Lifestyle interventions for the prevention and treatment of hypertension

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Abstract | Hypertension affects approximately one third of the world's adult population and is a major cause of premature death despite considerable advances in pharmacological treatments. Growing evidence supports the use of lifestyle interventions for the prevention and adjuvant treatment of hypertension. In this Review, we provide a summary of the epidemiological research supporting the preventive and antihypertensive effects of major lifestyle interventions (regular physical exercise, body weight management and healthy dietary patterns), as well as other less traditional recommendations such as stress management and the promotion of adequate sleep patterns coupled with circadian entrainment. We also discuss the physiological mechanisms underlying the beneficial effects of these lifestyle interventions on hypertension, which include not only the prevention of traditional risk factors (such as obesity and insulin resistance) and improvements in vascular health through an improved redox and inflammatory status, but also reduced sympathetic overactivation and non-traditional mechanisms such as increased secretion of myokines.

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Approximately one third of the world's adult population have arterial hypertension, traditionally defined as a clinic (or office) blood pressure (BP) of ≥140/90 mmHg[1]. In the past decade, the number of deaths attributable to high BP has risen by 56.1%, and hypertension remains a major cause of premature death worldwide despite substantial advances in pharmacological treatment[2]. The global direct medical costs associated with hypertension treatment are estimated to be US$370 billion per year, with the health-care savings from effective management of this condition projected to be about $100 billion per year[3]. However, recent changes in international guidelines might actually increase the prevalence of hypertension. According to the 2017 guidelines from the ACC/AHA[4], the threshold to define hypertension has now been established at 130/80 mmHg, with stage 1 hypertension defined as office systolic BP (SBP) of 130–139 mmHg and stage 2 hypertension defined as office SBP of ≥140 mmHg. The 2018 guidelines of the ESC/ESH[5] define a SBP of 130–139 mmHg as 'high–normal'. Therefore, many individuals who were not previously receiving medication might now be placed on treatment, leading to an increase in the number of individuals treated for hypertension in the near future.

The promotion of lifestyle interventions (notably exercise, body weight reduction and healthy diet recommendations) aimed at optimizing the prevention and management of hypertension (FIG. 1), including disease phenotypes with higher cardiovascular risk, such as resistant hypertension, should therefore be a priority. This approach is particularly relevant in light of the new stringent cut-off values. Indeed, the aforementioned ACC/AHA and ESC/ESH guidelines recommend lifestyle interventions for the prevention and treatment of hypertension (TABLE 1). The guidelines distinguish between effective lifestyle interventions for lowering BP, such as physical exercise, body weight loss, moderation in alcohol intake and healthy dietary patterns with low sodium intake and high potassium intake, and other interventions for which robust evidence of long-term BP-lowering effects is lacking, including behavioural therapies such as guided breathing, yoga, transcendental meditation or biofeedback. In this Review, we provide a summary of the epidemiological research supporting the benefits of major lifestyle interventions for the prevention and adjuvant treatment of hypertension and describe the main physiological mechanisms underlying these benefits.

Lifestyle versus genotype

Although both heritable and lifestyle risk factors contribute to increased BP levels, the latter can have a substantial effect on BP beyond genetic endowment. To investigate whether lifestyle factors offset the BP effect of an adverse genetic profile, Pazoki and colleagues constructed a genetic risk score for high BP with 314 published BP loci and used it to score 277,005 individuals without previous cardiovascular disease (CVD)

Key points

- Strong evidence supports the benefits of regular physical activity and exercise for the prevention and management of hypertension.
- Reducing body weight to normal in individuals with overweight or obesity reduces the risk of hypertension, but further evidence is needed on the long-term efficacy of this strategy.
- Sodium intake restriction reduces blood pressure, particularly in patients with hypertension, and the Dietary Approaches to Stop Hypertension (DASH) diet is the most effective dietary approach to prevent hypertension and to reduce blood pressure in individuals with pre-hypertension or hypertension.
- Shift work, short sleep duration or poor sleep and other forms of circadian disruption might increase the risk of hypertension.
- Some forms of psychological stress, such as post-traumatic stress disorder, seem to be associated with a higher risk of hypertension, but strong evidence on the potential antihypertensive benefits of stress management techniques is lacking.
- In contrast to common antihypertensive medications, lifestyle interventions, especially exercise, reduce blood pressure through multisystemic and 'non-traditional' mechanisms (for example, not only by improving vascular health or reducing sympathetic overactivation).

from the UK Biobank (age 40–69 years and median follow-up ~6 years)[6]. The investigators also scored participants according to lifestyle factors, including BMI, healthy diet, sedentary behaviour, alcohol consumption, smoking status and urinary sodium excretion levels measured at recruitment, and assessed the association between the genetic risk, lifestyle scores and BP levels. The healthy lifestyle score was strongly inversely associated with both SBP and diastolic BP (DBP) irrespective of the underlying BP genetic risk. Individuals with a favourable lifestyle had lower SBP (4–5 mmHg lower, on average) in all genetic risk groups than those with an unfavourable lifestyle. These data support population-wide efforts to lower BP through lifestyle modification.

Evidence from non-westernized populations, which have low rates of hypertension and a very low prevalence of age-related increases in BP and overall CVD despite receiving no pharmacological treatment, also provides support for the role of lifestyle factors in the prevention of hypertension[7–11] (FIG. 2). These low rates of hypertension and CVD are attributable, at least partly, to their traditional diets and lifestyles, which are similar to those that have characterized most of human evolutionary history — that is, non-westernized dietary patterns, regular physical activity, 'natural' sleep–wake cycles, and sun exposure, among others (FIG. 3) — all of which can influence BP levels and the risk of hypertension, as discussed in depth in the following sections.

Drugs and lifestyle: interaction effects

The role of lifestyle habits in the prevention and treatment of hypertension should be considered together with the potential interactions with antihypertensive medical treatments. An optimal lifestyle can be viewed as the first-line treatment of hypertension in some cases. The ESC/ESH guidelines indeed consider an optimal lifestyle as the only treatment needed for people with mild hypertension during the first 3–6 months after diagnosis, with the recommendation that pharmacological treatment is added after this period if hypertension is not well controlled[5]. In turn, the benefits of an optimal lifestyle should not be overlooked when considering antihypertensive medical treatment, because lifestyle intervention remains a cornerstone for the management of hypertension independently of the medical treatment received. For instance, physical exercise has been reported to improve BP in both pharmacologically treated and untreated individuals[12]. Exercise can markedly lower BP even in association with therapy with three or more drugs (such as in people with resistant hypertension)[13].

Dietary modifications such as the adoption of the Dietary Approaches to Stop Hypertension (DASH) diet are similarly effective in reducing BP in individuals with or without hypertension, as well as in patients with or without antihypertensive treatment[14]. Similarly, a reduction in sodium intake (one of the most popular recommendations for the dietary management of hypertension) is an effective strategy for reducing BP in patients with hypertension, and the effects might be additive to those of pharmacological interventions[15]. For instance, reducing sodium intake in patients aged 60–80 years with hypertension who were taking one antihypertensive drug resulted in a lower BP and a lower incidence of elevated BP, or resumption of medication, during a 28-month follow-up after withdrawal of the antihypertensive drug[16]. Likewise, a reduction in excessive body weight has been reported to be a beneficial strategy in patients with hypertension, in both those not receiving medication and, particularly, in those receiving medication[17].

In the next sections, we review the lifestyle interventions that are recommended by the ACC/AHA[4] and ESC/ESH[5] guidelines for the prevention and treatment of hypertension on the basis of robust evidence, that is physical exercise, body weight management, healthy dietary patterns, circadian entrainment and adequate sleep patterns, and stress management. The current evidence on the main lifestyle factors that can reduce BP and/or the risk of hypertension is summarized in FIG. 4.

Physical exercise

Despite the little attention that physical exercise has received in medical practice compared with drug therapy, guidelines from the Seventh and Eight US Joint National Committees, ACC, AHA, ESC, ESH, American College of Sports Medicine and Canadian Hypertension Education Program recommend increasing the levels of regular physical activity and exercise for the prevention and management of hypertension[18]. A 2019 umbrella review of 18 meta-analyses and systematic reviews including 594,129 adult participants provided strong evidence to support the role of physical activity in preventing hypertension in individuals with normal BP, as well as in reducing BP among individuals with pre-hypertension or hypertension[19]. A meta-analysis of longitudinal studies suggested that individuals who meet the minimum physical activity levels recommended by international guidelines have a 6% lower risk of hypertension than individuals with inactive lifestyles[20]. Moreover, an inverse dose–response relationship seems to exist between the level of physical activity and the

Clinic (or office) blood pressure
Blood pressure (BP) measured in the clinical setting (for example, an outpatient clinic). In this Review, 'BP' refers to 'clinic BP' unless otherwise stated.

Resistant hypertension
Clinic (or office) systolic blood pressure/diastolic blood pressure ≥140/90 mmHg (or ≥130/80 mmHg according to the 2017 ACC/AHA guidelines) in patients receiving at least three antihypertensive drugs (including one diuretic) at maximally tolerated doses.

Physical exercise
Also termed 'exercise training' or simply 'exercise'. A subset of physical activity that is planned, structured and repetitive and has a final or an intermediate objective of improving or maintaining physical fitness. In this Review, physical activity and exercise are sometimes used interchangeably to ease readability.

Non-westernized populations
Hunter–gatherers, traditional horticulturalists, pastoralists and farmers, and other populations minimally affected by western habits.

Non-westernized dietary patterns
Composed mainly of universal fresh food sources very low in refined oils, margarine, refined cereal grains, added sugars and ultra-processed foods.

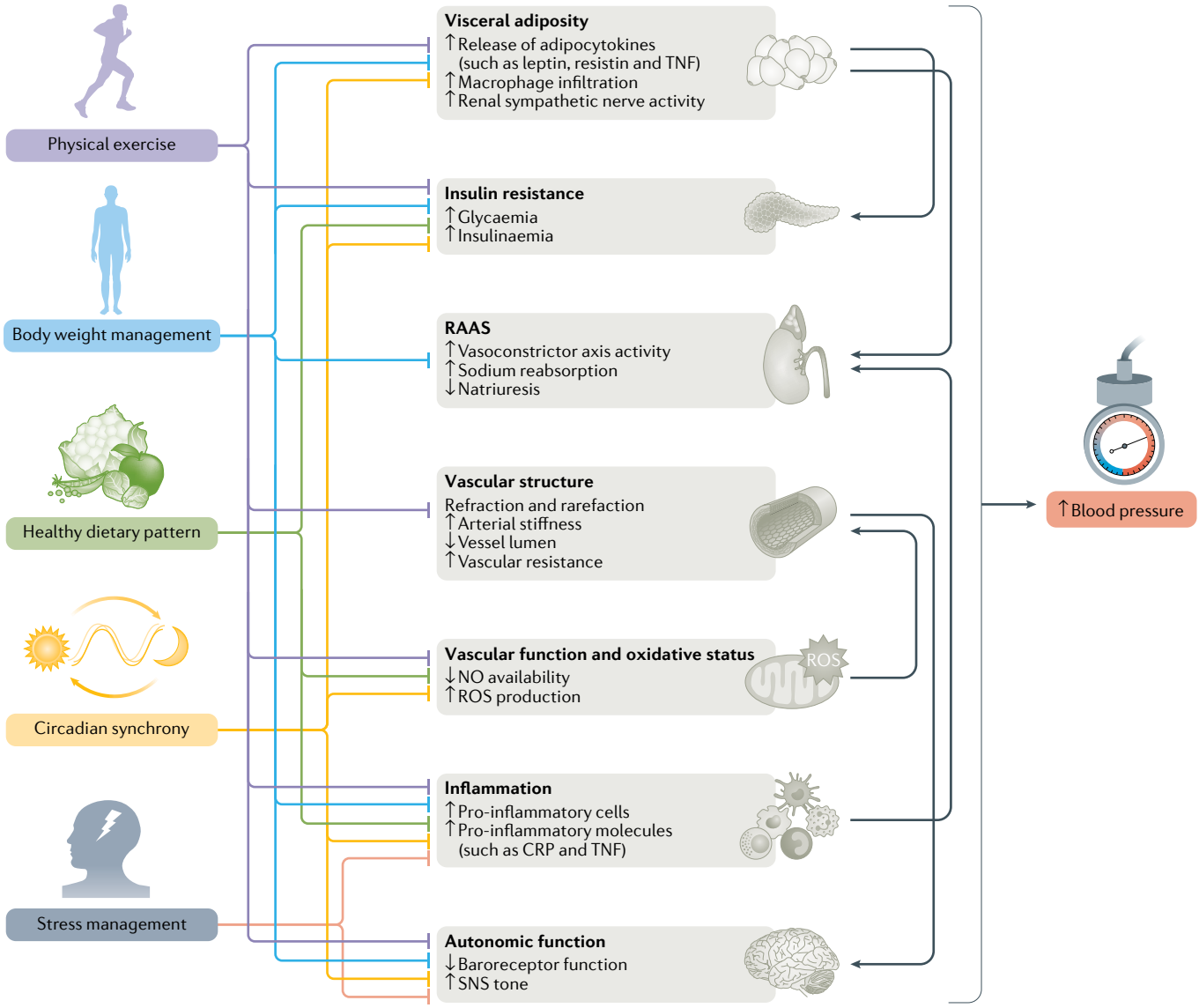

Fig. 1 | **Physiological mechanisms underlying the benefits of healthy lifestyle patterns on hypertension.** Each lifestyle factor can modulate one or more of the main physiological mechanisms that are involved in the development of hypertension: visceral fat accumulation, insulin resistance, stimulation of the renin–angiotensin–aldosterone system (RAAS), alteration of vascular structure, vascular endothelial dysfunction and oxidative stress, inflammation and autonomic dysfunction (with increased tone of the sympathetic nervous system (SNS)). CRP, C-reactive protein; NO, nitric oxide; ROS, reactive oxygen species; TNF, tumour necrosis factor.

risk of incident hypertension, with no cut-off to the amount of physical activity that confers benefit[19,20]. A network meta-analysis of 391 randomized controlled trials (RCTs) and 39,742 individuals found that both exercise interventions and antihypertensive drugs were similarly effective in reducing SBP in individuals with hypertension (SBP ≥140 mmHg)[21].

Physical exercise has also shown remarkable benefits in patients with resistant hypertension, although more research is needed to confirm these observations[22]. Greater physical activity levels have been associated with a lower risk of CVD in people with resistant hypertension[23,24], and two RCTs have shown that exercise interventions reduce 24-h ambulatory BP (average 20 mmHg decrease in SBP and 10 mmHg decrease in DBP) in this patient population[13,25]. Meta-analytical evidence also indicates that moderate exercise during pregnancy is associated with a significantly reduced risk of gestational hypertensive disorders[26,27]. Nonetheless, more evidence is needed on the sustainability of the benefits of exercise in the long term (BOX 1). Also, although exercise has beneficial effects per se on BP and in reducing the risk of hypertension, these beneficial effects might be maximized if combined with body weight reduction (BOX 2).

Physical activity
Any bodily movement produced by skeletal muscles that requires energy expenditure.

Exercise modalities

Different types of exercise have been shown to reduce BP. An umbrella review and a network meta-analysis concluded that all the main types of exercise (endurance exercise (also known as aerobic exercise), resistance exercise

Table 1 | **Lifestyle recommendations from major hypertension guidelines**

Lifestyle factor	ACC/AHA[4]	ESC/ESH[5]
Physical exercise and physical activity	Aerobic exercise (90–150 min per week, 65–75% of heart rate reserve)	Aim for 300 min per week of moderate-intensity or 150 min per week of vigorous-intensity aerobic physical activity, or an equivalent combination thereof
	Dynamic resistance exercise (90–150 min per week, 50–80% one repetition maximum, six exercises, three sets per exercise, ten repetitions per set)	Dynamic resistance exercises (2–3 days per week)
	Isometric resistance exercise (handgrip 4 × 2 min, 1 min rest between exercises, 30–40% maximal voluntary contraction, three sessions per week)	The effect of isometric exercises is less well established
Nutrition	Consume a diet rich in fruits, vegetables, whole grains and low-fat dairy products, with reduced content of saturated and total fat (DASH dietary pattern)	Increased consumption of vegetables, fresh fruits, fish, nuts and unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products
	Reduce intake of dietary sodium (optimal goal <1,500 mg per day)	Sodium intake restriction to <2,000 mg per day
	Increase intake of dietary potassium (aim for 3,500–5,000 mg per day)	
Body weight management	Best goal is ideal body weight	Avoid obesity (BMI >30 kg/m^2 or waist circumference >102 cm in men and >88 cm in women), and aim for healthy BMI (about 20–25 kg/m^2) and waist circumference values
Alcohol	Two or fewer drinks per day for men and one or fewer drinks per day for women	Drink <14 units per week for men and <8 units per week for women, and avoid binge drinking
Smoking	Not specified	Smoking cessation, supportive care and referral to smoking-cessation programmes

DASH, Dietary Approaches to Stop Hypertension.

(also known as strength exercise) or a combination thereof) are similarly effective in reducing BP in individuals with hypertension[19,21]. Although endurance exercise is probably the most commonly prescribed exercise modality for patients with hypertension, the benefits of resistance exercise (such as weight lifting) or the combination of endurance and resistance exercise remain largely unknown in the clinical setting, despite eliciting similar (or even greater) reductions in BP to those achieved with endurance exercise in patients with hypertension (SBP 8.7 mmHg for endurance exercise, 7.2 mmHg for resistance exercise and 13.5 mmHg for combined exercise)[21,28,29]. Moreover, growing evidence suggests that a specific type of resistance exercise, isometric exercise (such as handgrip), which has previously been associated with acute, potentially harmful hypertensive responses, might be effective in reducing BP (6–8 mmHg decrease in SBP and 3–4 mmHg decrease in DBP)[30,31]. A 2019 meta-analysis showed that the effects of isometric resistance exercise on BP reduction are significant and indeed similar to those provided by other exercise modalities (endurance, resistance or a combination thereof) when analysing individuals with or without hypertension together (mean 5.7 mmHg decrease in SBP)[21]. However, the BP changes did not reach statistical significance when analysing only patients with hypertension (4.9 mmHg decrease). Nonetheless, a potential matter of concern is the 'hypertensive response to exercise' phenomenon (BOX 3).

Dietary Approaches to Stop Hypertension
(DASH). A lifelong approach to healthy eating that is designed to help treat or prevent hypertension without medication, sponsored by the NIH. This diet is rich in fruits, vegetables, whole grains and low-fat dairy products, includes poultry, fish and nuts, contains small amounts of red meat, sweets and sugar-containing beverages, and results in a sodium intake within normal limits.

Minimum physical activity levels
WHO recommends that adults engage in ≥150 min per week of moderate-intensity physical activity (such as brisk walking) or ≥75 min per week of vigorous physical activity (such as very brisk walking or jogging), or a combination thereof, as well as in muscle-strengthening activities involving major muscle groups on ≥2 days per week.

Exercise intensity

Moderate-intensity and high-intensity exercise have similar beneficial effects on BP[21], although the latter has been suggested to be more effective in downregulating the pathophysiological mechanisms that contribute to the development of hypertension (such as arterial stiffness)[32]. However, according to a 2019 systematic umbrella review, insufficient evidence is available to determine the relationship between exercise intensity and BP[19].

Mechanisms

Adiposity. Obesity per se (that is, without other cardiometabolic conditions) is associated with a higher risk of hypertension[33], with the two main causative mechanisms being compression of the kidneys by visceral, perirenal and renal sinus fat, and increased renal sympathetic nerve activity with subsequent renin–angiotensin–aldosterone system (RAAS) activation[34] (FIG. 1). In addition, obese adipose tissue (particularly the visceral depot) is characterized by an increase in the production and secretion of cytokines and other peptides — the so-called adipocytokines (or adipokines), such as tumour necrosis factor (TNF), resistin and especially leptin — that have several negative multisystemic effects including increased inflammation, and contribute to a higher risk of hypertension[35]. Furthermore, leptin increases renal sympathetic nerve activity through stimulation of the melanocortin 4 receptor (MC4R) pathway in the central nervous system[34]. Patients with

24-h ambulatory BP
Also termed '24-h BP'. The mean result of blood pressure (BP) levels measured with a portable automated device at regular intervals during normal daily life over 24 h.

Endurance exercise
Also termed 'aerobic exercise'. A type of exercise that is performed for more than a few minutes and preferentially involves aerobic metabolism for energy production (for example, brisk walking, jogging, bicycling and swimming).

loss-of-function mutations in *MC4R* have diminished adrenergic activity and are less likely to develop hypertension than control individuals[36]. Exercise interventions, even without a concomitant hypocaloric diet[37] or body weight loss[38], are particularly effective in reducing visceral fat mass, which is more prone to induce insulin resistance than subcutaneous fat[39] and has a unique pro-inflammatory profile[40,41].

Insulin resistance. Insulin resistance and compensatory hyperinsulinaemia are traditionally associated with an increased risk of hypertension, as revealed in population studies showing correlations between these metabolic alterations and elevated BP in people with obesity and metabolic syndrome (so-called syndrome X)[42]. For instance, the prevalence of hypertension increased with worsening stages of impaired glucose metabolism in a cohort of Japanese individuals, with hyperglycaemia and hyperinsulinaemia being significant contributors to the risk of hypertension, at least in the early stages of impaired glucose metabolism[43]. However, the potential association between plasma insulin levels or insulin resistance and incident hypertension is much weaker in the absence of obesity (at least in men)[44], suggesting that obesity, especially when associated with excess visceral adiposity, is a confounder and that hyperinsulinaemia per se is not a primary cause of the development of hypertension[45].

Although compensatory hyperinsulinaemia owing to insulin resistance can acutely increase renal tubular sodium reabsorption and sympathetic nervous system (SNS) activity, these effects do not actually translate into increases in BP in humans or in animal models other than rodents and, therefore, do not increase the risk of hypertension in the absence of coexistent obesity and/or metabolic syndrome[42]. Nevertheless, the metabolic

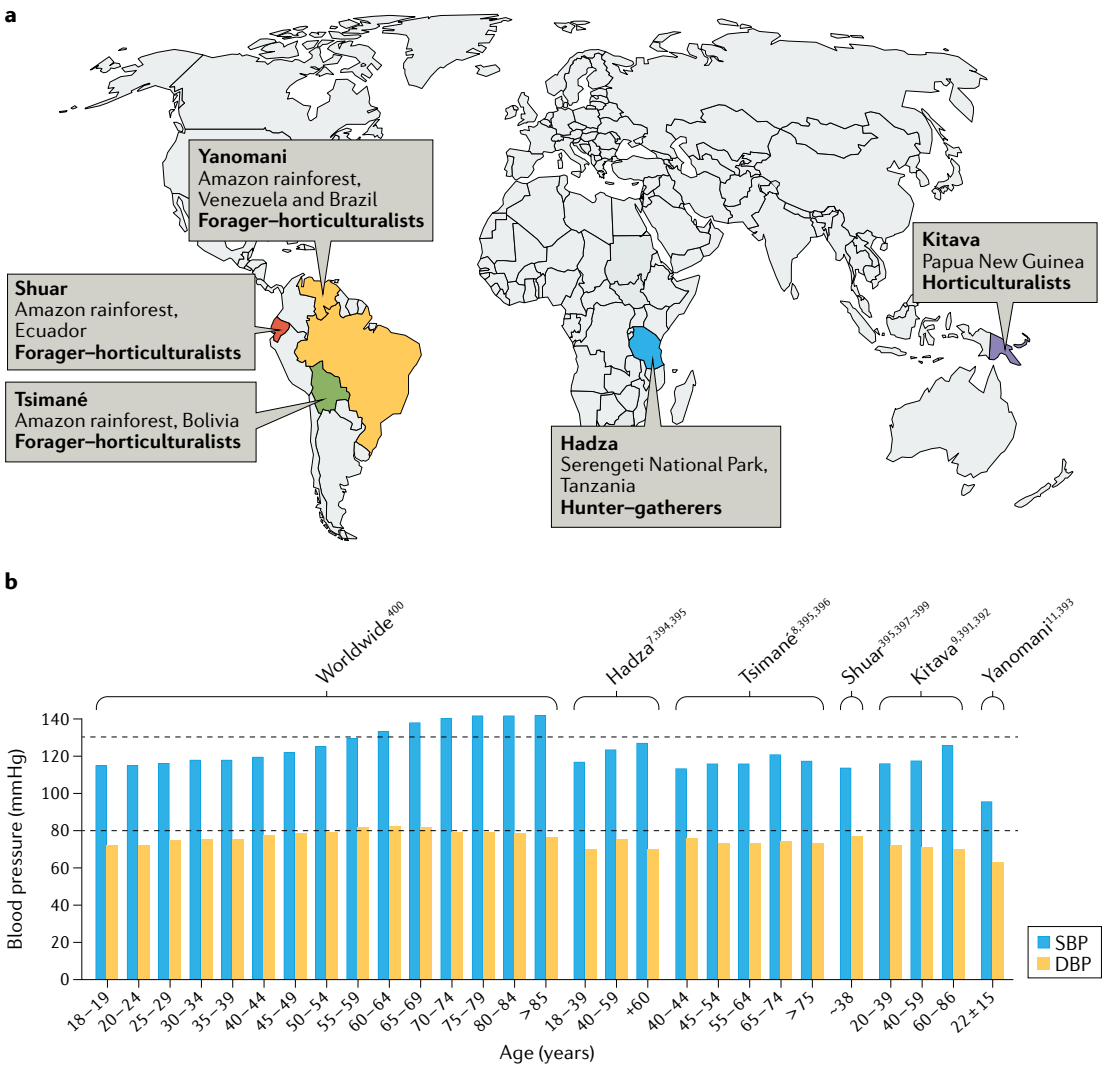

Fig. 2 | **Blood pressure profile of non-westernized populations.** The figure shows the geographical distribution (panel **a**) and blood pressure profiles (panel **b**) of representative non-westernized populations (Hadza, Kitava, Shuar, Tsimané and Yanomani) compared with the mean blood pressure values for the worldwide population. Non-westernized populations have low rates of hypertension and do not seem to show the typical age-related increase in blood pressure. Data from non-westernised populations were obtained from REFS[7–9,11,391–399]. World mean blood pressure levels were obtained from REF.[400]. DBP, diastolic blood pressure; SBP, systolic blood pressure.

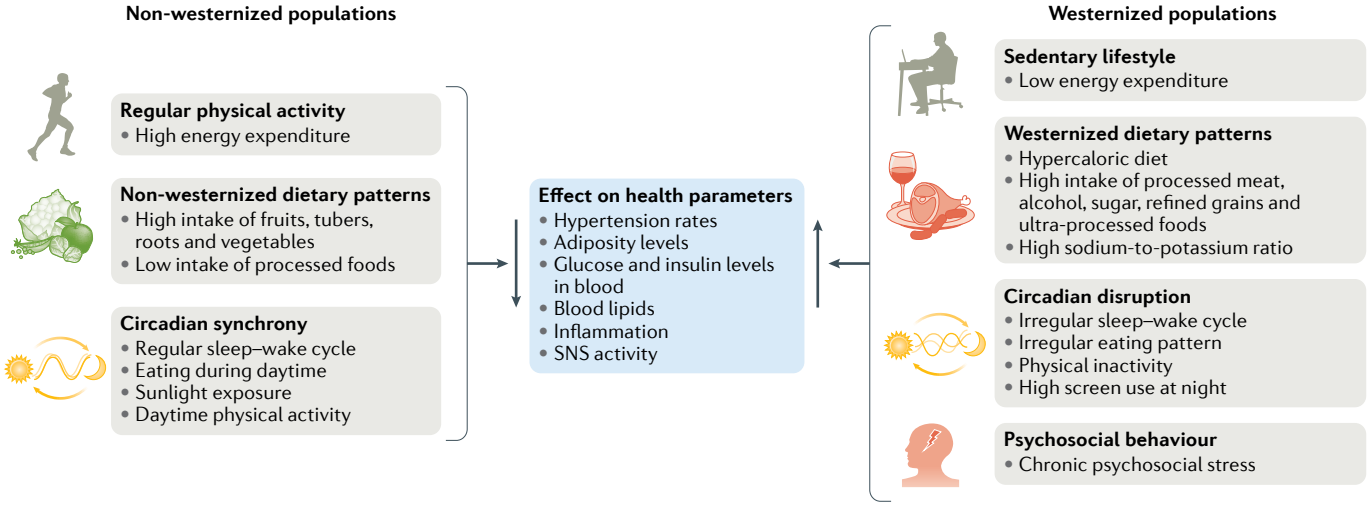

Fig. 3 | **Characteristic lifestyle factors in non-westernized and westernized populations.** The lifestyle pattern of westernized populations (frequently associated with a sedentary lifestyle, unhealthy diets, circadian disruption and high levels of chronic psychosocial stress) is likely to contribute to the high rates of hypertension and other associated risk factors commonly observed in these populations. By contrast, non-westernized populations usually have an opposite lifestyle (high physical activity levels, healthy diets and circadian synchrony) and, therefore, have a heathier cardiometabolic profile and lower rates of hypertension. SNS, sympathetic nervous system.

effects of insulin resistance (notably, hyperglycaemia and dyslipidaemia) can interact synergistically with pre-existing high BP to aggravate vascular and kidney injury and therefore exacerbate hypertension and its consequences[42]. Physical exercise per se has been reported to improve insulin sensitivity, at least when associated with some modest body weight reduction[46], and exercise alone has been shown to improve glucose control in healthy adults[47] and in patients with diabetes mellitus[48].

Renin–angiotensin–aldosterone system. The RAAS has a central role in regulating BP and is an important target in the treatment of hypertension[49]. The RAAS has two main axes, which counteract each other in terms of vascular control: the classic vasoconstrictive axis (renin–angiotensin-converting enzyme (ACE)–angiotensin II (Ang II)–type 1 Ang II receptor) and the opposing vasorelaxant axis (ACE2–Ang 1–7–Mas receptor)[50]. An abnormally high RAAS activity (for example, because of an imbalance between the two axes) can contribute to the development of hypertension[50]. Evidence from a meta-analysis does not support a clear role of physical exercise for targeting the RAAS[51]. Exercise interventions (≥4 weeks) reduced plasma renin activity concomitant with a reduction in BP, but with no significant relationship between the magnitude of improvements in both markers and no effect on plasma levels of Ang II or aldosterone.

Vascular structure. Structural changes in microcirculatory beds are responsible for the elevation in vascular resistance in hypertension, mediated mainly by a reduction in vessel lumen (remodelling) and in the number or length of small vessels (rarefaction)[52,53]. Hypertension is also associated with a reduced diameter and an increased wall thickness of large peripheral arteries[54]. Regular exercise has the opposite effect on artery remodelling to that associated with hypertension, eliciting an increase in the luminal diameter of conduit arteries and resistance arteries and in capillary density in skeletal muscles[55]. Exercise training can also reduce the carotid intima–media thickness in patients with hypertension[56].

Vascular function and oxidative status. Vascular endothelial dysfunction (VED) is a reversible functional condition[57], as opposed to the vascular damage or 'destruction' that occurs in hypertension-associated target-organ damage, and encompasses not only blunted endothelium-dependent vasodilatation but also endothelial inflammatory activation[58]. VED might contribute to hypertension, albeit with a less clear influence compared with its role in atherosclerosis development[58]. Reduced nitric oxide (NO) bioavailability seems to be an important characteristic of VED in hypertension[57], and might impair the inhibitory effect of NO on another endothelium-derived vasoactive molecule, endothelin 1 (REF.[59]). Endothelin 1 is a potent vasoconstrictor, meaning that the resulting imbalance between NO and endothelin 1 can result in increased vasoconstriction. An increased production of reactive oxygen species and a heightened inflammatory status also contribute to VED in patients with hypertension[60]. Oxidative stress causes NO inactivation[61] and might oxidize LDL particles thereby affecting their function, with resulting toxicity to endothelial cells and adhesion and migration of leukocytes to the arterial wall[62].

Meta-analytical evidence indicates that exercise improves endothelial function (typically assessed by flow-mediated dilatation of the brachial artery) and arterial stiffness (measured as pulse wave velocity and augmentation index), with a dose–response relationship between exercise intensity, at least in the case of aerobic exercise, and the benefits obtained[63,64]. Of note, the

Resistance exercise
Also termed 'strength exercise'. A type of exercise that is performed against a load or resistance (for example, weight lifting and leg press).

Isometric exercise
A type of exercise that usually involves small muscle groups and results in no displacement or joint movement (such as handgrip).

Renal sympathetic nerve activity
An important nerve regulator of the function of the renal vasculature, tubules and juxtaglomerular granular cells and, therefore, of renal haemodynamics, tubular reabsorption and renin secretion rate.

Renin–angiotensin–aldosterone system
(RAAS). A hormonal system that is a critical regulator of blood volume and systemic vascular resistance.

Adipocytokines
From the Greek *adipo* (fat), *cytos* (cell) and *kinos* (movement); also termed adipokines. Cytokines secreted by adipose tissue.

Sympathetic nervous system (SNS). One of the two main divisions of the autonomic nervous system, the other being the parasympathetic nervous system. Although its primary function is to stimulate the 'fight, flight or freeze' response, the SNS is constantly active at a basal level to maintain homeostasis in haemodynamics by inducing a vasoconstrictor effect in most vessels.

Conduit arteries
Also known as conducting arteries or elastic arteries. Arteries with many collagen and elastin filaments in the tunica media, which provides the capacity to stretch in response to each pulse. Conduit arteries include the largest arteries in the body (pulmonary arteries, the aorta and its branches).

beneficial effects of exercise on endothelial function and/or arterial stiffness have been confirmed in individuals with pre-hypertension and those with hypertension[65–67]. By contrast, aerobic exercise training for 8 months was not sufficient to reduce arterial stiffness in children with excess body weight, suggesting that longer interventions or concomitant body weight reduction might be required to improve arterial stiffness[68]. Physical exercise increases NO bioavailability[69], possibly owing to the beneficial effects of exercise on redox homeostasis and inflammation, mediated by the downregulation of nuclear factor-κB (NF-κB) signalling[70]. Physical exercise also stimulates the production of vasodilatory (NO and prostacyclin) and angiogenic (for example, vascular endothelial growth factor (VEGF)) agents by increasing shear stress[71]. Meta-analytical evidence supports the role of exercise training for the improvement of redox status in various populations[72], including women aged 60–75 years with hypertension[73].

Inflammation. Chronic systemic inflammation is involved in the pathophysiology of hypertension[74]. Elevated concentrations of inflammatory biomarkers have been associated with a higher prevalence of hypertension in a number of observational studies, which was confirmed in a 2019 meta-analysis showing that higher levels of circulating C-reactive protein (CRP), high-sensitivity CRP (hsCRP) and IL-6 are associated with the risk of developing hypertension[75]. Notably, a link between inflammation and increased activity of the RAAS vasoconstrictor axis has been reported, with high circulating levels of the pleiotropic cytokine IL-6 having a pathogenic role in Ang II-mediated hypertension[76].

In addition to clinical data, mechanistic evidence supports a causal role for inflammation in hypertension. Indeed, activation of the innate immune system after arterial wall injury might be an initial pathogenic event in hypertension, in which tissue injury leads to activation of Toll-like receptors (TLRs; notably TLR4) in endothelial cells and leukocytes, with subsequent secretion of various inflammatory cytokines and increased production of reactive oxygen species[77]. Among the known causes of chronic systemic inflammation is physical inactivity[78], whereas regular exercise has anti-inflammatory effects. For instance, a meta-analysis indicates that engaging in exercise training is associated with a decrease in circulating CRP levels regardless of age or sex[79]. At the mechanistic level, the anti-inflammatory milieu created by exercise training is largely mediated by myokines.

Myokines and adipokines. Working muscles act as endocrine organs that can produce and secrete small peptides (including cytokines) known as myokines, which can provide direct and indirect beneficial effects on cardiovascular phenotypes, including those related to BP[80]. Notably, muscle-released IL-6 — as opposed to that released from other sources in a non-exercise milieu — exerts anti-inflammatory effects by promoting the production of other cytokines with anti-inflammatory properties (such as IL-1 receptor antagonist and IL-10), while decreasing the circulating levels of pro-inflammatory factors (such as TNF)[81,82]. Exercise-induced myokines might also reduce BP through more direct mechanisms not necessarily linked to anti-inflammatory effects. In particular, irisin has been shown to reduce BP (with attenuation of VED mediated by the AMP-activated protein kinase (AMPK)–AKT–endothelial NO synthase (eNOS)–NO pathway) and stimulate vasorelaxation in hypertensive rats[83]. Muscle-released irisin might also prevent the elevation of BP induced by SNS outflow via activation of ATP-sensitive potassium channels in smooth muscle[84]. These preclinical findings are consistent with the reported inverse association between baseline plasma levels of irisin and SBP and DBP in women with pre-eclampsia[85]. However, other researchers have found a positive association between irisin and DBP in patients with renal disease[86], or between irisin, SBP and the risk of hypertension in a cohort comprising both individuals with normal BP and patients with hypertension[87], or no significant association between irisin and BP in individuals with central obesity[88]. Because irisin, and indeed most myokines, can also originate from tissues other than working muscles (such as adipose tissue) under

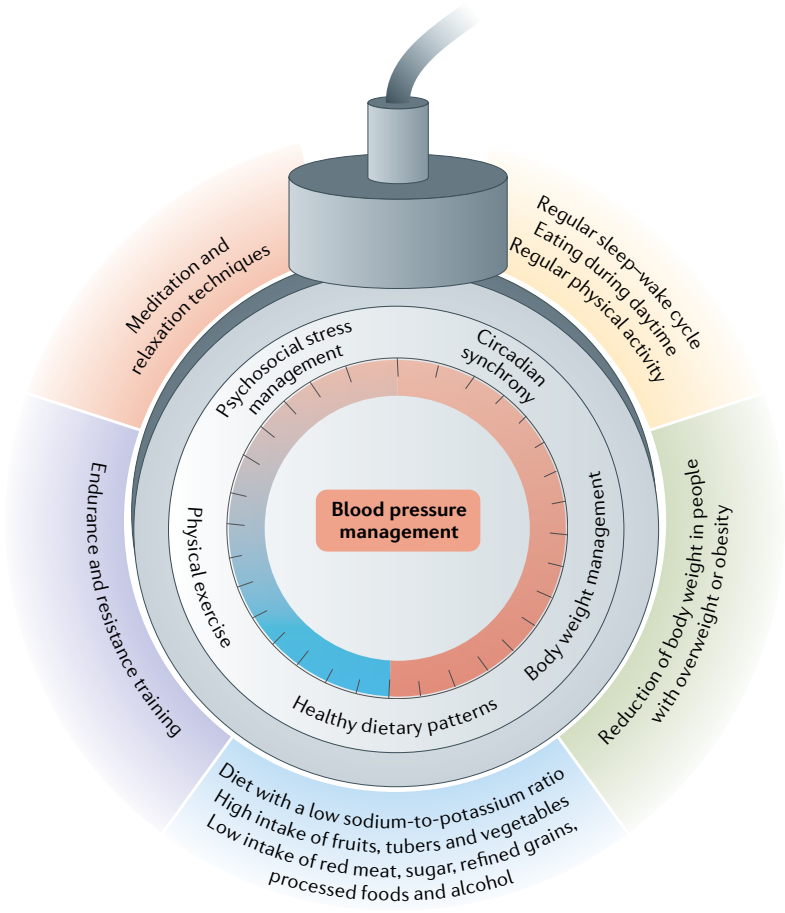

Fig. 4 | **Lifestyle factors with blood pressure-reducing effects.** Summary of the major, evidence-based lifestyle factors that reduce blood pressure levels and the risk of hypertension. A variety of lifestyle factors, including regular physical exercise, body weight management and adhering to a healthy diet, along with other potentially influencing factors, such as circadian entrainment and avoiding psychosocial stress, contribute to the adequate management of blood pressure.

Box 1 | Are the beneficial effects of exercise on blood pressure sustainable?

Some research suggests that the beneficial effects of exercise on blood pressure might still be observed with long-term interventions (≥12 months)[401–403]. However, a meta-analysis indicated that exercise interventions reduce systolic blood pressure (4.4 mmHg) and diastolic blood pressure (4.2 mmHg) in the short-to-medium term (3–6 months) in young adults with pre-hypertension or hypertension, but the benefits are lost at ≥12 months (systolic blood pressure −1.0 mmHg and diastolic blood pressure −0.9 mmHg)[404]. Therefore, further research is needed to confirm the long-term effectiveness of exercise interventions.

resting conditions[89], the beneficial effects of this and other myokines (such as IL-6) on BP might be specific to the exercise milieu.

Evidence from a meta-analysis suggests that regular exercise, even without major body weight reductions, decreases leptin levels[90]. Similarly, an acute bout of intense exercise reduces the circulating levels of pro-inflammatory adipokines linked to insulin resistance and obesity, such as omentin and resistin (with the reduction below baseline levels lasting up to 48–72 h after exertion)[91]. Therefore, regular exercise could provide benefits in individuals with hypertension, as in those with other chronic diseases[92], through the cumulative effects of acute increases in myokines and decreases in pro-inflammatory adipokines during and after each bout of exercise[93,94]. However, more research is needed in this area.

Autonomic function. The autonomic nervous system modulates BP by increasing SNS or parasympathetic nervous system (vagal) activity, with the former triggering systemic vasoconstriction. Patients with hypertension tend to present with chronic SNS activation[95], and the impaired function of carotid baroreceptors has been suggested to contribute to this neurogenic component of hypertension[96]. Evidence supports a role of exercise training in counteracting autonomic dysfunction, specifically in increasing vagal tone and decreasing SNS tone[97]. Exercise training improves arterial baroreflex control and therefore reduces BP in healthy individuals[98] and in patients with hypertension[99]. The benefits of exercise could result from both mechanical (reduced vascular stiffness and consequent increased barosensory vessel distensibility) and neural (adaptations in the afferent–efferent baroreflex control of cardiac vagal outflow) mechanisms related to baroreflex control[53].

Body weight management

Overweight and obesity are associated with an increased risk of hypertension. A meta-analysis of prospective studies including a total of 173,828 participants found that the risk ratios (RR) of incident hypertension were 1.52 (95% CI 1.37–1.67) and 2.17 (95% CI 1.84–2.50) for individuals with overweight or obesity, respectively, compared with individuals with normal body weight. A reduction in body weight to normal in individuals with overweight or obesity has indeed been reported to reduce the risk of incident hypertension by 24–40% and 40–54%, respectively[100]. Similarly, a meta-analysis of 25 RCTs concluded that for each 1 kg of body weight lost, both SBP and DBP were reduced by approximately 1 mmHg in individuals with or without hypertension[17]. A prospective study (including ~14,000 individuals) found that body weight loss reduced the risk of uncontrolled hypertension in individuals with hypertension and overweight or obesity[101].

Body weight-reducing strategies, particularly energy-restricted diets and physical exercise, have traditionally been considered major lifestyle interventions for the prevention and management of hypertension. In this regard, a meta-analysis concluded that interventions to reduce body weight, including energy-restrictive diets, induced greater reductions in both SBP (5 mmHg) and DBP (4 mmHg) than those including exercise interventions alone (2 mmHg)[17]. However, the opposite trend was observed, at least for DBP, when results were standardized for the amount of body weight lost[17]. More evidence is needed on the strength of the effect of body weight loss on BP reduction. A Cochrane review and meta-analysis of eight studies involving a total of 2,100 participants with high BP found significant and moderate-quality evidence for the body weight reduction effects of hypocaloric dietary interventions compared with no dietary intervention (mean difference of −4.0 kg)[102]. Nevertheless, the evidence for a BP reduction in the participants assigned to body weight-reducing diets, although significant compared with controls (SBP 4.5 mmHg and DBP 3.2 mmHg), was of low quality. The authors concluded that body weight-reducing diets reduce body weight and BP in people with primary hypertension but the magnitude of the effects is uncertain because of the small number of participants and studies included in the analyses. As for exercise interventions, controversy exists on the long-term sustainability of body weight reduction strategies (BOX 4).

Mechanisms

Adiposity. A high BMI, particularly if associated with excessive visceral fat[103], has been identified as a major risk factor for hypertension[35,104], and the role of adiposity in the pathophysiology of hypertension is described earlier in this Review. Beyond its obvious effects in reducing adiposity, the beneficial effects of intentional body weight reduction on hypertension can be mediated, at least partly, by additional mechanisms, as discussed in the sections below.

Insulin resistance. A strong correlation exists between insulin resistance (as determined by homeostatic model assessment of insulin resistance (HOMA-IR)) and most indicators of adiposity and obesity (total fat, visceral fat mass, BMI and waist circumference), with the strongest association for visceral fat mass[105]. Furthermore, moderate body weight reductions (average 9%) are accompanied by remarkable decreases in both HOMAR-IR (26%) and SBP and DBP (7 mmHg and 6 mmHg, respectively)[106]. In patients with obesity and diabetes, a 10% reduction in BMI attenuates insulin resistance and adipokine dysregulation (for example, with reductions in the circulating levels of leptin and resistin)[107]. Long-term (33-week) body weight reduction altered cytokine gene expression in peripheral immune blood cells of individuals with obesity (for example, reductions in *IL6*

Resistance arteries
Small-diameter blood vessels in the microcirculation with thick muscular walls and narrow lumen (usually arterioles and end point arteries) that contribute the most to the resistance to blood flow.

Nitric oxide
(NO). A volatile gas produced by endothelial cells that acts to relax vascular tone.

Oxidative stress
A process of cellular damage related to uncontrolled action of reactive oxygen species, a group of molecules, including oxygen and its derivatives, produced by the normal process of aerobic metabolism.

Chronic systemic inflammation
Usually referred to as simply 'inflammation'. A state of low-grade, non-infective ('sterile') inflammation at the systemic level that is characterized by activation of immune components that are often distinct from those engaged during an acute immune response and that can lead to major alterations in all cells, tissues and organs. This state is reflected by high baseline levels of specific biomarkers such as high-sensitive C-reactive protein.

Myokines
From the Greek *myo* (muscle) and *kinos* (movement). Molecules (mostly, but not only, small peptides such as cytokines) released from muscles, usually during exercise.

Baroreceptors
Mechanical receptors that sense blood pressure changes in both carotid sinuses and the aortic arch.

Arterial baroreflex
Also known as the baroreceptor reflex. A rapid negative feedback loop in which elevated blood pressure is sensed by baroreceptors, with their subsequent activation leading to rapid increases in parasympathetic outflow and decreases in sympathetic outflow and therefore to restoration of blood pressure levels.

Peripheral chemoreceptors
Located in the carotid and aortic bodies. Sensory extensions of the peripheral nervous system into blood vessels that detect changes in chemical homeostasis (hypoxaemia, hypercapnia and acidosis), which increases their firing with a subsequent increase in ventilation and sympathetic nervous system outflow.

Obstructive sleep apnoea
(OSA). A sleep-related breathing disorder characterized by repeated episodes of complete or partial upper-airway occlusion (and subsequent arterial hypoxaemia) during sleep.

and *IL1B* mRNA levels) that correlated with improvements in insulin sensitivity, although BP changes were not recorded[68]. The effects of body weight reduction on glucose homeostasis are associated with changes in the expression of many (80–100) genes in macrophages and adipocytes[108]. The changes induced by body weight reduction in the expression of genes associated with improved insulin sensitivity also involve downregulation of genes related to NF-κB activation[109].

Renin–angiotensin–aldosterone system. Body weight reduction, even of moderate magnitude (<10%) can reduce both RAAS activity and BP in individuals with obesity[110]. Notably, moderate body weight mass reductions (5%) can have an inhibitory effect on several RAAS components, such as reduced levels of plasma angiotensinogen (27%) and adipose tissue-derived angiotensinogen (20%), renin (43%) and aldosterone (31%) and reduced ACE activity (12%), that in turn is coupled with decreases in SBP (7 mmHg)[111]. In addition, reductions in waist circumference significantly correlate with reductions in plasma levels of angiotensinogen[111]. Reductions in plasma levels of angiotensinogen, Ang II, renin and the vasoconstrictor molecule endothelin 1 have been reported 6 months after bariatric surgery inducing an average reduction in BMI from 52.1 kg/m^2 to 40.4 kg/m^2, although changes in adiposity or RAAS components did not correlate with BP reductions[112].

Vascular function and oxidative status. Meta-analytical evidence suggests that obesity is associated with poorer arterial endothelial function (as assessed by flow-mediated dilatation of the brachial artery)[113], whereas body weight reduction has the opposite effect, with each 10-kg decrease in body weight being associated on average with a 1.1% increase in fasting flow-mediated dilatation[114]. However, whether improvements in endothelial function induced by body weight reduction translate into reductions in BP, as well as the potential mechanisms, remain to be elucidated. The overall evidence indicates that intentional body weight loss can reduce obesity-associated oxidative stress, typically assessed through determination of lipid oxidation products (such as 8-isoprostane)[115]. Whether the potential beneficial effects of body weight reduction on oxidative stress translate into a healthier BP profile also needs further investigation.

Pro-inflammatory adipokines. The involvement of obesity and adipose tissue-released adipokines in systemic inflammation is well documented[116]. In older individuals with obesity, higher adiposity is associated with higher blood levels of inflammatory markers such as CRP[117]. A meta-analysis has suggested a positive correlation between circulating leptin and inflammatory biomarkers (CRP, IL-6 and TNF)[118]. Obesity also results in dysfunction of the perivascular adipose tissue (PVAT), which in lean individuals has beneficial vasodilatory and anti-inflammatory functions[116]. Indeed, in obesity, the PVAT has an increased production of adipokines (IL-6, leptin, resistin and TNF) and chemokines that orchestrate inflammatory cell infiltration (mainly T cells) into PVAT and result in eNOS dysfunction[119].

Body weight reduction improves the inflammatory profile in individuals with obesity through a decrease in pro-inflammatory factors and an increase in anti-inflammatory molecules in subcutaneous adipose tissue[120]. Therefore, even modest body weight reductions (average 1.1 kg per month) in adults with overweight or obesity can reduce the plasma levels of inflammatory molecules (mainly CRP, IL-6 and TNF)[121]. In women with obesity, decreases in circulating CRP levels induced by a rapid body weight reduction intervention (4–6 weeks) are proportional to the magnitude of the body weight reduction[122]. The beneficial effects of body weight reduction on inflammation seem to be maintained in the long term: substantial body weight loss (average 15%) over 1 year inhibited the expression of genes related to vascular inflammation[123], and in people with morbid obesity, surgically induced body weight reduction was associated with marked decreases in renal and systemic inflammation as well as in SBP and DBP 1 year after surgery[124]. In addition, preclinical evidence shows that body weight reduction can reverse obesity-induced PVAT damage through a mechanism involving reduced inflammation and increased eNOS activity within the PVAT[125].

Autonomic function. Increased activity of the SNS has an important role in the development of obesity-related hypertension[126], with pharmacological α-/β-adrenergic receptor blockade resulting in a greater reduction in SBP in patients with hypertension who are obese than in those who are lean[127]. Causative mechanisms of SNS overactivation in obesity, especially central obesity, include abnormal adipokine secretion from adipose tissue (such as the role of leptin in stimulating the brain melanocortin system, as explained above), stimulation via the RAAS (with an existing reciprocal SNS–RAAS activation)[128], insulin resistance[129], baroreceptor dysfunction[130] and sustained activation of peripheral chemoreceptors[131]. Regarding the activation of peripheral chemoreceptors, obesity frequently coexists with obstructive sleep apnoea

Box 2 | **Can exercise without weight loss lower blood pressure?**

A classic study showed a decrease in blood pressure (6.4 mmHg in systolic blood pressure (SBP), 5.2 mmHg in diastolic blood pressure (DBP)) after an exercise intervention in men with or without hypertension even without changes in body weight[405]. However, a reduction in body weight led to a greater reduction in blood pressure even with no exercise (8.8 kg reduction in body weight: 9.2 mmHg reduction in SBP, 6.2 mmHg reduction in DBP)[405]. Other investigators have reported marked reductions in SBP and DBP (4.4 mmHg and 4.3 mmHg, respectively) in individuals with hypertension after an exercise intervention despite only a small reduction in body weight (1.8 kg)[406]. In turn, if exercise was combined with a body weight management programme and a dietary intervention that resulted in much greater body weight reductions (7.8 kg), the intervention induced greater reductions in SBP and DBP (7.4 mmHg and 5.6 mmHg, respectively)[406]. A meta-analysis found similar reductions in SBP and DBP (approximately 5 mmHg and 3 mmHg, respectively) with endurance exercise across different body weight reductions (≥1.5 kg reductions, or −1.5 kg to +0.2 kg), with SBP and DBP significantly reduced (by approximately 3 mmHg and 2 mmHg, respectively) even in those trials investigating exercise interventions in which body weight actually increased (by >0.2 kg)[407]. Therefore, the beneficial effects of exercise on blood pressure seem to occur independently of body weight reduction but the magnitude of the blood pressure reduction might increase, at least slightly, when both factors are combined.

Box 3 | **Hypertensive response to acute exercise**

Although long-term physical exercise interventions are associated with blood pressure reductions, blood pressure normally rises acutely during exercise as a result of increases in cardiac output in response to the higher demands for oxygen from working muscles. This response is usually physiological and is not associated with adverse events. However, some individuals have an exaggerated increase in systolic blood pressure during exercise, a condition known as a hypertensive response to exercise (HRE; usually defined as an increase in systolic blood pressure during exercise of ≥60 mmHg in men and ≥50 mmHg in women, or a systolic blood pressure of >210 mmHg in men and >190 mmHg in women)[408]. In individuals with normal blood pressure, a HRE might be a prognostic marker of the future development of hypertension and a greater incidence of cardiovascular disease[408]. Importantly, lifestyle interventions, including a healthy diet and regular exercise, have been reported to reduce the HRE[13,409].

(OSA), the most common condition associated with resistant hypertension, which is indeed observed in 30–40% of all patients with hypertension[132]. OSA leads to chronic intermittent hypoxia and sustained activation of carotid body chemoreceptors that reflexively upregulate SNS activity[133]. Body weight reduction per se (with or without a concomitant exercise intervention) has proven sympathoinhibitory benefits in individuals with obesity[134–136], which in turn are associated with improvements in baroreflex sensitivity and BP[136], with the opposite effects (increased parasympathetic and decreased SNS activity) observed with body weight increase[137]. However, some of the hypotensive effects of body weight reduction in individuals with severe obesity might be independent of the accompanying changes in the SNS[135].

Healthy dietary patterns

Sodium and potassium intake

Sodium restriction has been the most popular recommendation for the dietary prevention of hypertension and for BP reduction in general, and current dietary guidelines recommend reducing sodium (or salt) intake[4,5]. A 2020 meta-analysis showed that the magnitude of the BP decrease achieved with sodium reduction follows a dose–response relationship, being greater in older populations, non-white populations and those with higher BP[138]. A meta-regression analysis of 133 RCTs found strong evidence for a linear dose–response relationship between sodium restriction and BP (7.7 mmHg decrease in SBP and 3.0 mmHg decrease in DBP per 100 mmol sodium restriction)[139]. However, the relationship was weaker in the groups with mean SBP/DBP ≤131/78 mmHg, possibly because dramatically reducing sodium intake leads to compensatory increases in circulating aldosterone, renin and noradrenaline levels, with the magnitude of this effect being more pronounced in individuals with SBP <140 mmHg[140]. Moreover, different meta-analyses have suggested that the association between sodium intake and mortality might follow a U-shaped or J-shaped curve[141,142], which would be in accordance with the observation that the plasma levels of renin and aldosterone increase exponentially when sodium is restricted to <100 mmol per day[140]. However, these conclusions have been questioned because of methodological limitations (such as the use of unreliable methods for the assessment of sodium intake and confounding effects of comorbidities)[15,143,144], providing support for a linear dose–response relationship between salt restriction and cardiovascular benefits and therefore reinforcing salt reduction as a public health preventive measure against CVD[15]. However, further evidence on the effects of strict salt restriction in individuals without hypertension is warranted[145]. Furthermore, the effects of salt intake on BP must be considered together with the concomitant water load (BOX 5).

The ACC/AHA guidelines also recommend increasing potassium intake[4]. Potassium is an essential nutrient that is required for the maintenance of total body fluid volume, acid and electrolyte balance, and normal cell function. In pre-industrial era diets, potassium intake was very high, often exceeding 200 mmol per day[146]. However, in westernized societies, potassium intake is markedly lower. Food processing reduces the potassium content of food, and a diet high in processed foods and low in fresh fruits and vegetables is often lacking in potassium[146]. Global data suggest that the average potassium consumption in many countries is clearly below the values recommended by the European Union (90 mmol per day)[147] and WHO (≥90 mmol per day)[148] and in the USA (60–90 mmol per day)[149]. This observation is concerning, especially when considering the role of potassium in BP regulation, which has been demonstrated in multiple studies. A meta-analysis of 15 RCTs involving a total of 917 patients showed that potassium supplementation (particularly with intakes of 75–125 mmol per day) is associated with a decrease in BP in individuals who are not receiving antihypertensive medication, especially in patients with hypertension (mean 6.8 mmHg decrease in SBP and 4.6 mmHg decrease in DBP)[150]. A meta-regression analysis showed that both increased daily potassium excretion and decreased sodium-to-potassium ratio are associated with BP reduction[150]. These results overall confirm those of a previous meta-analysis reporting high-quality evidence that increased potassium intake reduces BP in patients with hypertension and has no adverse effect on blood lipid concentrations, catecholamine concentrations or renal function[151]. Similarly, a study showed that the population-wide (2,376 participants from six different villages in Peru) implementation of a salt-substitution programme (replacing regular salt with potassium-enriched substitutes (75% NaCl and 25% KCl)) resulted in an average 1.3 mmHg decrease in SBP and 0.8 mmHg decrease in DBP in individuals with or without hypertension (albeit of greater magnitude in those with hypertension)[152]. Moreover, salt substitution reduced the incidence of hypertension by 51% in participants without hypertension at baseline compared with a control group, which occurred along with increased urine levels of potassium but with no differences in urine sodium levels. However, the evidence from RCTs does not allow the identification of a precise optimal level of potassium intake for maximum health benefits. Nevertheless, if a person consumes both ≥90 mmol per day of potassium and the WHO-recommended sodium intake (<90 mmol per day)[153], their diet would have a molar ratio of sodium to potassium of approximately one-to-one, which is considered beneficial for health, particularly for individuals with sodium sensitivity[147].

Mediterranean diet
A diet abundant in fruits, vegetables, legumes, whole grains, olives, nuts and seeds, and containing extra-virgin olive oil associated with frequent consumption of fish, moderate consumption of dairy products and red wine, and low consumption of red meat and isolated sugars.

Diets

A number of dietary approaches have gained popularity owing to their purported beneficial effects not only on body weight, but also on overall cardiovascular health and hypertension in particular. Of note, the interventions described below have been typically compared with isocaloric control diets.

DASH diet. The first multicentre clinical trial of the DASH diet[154], published in 1997, showed that this diet can be effective in the prevention and management of hypertension. Subsequent evidence provided further support for the benefits of this diet. In the PREMIER trial[155], the DASH diet induced significant reductions in BP after 6 months in non-medicated individuals with above-optimal BP levels compared with an intervention consisting only of advice about lifestyle factors that affect BP (body weight reduction, sodium reduction, increased physical activity and limited alcohol intake). Of note, however, the DASH diet did not provide additional beneficial effects on BP compared with a third, behavioural 6-month intervention consisting of established lifestyle recommendations (body weight reduction, sodium restriction, increased physical activity and limited alcohol intake) but with no control or advice on the intake of fruits, vegetables or fat[155]. In the ENCORE trial[156], the DASH diet alone induced significant reductions in BP compared with usual diet in individuals with pre-hypertension or stage 1 hypertension (11.2 mmHg versus 3.4 mmHg for SBP, and 7.5 mmHg versus 3.8 mmHg for DBP).

The evidence accumulated over the years indicates that the DASH diet is one of the most effective approaches for the management of hypertension, especially if combined with calorie restriction[157]. A meta-analysis of 30 RCTs found that the DASH diet significantly decreased SBP (3.2 mmHg) and DBP (2.5 mmHg) in adults with or without hypertension[14]. Moreover, a long-term analysis of the ENCORE study showed that some beneficial effects of the 4-month DASH diet intervention on SBP were still present at 12 months (9.5 mmHg versus 3.9 mmHg decrease compared with baseline for the DASH diet and usual diet, respectively), although no significant differences between the groups were observed for DBP[158].

Mediterranean diet. Several studies have found that consuming foods typical of the Mediterranean diet might reduce the risk of hypertension, whereas food not typical of this dietary pattern, such as red meat, processed meat and poultry, has an unfavourable effect (reviewed previously[159]). A prospective study including 9,408 Spanish individuals without hypertension concluded that a high adherence to a Mediterranean diet did not reduce the risk of incident hypertension, but was associated with decreases in mean SBP (3.1 mmHg) and DBP (1.9 mmHg) from baseline to 6 years of follow-up compared with individuals with low adherence to the diet[160]. In the PREDIMED RCT[161] including 7,447 Spanish men and women (aged 55–80 years, >80% with hypertension), a Mediterranean diet that involved increasing the consumption of either extra-virgin olive oil or nuts led to decreases in SBP (5.9 mmHg and 7.1 mmHg, respectively) and DBP (1.6 mmHg and 2.6 mmHg, respectively) at 3 months compared with a low-fat control diet. After a follow-up of 4 years, SBP had not changed in either group, whereas DBP had decreased substantially and moderately in the extra-virgin olive oil group (15 mmHg) and the mixed nuts group (0.7 mmHg), respectively[162]. An RCT in Australian individuals aged >64 years showed that those who consumed a Mediterranean diet had a small but significant decrease in SBP and an improved endothelial function after either 3 or 6 months compared with individuals who maintained their habitual diet[163]. Similarly, a trial found that individuals aged >64 years who had adhered to a Mediterranean diet for 1 year showed a significant decrease in SBP (5.5 mmHg) but not in DBP compared with a control group that received standardized dietary advice[164]. However, the effect was significant only in male participants in separate analyses. Although the Mediterranean diet has a potentially favourable effect in reducing BP in healthy people and in patients with hypertension, data are lacking to determine how strong this effect is, and more studies are required[159].

Vegan diets. These diets are increasing in popularity and have beneficial effects on glycaemia and blood lipid profiles. Although the evidence on BP is less conclusive, preliminary evidence suggests that vegan diets could also have a beneficial effect in reducing high SBP. A meta-analysis including 983 individuals showed that a vegan diet without calorie restrictions did not significantly change SBP (1.3 mmHg decrease) or DBP (1.2 mmHg decrease) compared with less-restrictive diets (such as lacto-ovo-vegetarian diets or omnivorous diets)[165]. However, a subgroup analysis of studies including participants with a baseline SBP of ≥130 mmHg showed that

Box 4 | **Sustainability of weight reduction strategies**

Less than 20% of individuals who achieve a 10% reduction in body weight maintain that weight loss for more than 1 year[410]. A network meta-analysis found that different diets resulted in significant reductions in body weight at 6 months (4.6 kg, 4.4 kg and 3.1 kg for low-carbohydrate and low-fat diets and moderate intake of all macronutrients, respectively) together with significant decreases in systolic blood pressure (5.1 mmHg, 5.1 mmHg and 3.5 mmHg, respectively) and diastolic blood pressure (3.2 mmHg, 2.9 mmHg and 1.9 mmHg, respectively)[166]. However, the effects on weight loss (−3.2 kg, −3.3 kg and −1.9 kg), systolic blood pressure (−1.3 mmHg, 0.3 mmHg and −0.5 mmHg) and diastolic blood pressure (−0.8 mmHg, −0.2 mmHg and −0.1 mmHg) were reduced at 12 months with all diets. Evidence for the long-term sustainability of physical exercise interventions for promoting body weight reduction is also unclear. Body weight management programmes, including both exercise and diet, are more effective in reducing body weight mass in the short-to-medium term (3–6 months, mean difference −5.3 kg) and long term (12–18 months, mean difference −6.3 kg) than exercise interventions alone[411]. Moreover, although combined interventions seem similarly effective to diet alone for reducing body weight in the short-to-medium term (3–6 months, mean difference −0.6 kg), diet-only interventions seemed to be more effective in the long term (mean difference −1.7 kg)[411]. A meta-analysis of studies in individuals with obesity who had lost >5% of body weight concluded that lifestyle interventions focusing on both exercise and diet result in significant, albeit small, beneficial effects on body weight after 12 months (−1.6 kg)[412]. However, no evidence for efficacy was found when considering diet-only or physical activity-only interventions[412]. The evidence on the actual long-term sustainability of lifestyle interventions aimed at promoting body weight reduction is therefore unclear, although combining energy-restrictive diets and physical exercise interventions seems to maximize the likelihood of maintaining body weight reduction.

Box 5 | **Salt intake effects on blood pressure depend on concomitant water intake**

The association between salt intake and blood pressure has been known for at least a century, and low-salt diets were one of the first lifestyle interventions to prevent hypertension. Although the traditional thought is that the amount of salt is a critical factor driving acute blood pressure responses, the proposed mechanisms by which salt intake influences blood pressure have been evolving and, indeed, acute blood pressure responses to salt intake can be prevented by concomitant water loading[413]. Therefore, the capacity of salt intake to acutely increase blood pressure depends on the changes in plasma osmolality more than on the amount of salt intake per se.

Although the mechanisms involved in blood pressure elevation induced by salt-associated hyperosmolarity remain to be fully elucidated, they include: activation of osmosensitive neurons located in the subfornical organ, which sense osmotic changes in the plasma and stimulate the activity of the sympathetic nervous system[414]; activation of T cells by osmolarity-mediated pathways, which might have a role in the development of T cell-mediated autoimmune inflammation in the kidney and arterial walls[415]; increased vasopressin release and vasopressin V2 receptor activation[416]; and stimulation of the secretion of endogenous cardiotonic steroids (such as ouabain and marinobufagenin)[417] and the aldose reductase–fructokinase pathway in the hypothalamus, which might mediate blood pressure responses[418].

vegan diets significantly reduced both SBP (4.1 mmHg) and DBP (4.0 mmHg) in these individuals[165].

Diet comparisons

Numerous dietary approaches have a lowering effect on SBP and DBP compared with a control intervention. A network meta-analysis concluded that both low-fat (such as the Ornish diet) and low-carbohydrate (such as the Atkins, South Beach or Zone diets) diets and to a lesser extent those consisting of a moderate intake of all macronutrients (such as the DASH or Mediterranean diets) decrease SBP (5.1, 5.1 and 3.5 mmHg, respectively) and DBP (3.2, 2.9 and 1.9 mmHg, respectively) in the medium term (6 months) compared with a control intervention, although the effects attenuate in the long term (12 months)[166]. When separately analysing each individual diet, the Palaeolithic and Atkins diets were the most effective in decreasing SBP (14.6 mmHg with the Palaeolithic diet) and DBP (3.3 mmHg with the Atkins diet), although other popular diets such as the DASH diet were also among the most effective (4.7 mmHg decrease in SBP and 2.8 mmHg decrease in DBP)[166].

A systematic review and meta-analysis of studies including a total of 23,858 individuals of the effects of dietary pattern interventions (low-sodium, low-sodium–high-potassium, low-sodium–low-calorie, low-calorie, low-carbohydrate, Palaeolithic, high-protein, low-glycaemic index, and low-fat) on BP showed that the dietary interventions led to overall pooled decreases of 3.1 mmHg in SBP and 1.8 mmHg in DBP[167]. The DASH diet had the greatest effects, with a 7.6 mmHg decrease in SBP and 4.2 mmHg decrease in DBP. Low-sodium, low-sodium–high-potassium, low-sodium–low-calorie, and low-calorie diets also led to significant reductions in SBP and DBP. By contrast, the Mediterranean diet was associated with a significant reduction in DBP but not in SBP[167]. Another systematic review and network meta-analysis included 67 trials comparing 13 dietary approaches (DASH, low-fat, moderate-carbohydrate, high-protein, low-carbohydrate, Mediterranean, Palaeolithic, vegetarian, low-glycaemic index or load, low-sodium, Nordic, Tibetan, and control) involving 17,230 participants (including individuals with pre-hypertension or hypertension)[168]. The network meta-analysis showed that the DASH, Mediterranean, low-carbohydrate, Palaeolithic, high-protein, low-glycaemic index, low-sodium, and low-fat diets were significantly more effective in reducing SBP (–8.7 to –2.3 mmHg) and DBP (–4.9 to –1.3 mmHg) than the control diet. The DASH diet was ranked the most effective dietary approach for reducing SBP and DBP, followed by the Palaeolithic, low-carbohydrate and Mediterranean diets[168]. Overall, the DASH diet seems to be the most effective dietary approach to manage BP in patients with pre-hypertension or hypertension.

Dietary compounds

Food groups. Current dietary guidelines for the prevention of hypertension recommend high intake of specific food groups such as whole grains, fresh fruits, vegetables, nuts and legumes, and low intake of red and processed meats and sugar-sweetened beverages (SSBs)[4,5]. The overall available evidence supports these recommendations. A meta-analysis to assess the relationship between the risk of hypertension and the intake of 12 major food groups (whole grains, refined grains, vegetables, fruits, nuts, legumes, eggs, dairy products, fish, red meat, processed meat and SSBs) showed an inverse association for 30 g of whole grains per day, 100 g of fruit per day, 28 g of nuts per day and 200 g of dairy products per day[169]. By contrast, a positive association with the risk of hypertension was observed for 100 g of red meat per day, 50 g of processed meat per day and 250 ml of SSB per day. However, the quality of the evidence was very low or low. A meta-analysis with a more focused approach of selecting a few food items and including 351,819 individuals (5,000 with hypertension) showed that red meat (both processed and unprocessed) and poultry consumption were associated with a higher risk of hypertension, whereas egg consumption was associated with a lower risk[170]. A meta-analysis of eight RCTs found no differences in the effects on BP of consuming more than four whole eggs per week or four or fewer whole eggs per week[171]. A meta-analysis of 14 RCTs including 980 participants found that isocaloric substitution of a high-carbohydrate diet for a diet high in monounsaturated fatty acids (both in the context of low saturated fatty acids) did not affect BP levels in individuals with or without hypertension[172].

An increased sugar intake, particularly when maintained for >8 weeks, has been reported to increase BP[173]. A high fructose intake might lead to increased sodium absorption, as well as activation of renal sympathetic nerve activity and the RAAS[174]. However, whether an association exists between fructose (or raw fruit or fruit juice[175]) intake and the risk of hypertension is so far unclear[176,177]. Evidence from a meta-analysis supports an association between SSB consumption and hypertension, with each additional serving of SSB per day increasing the risk of hypertension by 8%[178], and with reductions in SSB consumption associated with a lower BP in the long term (1.8 mmHg for SBP and 1.1 mmHg for DBP per daily serving)[179]. The consumption of

artificially sweetened beverages has also been linked to an increased risk of hypertension (9% increase per additional serving per day)[178].

Alcohol. Strong evidence supports the detrimental effects of excessive alcohol intake on BP. A meta-analysis of longitudinal studies including a total of 361,254 participants concluded that alcohol intake beyond two drinks per day (12 g of pure ethanol per drink) was consistently associated with an increased incidence of hypertension in both men and women, although for lower intakes the results were significant only for men[180]. However, even low alcohol intakes (around one drink per day) are associated with a higher prevalence of CVD (including hypertension) and death, as supported by a combined analysis of 83 prospective studies including 599,912 current drinkers[181].

Both the ACC/AHA[4] and the ESC/ESH[5] guidelines recommend reducing alcohol intake for the management of hypertension. A meta-analysis including 36 trials and 2,865 participants concluded that alcohol intake reduction was not associated with BP reductions in individuals with moderate alcohol consumption (two or fewer drinks per day) but resulted in a significant BP reduction in those who consumed larger quantities (1.2 mmHg decrease in SBP and 1.1 mmHg decrease in DBP in those who consumed three drinks per day, and 5.5 mmHg and 4.0 mmHg, respectively, in those who consumed more than six drinks per day)[182]. Therefore, reducing alcohol intake might be an effective strategy for the management of hypertension in individuals who consume more than two drinks per day.

Mechanisms

Adiposity. Westernized dietary patterns are characterized by hyperpalatable processed foods with a high content of fat, sugar, salt and flavour additives that increase energy intake[183], thereby contributing to obesity, which, as previously discussed, can lead to hypertension.

Insulin resistance. Among the possible environmental causes of insulin resistance is the chronic adoption of westernized diets with a high energy content, as shown in short-term overfeeding studies in healthy individuals[184,185]. Despite the high energy content of westernized diets, these diets are high in ultra-processed foods and can be deficient in several micronutrients, such as magnesium[186]. Meta-analytical evidence supports an inverse association between magnesium intake and metabolic syndrome[187], and a beneficial effect of magnesium supplementation on glucose homeostasis[188,189]. Magnesium supplementation also reduces BP[190], including in patients with type 2 diabetes and independent of body weight status[191]. For instance, at a median dose of 368 mg per day for a median duration of 3 months, magnesium supplementation can reduce SBP by 2.0 mmHg and DBP by 1.8 mmHg[190]. Owing to their usual high content in processed foods or animal-derived foods high in fat and protein and cooked at high temperature and low humidity, western diets can be a substantial source of advanced glycation end-products (AGEs)[192]. AGEs can impair insulin sensitivity[193]. Diets low in AGEs (typically carbohydrate-rich foods such as vegetables, fruits and whole grains) can improve insulin sensitivity[194,195], albeit with no significant beneficial effects on BP[195]. However, in an animal model of hypertension associated with metabolic syndrome, pharmacological reduction of 24-h BP levels was associated with a decrease in the circulating levels of AGEs[196].

Renin–angiotensin–aldosterone system. Extreme reductions in sodium intake have been shown to activate the RAAS (by increasing renin and Ang II levels) in short-term studies[15]. This observation has been used as a counter-argument to salt reduction recommendations for the prevention and treatment of hypertension[15]. However, patients with hypertension seem to have a more sudden decrease in BP after acute reduction in salt intake than individuals with normal BP levels, which is, at least partly, attributable to a less responsive RAAS[197]. Conversely, a meta-analysis has suggested that a modest reduction in salt intake for ≥4 weeks causes significant and clinically important reductions in BP in individuals with or without hypertension, irrespective of sex and ethnic group, with a concomitant, small (or 'physiological') increase in plasma renin activity and aldosterone and noradrenaline levels[198]. This observation is in line with the finding that combining moderate salt restriction and RAAS blockers seems to work better than either strategy alone[199]. Notably, the DASH diet seems to have a priming effect on pathways affected by the RAAS (resulting in a natriuretic and diuretic effect) and results in a greater physiological response when combined with ACE inhibitors[200]. Chronic high alcohol intake induces increases in plasma renin concentration and BP[201]. Moderate alcohol intake also stimulates renin release[202], but repeated RAAS activation is not likely to mediate the pressor effect of regular moderate alcohol consumption[202].

Potassium. The effects of sodium intake on BP should be considered together with those of potassium. A low intake of dietary potassium (such as in westernized diets) reduces extracellular potassium content, which hyperpolarizes the plasma membrane and, at the kidney level, causes a reduction in intracellular chloride in the distal convoluted tubule. Low intracellular chloride concentration in turn activates the renal sodium chloride cotransporter (NCC), via WNK serine/threonine protein kinases, with subsequent extracellular retention of sodium and an increase in BP, even in the setting of high salt intake[203,204]. Conversely, high potassium intake (such as from diets rich in fruits, vegetables, tubers and legumes, such as the DASH and Mediterranean diets) suppresses the NCC, resulting in a positive sodium balance owing to pronounced natriuresis, with subsequent benefits for BP control[203].

Vascular function and oxidative status. High dietary salt intake can impair vascular endothelial function[205,206], although this effect can occur independent of changes in BP[206,207]. A potential mechanism for sodium-induced VED is oxidative stress in the microvasculature[207]. A diet rich in AGEs[208] and hypercaloric meals rich in *trans*-fatty

Advanced glycation end-products (AGEs). Proteins or lipids that become non-enzymatically glycated as a result of exposure to sugars.

acids and/or certain saturated fatty acids can trigger endothelial dysfunction[209]. Conversely, dietary AGE restriction might attenuate oxidative stress[210], and some dietary interventions can improve endothelial function through NO-related mechanisms. Indeed, the ingestion of foods rich in inorganic nitrite and/or nitrate, such as spinach, beetroot and other plants, improve endothelial function and reduce arterial stiffness and BP, because nitrites and nitrates can potentially be converted to NO[211]. Dietary nitrate is sequentially reduced to NO through an enterosalivary nitrate–nitrite–NO pathway that involves the oral microbiota[212]. The use of an antibacterial mouth rinse reduces the saliva and plasma concentrations of nitrate and nitrite, with a concomitant increase in BP[213].

Certain dietary components, most of which are characteristic of the Mediterranean diet, can also improve endothelial function, such as magnesium[214], fish-derived omega-3 fatty acids[215], olive oil[216] (with extra-virgin oil being associated with many of the cardiovascular benefits of the Mediterranean diet[217] and olive oil polyphenols with improvements in both VED and BP[218]), cocoa flavanols[219], anthocyanins (mainly berries, red grapes and red wine, with concomitant beneficial effects on VED and BP)[220], flavan-3-ols (also with beneficial effects on VED and BP)[221] and nuts[222].

Alcohol consumption might promote the release of endogenous vasoconstrictor substances such as Ang II, endothelin 1 and endothelin 2 (REFS[202,223,224]), which can increase oxidative stress and cause VED[224]. Preclinical evidence indicates that chronic alcohol ingestion induces VED by promoting inflammation and reducing the levels of NO, eNOS and vascular VEGFA, thereby hindering vasorelaxation[225].

Inflammation. High-glycaemic foods (containing added sugars and/or refined grains) can cause inflammation through increases in NF-κB activation in blood mononuclear cells[226]. Diets high in saturated fatty acids[227], meals rich in *trans*-fatty acids[228] and dietary AGEs (through the activation of the receptor for AGEs expressed on various cells including leukocytes) can also have a pro-inflammatory effect[229]. However, more evidence based on high-quality RCTs is needed before recommending dietary AGE restriction for the alleviation of the pro-inflammatory milieu[210].

Westernized diets are usually high in sodium, which can alter the composition of the gut microbiota and is associated with a pro-inflammatory phenotype in $CD4^+$ T cells and macrophages[230]. The pro-inflammatory effects of sodium are especially marked in the context of resistant hypertension, in which sodium accumulation together with a dysfunctional endothelial glycocalix causes microcirculation impairment, characterized by macrophage infiltration and vascular inflammation[231]. Westernized diets also tend to be low in nutrients and bioactive compounds involved in the regulation and resolution of inflammation, such as zinc[232], magnesium[233,234], potassium[235] or omega-3 fatty acids[236].

Some dietary interventions have been reported to inhibit or decrease inflammation, such as those high in fruits and vegetables[237], with a reduced glycaemic load[238], or those providing adequate amounts of micronutrients, such as zinc[232], magnesium[233] and potassium. Potassium supplementation could counteract the pro-inflammatory effects of sodium on T cells that are mediated through activation of the p38–MAPK–SGK1 pathway[235].

Autonomic function. Alcohol intake diminishes baroreflex sensitivity[239,240], and is associated with a higher SNS tone[241].

Gut microbiota. The gut microbiota has essential functions that are conserved from worms to humans, including regulation of nutrition, protection from pathogens and production of metabolites. Metabolites from the gut microbiota also signal to distant organs, contributing to the maintenance of host physiology[242]. In this context, alterations (dysbiosis) of the gut microbiota are associated with a higher risk of inflammation and CVD. A meta-analysis showed an association between the gut microbiota-derived metabolite trimethylamine *N*-oxide (TMAO) — which has been shown to be a biomarker for CVD events and death — and the risk of hypertension[243]. Preclinical evidence suggests an association between higher salt intake and gut microbiota dysbiosis[244,245]. Probiotics can reduce BP in patients with type 2 diabetes[246], as well as in healthy individuals and patients with hypercholesterolaemia, hypertension, obesity or metabolic syndrome, albeit with a modest effect[247].

Xenobiotics. With a high prevalence of fast-food meals, westernized diets can increase exposure to xenobiotics such as bisphenol A[248]. Bisphenol A exposure is associated with an increase in BP and a higher risk of hypertension[249–252] in observational studies, independent of race, ethnicity, smoking status, BMI or diabetes[252]. Furthermore, one RCT showed that a high exposure to bisphenol A (through consumption of beverages in cans instead of glass bottles) increased SBP by ~4.5 mmHg[253]. If combined with a high-fat intake, bisphenol A can induce hypertension in preclinical models through decreased NO bioavailability, increased oxidative stress and activation of the aryl hydrocarbon receptor signalling pathway[254] (a nuclear receptor with a primary function in mediating xenobiotic metabolism through transcriptional activation of drug-metabolizing enzymes). Other mechanisms for the association between bisphenol A exposure and risk of hypertension include endocrinal disturbance, inflammation and epigenetic changes[255] and Ang II–calcium/calmodulin-dependent protein kinase IIα-mediated uncoupling of eNOS[256]. Finally, bisphenol A exposure affects autonomic function (as reflected by a decreased heart rate variability), but this effect does not seem to be linked to increases in BP[250].

Circadian entrainment and sleep

Circadian entrainment

Most bodily functions and responses, including BP, vary over the course of a day[257]. Rhythmicity of biological activities is a crucial factor for survival, and the circadian rhythm is the most influential. In humans and

Polyphenols
A main class of plant secondary metabolite, existing in a wide variety of foods, typically divided into flavonoids and non-flavonoid polyphenols.

Anthocyanins
A type of flavonoid with antioxidant and colouring effects that give certain plants that are rich in these compounds (blueberry, raspberry, red and black grapes and black soybean, among many others) a red, blue, purple or black colour.

Flavan-3-ols
Sometimes referred to as 'flavanols', not to be confused with flavonols. Derivatives of flavans that include catechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, proanthocyanidins, theaflavins and thearubigins.

Gut microbiota
The collective microorganisms (bacteria, archaea, fungi and viruses) that reside in the gastrointestinal tract.

Probiotics
Live microorganisms with purported health benefits when consumed, mainly as a result of improving or restoring the gut microbiota.

Xenobiotics
Chemical substances found within an organism that are not naturally produced or expected to be present within the organism.

Bisphenol A
A ubiquitous plasticizing agent used in the manufacture of polycarbonate plastics and epoxy resins, found in food and beverage cans as well as in thermal receipt paper. Owing to a structural similarity to oestrogen, bisphenol affects various phenotypes that are regulated by the natural hormone oestrogen.

other mammals, the circadian rhythm is controlled by the central biological clock in the suprachiasmatic nucleus (SCN) of the hypothalamus and by peripheral clocks located in various cells throughout the body. The SCN evolved to synchronize activity, rest and energy intake to the circadian and circannual cycles using the autonomic nervous system. To entrain autonomic rhythms to the external environment, the SCN requires repeated cues from light exposure, sleep, activity and nutrient intake, at certain times.

Circadian rhythmicity is especially relevant to the cardiovascular system. Therefore, BP, cardiac output and heart rate have a marked circadian pattern, and the dysregulation of this circadian pattern, especially for BP, is associated with increased risk of CVD[257]. In this context, 24-h ambulatory BP monitoring provides clinically useful information and is a stronger prognostic factor for CVD and mortality than clinic BP[258–261]. The influence of circadian entrainment on hypertension risk is particularly relevant in light of the clinical importance of night-time ambulatory BP, which has been identified as a better predictor of adverse events than daytime ambulatory BP[262], and from which different risk levels can be identified. In patients with a good control of BP, a drop in BP of >10% is usually observed from daytime to night-time (known as the 'dipping pattern')[263]. However, other BP patterns such as 'extreme dipping' (drop in BP from daytime to night-time of >25%), 'non-dipping' (<10%) and 'riser' (increase in BP from daytime to night-time) are all characterized by an increased risk of CVD[264,265]. Therefore, an elevation in night-time BP regardless of the pattern, which can be exacerbated by an impaired circadian rhythm, along with an increased 24-h BP would be associated with a higher risk of CVD morbidity and death[266].

Disruption (misalignment) of the circadian rhythm (inverting behavioural and environmental cycles) is a common feature in individuals engaged in shift work. Evidence from a meta-analysis supports an association between shift work, particularly rotational shifts, and the risk of hypertension[267]. A non-dipper pattern can be observed from the first night shift, which recovers after 4 days of continuous shift work[268]. Circadian misalignment for 3 days can increase 24-h BP owing to a rise in night-time BP (5.6 mmHg for SBP and 1.9 mmHg for DBP)[269]. Exercise and eating schedules can also affect circadian entrainment. Therefore, aligning meals with circadian rhythms by restricting eating to early hours results in lower BP levels, along with other cardiometabolic benefits such as improved insulin sensitivity, lipid profile and redox status, in individuals with metabolic syndrome or pre-diabetes[270–272].

Sleep

The total daily sleep duration in the first humans was likely to have been >8 h during most of the year[273]. Those individuals living away from the equator were exposed seasonally to shortened (in winter) and lengthened (in summer) photoperiods that induced shorter sleep durations in summer and longer sleep durations in winter[274]. BP decreases by an average of 10–20% during sleep[275], meaning that less sleep in the summer results in a higher average 24-h BP and also extends the exposure to elevated SNS activity and to waking physical and psychosocial stressors. The effects of seasonally shortened sleep on BP were brief for our ancestors. However, today, short sleep durations and sleep disruptions are common throughout the year. For instance, >57% of participants in a 2013 study reported getting less sleep than needed on workdays[276]. Indeed, humans are now chronically exposed to many potential sleep disruptors, including shift work, multiple jobs, 24-h access to shopping, Internet, television, smart phones and travel across time zones, which can compete with sleep time and interrupt sleep schedules. Moreover, exposure to artificial light (especially in the blue spectrum) at night disturbs sleep quality and leads to irregular sleep schedules[277]. These alterations in sleep patterns can contribute to sleep-maintenance insomnia and disrupt circadian rhythmicity and autonomic balance. Even if individuals with insomnia can achieve adequate sleep durations by compensating for nocturnal awakenings by sleeping during the day, chronic insomnia has been found to be associated with a higher night-time SBP and blunted day-to-night decreases in SBP[278].

Other sleep-related variables can also negatively affect BP. Evidence from longitudinal and cross-sectional studies in young and middle-aged individuals of various ethnicities suggest an association between sleep duration and hypertension and/or higher BP. A meta-analysis including 1,074,207 individuals found that both short (≤5 h) and long (≥9 h) sleep durations were associated with increased BP levels[279]. A significant association between short sleep duration and the risk of hypertension was found in a large meta-analysis with 5,172,710 adults[280] and in another including adolescents only[281]. Sleep quality is another important aspect that can be associated with the risk of hypertension. A meta-analysis suggests that self-assessed poor sleep quality is associated with a greater likelihood of hypertension (OR 1.48, 95% CI 1.13–1.95)[282]. Variations in sleep architecture, such as decreased percentage of time in slow-wave sleep and low non-rapid eye movement sleep have also been shown to increase the risk of hypertension in older men[283] and middle-aged women[284].

The influence of sleep on hypertension risk is particularly relevant given the clinical importance of the night-time ambulatory BP as a predictor of adverse events[262]. In this regard, the presence of OSA or insomnia and a low number of sleeping hours in patients with hypertension can negatively affect the control of night-time BP and, consequently, increase the risk of CVD[285–287].

The observed association between sleep duration and hypertension has raised the hypothesis that interventions aimed at extending sleep duration and improving sleep quality could be effective measures for the prevention of hypertension[274]. Adequate treatment of OSA and the use of sleeping pills can improve the control of night-time ambulatory BP[288]. A RCT in patients with pre-hypertension or stage 1 hypertension and with habitual sleep durations of ≤7 h showed that a 6-week sleep extension intervention (resulting

Suprachiasmatic nucleus
(SCN). A small region of the brain in the hypothalamus, situated directly above the optic chiasm, that is responsible for controlling circadian rhythms.

Sleep quality
The self-reported, retrospective appraisal of the sleep experience. A good sleep quality typically means falling asleep in ≤30 min and sleeping soundly through the night (one or no awakenings and drifting back to sleep within 20 min of waking up).

Sleep-maintenance insomnia
A condition characterized by difficulty staying asleep, nocturnal awakenings and, in particular, waking too early and struggling to get back to sleep.

Slow-wave sleep
The phase of sleep that is considered to be restorative and is associated with the highest arousal threshold.

Low non-rapid eye movement sleep
The phase of sleep associated with better performance and learning as well as with decreased sympathetic nervous system activity and increased parasympathetic nervous system activity during the night.

in average sleep extensions of 35 min) significantly decreased beat-to-beat SBP (14 mmHg) and DBP (8 mmHg) averaged across a 24-h recording period compared with maintenance of habitual sleep duration[289]. However, a more recent RCT in individuals with mild sleep impairment did not find a beneficial effect of a sleep intervention on BP despite finding a beneficial effect on sleep quality[290]. Improvements in sleep could positively influence other common hypertension-related markers. Indeed, sleep deprivation is positively associated with the incidence of obesity, which is a risk factor for hypertension[291], and with deregulated fasting leptin levels and increased hunger[292]. Accordingly, adequate sleep might help with adherence to dietary interventions and body weight reductions[292] and might also help to achieve the necessary energy to engage in regular physical activity[274]. Shift work and the attendant changes in the sleep timing and circadian reversal is a risk factor for hypertension[267], particularly when coupled with short sleep duration[293]. Therefore, the promotion of adequate sleep should be coupled with circadian synchronization, such as maintaining regular sleep–wake times, adhering to time-restricted eating patterns, promoting the exposure to bright light during the day and minimizing exposure to bright light in the evening.

Mechanisms

Adiposity. Shift work is associated with altered eating patterns across the 24-h period (above the usual three meals every 24 h) including at night[294,295]. Circadian disruption or sleep deprivation can also impair the homeostatic control of food intake. For instance, partial sleep deprivation increases ghrelin levels and subjective appetite[296,297]. A meta-analysis of RCTs suggests that sleep restriction (to a total sleep time of 3.5–5.5 h) increases subjective hunger, calorie intake (average increase of 253 kcal per day) and body weight gain (albeit with modest average increases of 0.34 kg)[298]. However, whether these changes are associated with concomitant increases in BP is unknown. In addition, although long sleep duration (>9 h) is associated with a higher risk of obesity in adults[299,300], evidence to date does not support an association with incident hypertension[300].

Insulin resistance. Partial sleep deprivation can moderately decrease insulin sensitivity[298], but whether this concurrently affects BP remains to be determined. One potential mechanism is the generation of an insulin-resistant state in peripheral adipocytes, reflected by an impairment in the capacity of insulin to trigger an increase in the levels of phosphorylated AKT, a crucial step in the insulin signalling pathway[301]. Restructuring of the morning-to-evening transcriptome profile in white adipose tissue can also be involved, with uncoupling from the local clock machinery and a resulting increase in carbohydrate turnover and impairment in glucose homeostasis[302]. The adverse effects of sleep deprivation seem to be reversible, with two nights of recovery sleep (approximately 10 h per night) after four nights of sleep restriction restoring insulin sensitivity to baseline levels[303]. The circadian misalignment that occurs in individuals engaged in shift work might also increase insulin resistance independently of loss of total sleeping hours[304].

Renin–angiotensin–aldosterone system. The RAAS is closely related to sleep regulation, with an increase in activity during slow-wave sleep[305]. However, whether circadian alterations or sleep deprivation can mediate potential increases in BP through a RAAS-related mechanism remains to be elucidated. Nevertheless, OSA might cause hypertension, at least in part, by stimulating RAAS activity[306]. Mechanistically, this effect might involve the intermittent hypoxia caused by upper airway collapse. Preclinical evidence shows that recurrent hypoxia increases BP in part through increases in renal sympathetic nerve activity that increase RAAS activity by upregulation of Ang II receptors[307,308] and activates the RAAS in the carotid bodies[309]. In turn, continuous positive airway pressure therapy to treat OSA downregulates RAAS components and reduces BP[310].

Vascular function and oxidative status. Even short-term (5 days) partial sleep deprivation (<5 h) is sufficient to impair endothelial function, but with no apparent changes in BP[311]. However, OSA is associated with an increased risk of VED[312] and arterial stiffness[313], which is caused by oxidative stress and systemic inflammation (resulting in reduced NO availability)[314], increased levels of adhesion molecules[315] and leukocyte-derived microparticles[316], and disorders of coagulation and lipid metabolism[315].

Inflammation. Shift work is associated with systemic inflammation (reflected by increased levels of hsCRP) and with higher SBP and DBP[317]. Circadian misalignment (independently of sleep loss) increases inflammation, as determined by circulating levels of hsCRP[304] or CRP[317]. This pro-inflammatory pattern can be accompanied by an increase in SBP and DBP[317]. A meta-analysis suggested that sleep disturbance and longer sleep duration (>8 h), but not sleep restriction or deprivation, are associated with inflammation (higher circulating levels of CRP and IL-6)[318].

Autonomic function. Partial sleep deprivation causes a significant increase in SNS activity, but does not necessarily translate into higher SBP and DBP, at least in the short term (within days)[311]. However, total sleep deprivation has rapid effects on BP, with increases in both SNS activity and BP observed within only 24 h (REF.[319]) or 40 h (REF.[320]) of continuous non-sleep. These effects are mediated by a stress-induced resetting of arterial baroreceptors towards higher BP levels and a decrease in baroreflex sensitivity[319].

Stress management

A growing number of people in western countries are experiencing increased anxiety, depression and chronic psychosocial stress (herein mostly referred to as 'stress' for simplicity) brought about by globalization, cultural and socioeconomic changes, and stress in the work place[321,322]. Strong evidence indicates that stress and/or anxiety can transiently increase BP, being a prominent

Psychosocial stress
Also frequently referred to as 'mental stress'. The feeling of being overwhelmed or unable to cope as a result of pressures that are unmanageable.

component of white-coat syndrome[323]. Robust evidence also links the exposure to intensely traumatic life events with an increased risk of hypertension. For instance, an increased prevalence of hypertension has been reported in a large cohort of US veterans with post-traumatic stress disorder (PTSD) who had been deployed in Afghanistan or Iraq[324]. An increased risk of incident hypertension during a 22-year follow-up was also observed among civilian women with PTSD[325]. Similarly, PTSD was the main predictor of incident hypertension in a 2.4-year follow-up study in US veterans, whereas treatment for PTSD (with individual psychotherapy sessions or prescription of selective serotonin reuptake inhibitors) significantly reduced the risk of hypertension[326].

Whether chronic exposure to psychosocial stress can lead to an increased risk of hypertension is more controversial[327]. A meta-analysis showed that psychosocial stress is associated with an increased risk of hypertension (OR 2.40, 95% CI 1.65–3.49) and that patients with hypertension have a higher incidence of psychosocial stress than individuals without hypertension (OR 2.69, 95% CI 2.32–3.11)[321]. However, because of the heterogeneity between studies (particularly in the definition of stressors), more evidence (based on additional case–control and cohort studies) is needed to confirm that chronic psychosocial stress is a risk factor for hypertension.

Controversy also exists as to the effectiveness of stress management techniques for the prevention and treatment of hypertension[327]. A meta-analysis including 17 RCTs found no consistent benefits of different stress-reduction techniques, such as biofeedback or relaxation, on BP in patients with hypertension[328]. Another meta-analysis found decreases in both SBP (5.5 mmHg) and DBP (3.5 mmHg) with relaxation techniques in patients with hypertension, although the effects were not significant when the studies that included a sham therapy were analysed separately[329].

Some investigators argue that the 2017 ACC/AHA hypertension guidelines should have included meditation in the list of effective non-pharmacological interventions for the prevention and treatment of hypertension[330]. A 2019 meta-analysis including 851 adults with hypertension or CVD found no significant effects of transcendental meditation on SBP or DBP compared with their peers doing no transcendal meditation, but significant within-group (BP change from baseline) reductions in SBP and DBP were observed in the transcendental meditation group[331]. A RCT not included in this meta-analysis showed a significant effect of mindfulness meditation on lowering clinically measured SBP, 24-h SBP, at-rest SBP and DBP in individuals with high-normal BP or stage 1 hypertension compared with a control intervention involving health education talks[332]. The benefits seem to be greater if meditation or mental relaxation are combined with breathing techniques in yoga sessions (average 11 mmHg decrease in SBP and 6 mmHg decrease in DBP)[333]. Further evidence is needed to draw strong conclusions on the benefits of stress management techniques, including meditation, in the prevention or management of hypertension.

White-coat syndrome
Also known as 'white-coat hypertension'. A phenomenon in which people exhibit a blood pressure above the normal range in a clinical setting but not in other settings (at home or with 24-h ambulatory assessments).

Post-traumatic stress disorder
(PTSD). A mental health condition triggered by a terrifying event, either experiencing it or witnessing it, with symptoms including flashbacks, nightmares, severe anxiety or uncontrollable thoughts about the event.

Mechanisms

Adiposity. In the past four decades, the prevalence of stress has increased in parallel with that of obesity in industrialized societies[334]. Indeed, the presence of psychosocial stress has been associated with an increased adiposity[335], especially abdominal adiposity[334]. Obesity is itself a stress situation[336] that can undermine self-regulatory cognitive processes such as executive functioning[337], and interfere with the brain areas responsible for self-regulation[338]. Stress can affect behaviour by inducing over-eating and consumption of high-calorie foods[339–341]. In addition, a stress-induced, prolonged activation of the hypothalamic–pituitary–adrenal (HPA) axis might promote abdominal fat accumulation mediated by increases in cortisol secretion[334]. Greater stress is usually linked to lower physical activity[342] and disrupts sleep[343]. In turn, shorter sleep duration is associated with an increased subjective hunger and body weight[298], and poorer sleep quality is linked to a higher risk of obesity[344]. The evidence on the effects of stress management on body weight reduction is promising[345,346] but scarce, and whether it translates into clinical benefits for BP management remains to be determined.

Insulin resistance. Stress-induced chronic glucocorticoid exposure owing to the prolonged activation of the HPA axis can provoke insulin resistance through specific activation of glucocorticoid receptors in the hypothalamic arcuate nucleus, which stimulates neuropeptide Y (NPY) release[347]. In turn, increased NPY release from sympathetic nerves upregulates the production of NPY and its receptors in the abdominal fat in a glucocorticoid-dependent manner, leading to fat accumulation and a metabolic syndrome-like condition with reduced insulin sensitivity[347,348]. Glucocorticoids reduce insulin-mediated glucose uptake at the muscle tissue level via stimulation of serine kinases[349,350], resulting in phosphorylation and inactivation of the insulin receptor and insulin receptor substrate molecules[349]. In patients with coronary heart disease, a 16-week transcendental meditation intervention improved insulin resistance as well as BP levels, and the beneficial effects on the former were independent of potential confounders such as BMI, diabetes at baseline or physical activity[351].

Renin–angiotensin–aldosterone system. Acute stress stimulates the RAAS through SNS activation, but the evidence for chronic stress is not so clear. Nevertheless, data indicate that chronic stress increases plasma renin activity in humans (such as in people living alone)[352] and rats (such as after forced immobilization)[353].

Vascular function and oxidative status. Recurrent mental stress in mice (such as tail suspension) impairs endothelial function, with markedly reduced aortic mRNA levels of *Nos3* (which encodes eNOS) and increases in vascular oxidative stress, mediated by heart rate increases and reverted by adrenergic blockade[354]. In patients with major depressive disorder, exposure to everyday psychosocial stressors is associated with greater impairment of endothelial function (as assessed by acetylcholine-induced dilatation in cutaneous

microvessels)[355]. However, more evidence of the beneficial effects of stress management interventions on BP management is needed. The BP-reducing effects of a 16-week transcendental meditation programme in patients with coronary heart disease were not accompanied by improvements in endothelial function (as assessed by flow-mediated dilatation)[351].

Inflammation. Acute stress increases the production of pro-inflammatory molecules (IL-1β, IL-6, IL-10 and TNF)[356], and several forms of chronic stress (such as job stress or poverty) are associated with chronic systemic low-grade inflammation (as shown by increases in hsCRP or CRP)[357,358]. Mindfulness-based interventions have shown modest but significant effects in reducing the levels of biomarkers of low-grade inflammation (hsCRP, IL-6, NF-κB and TNF)[359]. The potential link between reduced inflammation and the beneficial effects on BP remains to be determined.

Autonomic function. Stress in adulthood can lead to pathophysiological changes including increased SNS activity with subsequent increases in BP[322]. In this context, a single session of mindfulness meditation can acutely decrease SNS activity and SBP and DBP in patients with hypertension and chronic kidney disease[360]. These findings are consistent with the benefits of regular meditation (up to 16 weeks) for improving autonomic balance (as assessed with heart rate variability)[351] and BP in patients with pre-hypertension or hypertension[361,362] or with coronary heart disease[351], and even for decreasing mortality (over a mean follow-up of 7.6 years) in patients aged ≥55 years with hypertension[363].

Unproven lifestyle interventions

This section summarizes lifestyle interventions that are increasingly gaining attention but for which conclusive evidence of efficacy for BP management is lacking.

Dietary components

Dietary acid load. When the dietary acid load is positive, excess acids must be excreted by the kidney to maintain the acid–base balance[146]. Therefore, in the setting of chronic kidney disease, a high dietary acid load invokes adaptive mechanisms to increase acid excretion despite a reduced number of nephrons, such as increased ammoniagenesis per nephron and augmented distal acid excretion mediated by the RAAS and endothelin 1, which might induce renal injury. In this context, a high acid load might increase the risk of hypertension. Meta-analytical evidence suggests a dose–response association between acid load (as determined by potential renal acid load), the risk of hypertension[364] and the risk of higher values of both SBP and DBP[364,365]. Therefore, consuming a net base-yielding diet could be expected to decrease BP, especially when characterized by a reduction in salt intake and an increase in the consumption of fruits, tubers, roots and vegetables, because it will also lead to an increase in magnesium content and a decrease in the sodium-to-potassium ratio. More evidence is needed on the potential BP-lowering effects of reducing dietary acid load.

Dietary fibre. An increased intake of dietary fibre could be one of the mechanisms underlying the beneficial effects on hypertension of fruit and vegetable consumption. A meta-analysis of 21 RCTs including 1,343 participants showed that viscous soluble fibre supplementation (β-glucan from oats and barley, guar gum, konjac, pectin and psyllium) at a median dose of 8.7 g per day for ≥4 weeks reduced SBP (1.6 mmHg) and DBP (0.4 mmHg) over a median follow-up of 7 weeks[366]. Therefore, inclusion of viscous soluble fibre in habitual diets might be beneficial.

Polyphenols. In the past decade, dietary polyphenols have been under the spotlight because of evidence of their association with positive health outcomes in numerous studies and their wide availability in a variety of commonly consumed foods. Among the most studied polyphenols are flavonoids. A meta-analysis of 15 cross-sectional studies and seven prospective cohorts, comprising 200,256 individuals (45,732 with hypertension), found no significant association between extreme quantiles of flavonoid intake and the risk of hypertension (RR 0.96, 95% CI 0.89–1.03)[367]. Although dietary intake of anthocyanins (a flavonoid subclass) was associated with a significant, albeit modest, reduction in the risk of hypertension when comparing highest versus lowest exposure (RR 0.92, 95% CI 0.88–0.97)[367]. Another meta-analysis of RCTs found significant effects of quercetin (a dietary flavonol) in reducing SBP and DBP at doses of ≥500 mg per day[368]. Evidence suggests that certain polyphenol-containing herbs and spices, notably ginger, can reduce BP in patients with pre-hypertension or hypertension[369]. A meta-analysis of six RCTs including 345 participants suggested that ginger supplementation reduces SBP (6.4 mmHg) and DBP (2.1 mmHg)[370]. Nevertheless, in separate subgroup analyses, SBP and DBP were significantly reduced only in the subset of studies that included participants with a mean age of ≤50 years, with a follow-up of ≤8 weeks and with ginger doses of ≥3 g per day.

Further evidence supporting the BP-lowering effects of polyphenols comes from studies on beetroot. This root vegetable has been postulated as a complementary treatment for hypertension because of its high content of inorganic nitrate, which has vasodilatory effects[371]. A systematic review and meta-analysis of 22 RCTs found lower SBP (3.6 mmHg) and DBP (1.3 mmHg) in groups receiving beetroot juice supplementation than in control groups[371]. However, the benefits were independent of nitrate content and, according to the investigators, other bioactive compounds in beetroot, such as polyphenols, might explain the observed BP-lowering effects.

The flavan-3-ols found in cocoa, particularly epicatechin, might increase the formation of endothelial NO, promoting vasodilatation and consequently BP reduction[372]. Indeed, the high intake of flavanol-rich cocoa in the non-westernized Kuna Indians has been suggested as one of the underlying causes of their low prevalence of high BP[373]. A Cochrane review including 35 trials concluded that cocoa consumption resulted in a small but significant reduction in SBP (1.8 mmHg) and DBP (1.8 mmHg), with stronger effects in patients with hypertension (SBP 4 mmHg, DBP 2.0 mmHg)[374].

Dietary acid load
The balance of net acid-yielding food items (meats, fish, shellfish, eggs, cheese, cereal grains and salt) and net base-producing food items (fruits, tubers, roots and vegetables).

Flavonoids
A type of polyphenol whose subclasses (for example, flavanols, flavonones and isoflavones) are present mostly in fruits, certain vegetables, seeds (such as flax), soy, whole grains, honey, tea, coffee, cocoa, some alcoholic beverages (such as wine) and a few spices.

Quercetin
The most abundant dietary flavonol, mainly found in onions, apples and berries.

Ginger
A flowering plant whose rhizome is frequently used as a spice, containing several bioactive compounds (such as gingerols) with the potential to affect human health.

Flaxseed
A seed from the flax plant with moderate-to-high contents of α-linolenic acid (an omega-3 fatty acid), lignans (a group of polyphenols), and soluble and insoluble fibre.

Flaxseed. The potential BP-lowering effects of flaxseed are probably related to its content of α-linolenic acid (an omega-3 fatty acid), fibre and lignans. A meta-analysis of 15 RCTs including 1,302 participants indicated that supplementation with flaxseed products significantly reduced SBP (2.9 mmHg) and DBP (2.4 mmHg) [375]. Of note, supplementation with flaxseed powder significantly reduced SBP but supplementation with oil preparations or lignan extract did not, and supplementation with flaxseed powder and oil preparations significantly reduced DBP, but supplementation with lignan extract did not.

Coffee and tea. Given that caffeine is widely consumed in coffee and other items, defining the possible BP effects associated with caffeine intake is important. Coffee consumption is associated with an acute (~3 h) increase in BP in both healthy individuals and patients with hypertension. For this reason, coffee consumption has traditionally been believed to increase the risk of hypertension, but this notion does not seem to be supported by scientific evidence. A meta-analysis (including 196,256 participants, 41,184 with hypertension) found that habitual drinking of one or two cups of coffee per day was not associated with an increased risk of hypertension compared with non-drinking[376]. Indeed, a small but significant protective effect of coffee consumption was found starting from the consumption of three cups of coffee per day (RR 0.97, 95% CI 0.94–0.99)[376]. A meta-analysis suggested that black or green tea can significantly reduce SBP and DBP in individuals with pre-hypertension or hypertension[377]. Green tea has also been shown to reduce SBP and DBP in individuals with overweight or obesity[378].

Vitamins. A poor vitamin status has been suggested to increase the risk of hypertension. A prospective study including 20,926 participants concluded that those with the highest plasma vitamin C concentrations at baseline had a 22% lower risk of high BP than those with vitamin C levels in the bottom quartiles[379]. This finding might be related to the role of vitamin C in the synthesis and bioavailability of NO[380]. A meta-analysis of 35 studies including 108,173 participants concluded that high plasma 25-hydroxyvitamin D concentrations are associated with a reduced risk of hypertension[381]. A meta-analysis of 12 RCTs concluded that multivitamin and multimineral supplementation has a lowering effect on BP (SBP 1.3 mmHg, DBP 0.7 mmHg), with the effect on SBP being much larger in patients with hypertension (8.0 mmHg)[382]. However, the low number of participants analysed precluded strong conclusions from being drawn. Indeed, a prospective study found no association between the use of multivitamin supplements and the risk of incident hypertension[383]. Regarding the effect of specific vitamin supplements, a meta-analysis of 29 RCTs concluded that vitamin C supplementation reduces BP, with the benefit remaining significant when analysing only patients with hypertension[384]. Greater controversy exists about the efficacy of vitamin D supplementation on BP, with meta-analytical evidence showing no or inconsistent benefits[385,386].

Smoking cessation

Cigarette smoking increases the risk of CVD through several mechanisms, including oxidative stress, impairment of endothelial function, arterial stiffness and inflammation, among others[387]. Cigarette smoking also has an acute hypertensive effect, principally through SNS stimulation[388]. The ESC/ESH guidelines[5], but not the ACC/AHA guidelines[4], recommend smoking cessation to prevent and manage hypertension. However, no clear evidence exists for a direct causal relationship between cigarette smoking and the risk of hypertension. A Mendelian randomization meta-analysis with 141,317 participants from 23 population-based studies found no strong association between smoking and SBP and DBP levels or the risk of hypertension[389]. Further research is warranted, because physiological mechanisms suggest that cigarette smoking can increase BP. Indeed, several meta-analyses have confirmed the deleterious effects of smoking on overall cardiovascular health[390].

Conclusions

The lifestyle changes brought by the westernized way of life (including, among others, a high prevalence of physical inactivity, unhealthy dietary patterns, disrupted circadian rhythms and high levels of psychosocial stress) contribute to increasing the risk of hypertension. This contribution is important because hypertension remains a major cause of premature death worldwide despite considerable advances in pharmacological treatments. As summarized in this Review, growing evidence supports the role of lifestyle interventions (mainly regular physical exercise and nutritional interventions, but also other less traditional approaches such as promotion of adequate sleep patterns coupled with circadian entrainment) for the prevention and adjuvant treatment of hypertension. These strategies act over a variety of physiological mechanisms at the multisystem level and have beneficial effects on BP and overall cardiovascular health. An optimal lifestyle should be the first-line strategy to prevent hypertension and an established adjuvant treatment in patients with hypertension.

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