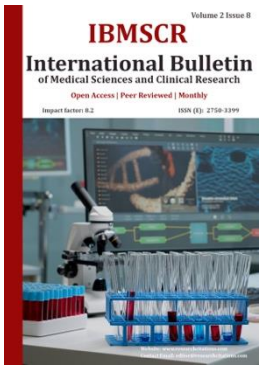

HYPERTENSION AND CARDIOVASCULAR DISEASE

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Abstract

The fragmented nature of previous research has obscured a comprehensive understanding of the causes of cardiovascular disease (CVD). Among the risk factors, high blood pressure (BP) has the strongest evidence for causality and a high prevalence. Normal biological levels of BP are significantly lower than what has traditionally been considered normal in both research and clinical practice. We propose that CVD is largely driven by a rightward shift in the population distribution of BP. Our view, which positions BP as the primary risk factor for CVD, is supported by conceptual frameworks tested in observational studies and clinical trials. Large cohort studies have identified high BP as a major risk factor for heart failure, atrial fibrillation, chronic kidney disease, heart valve disorders, aortic syndromes, and dementia, in addition to coronary heart disease and stroke. Multivariate modeling has shown that the attributable risk of high BP for stroke and coronary heart disease has increased as definitions of normal BP have shifted to lower values. Meta-analyses of BP-lowering randomized controlled trials have shown benefits closely matching predictions based on BP risk relationships in cohort studies. Preventing age-related increases in BP, along with intensive treatment of established hypertension, could significantly reduce the vascular outcomes typically associated with aging and alleviate much of the population's burden of BP-related CVD.

Keywords: blood pressure, cardiovascular disease causation, randomized controlled trials, cartesian evidence, attributable risk.

Proposed Causation of Cardiovascular Disease

High blood pressure (BP), smoking, diabetes, and lipid abnormalities are recognized as major modifiable risk factors for cardiovascular disease (CVD). Among these, high BP is supported by the strongest evidence for causation and is highly prevalent. However, biologically normal BP levels are significantly lower than those traditionally used in clinical settings and research, leading to an underestimation of BP's role as a CVD risk factor. We propose the following integrated theory for CVD causation, which is backed by a substantial body of consistent and coherent evidence:

"Cardiovascular disease in humans is primarily driven by a rightward shift in the distribution of BP."

While numerous theories exist in today's age of social media, few meet the essential criteria for causality. Scientific theories gain credibility by being well-structured and open to refutation through systematic observation and experimental testing. Our theory meets nearly all of the causality criteria set forth by Bradford Hill.

Shift in BP Distribution in Humans: Revealing a Selection Bias

At the end of the 19th century, Osler did not mention the risks of high blood pressure (BP) in his seminal textbook *The Principles and Practice of Medicine* because there was no practical way to measure BP noninvasively at the time. Shortly after noninvasive BP measurement techniques were developed and popularized, physicians and actuaries identified high BP as a potential cause of disease, particularly cardiovascular disease (CVD) events. In 1913, Janeway's study of 7,872 patients led to the conclusion that an average BP above 160 mm Hg was pathological.

Although these early studies linked high BP with CVD, they mainly compared the risk of CVD in individuals with extremely high BP to those with lower, yet still elevated, BP. What these early pioneers could not have known was that nearly all people, including those in the "lower" BP category, had BP levels above what is biologically normal. It took decades before BP was measured in populations with truly biologically normal BP, which was observed in isolated, non-acculturated societies. Studies later showed that almost all individuals in these isolated groups had much lower average BP levels compared to those in acculturated societies.

Although potential confounding factors exist between acculturated and unacculturated populations, many of these were controlled in a key study of two Amazonian tribes with similar backgrounds and cultural habits, but differing sodium intake. The Mundurucus, influenced by the Franciscans, included salt in their diet, while the Carajás, with minimal contact with Westerners, consumed almost no salt. In the Mundurucus, average BP increased with age, whereas in the Carajás, mean systolic BP remained around 110 mm Hg and diastolic BP around 60 mm Hg throughout their adult lives (Figure 1).

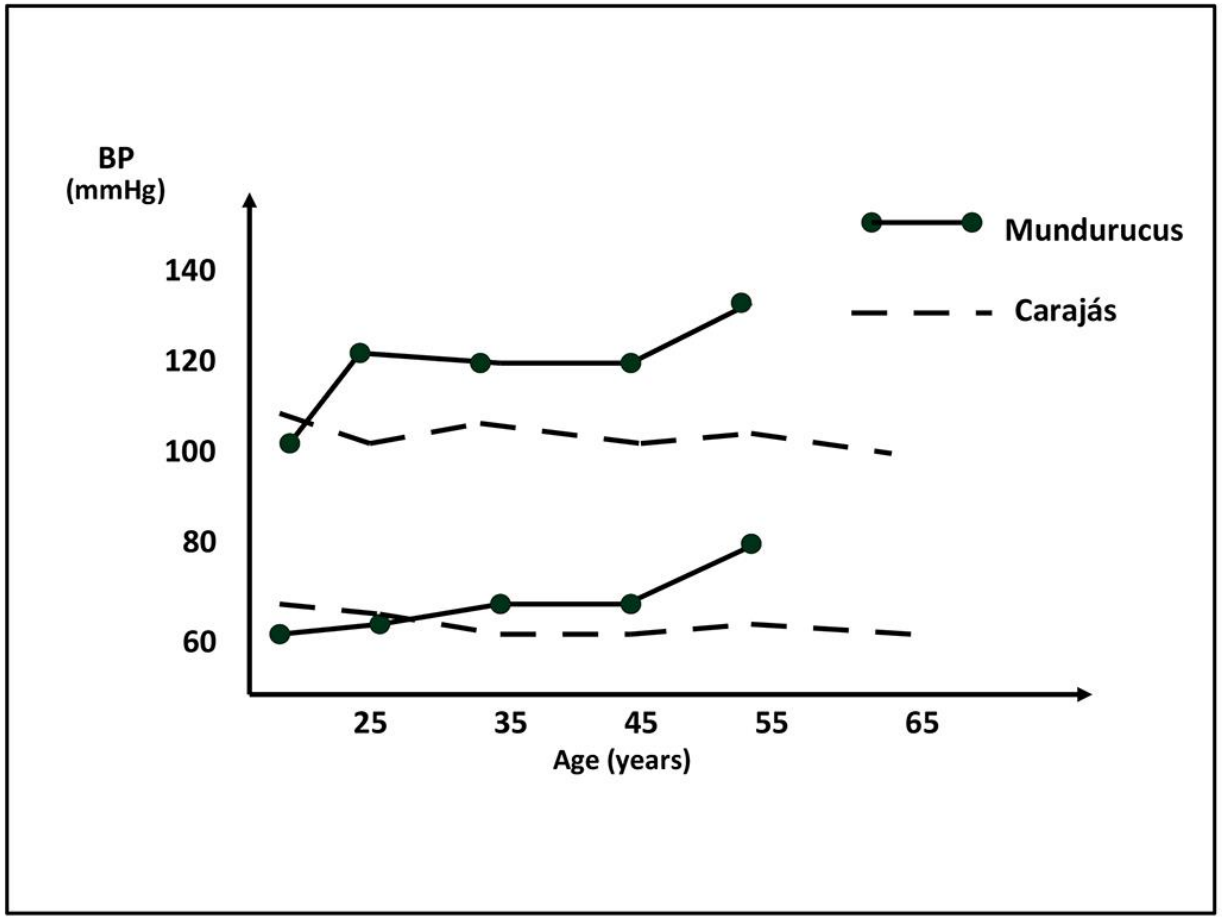

Figure 1.

Blood pressure for men by age in Mundurucus and Carajás Indians, showing a rise with aging in the "acculturated" Mundurucus but not in the "unacculturated" Carajás (reprinted with permission from the reference 8).

Another isolated society in Brazil, the Yanomamo Indians, who have very limited access to salt, also showed minimal or no increase in blood pressure (BP) with age. In addition to excreting very little sodium in their urine, they exhibited elevated levels of plasma renin activity and aldosterone. These findings suggest that biologically normal values for BP, renin activity, and aldosterone in unacculturated societies are vastly different from those observed in acculturated societies, where BP is higher, and plasma renin activity and aldosterone are lower due to exposure to high dietary sodium. Evidence from animal models, population studies, and clinical trials highlights the key role that excessive sodium intake plays in the age-related rise in BP.

The effects of two different definitions for identifying high BP are illustrated in Figure 2. The left panel shows the rightward shift in systolic and diastolic BP seen in acculturated societies. The shaded area in the unacculturated population represents high BP, using a threshold of systolic BP (SBP) ≥120 mm Hg or diastolic BP (DBP) ≥70 mm Hg, based on BP distributions from observational studies. In contrast, the shaded area for acculturated populations is based on the traditional high BP threshold of SBP ≥140 mm Hg or DBP ≥90 mm Hg. The right panel uses the SBP ≥120 mm Hg and DBP ≥70 mm Hg criteria to identify high BP in acculturated populations.

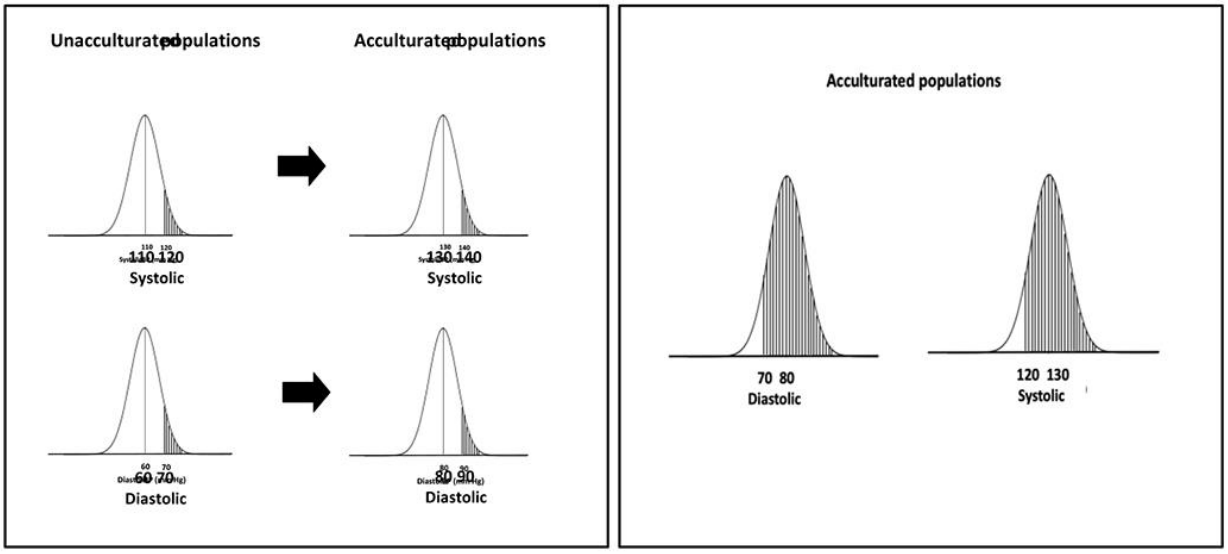

Figure 2.
Left-hand panel depicts distribution of systolic and diastolic BP in unacculturated and acculturated populations. Shaded areas identify distribution of a high blood pressure definition (systolic BP ≥120 mm Hg or diastolic BP ≥70 mm Hg) for adults in unacculturated societies and for their counterparts living in acculturated societies using the traditional definition for diagnosis of hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg). Shaded areas in the right-hand panel highlight distribution of high systolic and diastolic blood pressure applying the definition used for high blood pressure in unacculturated societies (SBP ≥120 mm Hg or diastolic BP ≥70 mm Hg).

According to these thresholds, approximately 70% of individuals in acculturated societies would be at a higher risk of developing cardiovascular disease (CVD). Using the hypertension diagnostic criteria from the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (SBP ≥130 mm Hg or DBP ≥80 mm Hg), around 63% of adults aged 45 to 75 in the United States and 55% in China have hypertension.

In recent decades, a leftward shift in BP distribution has been observed in high-income countries, leading to a decline in CVD incidence. However, globally, the absolute number of people with hypertension has increased due to a rightward shift in BP distribution in low- and middle-income countries.

Evidence from Cohort Studies

In an early cohort study, Keith, Wagner, and Barker reported on BP-related risks, categorizing participants by blood pressure levels, symptoms, electrocardiographic (ECG) abnormalities, albuminuria/hematuria, and optic fundi abnormalities. The mortality rate was proportional to the severity of these conditions, with more than 80% of participants experiencing fatal outcomes within one year if they had treatment-resistant BP, poor general health, abnormal ECG, albuminuria, hematuria, and optic edema (classified as Class IV). Despite these and other studies from the early 20th century suggesting that high BP caused cardiovascular disease (CVD), many influential figures at the time believed high BP was relatively harmless, often referring to it as “benign essential hypertension.” Among these opinion leaders, Paul Dudley White advocated the view that high BP was a compensatory physiological response and should not be treated.

In a series of landmark reports, the Prospective Studies Collaboration pooled data from numerous cohort studies, adjusting for regression dilution bias to provide precise estimates of the relationship between BP and CVD. One of their most important reports analyzed data from 61 cohort studies, representing 12.7 million person-years of follow-up and 56,000 deaths from coronary heart disease (CHD) and stroke. The study found that the risk of CVD steadily increased with higher baseline systolic BP (SBP) and diastolic BP (DBP), starting from a usual SBP of 115 mm Hg and DBP of 75 mm Hg. A 20 mm Hg increase in SBP and a 10 mm Hg increase in DBP doubled the risk of CVD (Figure 3, left panel, with log-transformed vertical axis). The right panel of Figure 3 shows an exponential increase in absolute risk for CHD and stroke as BP levels rise, with relatively small increases in CVD risk at lower BP levels and younger ages. This pattern helps explain why studies on younger and middle-aged populations typically only identify significant CVD risks at higher BP levels.

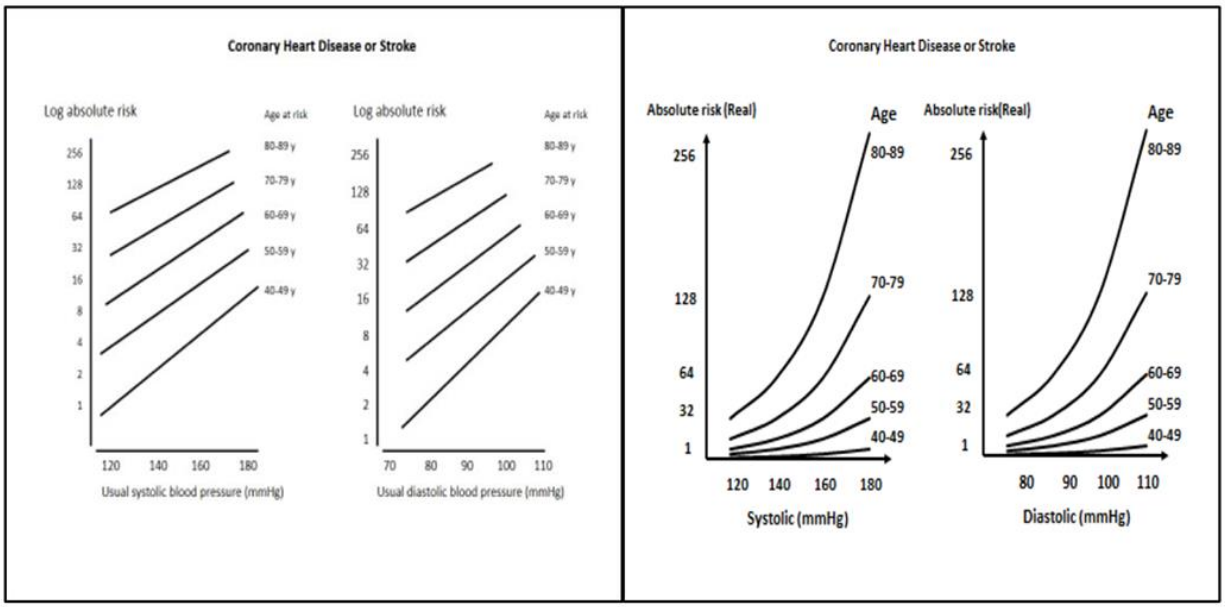

Figure 3.
Log transformed (left-hand panel) and untransformed (right-hand panel) absolute risk of coronary heart disease or stroke in adults, by systolic and diastolic blood pressure, stratified by age. (Reprinted with permission from references 20 and 21).

Most early observational studies focused on BP-related complications such as stroke and coronary heart disease (CHD), which tend to occur earlier and are more pronounced at higher BP levels. In older individuals, stroke and CHD are often accompanied by additional complications that develop after prolonged exposure to elevated BP, either due to the increased resistance of target organs or because of more moderate BP elevations sustained over time. The complications of high BP can be categorized into short-term and long-term consequences (as shown in the table). Consistent evidence from observational studies shows that high BP is the leading cause of long-term complications such as heart failure (both with and without preserved ejection fraction), atrial fibrillation, valvular heart disease, peripheral arterial disease, aortic syndromes, chronic kidney disease, end-stage renal disease, dementia, and Alzheimer's disease. Additionally, conditions like diabetes, erectile dysfunction, and age-related macular degeneration are likely linked to high BP as a contributing factor.

Table.
Short-term and long-term consequences of high BP

Short and long-term consequences
Stroke
Coronary heart disease
Heart failure
Cardiovascular death
Long-term consequences
Hypertensive cardiomyopathy
Heart failure with preserved ejection fraction

Atrial fibrillation

Valvular heart disease

Aortic syndromes

Peripheral arterial disease

Chronic kidney disease

Dementias

Diabetes mellitus

Erectile dysfunction

Centenarians

The primary reason centenarians live to 100 years or more is their remarkably low incidence of cardiovascular disease (CVD) and cancer. Coronary heart disease (CHD), stroke, dementia, and hypertension are significantly less common among centenarians compared to those who die younger (Figure 4). Vascular aging is closely linked to blood pressure (BP) levels, and it is not an inevitable process. Preventing age-related increases in BP could greatly reduce the vascular issues typically associated with aging. Interestingly, individuals who develop hypertension later in life are not at a higher risk of CVD earlier in life. Centenarians may also have a resistance to dietary sodium, as they appear to be able to manage sodium without needing the high pressure natriuresis seen in others.

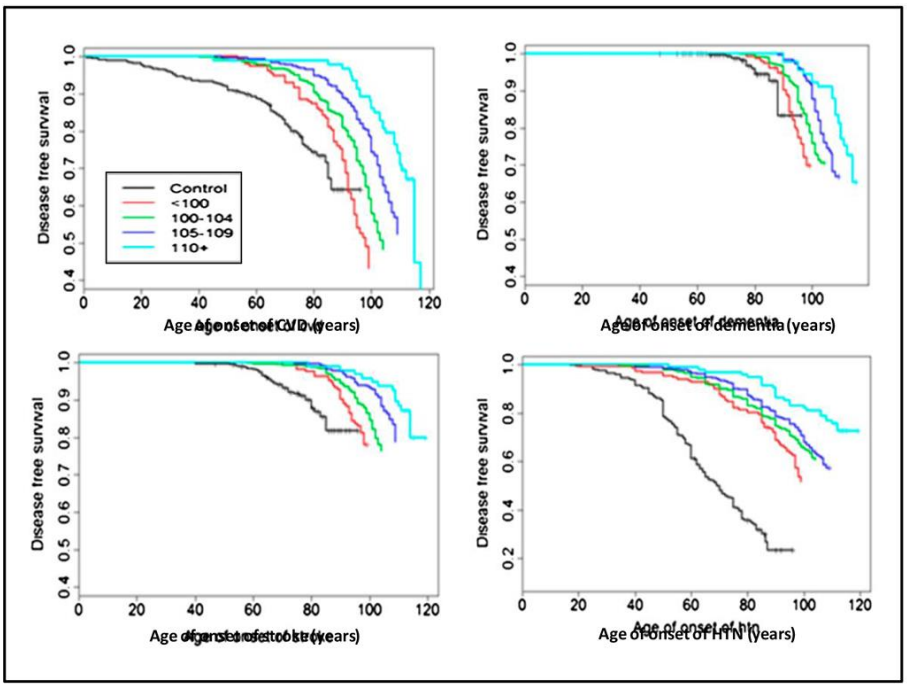

Figure 4.

Disease-free age survival for cardiovascular disease (CVD), dementia, stroke and hypertension (HTN) in controls (individuals without a familial predisposition for exceptional longevity (black line), and centenarians (color lines), stratified by age in years at death. The data demonstrate a consistent delay in onset of CVD, dementia and stroke when HTN starts late in life.

Cartesian Evidence

Experimental studies, which represent the highest level of proof for establishing causality, strongly support the theory of cardiovascular disease (CVD) causation. Key randomized controlled trials (RCTs) such as the 1967 Veterans Administration Cooperative Study on Antihypertensive Agents, the Systolic Hypertension in the Elderly Program (SHEP) trial, and the Systolic Blood Pressure Intervention Trial (SPRINT) have provided robust evidence for the effectiveness of blood pressure (BP) reduction in preventing CVD. For example, in the 1967 Veterans Administration trial, it was found that treating just six patients with diastolic BP averaging 115-129 mm Hg was enough to prevent one major CVD event per year.

Before the SHEP trial, many physicians considered isolated systolic hypertension a natural, benign consequence of aging. However, the trial demonstrated that chlorthalidone-based therapy reduced stroke incidence, the primary endpoint, by 36% compared to placebo. The SPRINT trial showed that participants aiming for a systolic BP goal of less than 120 mm Hg (intensive treatment) experienced a 25% lower incidence of the primary composite CVD endpoint compared to those with a goal of less than 140 mm Hg (standard treatment). Additionally, there were reductions of 43% in CVD mortality and 27% in all-cause mortality. The benefits extended to participants 75 years or older, including those with frailty or reduced gait speed.

High-quality meta-analyses have further confirmed the effectiveness of BP reduction for CVD prevention. These studies have compared the benefits observed in RCTs with the expected outcomes based on BP's role as a risk factor for CVD in observational studies. For instance, Law et al. calculated the CVD risk reduction in 147 RCTs, showing that a 10 mm Hg reduction in systolic BP led to decreases in stroke and coronary heart disease (CHD) incidence similar to those predicted in observational studies. Stroke risk showed a greater reduction, reflecting the higher sensitivity of cerebral vessels to elevated BP compared to coronary circulation.

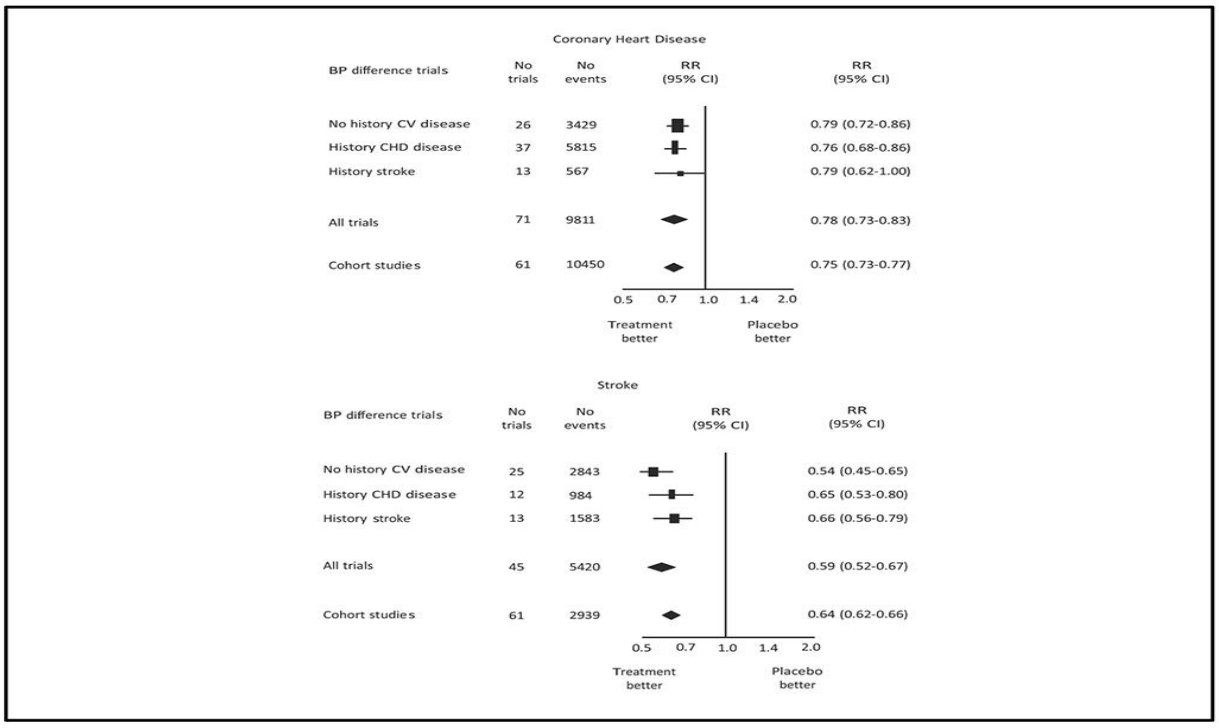

Figure 5.

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Relative risk estimates of coronary heart disease (top panel) and stroke (bottom panel) for systolic blood pressure reduction of 10 mm Hg or diastolic blood pressure reduction of 5 mm Hg in clinical trials meta-analysis and corresponding difference in meta-analysis of observational cohort studies.

A similar benefit was observed in a network meta-analysis by Bundy et al. This study found that the relative risk reduction for major cardiovascular disease (CVD) events in trials where participants were treated to a systolic blood pressure (BP) target of 120-124 mm Hg, compared to a target of 160 mm Hg or higher, was 64%. This closely aligns with the hypothetical 75% risk reduction predicted in the Prospective Studies Collaboration meta-analysis for a 40 mm Hg systolic BP reduction. The consistency between the risk reductions predicted in cohort studies and those demonstrated in randomized controlled trials (RCTs) supports Descartes' principle that the sum of the angles of any triangle equals 180 degrees. This close agreement between observed (clinical trials) and expected (cohort studies) benefits is remarkable, especially since the predicted benefits rely on imperfect measurements of a biological factor like BP.

There is limited experimental evidence regarding the prevention of long-term consequences of high BP, as such trials are difficult to design due to the extended duration of treatment required. However, some RCTs suggest benefits from BP lowering for these outcomes. For instance, in the SPRINT study, the composite outcome of mild cognitive impairment and dementia was significantly reduced during long-term follow-up.

The central importance of BP levels has also been highlighted in studies where increases in BP during treatment have led to CVD events. Examples include trials involving celecoxib, sibutramine, and torcetrapib. Conversely, the prevention of CVD events by sodium-glucose cotransporter 2 (SGLT2) inhibitors in adults with and without diabetes may be partially attributed to BP-lowering effects.

Attributable Risks

The estimation of high blood pressure's (BP) contribution to the development of cardiovascular disease (CVD) has progressively increased as the definitions of hypertension and analytical methods have evolved. Early estimates suggested that high BP accounted for 25% of coronary heart disease (CHD) cases and 50% of strokes. However, using the risks identified by the Prospective Studies Collaboration, the attributable risk for BP levels equal to or greater than 115/75 mm Hg was recalculated to be 49% for CHD and 62% for stroke. These estimates, though, likely understate the true impact of high BP on CVD development.

In many cohort studies, residual bias is probable because risk estimates are often based on only a few BP measurements. Vascular, cardiac, and renal damage occurs from long-term exposure to elevated BP, with repeated beat-to-beat fluctuations over time. A small number of BP readings cannot accurately capture this cumulative vascular load. Other CVD risk factors, such as smoking, dyslipidemia, and excess body weight, are subject to measurement error but are generally assessed with more precision compared to BP. More reliable methods, like ambulatory BP monitoring (particularly nighttime measurements), home BP monitoring, and automated office BP measurement, offer more accurate estimates of BP-related CVD risk and help identify risk at lower BP levels than traditional office measurements.

Another factor contributing to the underestimation of BP-related risks is the inclusion of intermediate consequences of high BP, such as left ventricular hypertrophy or vascular wall thickening, as direct causes of CVD in multivariate analyses. Even obesity and overweight, which are recognized CVD risk factors, are largely mediated by high BP. Despite these potential sources of underestimation, clinical trials have shown that nearly all of the predicted risk reduction for CVD is achieved through BP lowering, leaving little residual risk attributable to other concomitant factors.

What Is Missing?

In adults without cardiovascular disease (CVD), a strong association between blood pressure (BP) and CVD risk has been identified even at lower systolic (120-139 mm Hg) and diastolic (80-89 mm Hg) BP levels. Individuals within this BP range face an increased risk of developing higher BP levels over relatively short follow-up periods and often already show signs of target organ damage. Additionally, meta-analyses of event-based randomized controlled trials (RCTs) have demonstrated the benefits of antihypertensive treatment for secondary prevention in adults with CVD who have BP in this range. Trials have also shown that low-dose pharmacotherapy can lower BP and prevent incident hypertension in adults without CVD, with systolic BP of 130-139 mm Hg or diastolic BP ≤89 mm Hg.

The PREVER-Prevention trial further showed that low-dose diuretic therapy (chlorthalidone and amiloride) in adults with systolic BP of 120-139 mm Hg or diastolic BP of 80-89 mm Hg helped prevent the development of left ventricular hypertrophy, as measured by ECG.

However, no BP-lowering trial has yet demonstrated the prevention of CVD events in adults without CVD who have systolic BP below 140 mm Hg or diastolic BP below 90 mm Hg.

Despite strong evidence of BP-lowering benefits from clinical trials and meta-analyses, direct documentation of the benefits of intensive BP reduction is still lacking in adults with high BP who also have diabetes or a history of stroke. Ongoing trials in Brazil and China are exploring these questions in diabetic patients, and another trial in Brazil is investigating the impact of BP lowering in stroke survivors.

Conclusion and Perspectives

Our proposal that cardiovascular disease (CVD) is primarily driven by a rightward shift in the distribution of blood pressure (BP) is supported by coherent and substantial evidence. As with any theory, it is open to challenge and alternative interpretations. However, among current theories, ours aligns best with the principle of Occam's razor, being the hypothesis with the fewest assumptions. While other risk factors—such as lipid abnormalities, smoking, physical inactivity, and dietary factors beyond sodium—play significant roles in CVD development, elevated BP has the greatest impact on public health. That said, preventing CVD is most effective when addressed through a comprehensive approach that tackles all risk factors across the lifespan.

Regardless of its precise contribution, high BP remains a major risk factor for CVD development. Preventing age-related increases in BP would significantly reduce the vascular issues commonly attributed to aging. It is time to focus more on preventing typical age-related BP increases, alongside managing high BP in individuals with established hypertension. Even modest improvements in age-related BP trends could alleviate a substantial portion of the current burden of BP-related CVD.

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