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Review article

Vascular dementia: From pathobiology to emerging perspectives

Amy Elizabeth Morgan [a,*], Mark Tomás Mc Auley [b]

[a] School of Health and Sports Sciences, Hope Park, Liverpool Hope University, Liverpool L16 9JD, United Kingdom
[b] School of Science, Engineering and Environment, University of Salford Manchester, Salford M5 4NT, United Kingdom

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ABSTRACT

Vascular dementia (VaD) is the second most common type of dementia. VaD is synonymous with ageing, and its symptoms place a significant burden on the health and wellbeing of older people. Despite the identification of a substantial number of risk factors for VaD, the pathological mechanisms underpinning this disease remain to be fully elucidated. Consequently, a biogerontological imperative exists to highlight the modifiable lifestyle factors which can mitigate against the risk of developing VaD. This review will critically examine some of the factors which have been revealed to modulate VaD risk. The survey commences by providing an overview of the putative mechanisms which are associated with the pathobiology of VaD. Next, the factors which influence the risk of developing VaD are examined. Finally, emerging treatment avenues including epigenetics, the gut microbiome, and pro-longevity pharmaceuticals are discussed. By drawing this key evidence together, it is our hope that it can be used to inform future experimental investigations in this field.

1. Introduction

Dementia risk increases with age (Wahl et al., 2019). Specifically, it has been estimated to affect 6% of individuals aged 75–79 years, 18.3% of those aged 85–89 years, and 41.1% of those over the age of 95 years (Fig. 1) (Prince et al., 2014). Dementia impairs learning, cognition, language, and decision making (Mograbi et al., 2021). A decline in such intellectual skills can profoundly affect an individual, gradually eroding their independence and dignity (Duong et al., 2017; Torossian, 2021). Significantly, dementia was the leading cause of death in both males (13.5%) and females (21.3%) over the age of 80 years old in England and Wales in 2022 (Office for National Statistics (Office for National Statistics ONS, 2023). Moreover, it has been estimated that 5–10% of individuals ≥65 years of age have dementia (Langa et al., 2017; Matthews et al., 2013; Pierse et al., 2019). It is predicted >152.8 million people will be living with dementia by 2050 (GBD, 2019 Dementia Forecasting Collaborators, 2022). This is perhaps unsurprising given an ageing global population (Rudnicka et al., 2020). Of course, dementia is an umbrella term whose pathology is sub-type dependent (Elahi and Miller, 2017). After Alzheimer's disease (AD), vascular dementia (VaD) is recognised as the second most common type of dementia, accounting for approximately 20% of all dementia cases (Akhter et al., 2021; Plassman et al., 2007). VaD is the name given to a group of brain disorders which are characterised by cerebrovascular pathology (O'Brien and Thomas, 2015). It is estimated that the average age of VaD onset, diagnosis, and death, is 67.5 ±7.2, 73.5 ±7.0 and 77.0 ±6.9 years respectively. Interestingly the survival time from diagnosis is less for patients with VaD (3.2 ±1.4 years) when compared to patients with AD (5.8 ±2.0 years), Lewy body dementia (4.7 ±1.8 years), or frontotemporal lobe degeneration (4.9 ±2.2) (Liang et al., 2021).

There are many risk factors associated with VaD, including a poor diet (Dai et al., 2023), obesity (Albanese et al., 2017), hypertension (McGrath et al., 2017), hypercholesterolaemia (Iwagami et al., 2021), sustained heavy alcohol intake (Jeon et al., 2023), diabetes (Gudala et al., 2013), smoking (Choi et al., 2018), physical inactivity (Hansson et al., 2019), and air pollution (Grande et al., 2020). Specifically, co-morbidities are commonly observed (Fig. 2); for instance, one study revealed that two-thirds of patients had hypertension (65.9%) at the time of VaD diagnosis (Chung et al., 2023). Other comorbidities are also frequently observed; these include: chronic kidney disease (26.8%), atrial fibrillation (26.1%), stroke (25.3%), depression (22.2%), cancer (21.8%), diabetes (20.3%), angina (19.4%), congenital heart disease (16.1%), transient ischemic attack (15.5%), atherosclerotic heart disease (14.7%), thyroid dysfunction (12.9%), and heart failure (12.2%). Moreover, it has been observed that 79.4% of people have two or more comorbidities at the time of VaD diagnosis (Chung et al., 2023). Collectively, these risk factors contribute to the aetiology of VaD, and its significant burden on older people (Takeda et al., 2020). At present, no

* Corresponding author.
E-mail address: morgana1@hope.ac.uk (A.E. Morgan).

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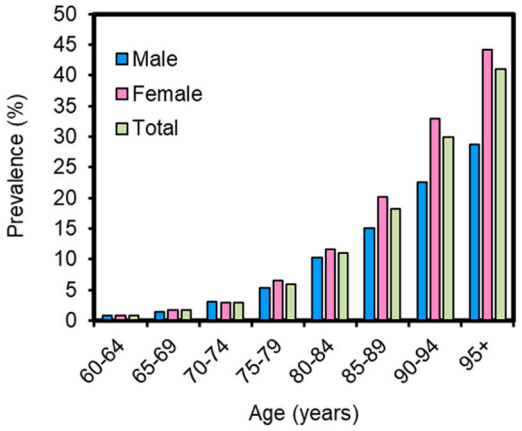

Fig. 1. Prevalence of late-onset dementia in the UK by age. Data from Prince et al. (2014).

pharmacological modality exists which can effectively treat or prevent VaD. Consequently, a biogerontological imperative exists to highlight the modifiable lifestyle practices which impact the onset and progression of VaD. This review critically examines the factors which have been empirically revealed to influence VaD risk. The overarching aim is to identify lifestyle strategies which could help to prevent or slow the progression of VaD. To successfully do this, it is necessary to have a contextual appreciation of the mechanisms which underpin the pathobiology of VaD. The next section will provide an overview of these processes.

2. Pathobiology

The pathobiology of VaD has been comprehensively reviewed previously (Kalaria, 2018; Sergi et al., 2023; Tian et al., 2022; Yang et al., 2022; Yu et al., 2022). What can be broadly concluded from this work is that the complete pathogenesis of VaD is complex, multi-factorial, and remains to be fully elucidated. The precise mechanisms and sequence of events which lead to VaD are most probably defined by the clinical subtype. Despite this uncertainty, a degree of mechanistic commonality links the subtypes (Prajjwal et al., 2023). These mechanisms are conceptually represented in Fig. 3. Vascular lesions are associated with several biological events which can lead to VaD (Bir et al., 2021). In older people vessel lesions tend to be caused by arteriosclerosis, atherosclerosis in cerebral arteries, or cerebral amyloid angiopathy (CAA) (Huang et al., 2021). Indeed, it is worth noting that midlife atherosclerosis has been associated with VaD in later years (Gustavsson et al., 2020). Atherosclerosis may cause ischemic stroke, the incidence of which strongly correlates with VaD (Koton et al., 2022). In terms of pathogenic mechanisms both atherosclerosis and arteriosclerosis have been linked to cortical cerebral microinfarcts (CMIs) (Arvanitakis et al., 2017; Hainsworth et al., 2024). Microinfarcts are a known pathology which is commonly associated with the ageing brain (Kövari and Gold, 2021). In fact, 51% of subjects in the 90+ oldest old study had microinfarcts (Corrada et al., 2016).

There are several processes that arteriosclerosis and atherosclerosis influence, which have the potential to impact the onset of CMIs (Huang et al., 2024). CMIs could be precipitated by cerebral hypoperfusion, that is caused by dysregulated cerebral blood flow, a secondary effect of atherosclerosis (de la Torre, 2012). Fig. 3 includes other downstream effects of atherosclerosis, that potentially contribute to the pathology of VaD. These mechanisms are not exhaustive, and interested readers are referred to a recent review, where five overlapping pathways were presented, which can lead to atherosclerosis associated VaD (Huang et al., 2021). The pathways centre on oxidative stress, micro RNAs (miRNAs), haemodynamic change, neurovascular unit damage and vascular morphogenesis.

It is widely regarded that arteriosclerosis also contributes to VaD (Wolters and Ikram, 2019). Arteriosclerosis accompanies ageing, and this process could adversely affect the blood brain barrier (BBB) (Qiu et al., 2023). The BBB is also affected by CAA, a condition which results in the build-up of amyloid β (Aβ) fragments of amyloid precursor protein in the cerebral vasculature (Rajeev et al., 2022). BBB leakiness can ensue due to damage to the vessel wall, which is the result of Aβ deposition (Gireud-Goss et al., 2021). Oxidative stress and inflammation are also considered to be significant players in the pathology of VaD (Finger et al., 2022). Animal models of cerebral hypoperfusion have shown that this process is associated with increased oxidative stress and inflammation (Du et al., 2017). Collectively, this dense tapestry of mechanisms and their complex interplay underscore the difficulties associated with fully delineating the sequence of events which culminate in VaD.

3. Comorbidities

In this section the relationship between VaD and some of its risk factors will be critically examined. Due to their significant role in dysregulating cardiovascular metabolism, particular attention will be placed on obesity, hypertension, CVD, and T2DM. However, it is imperative to reemphasise that VaD is a multifactorial disease. Its multifactorial nature is underscored by a number of recent studies. In one cross sectional study involving 46,011 Chinese participants (>60

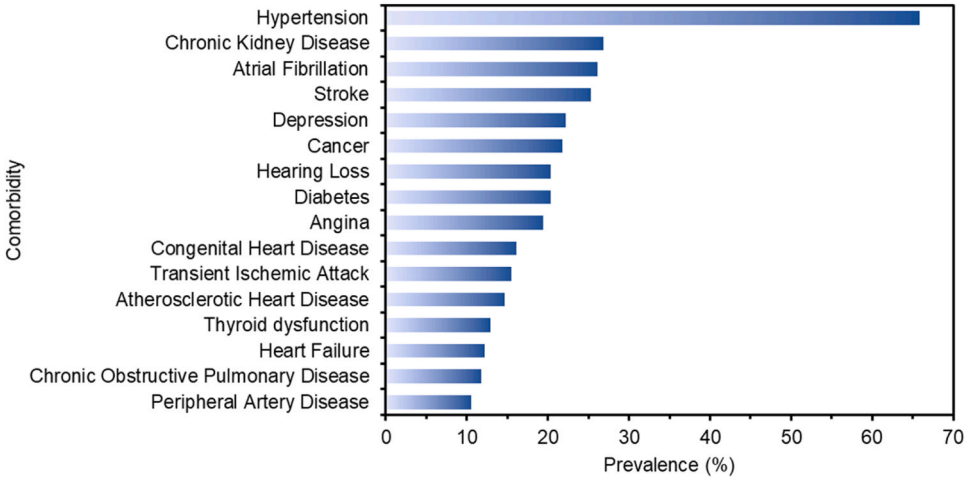

Fig. 2. Prevalence of comorbidities at time of VaD diagnosis. Data from Chung et al. (2023).

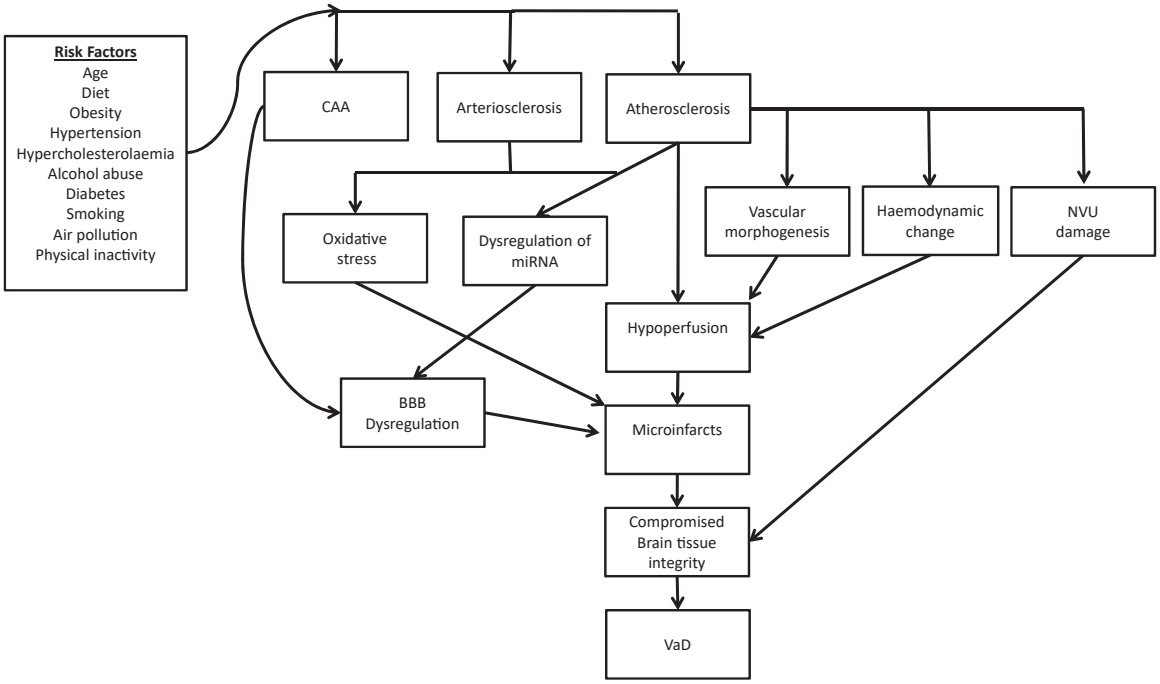

Fig. 3. Coarse grained conceptual overview of some of the putative mechanisms suggested to be involved in the pathobiology of vascular dementia. These mechanisms are discussed in Section 2. Abbreviations: CAA: cerebral amyloid angiopathy, BBB: blood brain barrier, NVU: neurovascular unit, VaD: vascular dementia.

years) many risk factors were identified including, age, sex, and family history (Jia et al., 2020). Nine modifiable risk factors were identified. These were: smoking, hypertension, hyperlipidaemia, diabetes, heart disease, cerebrovascular disease, living in rural areas, gaining fewer years of education and marital status. Most recently a Cox proportional hazards regression model was used to identify the main risk factors for VaD (Celis-Morales et al., 2022). Unsurprisingly age was identified as the main risk factor for VaD, with a relative influence of 47.84%. Diastolic (13.46%) and systolic (12.46%) blood pressure were revealed to be the second and third greatest influences on VaD risk. The fourth, fifth, and sixth factors with the greatest influence on VaD risk were T2DM duration (7.47%), presence of CVD (5.76%), and BMI (5.07%). Other risk factors include LDL-C (2.44%), HbA1c (1.78%), HDL-C (0.077%), and lipid medication (0.08%) (Celis-Morales et al., 2022). Such findings are consistent with experimental data which suggests that a higher frequency of comorbidities including: obesity, hypertension, diabetes and CHD, are often observed in individuals with VaD (Barbiellini Amidei et al., 2021; Fitzpatrick et al., 2009; Javanshiri et al., 2018; Malaguarnera et al., 2004; McGrath et al., 2017). This stresses the importance of viewing VaD in a holistic manner and not ascribing one or even a few factors to its aetiology.

3.1. Obesity

A number of studies have reported that a relationship exists between obesity and VaD risk (Fitzpatrick et al., 2009; Floud et al., 2020; Ma et al., 2016, 2020; Whitmer et al., 2007; Wong Zhang et al., 2023). For instance, one study examined the role of obesity at midlife (50 years) and later life (>65 years) on VaD development (Fitzpatrick et al., 2009). Mid-life obesity was associated with an increased risk of developing VaD, both with and without AD (HR 1.33, 95% CI 0.78–2.29). Similarly, when the impact of obesity in midlife (40–45 years) on VaD risk was examined, >30 years later in 10,136 subjects it was found that individuals with a BMI >30 (obese) at midlife were five times more likely to develop VaD (95% CI 2.98–8.43). Furthermore, being overweight at midlife was associated with a HR of 1.95 (95% CI 1.29–2.96) (Whitmer et al., 2007). A further meta-analysis involving 589,649 participants revealed that midlife obesity, was associated with a relative risk (RR) of 1.33 of developing any form of dementia in later life (Albanese et al., 2017). Being overweight in midlife was not associated with subsequent development of dementia. Moreover, although midlife obesity has been associated with the detection of dementia during a 15 year follow up period, with a RR of 1.21 (95% CI 1.16–1.26), inactivity at baseline was not (Floud et al., 2020). More recently, obese, >50-year-old participants from the English Longitudinal Study of Ageing exhibited a significantly increased risk of developing dementia (all types) (Ma et al., 2020). There was a 31% increased risk when compared to those with a normal BMI (mean follow up = 11 years). Overweight subjects also exhibited an increased risk of developing dementia when fully adjusted for other risk factors (HR 1.27, 95% CI 1.03–1.51) (Ma et al., 2020).

Some studies have focused specifically on women. To this end, waist circumference size and risk of developing dementia has been investigated. Women with abdominal obesity had a 39% increased risk of developing dementia (Ma et al., 2020). Other studies have used BMI to assess VaD risk. In one recent investigation, no association was found between low BMI, and low-calorie intake and the RR of dementia detection (15 year follow up period in >1 million subjects) (Floud et al., 2020). Paradoxically, it has been found that being underweight in later life (65+ years) has been associated with an increased risk of developing dementia (Fitzpatrick et al., 2009). In one study a lower percentage of participants were obese when diagnosis was received closer to baseline measurements. This could be in part due to the weight loss observed prior to diagnosis. For instance, 67.7% of patients with dementia lost weight during the decade prior to diagnosis. Moreover, 54% lost >2.5 kg during this period (Bowman et al., 2019). This is also consistent with findings from the Honolulu-Asia study which revealed that participants who developed dementia, exhibited an average weight loss 0.36 kg/year compared to 0.22 kg/year in males who did not develop dementia, during late life examinations (Stewart et al., 2005).

3.2. Hypertension

Hypertension potentially plays a significant role in VaD (Launer et al., 2000; McGrath et al., 2017; Ninomiya et al., 2011; Schliep et al.,

2021; Sierra, 2020). Autopsy reports have revealed that 74% of individuals with VaD suffered from hypertension (Javanshiri et al., 2018). Moreover, hypertension was more prevalent in patients with VaD, when compared to patients with AD or mixed dementia. Interestingly, the association between VaD and hypertension during midlife has been reported as more significant than in later-life. A multivariable-adjusted HR model for the development of VaD has been calculated as 2.38 (95% CI 0.77–7.30), 5.96 (95% CI 2.00–17.77), and 10.07 (95% CI 3.25–31.25) for patients with midlife prehypertension, stage 1 hypertension, and stage 2 hypertension respectively. Conversely, HRs of 3.01 (95% CI 0.68–13.31), 4.46 (95% CI 1.02–19.42), and 5.57 (95% CI 1.22–25.49) for later life patients with prehypertension, stage 1 hypertension and stage 2 hypertension were observed respectively (Ninomiya et al., 2011). Specifically, it has been estimated that every 10 mmHg increase in midlife systolic blood pressure is associated with a HR of 1.17 (95% CI 1.05–1.31) for the development of dementia (McGrath et al., 2017). Additionally, multivariable analysis indicated that midlife systolic hypertension was associated with a HR of 1.57 (95% CI 1.05–2.35). The continuation of systolic hypertension to later life was associated with a greater HR for developing dementia. Intriguingly, a rapid decline in systolic blood pressure from mid-life to later life was also associated with a greater risk of developing dementia (McGrath et al., 2017).

The Honolulu-Asia ageing study revealed an increasing risk of VaD with increasing diastolic blood pressure in mid-life untreated males (Launer et al., 2000). When controlling for age, education, the apo ε allele, smoking, and alcohol consumption, the associated risk for mixed, borderline high (90–94 mmHg), and high (>95 mmHg) diastolic blood pressure was 2.41 (95% CI 0.77–7.54), 3.26 (95% CI 0.79–13.40) and 2.78 (95% CI 0.54–14.25) respectively. Anti-hypertensive treatment reduced the HR to 1.32 (95% CI 0.54–3.21), 1.37 (95% CI 0.41–4.59), 1.47 (95% CI 0.59–3.66) in the mixed, borderline and high diastolic blood pressure groups (Launer et al., 2000). Interestingly, the development of hypertensive disorders during pregnancy has also been associated with a risk of VaD (HR 1.64, 95% CI 1.19–2.26), when adjusted for maternal age, year of childbirth and parity (Schliep et al., 2021).

The role of anti-hypertension medication on VaD pathogenesis has been investigated. A systematic review concluded that the antihypertensives ACE inhibitors and diuretics significantly reduced the risk and progression of dementia (Shah et al., 2009). It was also noted that calcium channel blockers may have a beneficial impact on the risk of dementia. Similarly, a systematic review concluded that antihypertensive medication, particularly calcium channel blockers and renin–angiotensin system blockers, could lower VaD risk (Rouch et al., 2015). Thus management of this condition using antihypertensive medication could be one way to lower VaD risk.

3.3. CVD

Cardiovascular disease (CVD) encompasses several diseases, including ischemic heart disease, stroke, and VaD. CVD is often a burden with advancing age, with ischemic heart disease and stroke the leading causes of global disability-adjusted life-years in people aged >50 years old (Vos et al., 2020). Inescapable crossover exists between the pathology of CVD and VaD (Zuo and Wu, 2022). This undoubtedly contributes to the recognition that CVD is a key risk factor for VaD (Justin et al., 2013). Indeed, analysis of autopsy data revealed an increased prevalence for moderate (46%) and severe (47%) aortic sclerosis in patients with VaD (Javanshiri et al., 2018). The prevalence of no (3%) and mild aortic sclerosis (4%) was significantly less extensive. Similar findings were observed for coronary sclerosis, with 5%, 15%, 32% and 48% of patients exhibiting no, mild, moderate and severe forms respectively. Moreover, signs of infarction or myocardial hypertrophy have been observed in 75% and 52% of deceased patients with VaD respectively (Javanshiri et al., 2018).

Cholesterol metabolism has a crucial role to play in CVD pathogenesis (Amarenco et al., 2020; Kwon et al., 2019; White et al., 2020). Certain patients with VaD have significantly higher levels of total cholesterol (5.6±0.5 mmol/L vs 5.1 ±0.4 mmol/L) and LDL-C (3.6 ±0.6 mmol/L vs 3.0±05 mmol/L) (Malaguarnera et al., 2004). However, lipid lowering therapy does not appear to impact VaD risk. For instance, a meta-analysis of observational studies revealed no statistical difference between VaD risk and statin use (RR 0.93, 95% CI 0.74–1.16, $p = 0.54$), despite an association between statin use and all-cause dementia (RR 0.83, 95% CI 0.793–0.872, $p < 0.0001$) and AD (RR 0.69, 95% CI 0.60–0.80, $p < 0.0001$) (Poly et al., 2020). Similarly, another meta-analysis demonstrated that statin use was associated with a risk reduction for AD (RR 0.81; 95% CI, 0.73–0.89) and non-AD dementia (RR 0.81; 95% CI, 0.73–0.89), although VaD was not included in this work (Zhang et al., 2018).

Aspirin, commonly used for the prevention of atherosclerotic cardiovascular disease, has been investigated as a potential preventative therapy for VaD development. Results have indicated that low doses of aspirin are associated with a 69% reduction in VaD risk in participants with CHD (Nguyen et al., 2022). Moreover, a meta-analysis of cohort studies revealed that low dose treatment with aspirin had a protective effect against the risk of all-cause dementia (Nguyen et al., 2022). However, these results are not consistent with some other studies. A recent meta-analysis of randomised control trials was not able to establish a similar relationship (Li et al., 2021). Likewise, no relationship was established between low-dose aspirin use and the prevention of dementia in patients with T2DM (Matsumoto et al., 2020). However, when sex differences were examined, results were significant for women (Matsumoto et al., 2020).

3.4. Type 2 diabetes mellitus

An inextricable link exists between poor glycaemic control in type 2 diabetes mellitus (T2DM) patients and vascular cognitive impairment (Lyu et al., 2020). Indeed, optimum glycaemic control has been identified as a crucial factor in preventing VaD (Celis-Morales et al., 2022). It is estimated that patients with diabetes mellitus have a 34–127% increased risk of developing VaD (Celis-Morales et al., 2022; Gudala et al., 2013). Furthermore, diabetes is more prevalent in deceased patients with VaD when compared with other forms of dementia. In fact, autopsy reports revealed that 31% of patients with VaD also had diabetes (Javanshiri et al., 2018). In contrast, diabetes was only present in 12% of patients with mixed dementia. Animal experiments underscore how diabetes can impact brain integrity. Male Wistar rats with streptozotocin-induced diabetes suffer from significant learning and memory deficits (Gocmez et al., 2019). Mechanistically, T2DM has been associated with diminished cerebral perfusion and vasoreactivity, and grey matter atrophy (Last et al., 2007). Specifically HbA1c, an indicator of glucose control over the previous 2–3 months, has been positively correlated with the degree of atrophy ($r = 0.72$, $p = 0.002$) (Last et al., 2007). Moreover, a 1 mmol/mol increase in HbA1c has been associated with a greater rate of decline in global memory and executive functioning z scores (Zheng et al., 2018). Similarly, it has been reported that each percentage increase in historical HbA1c was associated with a 24% increased odds of poor cognitive function, and a 21% increased odds of accelerated 4 year decline (Feinkohl et al., 2015).

One UK-based longitudinal cohort study found that earlier onset diabetes was associated with a higher HR for all cause dementia (Barbiellini Amidei et al., 2021). The HR of dementia was 1.11 in 70-year-old participants who developed diabetes within the last 5 years, when compared with 70-year-old participants without dementia. This increased to 1.49 if diabetes onset was 6–10 years prior, and 2.12 if diabetes onset was more than 10 years earlier. Moreover, a correlation existed between developing diabetes at a younger age and developing dementia earlier in life. For instance, the mean age of dementia diagnosis was 75.8 years in participants who developed diabetes before 60 years of age. This rose to 76.7 years in participants who developed diabetes between the ages of 61–65 years; and 77.5 years in individuals

without diabetes. Further work recapitulates the key role increasing age plays in both dementia and diabetes risk. In a study which examined modifiable and non-modifiable risk factors associated with both T2DM and VaD it was revealed that ageing has the greatest influence on VaD risk (47.84%) compared with T2DM duration (7.74%) and HbA1c (1.78%) (Celis-Morales et al., 2022).

4. Nutrition and vascular dementia

It is increasingly recognised that a major contributor to the malleability of the ageing process is diet (Kim et al., 2022; Mazza et al., 2021; Mc Auley, 2020). Nutrition is a significant factor in disease prevention, and as such it is crucial to maintaining healthspan (Leitão et al., 2022; Longo and Anderson, 2022). The relationship between VaD and a wide variety of nutrients, minerals and supplements have been extensively examined (Azuma et al., 2022; Ghahremani et al., 2023; Gil Martínez et al., 2022; Jia et al., 2018; Masaki et al., 2000; McCleery et al., 2018; Zhao et al., 2022), however it is beyond the scope of this review to critically discuss all of these. Rather, the aim is to highlight some nutrients which have been suggested to significantly impact either the onset or progress of VaD. Due to its pivotal importance in one-carbon metabolism and homocysteine (Hcy) homeostasis, which is a known risk factor in vascular pathology, the nutritional biochemistry of B vitamins is an area of crucial investigative significance (Chang et al., 2023; Nilsson et al., 2013; Wald et al., 2002; Z. Wang et al., 2022). For these reasons it is biologically cogent to dedicate the first part of this section to discussing the role of folate, vitamin B12 and Hcy in the pathogenesis of VaD.

4.1. Folate

Folate (vitamin B9), is naturally found in leafy green vegetables, liver, legumes, nuts and fruit, with many foods fortified with its synthetic variant, folic acid (FA) (Dietrich et al., 2005; Mc Auley et al., 2018; Suitor and Bailey, 2000; West et al., 2020). This water-soluble vitamin is a key regulator in several biochemical processes, including DNA synthesis, protein formation, and erythropoiesis (Bailey et al., 2015; Ducker and Rabinowitz, 2017). An association exists between folate deficiency and VaD risk (Malaguarnera et al., 2004; Nilsson et al., 2013). In one study VaD patients had significantly reduced folate levels compared to controls (10.8±3.03nmol/l vs 13.9±3.03nmol/l respectively) (Malaguarnera et al., 2004). However, not all studies are consistent with these findings. Intriguingly, folate deficiency has been observed in 23.3% of VaD patients who were <75 years, compared to 17.1% of those >75 years of age (Nilsson et al., 2013). Other work reported no significant difference between serum folate levels in VaD patients and controls (Quadri et al., 2004). Although it was sometime a go since this study was conducted, and it would be worthwhile if more recent work investigated this relationship further.

The relationship between FA intake and cognitive function has also been investigated. In a nutritional intervention study, supplementation with 400 μg/day resulted in an increase in serum FA, and a decline in Hcy, IL-6 and TNF-α and Aβ−42 after 12 months. Significantly, this dietary treatment correlated with improved cognitive function (Ma et al., 2016). A caveat of this being that participants had mild, rather than advanced cognitive impairment.

Other lines of evidence suggest supplementation with FA could help reduce VaD risk. Intriguingly, a recent study of Mthfr+/− mice revealed that FA supplementation resulted in a significant reduction in DNA methylation (DNAm), within the lipolysis-stimulated lipoprotein receptor (*Lsr*) gene (Leclerc et al., 2021). The decline in DNAm was associated with increased *Lsr* expression; which could have contributed to the rise in plasma cholesterol, and the decrease in hepatic cholesterol, which was also observed in this work. This finding is worth noting because elevated plasma cholesterol levels strongly correlate with increased VaD risk (Iwagami et al., 2021; Malaguarnera et al., 2004).

4.2. Vitamin B12

The role of vitamin B12 (cobalamin), in VaD risk is an intriguing one. Many studies report that VaD sufferers are vitamin B12 deficient (Goebels and Soyka, 2000; Moore et al., 2012; Moretti et al., 2017). As an example, one study observed vitamin B12 levels of 230.17±7.26 pg/mL in VaD patients compared with 389.7±20.58 pg/mL in controls (Köseoglu and Karaman, 2007). Moreover, vitamin B12 supplementation studies suggest that an adequate intake of this vitamin could help prevent cognitive decline. For instance, it was recently revealed that 84% of patients with minimal cognitive impairment, reported a marked improvement in their symptoms following supplementation (Jatoi et al., 2020). In contrast, a study involving almost 3000 subjects, observed that although vitamin B12 deficiency is a contributing factor to cognitive decline, sub-optimal intake is not a direct VaD risk factor (Soh et al., 2020).

Other studies have reported no statistical correlation between B12 and VaD risk (Arendt et al., 2021; McIlroy et al., 2002; Quadri et al., 2004). For instance, one investigation reported no significant difference between the mean serum vitamin B12 of 15 VaD sufferers and 55 matched controls (254±104pmol/L vs. 278±99pmol/L respectively) (Quadri et al., 2004). A non-significant difference between the vitamin B12 levels of VaD patients and a control group was also reported by Malaguarnera et al. (2004). In this study, VaD patients on average exhibited vitamin B12 levels of 399.8±72.62pmol/L, compared with 438.6 ±61.62pmol/L in controls. One potential explanation for this finding is found in Nilsson et al. (2013) who observed vitamin B12 deficiency in only 9% of VaD patients who were <75 years of age. This figure only increased to 9.8% in VaD patients >75 years (Nilsson et al., 2013). Moreover, a recent investigation involving >100,000 subjects (median 63 years of age) found no association between plasma levels of B12 and dementia (Arendt et al., 2021).

4.3. Homocysteine

The amino acid Hcy is key to protein synthesis; specifically, it is converted to methionine (met) and cysteine by vitamins B12, B6, and folate (Fig. 4) (Finkelstein and Martin, 2000; Škovierová et al., 2016). A negative correlation has been observed between Hcy concentration and circulating plasma B vitamin levels (Clarke et al., 2014; Gofir et al., 2021; Köseoglu and Karaman, 2007; Leblhuber et al., 2000). Specifically, in a seminal study involving 1160 participants from the original Framingham cohort (67–96 years), Hcy was inversely correlated with plasma vitamin B12, and the dietary intake of folate and vitamin B6 (Selhub, 1993). Crucially, in 67% of cases of hypercysteinemia, inadequate plasma concentrations of one or more B vitamin were deemed to be a contributing factor.

Hcy increases with age (Nilsson et al., 2013; Seshadri et al., 2002). This is pathologically significant because elevated Hcy is associated with several age-related diseases, including coronary artery disease (Shenoy et al., 2014), stroke (Shi et al., 2015), AD (Seshadri et al., 2002), and VaD (Nilsson et al., 2013; Ravaglia et al., 2005). In VaD patients (mean age 75.8 ±6.47 years), Malaguarnera et al. (2004) reported significantly elevated Hcy levels, when compared to controls (26±6.58μmol/L vs 10.7±3.0 μmol/L). Similarly, plasma Hcy levels of 18.6±4.15 μmol/l have been recorrded in VaD patients (mean age 80±4.79 years), compared to 10.3± 1.28 μmol/l in controls (Köseoglu and Karaman, 2007). This is consistent with other work which also observed VaD patients to have circulating Hcy levels of 17.0μmol/L (IQR 12.6–23.9, mean age 77.3±9.3 years), compared to controls (10.7μmol/L, IQR 8.1–13.3) (McIlroy et al., 2002).

Reduced levels of plasma B vitamins (B6, 12 and folate), and elevated Hcy, could predict cognitive decline (Dominguez et al., 2021; Tucker et al., 2005). Part of the rationale for this assertion is that Hcy levels have been observed to correlate with brain atrophy rate (Smith et al., 2010; Song et al., 2023). To prevent cognitive decline, it has been

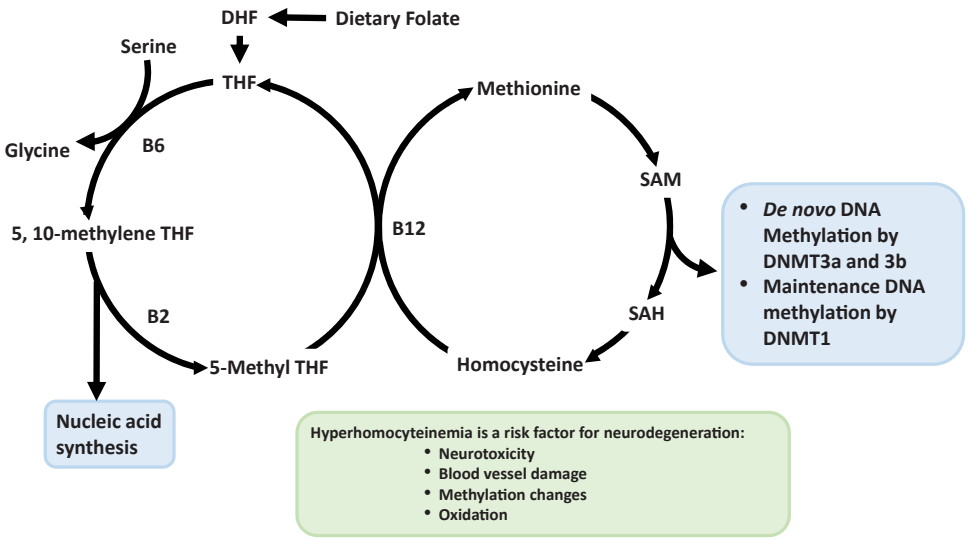

Fig. 4. The folate and methionine cycles. Hyperhomocysteinemia is a risk factor for neurodegeneration. Abbreviations: DHF: dihydrofolate, DNMT: DNA methyltransferase, SAH: S-adenosylhomocysteine, SAM: S-adenosyl-methionine, THF: tetrahydrofolate.

suggested that supplementation might be key (Smith et al., 2010). Indeed, it has been estimated that reducing Hcy levels via supplementation with B vitamins, to prevent dementia, could save >£60,000 per quality-adjusted life years gained (Tsiachristas and Smith, 2016). In one randomised controlled study, participants who received 800 μg/day of FA saw their serum folate increase from 12nmol/L to 76nmol/L, their Hcy decrease from 13.0 to 10.1μmol/L, and their cognitive function improve significantly after 3 years (Durga et al., 2007). Furthermore, it has been observed that treatment with FA, vitamin B6 and vitamin B12 results in a reduced level of brain atrophy in individuals >70 years of age compared to controls (0.76% vs 1.08%). The rate of brain atrophy was reduced by 53.3% in those with Hcy levels >13.0μmol/L who received treatment compared to controls (Smith et al., 2010).

Disappointingly, many studies have reported a reduction in Hcy with supplementation, without subsequent improved cognitive functioning (Clarke et al., 2014; Gofir et al., 2021; Stott et al., 2005). For instance, in a double-blind randomised control study of 3680 adults with nondisabling cerebral infarction, it was reported that a high dose of B vitamins (5 mg of vitamin B6, 0.4 mg of vitamin B12, and 2.5 mg of FA), reduced the level of Hcy by 2.4 μmol/L after 1 month of treatment (Toole et al., 2004). Furthermore, treatment with a low dose (200 μg of vitamin B6, 6 μg of vitamin B12, and 20 μg of FA) resulted in a 0.3 μmol/L reduction over the same time period. Despite this, there was no effect on vascular outcomes over the trial period (Toole et al., 2004). Similarly, it was reported that daily treatment with 2.5 mg of FA, 50 mg of vitamin B6, and 1 mg of vitamin B12 resulted in a 2.4 μmol/l reduction in Hcy in VaD patients or diabetes after 5 years (Lonn et al., 2006). However, the risk of major cardiovascular events was not affected in vascular disease patients (Lonn et al., 2006).

Interestingly, combined FA and B12 vitamin treatment was not associated with a reduction in the risk of recurrent CVD in patients who previously had an acute myocardial infarction, despite a 27% reduction in Hcy (Bønaa et al., 2006). Moreover, one meta-analysis of 11 trials containing 22,000 participants, concluded that although B vitamins reduced Hcy levels by 28%, cognitive function was unaffected (Clarke et al., 2014). Similarly, a recent meta-analysis revealed that although a 6 month FA treatment was useful in lowering Hcy levels by on average 6.16 μmol/l, there was no impact on cognitive function (Gofir et al., 2021). Other work has concluded that the beneficial effects of B vitamin supplementation on brain atrophy can only be observed in people (≥70 years old), who have higher levels of omega 3 fatty acids (Jernerén et al., 2015).

4.4. Specific dietary regimes

Certain diets have been found to influence VaD risk. The dietary approach to stop hypertension (DASH) and the Mediterranean diet have both been associated with a reduced rate of cognitive decline in older persons (Barnes et al., 2023; Charisis et al., 2021b; Tangney et al., 2014). In the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD), it was revealed that consumption of an anti-inflammatory diet may be protective against the development of dementia (Charisis et al., 2021a). It was observed that each unit rise of the dietary inflammatory index resulted in a 21% increase in dementia risk. This is perhaps an unsurprising finding given that it has been suggested reducing the intake of pro-inflammatory saturated fatty acid could abrogate VaD associated cognitive decline (Blake et al., 2022). This view is further supported by the finding that every 10% increase in the consumption of ultra-processed food is associated with a 28% rise VaD risk (H. Li et al., 2022). Other components of human diet have been investigated for their VaD link. For example, it has been reported that tea and coffee intake were associated with lower risk of developing VaD (Zhang et al., 2021). Daily consumption of 2–3 cups of tea and >4 cups of coffee was associated with the lowest hazard ratio (HR) when compared to coffee or tea drinkers. Furthermore, it has been reported that moderate intake of flavanols, a compound commonly found in tea, and flavanol oligo/polymers were associated with lower VaD risk (Bondonno et al., 2021). This finding could be part of the reason why herbal medicine has been advocated as a treatment option for VaD (Bai and Zhang, 2021; Chang et al., 2016; Zhang et al., 2022).

4.5. Dietary restriction modalities

Dietary restriction (DR) is a term which captures a broad range of food manipulation modalities (Green et al., 2022; Mc Auley, 2022). DR includes caloric restriction (CR) (Hofer et al., 2022), time restricted feeding (TRF) (Longo and Panda, 2016), protein restriction (PR) (Simpson et al., 2017), amino acid restriction (D. Wang et al., 2022) and intermitting fasting (IF) (de Cabo and Mattson, 2019). CR is the most well documented regime (Flanagan et al., 2020). Typically, CR involves decreasing calorie intake by between 30% and 40%, without provoking nutrient deficiency or malnutrition (Erbaba et al., 2021). It has been widely documented that CR can extend healthspan and lifespan in many organisms (Hwangbo et al., 2020). In humans, it has been reported that a 30% CR diet for 3 months can result in a 20% increase in verbal memory scores in individuals aged 60 ±7.6 years (Witte et al., 2014).

More recent work suggests that two years of 25% CR in healthy human male and females (21–50 years) can improve working memory (Leclerc et al., 2020). The mechanism(s) which underpin these associations remain unknown. However, findings in rodents have shed some light on the metabolic and structural changes associated with CR. For instance, 40% CR in aged rats has been found to attenuate oxidative stress, preserve Nrf2-driven antioxidant defence mechanisms, inhibit apoptosis, reduce pro-inflammatory cytokine secretion, increase endothelial cell proliferation, improve adhesion to collagen, and promote the formation of capillary-like structures in cerebromicrovascular endothelial cells (Csiszar et al., 2014). However, not all rodent studies suggest CR is beneficial. In a recent study, late-onset CR worsened cognitive performance in female rats (Prvulovic et al., 2022).

TRF recapitulates the effects of CR and helps prevent vascular cognitive impairment in model organisms (Balasubramanian et al., 2020). TRF involves eating within a particular time window. What defines TRF from CR is that it does not require a reduction in the overall calories consumed by an organism (Gallop et al., 2023). In ageing rats TRF has been observed to be neuroprotective (Bhoumik et al., 2022). However, in humans one recent study observed that TRF was associated with poor cognitive performance among 1353 community-dwelling Chinese older adults (Li et al., 2023).

IF has also been suggested as a therapeutic approach for preventing VaD (Yoon and Song, 2019). In one study mice subjected to IF had enhanced learning capacity compared to their counterparts fed *ad libitum* (Selvaraji et al., 2022). PR has similar efficacy. It can mimic the effects of CR and has been shown to be neuroprotective in rodents. This is underscored by a study which examined hippocampus integrity in mice subjected to 20% CR, compared to mice who received access to one of three *ad libitum* low-protein, high-carbohydrate diets (Wahl et al., 2018). Hippocampus RNA expression was similar between all dietary protocols.

The effects of CR can also be elicited by decreasing the intake of certain amino acids. For example, met restriction (MR) extends life/health span in several model organisms (Fang et al., 2022; Kosakamoto et al., 2023; Thyne and Salmon, 2022). MR has been observed to improve working, short term, and spatial memory in aged mice (Bo Ren et al., 2021). The improvements were accompanied by synaptic ultrastructure preservation, increased mitochondrial biogenesis, and reduced MDA levels in the hippocampi of the mice. MR has also been observed to improve cognition in mice (Lail et al., 2023).

5. Emerging perspectives

5.1. Epigenetics

In the last decade epigenetics has significantly impacted biogerontology. Epigenetic clocks can correlate biological age with chronological age to a high degree of statistical precision (Bergsma and Rogaeva, 2020; Duan et al., 2022; Margiotti et al., 2023). Moreover, age related epigenetic changes have been implicated in many diseases, including cancer (Morgan et al., 2018), CVD (Krolevets et al., 2023), T2DM (Ling et al., 2022), and osteoarthritis (Richard et al., 2023). The nexus between epigenetics, ageing and VaD is a burgeoning area of investigation. DNAm is the most extensively studied aspect of epigenetics (Duan et al., 2022; Mc Auley, 2023, 2021; Morgan et al., 2020; Ryan, 2021; Zagkos et al., 2021). As the hippocampus is a pathological substrate for dementia (Laakso et al., 1996; McAuley et al., 2009), and given that atrophy of this tissue is a characteristic of subcortical VaD (Kim et al., 2015; van de Pol et al., 2011) it is a key target for epigenetic investigation. In a recent study which focused on the hippocampus of rats with VaD, the vascular endothelial growth factor (VEGF), and kinase insert domain receptor genes were found to be hypomethylated (Park et al., 2018). Both were identified out of 1180 differentially DNAm genes. There is a significant degree of logic underpinning this finding, given that increased levels of VEGF are associated with VaD (Tarkowski et al., 2002). Moreover, elevated VEGF expression is suggested to occur after cerebral hypoperfusion (Jun et al., 2020), which is a critical feature of vascular impairment (Rajeev et al., 2023).

The nexus between DR, epigenetics and VaD is another growing area of exploration. The impact of IF on the DNAm landscape of a chronic cerebral hypoperfusion mouse model of VaD has revealed how the DNAm landscape can change during brain pathology (Selvaraji et al., 2022). AL-fed and IF mice had overlapping differential expressed genes (DEGs), all of which were associated with dementia related pathology including VaD. The ABCC4 gene was hypermethylated in AL-fed mice and hypomethylated in IF mice. ABCC4 is crucial for vascular integrity as it helps to maintain appropriate levels of cyclic adenosine monophosphate (cAMP) (Belleville-Rolland et al., 2016). Smooth muscle vasodilation is regulated by cAMP (Inoue et al., 2023). Given the neurodegenerative significance of DNAm changes to ABCC4, the authors posited that its hypomethylation in IF mice compared to its hypermethylation in AL-fed mice implies a rescuing of its function due to DR. However, given this study found that other genes, including, SPEG, ECE1 and FGFR2 were hypermethylated in AL fed mice and hypomethylated in IF mice, it is unlikely that one single epigenetic alteration is responsible for the putative benefits IF has on VaD.

miRNAs are non-coding RNA that modulate gene expression post-transcriptionally (Shang et al., 2023). Differentially expressed circulating miRNA have been suggested as blood biomarkers for VaD (Hosoki et al., 2021; Prabhakar et al., 2017). Given this finding, it is conceivable that regulators of miRNA signalling could present a therapeutic approach for VaD treatment (D. Li et al., 2022; Zhai et al., 2022). This assertion is supported by recent work in a rat model of VaD which investigated tilianin treatment (Sun et al., 2023). Tilianin ameliorated the cognitive deterioration associated with VaD by modulating the miR-193b-3p/CaM- and miR-152–3p/CaMKIIα-mediated inflammatory and apoptotic pathways. Other work underscores how miRNAs could act as novel clinical biomarkers/therapeutic targets for VaD (D. Li et al., 2022; Zhai et al., 2022). For instance, miR-409–3p, miR-502–3p, miR-486–5p, and miR-451a have been suggested as viable biomarkers for VaD (Prabhakar et al., 2017; Zhai et al., 2022).

Histone modifications are also pivotal to how the epigenetic landscape is transformed during ageing (Zhang et al., 2020). Considerable attention has centred on histone deacetylase 6 (HDAC6). HDAC6 catalyses histone deacetylation. It also deacetylates non-histone proteins, including microtubules and α-tubulin (Pulya et al., 2021). Inhibition of HDAC6 is an effective treatment for heart failure, cancer, inflammatory disorders, and certain neurodegenerative conditions (Faridoon et al., 2023). HDAC6 has been suggested to be a potential therapeutic target for VaD. To test this idea a recent study administered the AD drug Donepezil to a rat model of VaD (Jian et al., 2020). This reduced the nuclear translocation of HDAC6 and its binding with the brain-derived neurotrophic factor (BDNF) gene promoter IV in the cortex. Donepezil abrogated neurodegeneration and restored the synapse dendritic spines density in the cortex. This finding resonates with the observation that HDAC inhibition protects chronic cerebral hypoperfusion and oxygen-glucose deprivation injuries via lysine 14 residue of histone 3 (H3K14) and lysine 5 of histone 4 (H4K5) acetylation-mediated BDNF expression (Fang et al., 2020). HDAC inhibition was associated with an increase in the acetylation status on H3K14 and H4K5.

5.2. The gut microbiome

A complex bidirectional relationship exists within the gut-brain axis which emerging evidence suggests plays a role in dementia (Aziz et al., 2021; Ji et al., 2024; Łuc et al., 2021; Marizzoni et al., 2023). In fact, dementia is associated with changes in the beta diversity and taxonomic composition of the gut microbiome (Stadlbauer et al., 2020). Furthermore, dementia has been associated with increased intestinal permeability and systemic inflammation (Stadlbauer et al., 2020). Moreover, a relationship exists between several gut microbiome-associated

metabolites and the presence of dementia. Most notably, elevated ammonia, and reduced lactic acid have been associated with an increased risk of dementia (Saji et al., 2020). Intriguingly, the combination of these metabolites had a predictive value similar to that of biomarkers traditionally used to identify dementia.

Environmental factors including stress (e.g. hypoxia), and diet are associated with perturbed cognitive functioning and gut microbiome dysbiosis. For instance, in mice, the combination of a ketogenic diet and hypoxic conditions led to increased levels of the pathobiont *Bilophila*. Monocolonisation with *Bilophila wadsworthia* has been shown to result in impaired cognitive behaviour, and reduced hippocampal activity and neurogenesis (Olson et al., 2021). Moreover, several genes associated with neuronal excitation, mitochondrial processes, neuronal interactions, ubiquination, and immune response were differentially expressed following colonisation. These findings tentatively imply that providing the gut microbiome with pre- and probiotics may be useful in the treatment of dementia. This claim is supported by a meta-analysis which concluded that in patients with mild cognitive impairment, probiotic supplementation resulted in significant improvements in cognitive function (Zhu et al., 2021). Furthermore, a meta-analysis of 5 clinical studies revealed that probiotics had a significant effect on cognitive function, while a meta-analysis of 10 preclinical studies showed that patients in the probiotic group had significant improvement in spatial and non-spatial memory (Ruiz-Gonzalez et al., 2021). This work highlighted that probiotic administration was associated with an increase in BDNF. This is an intriguing finding given that a reduction in BDNF levels is associated with ageing, poor memory performance, and reduced hippocampal volume (Erickson et al., 2010). Other work further underscores the therapeutic potential of probiotics. In a double-blind randomised control trial, it was observed that in patients with mild cognitive impairment, daily administration of the probiotic *Bifidobacterium breve* MCC1274 resulted in an increase in the "orientation" score of the cognitive test Japanese version of AD Assessment Scale (Asaoka et al., 2022). Further to this, the "orientation in time" and "writing" subscales of the Mini-Mental State Examination were significantly improved. Additionally, a systematic review of AD in animal models revealed that probiotic administration resulted in improved cognitive functioning, increased bacterial richness, elevated short chain fatty acid levels and reduced inflammation (Krüger et al., 2021). However, it is important to note that not all studies are therapeutically promising. A recent meta-analysis of three random control trials of human participants with AD showed no improvement in cognitive function after probiotic supplementation (Krüger et al., 2021).

5.3. Pro-longevity molecules

5.3.1. Metformin

Metformin is a drug used to successfully treat diabetes (Hostalek and Campbell, 2021; Pernicova and Korbonits, 2014). The efficacy of metformin has led to it being proposed as an anti-ageing drug (Chen et al., 2022; Johnson et al., 2022; Piskovatska et al., 2020). Given this level of confidence in metformin it is perhaps unsurprising that a meta-analysis revealed that cognitive impairment was found to be significantly less prevalent in T2DM patients who take metformin (Campbell et al., 2018). This observation is consistent with other studies (Bitto et al., 2016; Chin-Hsiao, 2019; Teng et al., 2021). In an investigation involving US veterans (mean age 63.2 ±10.9 years) metformin administration was associated with a reduction in neurodegenerative disease prevalence by approximately half (Shi et al., 2019). Metformin has also been associated with a reduced risk of dementia in a retrospective cohort study (Chin-Hsiao, 2019). Interestingly, this study identified a dose-response pattern between metformin and dementia risk. More recently, it was revealed that metformin administration was associated with a reduced risk of cognitive impairment, and a reduction in cerebral small vessel disease burden score in T2DM patients (Teng et al., 2021). As outlined earlier small vessel disease causes cognitive impairment and VaD (Wardlaw et al., 2019). Thus, this finding suggests a potential mechanism of action for metformin in VaD treatment.

5.3.2. Rapamycin

The mammalian target of rapamycin (mTOR) inhibitor rapamycin has been shown to be effective as a treatment for insulin resistance (Blagosklonny, 2019), cancer (Blagosklonny, 2023), atherosclerosis (Van Skike et al., 2023), and AD (Van Skike et al., 2023). Rapamycin has also been licenced as an immunosuppressant for organ transplantation (Nguyen et al., 2019). Furthermore, it has been shown to increase longevity in a range of organisms (Aiello et al., 2022; Alvers et al., 2009; Bitto et al., 2016; Juricic et al., 2022; Lind et al., 2017; Robida-Stubbs et al., 2012). Focusing specifically on VaD, rapamycin has been observed to inhibit neuronal apoptosis, alleviate neuronal injury and mitochondrial dysfunction, and enhance mitophagy associated with VaD in rats (Zheng et al., 2021). The authors postulated this occurred due to the suppression of the PI3K/AKT/mTOR pathway. Cognitive improvement was observed in this study. This tentatively suggests rapamycin could be used to treat VaD. However, more studies are needed, particularly in humans, in order to consolidate this notion. At present limited investigations have been conducted in humans. In the ones that have been undertaken the results are inconclusive. For example, in one study involving healthy human volunteers, aged 70–95 years (n=11), who consumed 1 mg/day of rapamycin for 8 weeks, improvements in cognition or physical function were not observed (Kraig et al., 2018). Importantly, however, the author suggested that trials using a larger sample size and longer duration should be conducted to further our understanding of the role of rapamycin in age associated disease.

5.3.3. Resveratrol

Heavy alcohol intake is a risk factor for VaD (Schwarzinger et al., 2018). However, light to moderate alcohol use has been linked with a reduced risk of cognitive impairment and dementia (Rehm et al., 2019). Specifically, red wine has been investigated due to the high levels of the polyphenol resveratrol found naturally within red grapes (Lucerón-Lucas-Torres et al., 2022). Resveratrol has been studied for its anti-microbial (Abedini et al., 2021), anti-inflammatory (Gacar et al., 2023), anti-oxidative (Zhang et al., 2019), anticarcinogenic (Boxu Ren et al., 2021), cardio-protective (Raj et al., 2021), and neuro-protective properties (Ma et al., 2013).

The effect of resveratrol on rats with VaD has been examined. In one study resveratrol treatment substantially improved spatial learning and memory (Zhang et al., 2019). In addition, hippocampal expression of the antioxidant enzyme superoxide dismutase (SOD) and the Bcl-2 anti-apoptotic gene were significantly increased, while the oxidative stress marker malondialdehyde, the apoptosis-promoting gene Bax, and the pro-apoptotic enzyme caspase-3 decreased. It was postulated that the neuroprotective effects of resveratrol may be due to downregulation of the apoptosis pathway and a dampening of oxidative stress. This idea is supported by other work (Gocmez et al., 2019; Ma et al., 2013). For instance, resveratrol treatment improved cognitive decline in a streptozotocin-induced diabetic rat model of VaD (Gocmez et al., 2019). Specifically, resveratrol administration was associated with an increase in SOD levels, and increased levels of the endothelial homeostasis regulator protein eNOS, and BDNF mRNA. In another study involving a VaD rat model, supplementation with 25 mg/kg resveratrol was associated with improved memory and learning (Ma et al., 2013). SOD was elevated, in addition to glutathione in the hippocampus and cerebral cortex, while malonyldialdehyde decreased; further underscoring the potential neuroprotective effects of resveratrol.

Resveratrol has been examined in humans. In one study involving 10 patients with mild cognitive decline, supplementation with an active grape formulation resulted in no decline in metabolism in the standardized volumes of interest of the right posterior cingulate cortex and left superior posterolateral temporal cortex (Lee et al., 2017). The

placebo group demonstrated a reduction in these parameters after 6 months. In another study, 75 mg weekly resveratrol increased cerebral vasodilator responsiveness in T2DM patients (49–78 years) (Wong et al., 2016). This is potentially significant because microvascular disfunction has been associated with reduced cognitive performance (Rensma et al., 2020).

In further work, retention of words over a 30-minute period was significantly increased in 23 overweight (BMI 25–30 kg/m^2) adults aged 50–80 years who took 200 mg/d of resveratrol for 26 weeks, compared to pairwise matched controls (Witte et al., 2014). Supplementation also significantly reduced HbA1c levels, which correlated with increased leptin ($r = -0.5$, $p = 0.013$) and functional connectivity in the medial prefrontal cortex ($r = -0.67$, $p < 0.001$). In another study, resveratrol supplementation (75 mg twice daily) improved cerebrovascular responsiveness to hypercapnic and cognitive stimuli, verbal memory and overall cognitive performance in post-menopausal women after 14 weeks (Evans et al., 2017). Taken together, these findings suggest that resveratrol supplementation could be a promising therapeutic strategy for the prevention of cognitive decline associated with ageing and VaD.

6. Discussion and conclusions

This review aimed to critically examine the relevant literature in order to identify the factors which underpin VaD risk, and the mechanisms which contribute to its pathobiology. It is evident from surveying the literature that a substantial amount of current VaD knowledge is based on inferences derived from observational studies. A significant limitation of observational studies is that they make it challenging to disentangle cause from effect. Despite this drawback general learnings can be taken from this review. Firstly, it is reasonable to conclude that suboptimal diet is a risk factor for VaD. Empirical evidence implies that deficiencies in B vitamin intake increases the risk of developing VaD (Jatoi et al., 2020; Ma et al., 2016; Malaguarnera et al., 2004). Moreover, it can be concluded with a reasonable degree of confidence that dysregulated B vitamin metabolism, and in particular elevated hcy is detrimental to the neurovascular system (Nilsson et al., 2013; Yuan et al., 2022). What can also be taken from this review is that a wide range of comorbidities are associated with VaD. Effective management of comorbidities such as hypertension and T2DM is one way to lower VaD risk (Campbell et al., 2018; Chin-Hsiao, 2019; Javanshiri et al., 2018; McGrath et al., 2017; Rouch et al., 2015; Teng et al., 2021). This conclusion is further supported by recent work which showed that administration of antihypertensive medication over a seven-year period was associated with a decreased risk of developing dementia (Schroevers et al., 2023).

The importance of ageing to VaD risk and progression was a recurring theme of this review. Our understanding of ageing has increased significantly in the last few decades. Indeed, based on current evidence, human ageing can be viewed as an immutable process, whose trajectory can be moulded by appropriate lifestyle, pharmaceutical or medical interventions (Chmielewski, 2020; Johnson et al., 2022; Lee et al., 2021). However, it is important to emphasize that a complete picture of the mechanisms which underpin ageing remains elusive (Rattan, 2024). This is a key point because it is clear from this review that the pathobiology of VaD is shaped by fundamental ageing processes. This makes untangling VaD pathobiology incredibly challenging. If the root causes of ageing are elucidated further this will lead to a commensurate understanding of VaD.

This review does have several limitations. For example, some VaD risk factors were not discussed. The rationale underpinning this decision was that it was deemed cogent to examine those risk factors that are recognised as being critical to VaD. Moreover, it was simply unfeasible to evaluate every risk factor for VaD. However, it is worth briefly mentioning within the context of the findings of this review some risk factors that may impact those discussed in this survey. For instance, a lack of physical activity (PA) and vitamin D status have recently been highlighted as potentially important to the onset of VaD (Vítor et al., 2023). Optimal vitamin D status and adequate levels of PA are suggested to be neuroprotective. In the case of vitamin D, findings from a mouse model of VaD suggests that neuroprotection is mediated via a reduction in the inflammatory markers IL-1β and TNF-α (Sadeghzadeh et al., 2023). Focusing on PA, recent experimental findings in a rat model tentatively suggest its neuroprotective effects are elicited by provoking the up-regulation of dopamine and 5-hydroxytryptamine levels. However, substantially more work is required to fully delineate the relationship between PA and VaD.

Despite the limitations discussed in the previous paragraph this review did reveal some worthwhile therapeutic avenues that merit further investigation. For example, the emerging role of epigenetics was outlined. An epigenetic exploration of genes linked to VaD pathobiology is very much in its infancy. Thus, this is a research path which necessitates further exploration. Investigations exploring the nexus between the gut microbiome and VaD are also at a preliminary stage. Our understanding of VaD will progress if this line of inquiry is followed. Particularly if additional research is conducted into the relationship between probiotics and cognitive health. However, arguably the most intriguing area that was expounded in this review is that of pro-longevity molecules such as metformin. These molecules are being ubiquitously investigated currently, and it will be interesting to observe if they become a common feature of VaD studies. If they prove effective at preventing/treating VaD this will be of significant benefit to the health and wellbeing of older people.

CRediT authorship contribution statement

Amy Morgan: Conceptualisation, writing – original draft, writing – review & editing. **Mark Mc Auley:** Conceptualisation, writing – original draft, writing – review & editing.

Declaration of Competing Interest

None.

Data Availability

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