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# Critical review of nutrition, blood pressure and risk of hypertension through the lifecycle: do B vitamins play a role?

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## Abstract

Hypertension is the leading cause of preventable mortality worldwide, contributing to over 9 million deaths per annum, predominantly owing to cardiovascular disease. The association of obesity, physical inactivity and alcohol with elevated blood pressure (BP) is firmly established. Weight loss or other dietary strategies, such as the Dietary Approaches to Stop Hypertension (DASH) diet, have been shown to be effective in lowering BP. Additionally, specific nutrients are recognised to contribute to BP, with higher sodium intake linked with an increased risk of hypertension, while potassium is associated with a reduced risk of hypertension. Of note, emerging evidence has identified a novel role for one-carbon metabolism and the related B vitamins, particularly riboflavin, in BP. Specifically in adults genetically at risk of developing hypertension, owing to the common C677T polymorphism in *MTHFR*, supplemental riboflavin (co-factor for MTHFR) was shown in randomised trials to lower systolic BP by up to 13 mmHg. A BP response to intervention of this magnitude could have important clinical impacts, given that a reduction in systolic BP of 10 mmHg is estimated to decrease stroke risk by 40%. This review aims to explore the factors contributing to hypertension across the lifecycle and to critically evaluate the evidence supporting a role for nutrition, particularly folate-related B vitamins, in BP and risk of hypertension. In addition, gaps in our current knowledge that warrant future research in this area, will be identified.

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**Keywords:** Blood pressure; Hypertension; Hypertension in pregnancy; One-carbon metabolism; Folate-related B vitamins

## 1 Introduction

Hypertension is recognised as the leading preventable cause of morbidity and mortality worldwide, predominantly owing to cardiovascular disease (CVD), especially stroke [1,2]. Hypertension in adults and in pregnancy is defined as a systolic/diastolic blood pressure (BP) of 140/90 mmHg or more at rest [3,4]. The relationship between BP and disease risk is continuous. In middle-aged and older individuals who have a BP >115/70 mmHg, it is estimated that the risk of developing CVD doubles for every 20 and 10 mmHg rise in systolic and diastolic BP, respectively [5]. This not only suggests that cardiovascular risk can be reduced through lowering of BP in hypertensive individuals, but that reduction in BP could also have substantial impacts in terms of CVD risk in normotensive individuals. A number of lifestyle and nutritional factors are known to influence BP throughout life and can contribute to the pathogenesis of hypertension. This review explores the factors contributing to BP variability and risk of hypertension across the lifecycle, with critical evaluation of the evidence for the role of nutrition, and in particular folate-related B vitamins, in preventing or delaying the onset of hypertension.

## 2 Global burden of hypertension and hypertension in pregnancy

Hypertension and its complications account for over 9 million deaths per annum [1]. The prevalence of hypertension worldwide rose from an estimated 600 million people in 1980 to almost 1 billion people in 2008; it is predicted to rise even further to 1.56 billion people by 2025 [6,7]. Given that hypertension is the second leading risk factor for disease burden worldwide, elevated BP is a public health concern of global proportions [2]. Moreover, hypertension in pregnancy may lead to serious adverse complications and outcomes. Hypertensive disorders during pregnancy carry risks for both the pregnant woman and the foetus and have been implicated in the development of one-third of severe maternal morbidity in the United Kingdom [8] and one-tenth of preterm births [9], which are the leading cause of neonatal morbidity and mortality [10]. Thus, hypertension in pregnancy, as in non-pregnancy, is of major concern.

Apart from the adverse health impacts, the financial burden associated with hypertension and hypertension in pregnancy is enormous. In the United States, the estimated direct and indirect healthcare costs for hypertension were \$53.2 billion in 2013, whilst the direct costs of hypertension are projected to rise to a staggering \$220.9 billion by 2035 [11]. Furthermore, the costs associated with a pregnancy complicated by pre-eclampsia, a serious hypertensive disorder of pregnancy, are more than double compared to the costs associated with each case of an uncomplicated pregnancy [12]. In 2012, the total cost burden of pre-eclampsia during the first year after delivery was reported at \$2.18 billion in the United States [13].

Evidence from the National Health and Nutrition Examination Survey (NHANES) in the United States suggests that awareness of hypertension varies between different life stages with young adults (18–39 years old) being less aware of being hypertensive compared to middle aged (40–59 years) and older (60 years or older) individuals [14]. Treatment rates and BP control rates followed a similar pattern, with the older adults achieving the highest rate of BP control (54%). A recent study of 526,336 participants showed that whilst hypertension awareness and BP control rates have substantially improved over the last few decades in the developed world [15], these trends have not been observed in the developing world where BP control rates are poor. The proportion of the population that is aware of their hypertensive status in developing countries is also reported to be low (3% in Nigeria and Namibia) [16]. Furthermore, the majority of women suffering from hypertension and hypertensive disorders during pregnancy in developing countries were reported to be unaware of their condition [17–19]. Lack of awareness compromises treatment and BP control rates, which in turn can lead to an increase in the occurrence of complications associated with hypertension, such as end-organ damage and pathological

vascular and neurological changes [3]. Thus, awareness campaigns on hypertension might benefit BP control rates by increasing the proportion of people adhering to their antihypertensive medication.

### 3 Regulation, measurement and treatment of blood pressure

Homeostasis, and hence BP control is primarily regulated by the renin-angiotensin-aldosterone system (RAAS), the baroreceptor reflex and the presence of vasoactive factors in the circulatory system [20,21]. The complex RAAS is involved in the long-term regulation of BP and essentially modulates systemic vascular resistance and the reabsorption of sodium and water which ultimately leads to a BP increase. The proteolytic renin enzyme, which is released in the blood stream by the granular cells of the juxtaglomerular apparatus in the kidney, cleaves angiotensinogen to angiotensin I. The angiotensin-converting enzyme (ACE) then facilitates the conversion of the inactive peptide angiotensin I to the active peptide angiotensin II. Angiotensin II acts directly on angiotensin type I and II receptors in the vascular system to cause vasoconstriction and thereby a BP rise. In addition, angiotensin II also stimulates the release of the steroid hormone aldosterone from the adrenal cortex to further promote sodium and water reabsorption. As a result, blood volume increases further and, therefore, BP increases [20,21]. Moreover, the short-term regulation of BP is mediated by the baroreceptor reflex. In response to vessel wall distention, baroreceptors, which are located on the aortic arch and carotid sinus, increase the afferent impulse activity [20,22]. This causes a decrease in the activity of the efferent sympathetic nervous system and an increase in the activity of the parasympathetic nervous system to augment vagal tone, stimulate bradycardia and vasodilation and eventually lower BP. As well as RAAS and the baroreceptor reflex, endothelial mechanisms are implicated in BP regulation [20]. The vascular endothelium, which constitutes the inner cellular lining of blood vessels, synthesises vasoactive factors such as nitric oxide and endothelin-1. Nitric oxide mediates vasodilation and hence, BP lowering, whilst endothelin-1 causes vasoconstriction and in turn an increase in BP. Given that BP is the product of cardiac output, systemic vascular resistance and arterial elasticity, an imbalance of sodium reabsorption, impaired neurogenic control, endothelial dysfunction and/or increased arterial stiffness can increase the risk of developing hypertension [20,21].

BP refers to the force exerted by blood on the walls of the large arteries in the systemic circulation. Specifically, systolic BP refers to the maximum pressure in the arteries during a contraction of the heart muscle (systole), and diastolic BP refers to the lowest pressure measured within the arteries when the heart muscle relaxes between beats (diastole) [22]. In a clinical setting, BP is predominantly measured using the auscultatory method to detect the appearance and disappearance of Korotkoff sounds in the brachial artery, which represent systolic and diastolic BP, respectively [23]. An alternative non-invasive BP monitoring method is the oscillometric technique, wherein BP is measured using an automated cuff that yields estimates of systolic and diastolic BP by the observation of oscillations in the cuff pressure [23]. Given that patients may present to the clinic with white coat hypertension (hypertensive BP levels in the clinic but not outside the clinic) or masked hypertension (hypertensive BP levels outside the clinic but not at the clinic) and that BP varies throughout the day and night, an out of office BP measurement over an extended period of time should be considered for the diagnosis of hypertension [3,23]. Ambulatory BP monitoring (ABPM) is the reference standard as it records BP over a 24-h period and can, therefore, track circadian rhythm and prevent false diagnosis. In the case that an ABPM is not suitable or tolerated by the patient, a home BP monitoring would be recommended to confirm the diagnosis of hypertension [3].

The main goal of antihypertensive therapy is to treat and control hypertension, and in turn, to prevent the associated complications, particularly myocardial infarction and stroke. The National Institute of Health and Care Excellence (NICE) advises that in adults under 80 years, BP should be reduced to <140/90 mmHg, whereas for

older adults over 80 years, BP should be reduced to <150/90 mmHg [3]. In women who are pregnant or planning to become pregnant, the target BP is 135/80 mmHg [4]. In infants and children, the targets are BP < 99<sup>th</sup> and 95<sup>th</sup> percentile for age, sex and height, respectively [24,25]. In hypertensive children and adolescents who have specific conditions (e.g. chronic renal disease, diabetes or hypertensive end-organ damage), it is recommended that BP be reduced to less than the 90<sup>th</sup> percentile for age, sex and height [25]. Pharmacologic treatment of hypertension involves the use of antihypertensive agents, such as ACE inhibitors, angiotensin II receptor blockers,  $\alpha$ -adrenergic receptor blockers,  $\beta$ -blockers, calcium-channel blockers (CCBs) and diuretics; polytherapy is recommended whereby two or more antihypertensive medications are used in combination [3]. However, in pregnancy and breastfeeding, certain antihypertensive agents, such as ACE inhibitors, are contraindicated as they could be harmful to mother, foetus and offspring [4,26]. During the perinatal and antenatal periods, labetalol ( $\beta$ -blocker), nifedipine (CCB) and methyldopa (centrally acting antiadrenergic) are recommended as suitable options for the treatment of hypertension [4]. Furthermore, in women who have chronic hypertension or are at high risk for pre-eclampsia, aspirin is recommended from 12 weeks of pregnancy until birth [4]. In infancy, the only antihypertensive agent proven to effectively reduce BP is captopril (ACE inhibitor) [27]. Apart from antihypertensive medications, statin therapy for the treatment of hyperlipidaemic hypertensive patients has been shown to result in a BP reduction and improved BP control rates, irrespective of antihypertensive medication [28]. Furthermore, the BP-lowering effect of statins seems to be independent of statin type or dosage administered [29]. Moreover, weight loss resulting from pharmacological (orlistat, rimonabant and topiramate) and surgical (bariatric surgery) interventions has also been shown to lead to a decrease in BP and improved BP control rates [30–34].

### **3.1 Factors contributing to hypertension**

It is widely recognised that hypertension is a multifactorial condition involving the interaction of modifiable and non-modifiable risk factors.

### **3.2 Modifiable risk factors for hypertension**

The link between obesity and hypertension is well documented. An estimated 15, 25 and 40% of normal weight, overweight and obese individuals, respectively, are reported to have hypertension [35]. Excess body mass not only affects BP in the general adult population but can also have an adverse effect on BP in pregnancy and childhood. One systematic review showed that women who had a pre-pregnancy body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup> were up to 10 times more likely to develop gestational hypertension and pre-eclampsia [36]. Furthermore, evidence from a prospective birth cohort study in childhood showed that children who were overweight at 5 and/or 14 years of age had a higher systolic and diastolic BP at age 14 years compared to those who had a normal BMI at 5 and 14 years [37]. Therefore, controlling the global obesity epidemic for the prevention and treatment of hypertension at all life stages is of paramount importance.

It is well established that lack of regular physical activity adversely influences BP, irrespective of whether the individual is normotensive or hypertensive. One meta-analysis of 65 studies investigating the acute effects of exercise on BP showed that in the hours following an exercise session, systolic and diastolic BP were reduced by 4.8 and 3.2 mmHg [38], respectively. Another systematic review of 27 randomised controlled trials (RCTs) in individuals with hypertension reported that regular medium-to-high intensity aerobic activity was associated with lower systolic BP by 11 mmHg and diastolic BP by 5 mmHg [39].

Although the evidence in relation to the effect of smoking on BP is conflicting [40], most studies report smoking as an important determinant of hypertension [41,42]. Not only is active smoking associated with an increased

risk of incident hypertension [41], but passive smoking can also have detrimental effects on BP. Of note, Cabral et al. [42] recently reported a higher BP at 4 years of age in children whose mothers smoked prior to conception through pregnancy and childhood compared with those children of non-smoker mothers. This reinforces the importance and need of effective smoking cessation programmes and smoke-free environments from early life through older age in order to maintain more optimal BP, and thus better cardiovascular health.

Alcohol and caffeine consumption have also been associated with BP. A recent meta-analysis of 36 alcohol intervention trials with a total of 2,865 participants estimated that a reduction in alcohol consumption for at least 7 days in normotensive or hypertensive individuals who drank more than 2 drinks per day was associated with a lowering of systolic and diastolic BP by 5.5 and 4.0 mmHg, respectively [43]. Caffeine intake has also been associated with BP, but the evidence is somewhat unclear. Caffeine intakes of 200–300 mg have been shown to lead to an acute increase in systolic BP of 8.1 mmHg and diastolic BP of 5.7 mmHg [44], whilst the BP response to caffeine seems to be exacerbated in hypertensive patients [45]. Although the evidence on the effect of habitual consumption of caffeine on BP and hypertension risk is inconsistent [46,47], most studies indicate that regular caffeine intake does not increase BP or hypertension risk [44]. This may relate to the development of partial haemodynamic tolerance, whereby the antagonising effect of caffeine is dampened by an eventual upregulation of adenosine receptors [44,48].

There is considerable evidence that certain dietary patterns and specific nutrients can strongly influence BP and potentially prevent or treat hypertension. Such evidence will be discussed in section 6 of this review.

### **3.3 Non-modifiable risk factors for hypertension**

Advancing age results in structural modifications in the arteries and in particular large arterial stiffness, which in turn leads to BP changes over time [49]. Findings from the longitudinal Framingham Heart Study demonstrated that systolic BP increases linearly between the ages of 30 and 84 years, whilst diastolic BP increases until 50–60 years and then slowly declines [50]. Consequently, isolated systolic hypertension predominantly affects older adults [51]. The third NHANES in the United States showed that 3 of every 4 hypertensive adults is aged  $\geq 50$  years, reiterating that advancing age is a key determinant of hypertension [52].

Sex differences in BP and risk of hypertension are also observed. The prevalence of hypertension is higher in males up to 65 years, whereas after 65 years the risk of hypertension appears to be higher in females [11,53]. It has been suggested that these sex differences in the epidemiology of hypertension might be due to a potential protective effect against hypertension development of sex hormones in women of reproductive age, which is reversed after menopause [54]. However, research investigating the effect of hormone replacement therapy on BP in postmenopausal women is controversial, indicating that the sex-related differences on BP may be more complex than initially perceived [55–57].

Racial and ethnic differences have also been shown in epidemiological studies to affect the incidence and prevalence of hypertension. A study conducted in American adults, aged 20 years or older, showed that the age-adjusted prevalence of hypertension in Asians, Hispanics, Whites and Blacks was 27.0, 29.0, 29.2 and 42.4%, respectively [53]. The same study also showed that, compared to Hispanic adults, the life expectancy of Black Americans was shorter by 7 years, possibly owing to higher rates of hypertension. Given that the difference in BP observed between Blacks and Whites was shown to begin at 15 years of age and that BP tracks with age, interventions to prevent hypertension in this at-risk population should ideally be commenced in adolescence [58].

There is strong evidence suggesting that an estimated 48–60% of systolic and 34–67% of diastolic BP variance may be attributed to heritability [59,60]. The prevalence of hypertension was shown to be significantly higher in individuals who have family history of hypertension compared to those without [61]. In addition, BP levels amongst normotensive individuals were also found to be higher in those with a positive family history [62]. Furthermore, Ness et al. [63] demonstrated that the risk of developing hypertension in pregnancy and pre-eclampsia in women who had at least two first-degree family members with hypertension was twofold higher than those who had no family history. Thus, BP should be closely monitored in individuals with a family history of hypertension, even when BP is normal.

## 4 Blood pressure and risk of hypertension through the lifecycle

### 4.1 Pregnancy

Multiple physiological changes occur during pregnancy, leading to an initial decrease in BP until the 20<sup>th</sup> gestational week, followed by a progressive increase until term [64–66]. Hypertension is not only a risk factor in the general population but is of particular concern in pregnant women, with up to 15% of pregnancies complicated by hypertension [67]. In such pregnancies, the BP pattern deviates from the typical one. A recent meta-analysis by de Haas et al. [68] showed that the mid-gestational systolic BP drop is absent in hypertensive pregnancies, while diastolic BP initially decreases and after mid-pregnancy both systolic and diastolic BP rise to higher levels and in a steeper slope than in normotensive pregnancies.

Hypertension in pregnancy can be defined as i) chronic hypertension, ii) gestational hypertension or iii) pre-eclampsia [4]. Chronic hypertension refers to pre-existing hypertension or hypertension diagnosed before the 20<sup>th</sup> week of gestation, whereas gestational hypertension is defined as high BP occurring for the first time after the 20<sup>th</sup> week of gestation. Gestational hypertension usually resolves postpartum, however, if high BP persists beyond the 12<sup>th</sup> week after pregnancy, then the diagnosis of chronic hypertension can be assigned [69]. Pre-eclampsia is a condition unique to human pregnancy and is characterised by the presence of hypertension and proteinuria or hypertension and end-organ dysfunction with or without proteinuria [4]. The occurrence of seizures in combination with the pre-eclamptic phenotype leads to the diagnosis of eclampsia.

The prevalence of hypertension and pre-eclampsia has increased in the recent years, possibly due at least in part to advanced maternal age and the obesity epidemic [70,71]. Chronic hypertension, gestational hypertension and pre-eclampsia or eclampsia complicate 1–5%, 6–7% and up to 5–7% of all pregnancies, respectively [72]. Compared to women who had normotensive pregnancies, women with a history of hypertension in pregnancy are at an increased risk for hypertension and stroke in later life [69]. Furthermore, women with a history of hypertensive disorder of pregnancy are typically diagnosed with hypertension on average 8 years earlier than those with no such history [73]. This suggests that hypertension in pregnancy not only influences pregnancy outcomes, but also increases the risk of hypertension and age of onset of hypertension in later life.

### 4.2 Infancy

Defining normal BP in infants, especially neonates, is extremely complex as BP and the pattern of BP at this stage of life are strongly correlated with birth weight, size, gestational age, chronological age and postmenstrual age (i.e. gestational age plus chronological age) [74–76]. BP of term newborns remains unchanged in the first 15 minutes fifteen minutes after birth, whereas BP of newborns who were born preterm decreases steadily within the first 3 hours three hours of life [77,78]. Eventually, BP spontaneously rises during the first 5–7 days in neonates, after which point the rise in BP is less rapid [75,79,80]. It has also been reported that the rate of

increase in systolic BP during infancy is greater than the rate of increase in diastolic BP [81]. Moreover, the BP rise in preterm newborns is reported to be more pronounced than in term newborns [79,82]. However, after 14 days of life, BP in preterm neonates appears to stabilise and is found to be similar to that of term infants [82].

Hypertension in infants aged 1 month to 1 year is defined as a BP  $\geq$  95<sup>th</sup> percentile for age, sex, height and weight [74], whereas hypertension in neonates is defined as a systolic BP greater or equal to the 95<sup>th</sup> percentile for chronological age, postmenstrual age, sex, birth weight and appropriateness of size for age [24,74]. Although 5% of infants are hypertensive by definition, the reported incidence of infantile hypertension ranges from 0.2% in healthy newborns, to 3.0% in the neonatal intensive care unit [74,83].

### 4.3 Childhood and adolescence

In children, BP increases progressively and is similar between the two sexes before puberty. The upward trend in BP continues during adolescence, albeit the incline is steeper. In particular, males experience a more marked pubertal rise than females and the widely accepted sex-related differences in BP are slowly established [84]. The prevalence of hypertension and pre-hypertension in British children and adolescents was estimated at 2.3 and 6.9%, respectively, in 2007 [84].

In the United Kingdom, hypertension in children and adolescents is defined as a BP above the 98<sup>th</sup> percentile for age [84]. Hypertension in childhood and adolescence is becoming a major concern as a strong association has been established of paediatric hypertension and pre-hypertension with hypertension and CVD risk in adulthood [85,86]. An estimated 1 in every 2 hypertensive adults had elevated BP in childhood [87]. As in adulthood, paediatric hypertension may also result in irreversible end-organ and vascular damage [88,89]. The collated evidence suggests that BP monitoring in children and adolescents is important, but in practice, BP is likely to be overlooked in most paediatric settings. Despite having their BP measured and recorded, three quarters of all hypertensive and pre-hypertensive paediatric patients remain undiagnosed [90].

### 4.4 Adulthood

Systolic and diastolic BP continuously increase from early adulthood to middle-age with a systolic/diastolic BP of <120/80 mmHg considered as normal BP, since it is associated with the lowest CVD risk and related adverse outcomes [51]. The prevalence of hypertension in adults aged 18–39 years and 40–59 years is reported to be 7.3 and 32.7%, respectively [14]. Of note, normotensive individuals at age 55 are reported to have a 90% lifetime risk of developing hypertension [91]. In addition, individuals who experience a reduction or no change in BP by the age of 55 have the lowest lifetime risk for CVD (22–41%), compared to those who had or developed hypertension by that age (42–69%) [92]. Thus, primary prevention of hypertension is crucial to alleviate a potential public health burden. It is extensively documented that the use and duration of use of hormonal contraceptives (the most widely used method of birth control by women) are associated with increased BP and risk of hypertension [93]. However, cessation of hormonal contraceptives eventually cancels the excess hypertension risk and restores BP to baseline levels [94]. Hence, the BP of women who are taking hormonal contraceptives should be regularly monitored and if needed, an alternative method of birth control considered.

In adults aged 18–39 years, BP within the normal range is associated with a reduced risk of heart failure compared with a systolic or diastolic BP of 130 mmHg or 80 mmHg or more, respectively [95]. These cardiovascular outcomes are thought to be a result of pathological changes in the heart and the vasculature, which are caused by elevated BP. Recently, three-dimensional echocardiography revealed that, even after adjusting for relevant confounders, higher cumulative BP from early adulthood to middle age is linked to left



atrial remodelling and dysfunction [96]. Additionally, findings from the 'Insight 46' epidemiological study of dementia-free individuals showed that high BP in midlife is associated with increased white matter hyperintensity volume and smaller whole-brain volume at 70 years of age, suggesting that BP within this age group is a predictor for potential adverse outcomes in later life [97].

## 4.5 Older age

Systolic BP is known to increase with age throughout life whereas diastolic BP increases until about 60 years and then declines [98]. Evidence from the United States showed that two thirds of adults (60 years or older) were hypertensive [14]. Interestingly, recent results from a population-based cohort study of older participants over a 20-year period revealed that both systolic and diastolic BP decline during the 18 to 14 years before death; 64% of these individuals experienced a reduction in systolic BP of greater than 10 mmHg [99]. In line with the findings of Ravindrarajah et al. [100], the decline in BP was shown to be accelerated in the last two years of life [99].

BP reduction and control in older age remain important for the prevention of CVD [5,101]. Evidence shows that standard BP control (systolic BP of <140 mmHg) in older hypertensive patients led to a reduction of cardiovascular events as expected [102]. Of note, the Systolic BP Intervention Trial (SPRINT) showed that compared to standard BP treatment, intensive BP treatment (BP target of <120 mmHg) in older adults with hypertension resulted in lower death rates from CVD (by 43%) and any cause (by 27%) [103]. In contrast to the beneficial effects of intensive treatment reported in the SPRINT trial, another study found that older, treated hypertensives with a systolic BP of <135 mmHg and 125 mmHg were at increased risk of mortality and incident heart failure, respectively [104]. Thus, the issue of BP management in older adults is somewhat controversial. Also, use of antihypertensives and low BP in older adults have been linked with increased risk for serious fall injuries in some studies [105,106], whilst other studies show no such associations [107]. Apart from the importance of effective BP management for cardiovascular health and mortality, BP plays a key role in cognitive function and brain health. A systolic BP of  $\geq 130$  mmHg in treated hypertensive patients aged 75 years or older was associated with less cognitive decline after 1 year [108]. Collectively, the evidence suggests that BP in older age should be regularly monitored and tightly regulated in order to maintain health and wellness.

# 5 Nutrition interventions to lower blood pressure

## 5.1 Energy intake and obesity

Body weight, weight gain and obesity are strongly associated with BP [35,109]. Thus, lifestyle modifications to induce weight reduction is the first line of treatment in pre-hypertensive and hypertensive patients [3,4,25], with reports estimating that for every 10 kg of weight loss, systolic BP potentially decreases by an estimated 5–20 mmHg [51]. However, weight loss of this magnitude is extremely difficult to achieve in practice for both health professionals and patients, and even harder to sustain in the longer term. Of note, the Look AHEAD (Action for Health in Diabetes) study, a multicentred RCT of 5,145 overweight or obese individuals with type 2 diabetes, tested the effectiveness of two approaches to weight loss over one year [110]. One approach was an intensive lifestyle intervention involving a programme of behavioural modifications for weight management, a diet plan with caloric restriction and increased physical activity. The other approach was 'usual care', comprising of a programme of diabetes support and education. After one year of follow-up, the percentage of initial body weight loss was greater in those assigned to the intensive lifestyle intervention (8.6%) compared with those assigned to receive usual care (0.7%). Furthermore, the weight loss achieved by the intensive lifestyle intervention group led to greater reductions in systolic/diastolic BP ( $-6.8/-3.0$  mmHg) compared to the usual

care group ( $-2.8/-1.8$  mmHg) and prevented the increase in antihypertensive medication users at one year ( $-0.1\%$  vs  $2.2\%$ ).

## 5.2 Dietary patterns

Emerging evidence has identified certain dietary patterns to be linked with BP across all age groups, most notably, the Dietary Approaches to Stop Hypertension (DASH) diet, which is characterised by a high consumption of fruits, vegetables, whole grains and low-fat dairy and a reduced consumption of saturated and total fat (Table 1). In comparison to a control typical ‘American’ diet, comprised of low fruit, vegetable and dairy product consumption and high consumption of saturated and total fat, the DASH diet was shown to be highly effective in reducing systolic/diastolic BP among normotensive (by  $3.5/2.1$  mmHg) and hypertensive individuals (by  $11.4/5.5$  mmHg) after 8 weeks of intervention [111]. Of interest, the effect of the DASH diet on BP was found to be maintained at 8 months after completion of the trial [112]. Moreover, the DASH diet is not only effective in non-pregnant adults, but it has also been shown to have a BP-lowering effect in pregnant women and adolescents [113–115]. The effects of the DASH diet on BP may be at least partly explained by dairy-rich nutrients including calcium, as the recently published INTERnational study on MAcro/micronutrients and blood Pressure (INTERMAP) confirmed that low-fat dairy consumption was associated with lower BP in 2,694 participants aged 40–59 years [116]. Unsurprisingly, modifications to the DASH diet to reduce sodium intake or body weight have been shown to further lower BP compared to the DASH diet alone [112,117,118]. Taken together, this evidence supports the implementation of the DASH diet or its modified versions as an effective lifestyle intervention for the prevention, and potentially the treatment, of hypertension through the lifecycle.

alt-text: Table 1

Table 1

*i* The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purpose for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Effectiveness of selected nutritional interventions to lower systolic blood pressure.

Author	Population	Cohort	Intervention	Main findings
Dietary patterns				
Appel et al. [111] 1997	United States	$n = 459$ 44–45 years (Pre)hypertensive	8-week intervention with the ‘DASH’ diet vs a diet rich in fruits and vegetables only vs a control diet <i>DASH diet</i> : rich in fruits, vegetables, whole grains and low-fat dairy and low saturated and total fat <i>Control ‘American’ diet</i> : low in fruits, vegetables and dairy products and	Compared with the control diet, the DASH diet lowered systolic BP by 5.5 mmHg overall, by 3.5 mmHg in normotensives and by 11.4 mmHg in hypertensives. The BP-lowering effect of the DASH diet was greater than that of the diet rich in fruits and vegetables only

			high in saturated and total fat	
Estruch et al. [120] 2006	Europe	<i>n</i> = 772 69–70 years (Pre)hypertensive and at high CVD risk	A 3-month intervention with a ‘Mediterranean’ diet with virgin olive oil (1 L/week) vs a Mediterranean diet with nuts (30 g/day) vs a low-fat diet <i>Mediterranean diet:</i> high in olive oil, nuts, fruits and vegetables, and low in red meat and processed foods	Compared with the low-fat control diet, systolic BP decreased in response to the Mediterranean diet with olive oil by 5.9 mmHg and the Mediterranean diet with nuts by 7.1 mmHg

### *Specific nutrients*

Gu et al. [200] 2001	China	<i>n</i> = 150 56.9 years (Pre)hypertension	12-week RCT with potassium chloride (60 mmol/day) vs placebo	Potassium chloride supplementation lowered systolic BP by 5.0 mmHg
He et al. [201] 2009	Europe	<i>n</i> = 338 50 years Untreated hypertensive	A 2-week reduced-salt diet followed by the addition of slow sodium (90 mmol/day) vs placebo; 6-week crossover RCT	Reduction in salt intake lowered systolic BP by 5.0 mmHg
Forman et al. [150] 2013	United States	<i>n</i> = 283 51 years Predominantly normotensive	3-month RCT during winter time with 1000, 2000 or 4000 IU/day cholecalciferol vs placebo	A dose-response relationship of cholecalciferol supplementation and systolic BP was shown, with a BP-lowering response up to 4.0 mmHg

### *B vitamins*

Van Dijk et al. [190] 2001	Europe	<i>n</i> = 130 45–46 years Siblings of patients with premature atherothrombosis	2-year RCT with FA (5 mg/day) plus pyridoxine (250 mg/day) vs placebo	B vitamin intervention lowered systolic BP by 3.7 mmHg
Toole et al. [188] 2004	United States, Canada, Europe	<i>n</i> = 3,649 66 years Cerebral infarct	2-year RCT with high dose combined FA (2.5 mg), pyridoxine (25 mg) and cobalamin (0.4 mg) vs negligible dose	B vitamin intervention did not affect BP
McMahon et al. [189] 2007	New Zealand	<i>n</i> = 249 73–74 years Elevated homocysteine	2-year RCT with combined L-5-methylTHF (1 mg), vitamin B12 (500 µg)	B vitamin intervention did not affect BP

			and vitamin B6 (10 mg) vs placebo	
Huo et al. [173] 2015	China	n = 20,702 60.0 years Hypertensive	5-year RCT with FA (0.8 mg/day) in combination with enalapril (10 mg/day) vs enalapril (10 mg/day) alone	No difference in systolic BP response between FA combined with enalapril (−27.1 mmHg) and enalapril alone (−27.1 mmHg). However, FA reduced the risk of first stroke by 21%
<b><i>B vitamins in MTHFR genotype stratified groups</i></b>				
Horigan et al. [185] 2010	Europe	n = 197 53–54 years Hypertensive with CVD	16-week RCT with riboflavin (1.6 mg/day) vs placebo	Riboflavin lowered systolic BP by 13.4 mmHg, specifically in those with the <i>MTHFR</i> 677 TT genotype. No BP response in CC or CT genotypes
Wilson et al. [186] 2012	Europe	n = 62 58.2 years Hypertensive with CVD and the TT genotype	16-week crossover trial with riboflavin (1.6 mg/day) vs placebo	Riboflavin lowered systolic BP by 9.2 mmHg
Wilson et al. [187] 2013	Europe	n = 91 69.1 years Hypertensive without CVD, but with the TT genotype	16-week RCT with riboflavin (1.6 mg/day) vs placebo	Riboflavin lowered systolic BP by 5.6 mmHg. BP control rates increased from 32% to 57% in response to riboflavin supplementation

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; BP, blood pressure; CVD, cardiovascular disease; RCT, randomised controlled trial; FA, folic acid; THF, tetrahydrofolate; *MTHFR*, methylenetetrahydrofolate reductase.

Apart from the DASH diet, other dietary patterns or foods have been linked with improved BP and cardiovascular health. The ‘Mediterranean’ diet, which includes high intakes of extra virgin olive oil, nuts, fruits, vegetables, and minimal intakes of red meat and processed foods [119], has been the subject of a number of studies. The Prevención con Dieta Mediterránea (PREDIMED) randomised trial reported on the effects of this dietary pattern in older adults at high cardiovascular risk [120]. Compared to a low-fat control diet, the Mediterranean diet with extra virgin olive oil or with nuts resulted in significant reductions in systolic BP of 5.9 and 7.1 mmHg, respectively, at 3 months [120]. Although the mechanism explaining the BP-lowering effect of the Mediterranean diet is unclear, it may be mediated by the typically high polyphenol content of this dietary pattern. Dietary polyphenols are associated with an increase in the endothelial production of nitric oxide which, in turn, stimulates vasodilation and hence mediates a reduction in BP [121]. Although there is evidence of the beneficial effects of the Mediterranean diet on BP, data on the prevention and treatment of hypertension with this dietary pattern are not conclusive [122]. Accumulating evidence also indicates that increased fruit and vegetable consumption is inversely associated with hypertension and CVD [123]. Of interest, a crossover RCT investigating the acute BP effect of beetroot juice (with four doses of either 0, 100, 250 and 500 g) showed that BP was significantly reduced over the 24-h post-ingestion period, in a near dose-response manner [124]. The mechanism by which beetroot juice reduces BP may be mediated through the nitric oxide pathway [125]. Nitrates, which are abundantly found in beetroot juice, are reduced to nitrites by the microbiome in the oral cavity. Endothelial nitric oxide synthase (eNOS) further reduces nitrites to nitric oxide and stimulates relaxation of the vascular smooth muscle, thus leading to a reduction in BP [125].

### 5.3 Specific nutrients

A meta-analysis of 34 randomised trials (3,230 participants) showed that a reduction of 4.4 g in daily salt intake for at least four weeks resulted to a decline of 4.2 mmHg in systolic BP and 2.1 mmHg in diastolic BP [126]. Given that the current average dietary salt intake is estimated to be 9–12 g/day [127], a reduction of at least 4.4 g in daily salt intake to comply to the World Health Organisation's target of less than 5 g/day [128], could have major beneficial impact on cardiovascular and public health. In fact, a modest decrease of 2 mmHg in diastolic BP at a population level (potentially achievable via a reduced salt intake) could be predicted to result in 17, 6 and 15% reduction in hypertension prevalence, coronary heart disease risk and stroke risk, respectively [129]. A recently published meta-analysis of 133 randomised trials including 12,197 participants showed a dose-response relationship of sodium reduction with BP, whereby each 50 mmol reduction in 24-h sodium excretion (i.e. the best measure of salt intake) was associated with a decrease in systolic and diastolic BP of 1.10 and 0.33 mmHg, respectively [130]. However, evidence suggests that the effect of sodium intake on BP varies greatly between individuals since the BP of some individuals rises after sodium loading, whilst the BP remains unaffected in others [131,132]. In those who do experience a BP change with reduced sodium intake or sodium loading, the diagnosis of 'sodium sensitivity' can be assigned [131]. Furthermore, sodium sensitivity has been shown to exist in normotensives as well as those with hypertension, albeit with a higher prevalence among the latter [131,132]. However, currently there is no agreement on the characterisation of the sodium sensitive individuals [133,134].

BP responses to potassium have been examined in numerous observational and interventional studies. A meta-analysis of 22 RCTs and 11 cohort studies in adults by Aburto et al. [135] showed an inverse association of potassium intake with BP and stroke, though a dose-response relationship was absent. Additionally, the most marked systolic BP reduction (7.2 mmHg) was exhibited when potassium intake was 90–120 mmol/day [135]. Furthermore, observational studies in pregnancy found serum potassium to be significantly lower in hypertensive pregnancies than in normotensive pregnancies [136].

Calcium supplementation (1 g/day) has been shown to reduce BP in most, but not all studies [137–139]. Moreover, calcium supplementation during pregnancy resulted in lower maternal BP, lower risk of pre-eclampsia and lower offspring BP in the early years of life [140–142]. These findings suggest that, apart from a potential role in the treatment of hypertension, calcium may have a role in maintaining healthy BP from in utero to older age.

Magnesium is another nutritional factor that may influence BP. A meta-analysis of 34 randomised trials involving 2,028 individuals demonstrated very small, but significant, BP reductions with magnesium supplementation [143]. Interestingly, co-administration of magnesium with antihypertensive medication has been shown to have an additive effect on BP reductions compared to antihypertensive medication alone. Hence, magnesium therapy for hypertension could lead to improved BP control in hypertensive patients [144].

A protective role of polyphenols in CVD and hypertension has been suggested [145,146]. An RCT using a diet with either polyphenol-rich olive oil (~30 mg/day) or polyphenol-free olive oil in young women with pre-hypertension and mild hypertension demonstrated a notable decrease in systolic and diastolic BP of 7.9 and 6.7 mmHg, respectively, in response to the polyphenol intervention [147]. Furthermore, recent findings have shown that the effect of polyphenols on BP might be sex specific and confined to certain polyphenol classes and subclasses [148,149].

The role of vitamin D in bone health and calcium metabolism is well established, whereas its effect on BP and hypertension remains unclear. A 3-month RCT with placebo or 1000, 2000 or 4000 international units of

vitamin D3 per day showed that vitamin D3 supplementation had no effect on diastolic BP, whilst systolic BP was significantly reduced in a dose-response manner [150]. In contrast, a recent systematic review and meta-analysis of randomised trials (1,687 participants) showed that BP remained unchanged in response to vitamin D3 supplementation in vitamin D deficient adults [151]. Therefore, the role of vitamin D supplementation in BP is unclear.

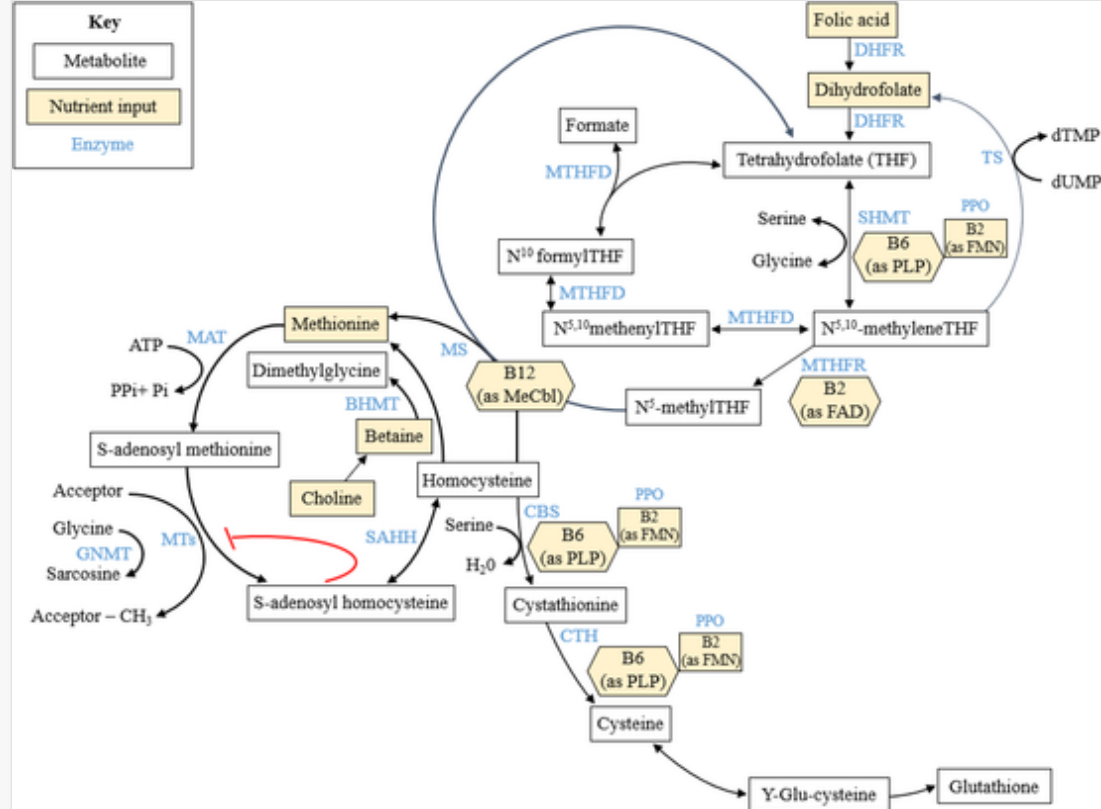
## 6 One-carbon metabolism, related B vitamins and blood pressure

### 6.1 Role of B vitamins within one-carbon metabolism

Tetrahydrofolate (THF)-mediated one-carbon metabolism encompasses a complex network of interdependent pathways that support a variety of processes, including purine and thymidine biosynthesis, amino acid homeostasis and epigenetic mechanisms (Fig. 1). Biologically active folates are present as reduced co-factor forms, i.e. THF, with the predominant form in plasma and cells carrying a methyl group, i.e. 5-methylTHF (5-MTHF). Folic acid, the synthetic form of folate, has to be sequentially reduced to form dihydrofolate and then THF via dihydrofolate reductase. THF then enters the folate cycle and the pyridoxal 5'-phosphate (PLP; active form of vitamin B6)-dependent conversion of serine to glycine donates a methyl group to THF to form 5, 10-methyleneTHF, which is then converted to 5-MTHF [152]. Riboflavin (vitamin B2) is also involved in one-carbon metabolism in one of two co-factor forms, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) [153]. FMN is required by pyridoxine-phosphate oxidase to biologically convert most naturally available vitamin B6 to the active co-factor form PLP in tissues, whereas FAD is required as a co-factor for the key folate-metabolising enzyme, methylenetetrahydrofolate reductase (MTHFR) [152,153]. The flavoprotein MTHFR catalyses the conversion of 5,10-methyleneTHF to 5-MTHF which then serves as a methyl donor for the regeneration of methionine from homocysteine [152]. The reaction responsible for homocysteine remethylation and consequent THF regeneration links the folate cycle with the methionine cycle and is catalysed by the methylcobalamin (vitamin B12)-dependent methionine synthase. Remethylation of homocysteine to methionine is of particular importance as methionine and adenosine triphosphate act as the substrates for S-adenosylmethionine synthetase to form S-adenosylmethionine; the universal methyl donor which plays a key role in epigenetics, biosynthetic processes and in sulphur metabolism [152].

alt-text: Fig. 1

Fig. 1



(Colour online and in press) B vitamins and one-carbon metabolism. B2, vitamin B2 (riboflavin); B6, vitamin B6; B12, vitamin B12; BHMT, betaine-homocysteine methyltransferase; CBS, cystathionine  $\beta$ -synthase; CTH, cystathionine  $\gamma$ -lyase; DHFR, dihydrofolate reductase; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; GNMT, glycine N-methyltransferase; MAT, methionine adenosyltransferase; MeCbl, methylcobalamin; MS, methionine synthase; MT, methyltransferases; MTHFR, methylenetetrahydrofolate reductase; MTHFD, methylenetetrahydrofolate dehydrogenase; PLP, pyridoxal 5'-phosphate; PPO, pyridoxine-phosphate oxidase; SAHH, S-adenosylhomocysteine hydrolase; SHMT, serine hydroxymethyltransferase; TS, thymidylate synthase. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

## 6.2 One-carbon metabolism in relation to adverse pregnancy outcomes and cardiovascular disease

One-carbon metabolism requires an adequate supply of folate, along with vitamin B12, vitamin B6 and riboflavin. Sub-optimal status of any of these B vitamins and/or genetic polymorphisms on B vitamin-dependent enzymes in one-carbon metabolism, can result in a disruption of one-carbon metabolic pathways which can lead to adverse phenotypes, even if dietary folate and related B vitamin intakes are adequate [154,155].

Folate is of particular importance in pregnancy and foetal development owing to its essential role in cell division and tissue growth. The role of periconceptional maternal folate in the prevention of neural tube defects is widely recognised, however, folate has a number of other roles throughout pregnancy with important impacts for maternal and offspring health [156]. Supplementation with folic acid has been shown to prevent the decline in maternal folate concentrations that typically occurs during pregnancy [157] and hence, prevent the occurrence of megaloblastic anaemia of pregnancy [158]. Given that the regeneration of methionine from homocysteine is dependent on folate, a low folate status leads to elevated homocysteine concentrations, a phenotype that can be alleviated in response to intervention with folic acid alone or in combination with related B vitamins [159].

There is extensive evidence to link low folate status (and/or elevated homocysteine concentrations) with an increased risk of adverse pregnancy complications and outcomes including gestational hypertension [160], preeclampsia [161–163], placental abruption [164], pregnancy loss [165,166], low birth weight and intrauterine growth restriction [167]. The risk of gestational hypertension and pre-eclampsia was shown in some studies to be reduced by folic acid supplementation during pregnancy [160], albeit the evidence is somewhat conflicting [168]. Of note, recent evidence from an RCT with high dose folic acid beyond the first trimester of pregnancy showed that folic acid had no beneficial effect on pre-eclampsia in women at high risk for this condition [168]. Such inconsistencies might be explained by intra- and inter-population genetic variation and/or differences in nutritional status of folate and related B vitamins. Of interest, genome-wide association studies (GWAS) and epidemiological studies have linked the common *MTHFR* C677T polymorphism with hypertension and hypertension in pregnancy [155,169–171]. The role of this polymorphism in BP will be discussed further in section 7.3.

Considerable evidence links one-carbon metabolism with CVD, especially stroke [172]. Most notably, findings from the 5-year China Stroke Primary Prevention Trial (CSPPT) of 20,702 hypertensive patients showed that intervention with folic acid resulted in no BP-lowering effect, but significantly reduced the incidence of first stroke by 21% (Table 1) [173]. Of note, the *MTHFR* C677T polymorphism has been linked with several adverse health outcomes, including an increased CVD risk by up to 40% [172]. Less well recognised is evidence showing that the *MTHFR* C677T polymorphism is associated with an increased risk of hypertension and hypertension in pregnancy by up to 87% [169,174–177].

Most relevant studies examining adverse pregnancy and CVD outcomes in relation to folate have focused on plasma homocysteine as the relevant risk factor, but it is likely that folate and metabolically related B vitamins have protective roles against disease that are independent of their homocysteine-lowering effects [178].

### 6.3 One-carbon metabolism, *MTHFR* and blood pressure

The frequency of the *MTHFR* 677-TT genotype is 10% worldwide, however, the distribution varies according to geographical area, in that it ranges 0–3% (in Africa), 8–11% (in Australia), 3–18% (in United States), 8–20% (in China) and 4–26% (in Europe) [179]. The highest reported frequency of the TT genotype is in Mexico (32%) [179]. In addition, geographical gradients in *MTHFR* genotype frequencies in Europe (north to south increase) and China (south to north increase) have been reported [179,180]. As well as geographical variations, ethnicity also appears to influence the frequencies of *MTHFR* genotypes; populations of African, European and American Hispanic ancestry have a low, intermediate and high TT genotype distribution, respectively [179]. Notably, in Mexico, the TT genotype has been shown to be as high as 44% in Mexican Amerindians [181]. Collectively, these findings confirm the impact of ethnogeographic variations in the frequency and distribution of the *MTHFR* 677-TT genotype.



At a molecular level, the C677T polymorphism in the *MTHFR* gene is known to cause a substitution of the amino acid alanine to valine in the protein, producing a thermolabile enzyme with a reduced activity [182]. Elevated homocysteine concentrations occur in individuals with the *MTHFR* 677TT genotype and is the widely recognised phenotype [182]. Hyperhomocysteinaemia has in turn been causatively associated with an increased risk of CVD although its role remains somewhat controversial [154]. Molecular evidence shows that the increased propensity for the variant form of MTHFR to dissociate from its FAD co-factor is responsible for the reduced enzyme activity of the variant enzyme in the TT genotype [183]. Interestingly, human intervention trials have reported a marked decrease in homocysteine concentrations in response to riboflavin supplementation, specifically in individuals with the TT genotype, suggesting that riboflavin can restore reduced MTHFR enzyme activity *in vivo* [184].

As previously mentioned, evidence from GWAS and clinical studies points to a role for one-carbon metabolism in BP and raises the possibility that intervention with relevant B vitamins may have a role in modulating BP. In this regard, a highly novel role for riboflavin in BP has emerged over the last decade from studies conducted at this Centre. The first of these was a 16-week RCT with riboflavin (1.6 mg/day) in premature CVD patients which showed that specifically in those with the *MTHFR* 677TT genotype, systolic (−13.4 mmHg) and diastolic (−7.5 mmHg) BP was highly responsive to riboflavin [185]. At a 4-year follow-up study, these high-risk patients with the TT genotype remained hypertensive despite the fact that antihypertensive polytherapy had been introduced in the intervening period; BP control was achieved again only in response to riboflavin [186]. In a third trial, it was shown that the genotype-specific lowering of BP in response to riboflavin was not confined to high-risk CVD patients, but was also demonstrated in hypertensive individuals without overt CVD [187]. In summary, these randomised trials show that targeted riboflavin supplementation in genetically at-risk hypertensive adults with or without CVD can effectively lower systolic BP by between 6 and 13 mmHg, irrespective of antihypertensive medication. The magnitude of such BP reductions could have an important clinical impact, given that a reduction in systolic BP of 10 mmHg is estimated to decrease stroke risk by 40% [5]. However, the effect of riboflavin supplementation on BP in individuals with the TT genotype has not yet been investigated in other populations outside of Northern Ireland or in pregnancy.

In addition to the genotype-specific BP benefits observed in response to riboflavin, evidence for an effect of B vitamins on BP in the general population is far weaker (Table 1). In the Vitamin Intervention for Stroke Prevention (VISP) trial, 3,649 adults with nondisabling cerebral infarction were randomised to a multivitamin containing either a low dose or a high dose of B vitamins (pyridoxine, cobalamin and folic acid) for 2 years, with results showing no BP response to B vitamin intervention [188]. Similar findings were also reported by McMahon et al. [189], who investigated the effect of combined folic acid, vitamin B6 and B12 on BP in older adults and also showed no BP response. In contrast, another 2-year RCT with folic acid (5 mg/day) and pyridoxine (250 mg/day) found significant reductions in both systolic (of 3.7 mmHg) and diastolic (of 1.9 mmHg) BP in response to intervention [190].

## 6.4 Biological mechanisms linking one-carbon metabolism with blood pressure

The precise mechanisms linking one-carbon metabolism with BP, or explaining the novel role of riboflavin in BP in individuals with the TT genotype, are currently unknown. MTHFR enzyme activity is compromised in individuals with the homozygous variant *MTHFR* 677TT genotype, but appears to be particularly sensitive to changes in riboflavin status [184,191]. It could therefore be speculated that in individuals with this genotype, there is a higher capacity to replace the inactivated enzyme with optimal riboflavin than with low riboflavin status, or that higher riboflavin status prevents the dissociation of the MTHFR co-factor, FAD, from the active

site or allows its quick replacement, and in turn stabilises the variant MTHFR enzyme [192]. In this way, individuals with the TT genotype may have increased riboflavin requirements in order to sustain normal MTHFR activity. Restoration of cellular concentrations of 5-MTHF by riboflavin supplementation in those with the variant TT genotype may also correct any perturbations in one-carbon metabolism owing to this genetic variant, but this remains to be demonstrated [193].

As reviewed elsewhere, the effect of MTHFR on BP is likely to be mediated by nitric oxide, a potent vasodilator which regulates endothelial function [192]. It has been shown that patients with the TT genotype have lower vascular tissue concentrations of 5-MTHF, which in turn are linked with nitric oxide bioavailability and endothelial function [194,195]. Given that riboflavin supplementation appears to restore MTHFR activity in these genetically at-risk individuals [184], it could be speculated that 5-MTHF concentrations in the vascular tissue would increase in response to riboflavin supplementation, leading to the stimulation of eNOS and an increase in nitric oxide bioavailability, thus vasodilation and BP-lowering. Furthermore, apart from reducing 5-MTHF concentrations, impaired one-carbon metabolism could also compromise the activity of dihydrofolate reductase and dihydrobiopterin reductase, impairing the conversion of dihydrobiopterin to tetrahydrobiopterin [196]. Whereas an increase in the bioavailability of tetrahydrobiopterin stimulates eNOS to produce nitric oxide to ultimately induce vasodilation, an accumulation of dihydrobiopterin leads to the generation of superoxide by eNOS [197,198]. Of note, given that riboflavin supplementation has been shown to elicit a BP-lowering response that is specific to individuals with the variant TT genotype in *MTHFR*, a direct effect at the flavoprotein binding domain of eNOS is unlikely to be the major mechanism explaining the BP-lowering role of riboflavin shown in the aforementioned intervention trials, as such an effect would likely impact BP generally and not in the observed *MTHFR* genotype-specific manner [199]. Furthermore, although some observational studies have suggested a role for homocysteine in BP, randomised trials primarily designed to lower homocysteine as a means to reduce CVD showed no corresponding BP response [188,189]. Therefore, homocysteine is unlikely to be directly involved in explaining the relationship of one-carbon metabolism with BP. Further research in this area is clearly required in order to fully explore these and other biological mechanisms linking one-carbon metabolism with BP and hypertension.

## 7 Conclusions and future work

Hypertension is a public health challenge of global proportions. Currently, antihypertensive treatment for the achievement of BP control is ineffective for over 40% of individuals suffering from hypertension. This emphasises the need for identification of alternative prevention and treatment strategies for hypertension. Nutrition is inextricably linked to BP and is involved in the pathogenesis and treatment of hypertension across the lifecycle. At this time, the evidence for a protective effect against hypertension is strongest in relation to the DASH diet, reduced sodium intake and increased potassium intake. Of interest, emerging evidence implicates one-carbon metabolism and related B vitamins in BP. Most notably, supplemental riboflavin may offer an effective personalised approach for managing BP in genetically at-risk individuals, albeit all the evidence in this area to date comes from trials conducted in Northern Ireland. Hence, further research is warranted to replicate such studies in different populations and in cohorts with and without existing hypertension. Mechanistic studies which will add to our understanding of the role of this gene-nutrient interaction in BP are also needed. Given that BP is known to track from early life, and hypertension in pregnancy is a major risk factor both for adverse pregnancy outcomes and later life cardiovascular events, the effect of supplementation with B vitamins on BP in pregnant women genetically at-risk of hypertension should be investigated. If a beneficial effect of relevant B vitamins on BP during pregnancy is demonstrated, a public health strategy to improve B vitamin status during

the periconceptual and antenatal period may alleviate the health and economic burden of hypertension in pregnancy.


## Author contributions

E.P. drafted the original manuscript; H.McN., K.P., M.W. and E.P. critically revised the manuscript for important intellectual content. All the authors have read and approved the final manuscript.

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 The corrections made in this section will be reviewed and approved by a journal production editor. The newly added/removed references and its citations will be reordered and rearranged by the production team.

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## Highlights

- Hypertension is the leading cause of mortality worldwide, typically from CVD.
  - Intervention to effectively lower blood pressure (BP) can reduce CVD risk.
  - Nutritional factors can influence BP and risk of hypertension across the lifecycle.
  - Emerging evidence points to a novel role for one-carbon metabolism in BP.
  - Riboflavin (MTHFR co-factor) lowers BP in individuals with the *MTHFR* 677TT genotype.
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