Inflammation and Elevated Systemic Blood Pressure. J Vasc Res. 2015;52:299-305. https://doi.org/10.1159/000443885

86. Aghamohammadzadeh R, Greenstein AS, Yadav R, Jeziorska M, Hama S, Soltani F, et al. Effects of bariatric surgery on human small artery function: evidence for reduction in perivascular adipocyte inflammation, and the restoration of normal anticontractile activity despite persistent obesity. J Am Coll Cardiol. 2013;62:128-135. https://doi.org/10.1016/j.jacc.2013.04.027

87. Torok J, Zemancikova A, Valaskova Z, Balis P. The role of perivascular adipose tissue in early changes in arterial function during high-fat diet and its combination with high-fructose intake in rats. Biomedicines. 2021;9. https://doi.org/10.3390/biomedicines9111552

88. Watts SW, Flood ED, Garver H, Fink GD, Roccabianca S. A New Function for Perivascular Adipose Tissue (PVAT): Assistance of Arterial Stress Relaxation. Sci Rep. 2020;10:1807. https://doi.org/10.1038/s41598-020-58368-x

89. Saxton SN, Toms LK, Aldous RG, Withers SB, Ohanian J, Heagerty AM. Restoring perivascular adipose tissue function in obesity using exercise. Cardiovasc Drugs Ther. 2021;35:1291-304. https://doi.org/10.1007/s10557-020-07136-0

90. Azul L, Leandro A, Boroumand P, Klip A, Seiça R, Sena CM. Increased inflammation, oxidative stress and a reduction in antioxidant defense enzymes in perivascular adipose tissue contribute to vascular dysfunction in type 2 diabetes. Free Radic Biol Med. 2020;146:264-274. https://doi.org/10.1016/j.freeradbiomed.2019.11.002

91. Li XY, Zhang M, Xu W, Li JQ, Cao XP, Yu JT, et al. Midlife Modifiable Risk Factors for Dementia: A Systematic Review and Meta-analysis of 34 Prospective Cohort Studies. Curr Alzheimer Res. 2019;16:1254-1268. https://doi.org/10.2174/1567205017666200103111253

92. Leigh SJ, Morris MJ. Diet, inflammation and the gut microbiome: Mechanisms for obesity-associated cognitive impairment. Biochim Biophys Acta Mol Basis Dis. 2020;1866:165767. https://doi.org/10.1016/j.bbadis.2020.165767

93. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog Neurobiol. 2014;117:20-40. https://doi.org/10.1016/j.pneurobio.2014.02.004

94. Liu H, Yang Y, Xia Y, Zhu W, Leak RK, Wei Z, et al. Aging of cerebral white matter. Ageing Res Rev. 2017;34:64-76. https://doi.org/10.1016/j.arr.2016.11.006

95. García-García I, Michaud A, Jurado M, Dagher A, Morys F. Mechanisms linking obesity and its metabolic comorbidities with cerebral grey and white matter changes. Rev Endocr Metab Disord. 2022;23:833-843. https://doi.org/10.1007/s11154-021-09706-5

96. Buie JJ, Watson LS, Smith CJ, Sims-Robinson C. Obesity-related cognitive impairment: The role of endothelial dysfunction. Neurobiol Dis. 2019;132:104580. https://doi.org/10.1016/j.nbd.2019.104580

97. Zhao X, Gang X, Liu Y, Sun C, Han Q, Wang G. Using metabolomic profiles as biomarkers for insulin resistance in childhood obesity: a systematic review. J Diabetes Res. 2016;2016:8160545. https://doi.org/10.1155/2016/8160545

98. Iacomino G, Siani A. Role of microRNAs in obesity and obesity-related diseases. Genes Nutr. 2017;12:23. https://doi.org/10.1186/s12263-017-0577-z

99. Salama, II, Salama SI, Elmosalami DM, Saleh RM, Rasmy H, Ibrahim MH, et al. Risk factors associated with mild cognitive impairment among apparently healthy people and the role of microRNAs. Open Access Maced J Med Sci. 2019;7:3253-61. https://doi.org/10.3889/oamjms.2019.834

100. Yuen SC, Liang X, Zhu H, Jia Y, Leung SW. Prediction of differentially expressed microRNAs in blood as potential biomarkers for Alzheimer's disease by meta-analysis and adaptive boosting ensemble learning. Alzheimers Res Ther. 2021;13:126. https://doi.org/10.1186/s13195-021-00862-z

101. Bazrgar M, Khodabakhsh P, Prudencio M, Mohagheghi F, Ahmadiani A. The role of microRNA-34 family in Alzheimer's disease: A potential molecular link between neurodegeneration and metabolic disorders. Pharmacol Res. 2021;172:105805. https://doi.org/10.1016/j.phrs.2021.105805

102. Ineichen BV, Sati P, Granberg T, Absinta M, Lee NJ, Lefeuvre JA, et al. Magnetic resonance imaging in multiple sclerosis animal models: A systematic review, meta-analysis, and white paper. Neuroimage Clin. 2020;28:102371. https://doi.org/10.1016/j.nicl.2020.102371

103. Su YY, Yang GF, Lu GM, Wu S, Zhang LJ. PET and MR imaging of neuroinflammation in hepatic encephalopathy. Metab Brain Dis. 2015;30:31-45. https://doi.org/10.1007/s11011-014-9633-1

104. Kroll DS, Feldman DE, Biesecker CL, McPherson KL, Manza P, Joseph PV, *et al.* Neuroimaging of sex/gender differences in obesity: a review of structure, function, and neurotransmission. Nutrients. 2020;12. https://doi.org/10.3390/nu12071942

105. Letra L, Pereira D, Castelo-Branco M. Functional neuroimaging in obesity research. Adv Neurobiol. 2017;19:239-48. https://doi.org/10.1007/978-3-319-63260-5_10

106. Schlögl H, Horstmann A, Villringer A, Stumvoll M. Functional neuroimaging in obesity and the potential for development of novel treatments. Lancet Diabetes Endocrinol. 2016;4:695-705. https://doi.org/10.1016/S2213-8587(15)00475-1

107. Cui Y, Tang TY, Lu CQ, Ju S. Insulin resistance and cognitive impairment: evidence from neuroimaging. J Magn Reson Imaging. 2022. https://doi.org/10.1002/jmri.28358

108. Drelich-Zbroja A, Matuszek M, Kaczor M, Kuczyńska M. Functional magnetic resonance imaging and obesity-novel ways to seen the unseen. J Clin Med. 2022;11. https://doi.org/10.3390/jcm11123561

109. Consortium HMP. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486:207-214. https://doi.org/10.1038/nature11234

110. Aagaard K, Petrosino J, Keitel W, Watson M, Katancik J, Garcia N, *et al.* The Human Microbiome Project strategy for comprehensive sampling of the human microbiome and why it matters. Faseb j. 2013;27:1012-1022. https://doi.org/10.1096/fj.12-220806

111. Gevers D, Knight R, Petrosino JF, Huang K, McGuire AL, Birren BW, *et al.* The Human Microbiome Project: a community resource for the healthy human microbiome. PLoS Biol. 2012;10:e1001377. https://doi.org/10.1371/journal.pbio.1001377

112. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol. 2021;19:55-71. https://doi.org/10.1038/s41579-020-0433-9

113. Hou K, Wu ZX, Chen XY, Wang JQ, Zhang D, Xiao C, *et al.* Microbiota in health and diseases. Signal Transduct Target Ther. 2022;7:135. https://doi.org/10.1038/s41392-022-00974-4

114. Nagpal R, Yadav H, Marotta F. Gut microbiota: the next-gen frontier in preventive and therapeutic medicine? Front Med (Lausanne). 2014;1:15. https://doi.org/10.3389/fmed.2014.00015

115. Iatcu CO, Steen A, Covasa M. Gut microbiota and complications of Type-2 Diabetes. Nutrients. 2021;14. https://doi.org/10.3390/nu14010166

116. Liu BN, Liu XT, Liang ZH, Wang JH. Gut microbiota in obesity. World J Gastroenterol. 2021;27:3837-3850. https://doi.org/10.3748/wjg.v27.i25.3837

117. Portincasa P, Bonfrate L, Vacca M, De Angelis M, Farella I, Lanza E, *et al.* Gut Microbiota and Short Chain Fatty Acids: Implications in Glucose Homeostasis. Int J Mol Sci. 2022;23. https://doi.org/10.3390/ijms23031105

118. Cox AJ, West NP, Cripps AW. Obesity, inflammation, and the gut microbiota. Lancet Diabetes Endocrinol. 2015;3:207-215. https://doi.org/10.1016/S2213-8587(14)70134-2

119. Scheithauer TPM, Rampanelli E, Nieuwdorp M, Vallance BA, Verchere CB, van Raalte DH, *et al.* Gut microbiota as a trigger for metabolic inflammation in obesity and Type 2 Diabetes. Front Immunol. 2020;11:571731. https://doi.org/10.3389/fimmu.2020.571731

120. Maruvada P, Leone V, Kaplan LM, Chang EB. The Human Microbiome and Obesity: Moving beyond Associations. Cell Host Microbe. 2017;22:589-599. https://doi.org/10.1016/j.chom.2017.10.005

121. Patterson E, Ryan PM, Cryan JF, Dinan TG, Ross RP, Fitzgerald GF, *et al.* Gut microbiota, obesity and diabetes. Postgrad Med J. 2016;92:286-300. https://doi.org/10.1136/postgradmedj-2015-133285

122. Torres-Fuentes C, Schellekens H, Dinan TG, Cryan JF. The microbiota-gut-brain axis in obesity. Lancet Gastroenterol Hepatol. 2017;2:747-756. https://doi.org/10.1016/S2468-1253(17)30147-4

123. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, *et al.* The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004;101:15718-15723. https://doi.org/10.1073/pnas.0407076101

124. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, *et al.* Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341:1241214. https://doi.org/10.1126/science.1241214

125. Sandhu KV, Sherwin E, Schellekens H, Stanton C, Dinan TG, Cryan JF. Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry. Transl Res. 2017;179:223-244. https://doi.org/10.1016/j.trsl.2016.10.002

126. Everard A, Cani PD. Gut microbiota and GLP-1. Rev Endocr Metab Disord. 2014;15:189-196. https://doi.org/10.1007/s11154-014-9288-6

127. Hibberd AA, Yde CC, Ziegler ML, Honoré AH, Saarinen MT, Lahtinen S, et al. Probiotic or synbiotic alters the gut microbiota and metabolism in a randomised controlled trial of weight management in overweight adults. Benef Microbes. 2019;10:121-135. https://doi.org/10.3920/BM2018.0028

128. Kim J, Yun JM, Kim MK, Kwon O, Cho B. Lactobacillus gasseri BNR17 Supplementation Reduces the Visceral Fat Accumulation and Waist Circumference in Obese Adults: A Randomized, Double-Blind, Placebo-Controlled Trial. J Med Food. 2018;21:454-461. https://doi.org/10.1089/jmf.2017.3937

129. Thuny F, Richet H, Casalta JP, Angelakis E, Habib G, Raoult D. Vancomycin treatment of infective endocarditis is linked with recently acquired obesity. PLoS One. 2010;5:e9074. https://doi.org/10.1371/journal.pone.0009074

130. Million M, Thuny F, Angelakis E, Casalta JP, Giorgi R, Habib G, et al. Lactobacillus reuteri and Escherichia coli in the human gut microbiota may predict weight gain associated with vancomycin treatment. Nutr Diabetes. 2013;3(9):e87. https://doi.org/10.1038/nutd.2013.28

131. Rahman MM, Islam F, Or-Rashid MH, Mamun AA, Rahaman MS, Islam MM, et al. The gut microbiota (microbiome) in cardiovascular disease and its therapeutic regulation. Front Cell Infect Microbiol. 2022;12:903570. https://doi.org/10.3389/fcimb.2022.903570

132. Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease. Circ Res. 2020;127:553-570. https://doi.org/10.1161/CIRCRESAHA.120.316242

133. Bauer KC, Huus KE, Finlay BB. Microbes and the mind: emerging hallmarks of the gut microbiota-brain axis. Cell Microbiol. 2016;18:632-644. https://doi.org/10.1111/cmi.12585

134. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011;472:57-63. https://doi.org/10.1038/nature09922

135. Tang WH, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. Circ Res. 2017;120:1183-1196. https://doi.org/10.1161/CIRCRESAHA.117.309715

136. Lam V, Su J, Hsu A, Gross GJ, Salzman NH, Baker JE. Intestinal microbial metabolites are linked to severity of myocardial infarction in rats. PLoS One. 2016;11:e0160840. https://doi.org/10.1371/journal.pone.0160840

137. Lam V, Su J, Koprowski S, Hsu A, Tweddell JS, Rafiee P, et al. Intestinal microbiota determine severity of myocardial infarction in rats. Faseb j. 2012;26:1727-1735. https://doi.org/10.1096/fj.11-197921

138. Gan XT, Ettinger G, Huang CX, Burton JP, Haist JV, Rajapurohitam V, et al. Probiotic administration attenuates myocardial hypertrophy and heart failure after myocardial infarction in the rat. Circ Heart Fail. 2014;7:491-499. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000978

139. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Nutrition. 2016;32:315-320. https://doi.org/10.1016/j.nut.2015.09.003

140. Vaghef-Mehrabany E, Alipour B, Homayouni-Rad A, Sharif SK, Asghari-Jafarabadi M, Zavvari S. Probiotic supplementation improves inflammatory status in patients with rheumatoid arthritis. Nutrition. 2014;30:430-435. https://doi.org/10.1016/j.nut.2013.09.007

141. Varesi A, Pierella E, Romeo M, Piccini GB, Alfano C, Bjørklund G, et al. The potential role of gut microbiota in Alzheimer's disease: From Diagnosis to Treatment. Nutrients. 2022;14. https://doi.org/10.3390/nu14030668

142. Goyal D, Ali SA, Singh RK. Emerging role of gut microbiota in modulation of neuroinflammation and neurodegeneration with emphasis on Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2021;106:110112. https://doi.org/10.1016/j.pnpbp.2020.110112

143. Angoorani P, Ejtahed HS, Hasani-Ranjbar S, Siadat SD, Soroush AR, Larijani B. Gut microbiota modulation as a possible mediating mechanism for fasting-induced alleviation of metabolic complications: a systematic review. Nutr Metab (Lond). 2021;18:105. https://doi.org/10.1186/s12986-021-00635-3

144. Deledda A, Annunziata G, Tenore GC, Palmas V, Manzin A, Velluzzi F. Diet-Derived Antioxidants and Their Role in Inflammation, Obesity and Gut Microbiota Modulation. Antioxidants (Basel). 2021;10. https://doi.org/10.3390/antiox10050708

145. Forslund SK. Fasting intervention and its clinical effects on the human host and microbiome. J Intern Med. 2023;293:166-183. https://doi.org/10.1111/joim.13574

146. Hainsworth AH, Oommen AT, Bridges LR. Endothelial cells and human cerebral small vessel disease. Brain Pathol. 2015;25:44-50. https://doi.org/10.1111/bpa.12224

147. McGonigle P, Ruggeri B. Animal models of human disease: challenges in enabling translation. Biochem Pharmacol. 2014;87:162-171. https://doi.org/10.1016/j.bcp.2013.08.006