Chapter 1

Prevalence and Long-term Consequences of Hypertension

Sergey Gilyarevsky
Russian Medical Academy of Continuous Professional Education,
Department of Clinical Pharmacology and Therapy

Global surveys of blood pressure (BP) have shown that at least one person in four world-wide has hypertension. Moreover, the number of people with hypertension has increased markedly in recent decades. High blood pressure increases the risk of adverse cardiovascular events (coronary heart disease, heart failure and stroke) and premature death, among other adverse outcomes. Controlling high BP with antihypertensive therapies is proven to improve clinical outcomes in people with hypertension.

Definitions of hypertension

The BP cut-off values used to diagnose arterial hypertension differ to some extent between guidelines and regions. Moreover, classifications of the severity of hypertension also differ. Table 1 summarises these classifications from three influential guidelines proposed by the European Society of Cardiology (ESC) [1], the American Heart Association (AHA)

and the American College of Cardiology (ACC) [2], and the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) [3]. The two guidelines originating from Europe set the cut-off for systolic/diastolic BP (SBP/DBP) at 140/90 mmHg, although the ESC guideline considers three categories of non-hypertensive BP as "optimal", "normal" and "high normal" BP. Further grades of increasing severity of hypertension are diagnosed using cut-off values of 160/100 mmHg and 180/110 (or 120) mmHg. The US guideline considers that an individual with BP even slightly above 140/90 mmHg already has Stage 2 hypertension, having defined normal BP as <130/80 mmHg. No further categories of severity of hypertension are provided by the US guideline. Using higher or lower cut-off values to diagnose hypertension will lead to lower and higher (respectively) estimates of the prevalence of hypertension, and this should be remembered when interpreting the results of epidemiological studies in this field.

Table 1 Examples of current definitions of hypertension from major guidelines.

	ESC (2018) [1]	AHA/ACC (2017) [2]	NICE (2022) [3]
Normal BP	<120/<80 mmHg (= "**Optimal**" BP) 120–129/80–84 mmHg (= "**Normal**" BP) 130–139/85–89 mmHg (= "**High normal**" BP)	<120/<80 mmHg 120–129/<80 mmHg ("**elevated**" BP)	<140/90 mmHg
Cut-off for diagnosis of hypertension	≥140/90 mmHg (**Grade 1 hypertension**)	≥130/80 mmHg (**Stage 1 hypertension**)	140/90 mmHg (**Stage 1 hypertension**)
Additional grades of severity of hypertension	≥160–179/100–109 mmHg (**Grade 2 hypertension**) ≥180/110 mmHg (**Grade 3 hypertension**)	≥140/≥90 mmHg (**Stage 2 hypertension**)	≥160/100 but <180/120 mmHg (**Stage 2 hypertension**) SBP ≥180 mmHg or DBP ≥120 mmHg (**Stage 3** or "**severe**" **hypertension**)

ACC: American College of Cardiology; AHA: American Heart Association; BP: blood pressure; ESC: European Society of Cardiology; SBP/DBP: systolic/diastolic blood pressure.

Prevalence of hypertension

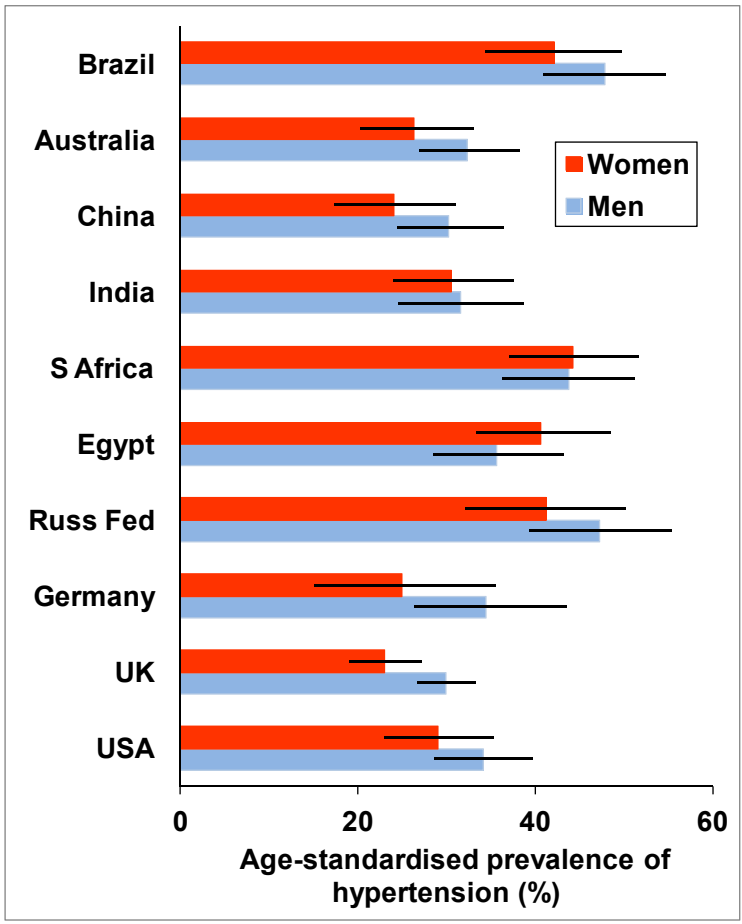
Global prevalence of hypertension

Figure 1 shows the age-standardised prevalence of hypertension in adults for the year 2019 in selected countries around the world, from a global survey conducted by the Non-Communicable Diseases (NCD) Risk Factor Collaboration under the auspices of the World Health Organization (WHO) [4]. For this study, hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, or receipt of antihypertensive medication. There is no doubt that the prevalence of hypertension is high worldwide: the proportions of people with hypertension in the countries highlighted in Figure 1 range from about 1 in 4 individuals to about 2 in 5. This survey also found that the number of people with hypertension worldwide approximately doubled between 1990 and 2019, from 648 million people to 1.3 billion. This doubling increased in the absence of a marked change in the age-standardised prevalence of hypertension, in the setting of a global population that is increasing in number and increasing in average age. Another global survey estimated the prevalence of hypertension to be 31.1% in 2010, with a higher prevalence in low or middle income countries (31.5%) compared with high-income countries (28.5%) [5].

The problem of unawareness of hypertension

Unawareness of hypertension is also common and Figure 2 illustrates the magnitude of the problem in the same selection of countries from the global hypertension survey [4]. Among these countries, the proportion of patients unaware of/with undiagnosed hypertension was lowest in the United States of America (USA) and the Russian Federation (especially for women), where about 80% of people with hypertension were aware of having the condition. The proportion with diagnosed hypertension was lower in other countries, including some relatively high-income countries like the UK and Australia, where about 60% of the total population with hypertension were aware of having it. Rates of awareness of hypertension had increased from the 1990s to the

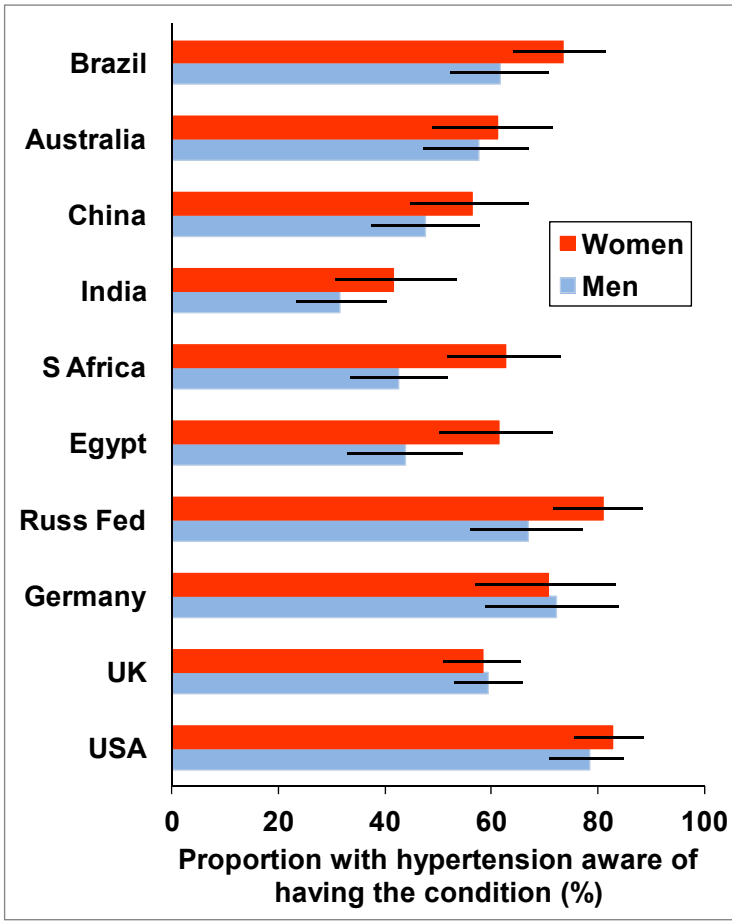
Figure 1 Age-standardised prevalence of hypertension in men and women aged 30–79 years in selected countries [4].



Bars are 95% credible intervals. Drawn from data presented by the Non-Communicable Diseases (NCD) Risk Factor Collaboration [4]. Russ Fed: Russian Federation; S Africa: South Africa; UK: United Kingdom; USA: United States of America.

early 2000s, but progress has plateaued more recently, with continuing marked variation in the rates of awareness of hypertension between countries [6].

Figure 2 High prevalence of unawareness of hypertension in selected countries from a global survey of hypertension in adults [4].



Bars are 95% credible intervals. Drawn from data presented by the Non-Communicable Diseases (NCD) Risk Factor Collaboration [4]. Russ Fed: Russian Federation; S Africa: South Africa; UK: United Kingdom; USA: United States of America.

High prevalence of hypertension conditions associated with insulin resistance

Some populations have an especially high prevalence of hypertension. For example, high BP is one of the five criteria for diagnosing metabolic syndrome, so it is perhaps unsurprising that the prevalence of hypertension approaches 80% among this population [7]. Type 2 diabetes, which accounts for about nine people in ten with diabetes, is also associated patho-physiologically with insulin resistance, metabolic syndrome and associated cardiovascular risk factors. Accordingly, hypertension is common among people with diabetes, as shown by data from the USA, where 69% of people with diabetes have hypertension [8]. Similarly, a study in Jordan found that 75% of people with diabetes also have hypertension, with a 1-year incidence of hypertension of 26% among people with diabetes who were normotensive at baseline [9]. Other cross-sectional studies found that 60% of 378 people with type 2 diabetes at a tertiary hospital in Ethiopia also had hypertension [10], and that 60% of 3,092 people with diabetes in India had uncontrolled hypertension [11]. A systematic review of observational studies demonstrated that the prevalence of hypertension in diabetes is as high as 80–90% in some countries [12]. The presence of obesity, also associated closely with insulin resistance, metabolic syndrome and type 2 diabetes, almost doubles the likelihood of having hypertension compared with people of normal weight [13].

Epidemiological transitions in the developing world

Historically, infectious diseases have been a leading cause of morbidity and mortality in the developing world. Advances in recent decades in the management of infectious and deficiency diseases (particularly HIV in sub-Saharan Africa) and general improvements in healthcare provision are driving an epidemiological shift from infectious diseases to non-communicable diseases (NCDs) as the predominant burden of illness in these countries [14–16]. The underlying reasons for the epidemiological shift are complex, and include a greater likelihood of living to an age when NCDs may develop, access to high-energy diets, increased use of alcohol and tobacco, and increased sedentariness secondary to shifts of the

population from a rural to an urban setting [14–17]. As an example, deaths from NCDs have risen by 31% during the last 25 years in India, with hypertension the main driving force for the development of cardiovascular diseases [18]. The developing world already bears a disproportionate burden of hypertension, and the continued emergence of hypertension, diabetes, cardiovascular disease and other NCDs will provide an increasing challenge to healthcare systems there.

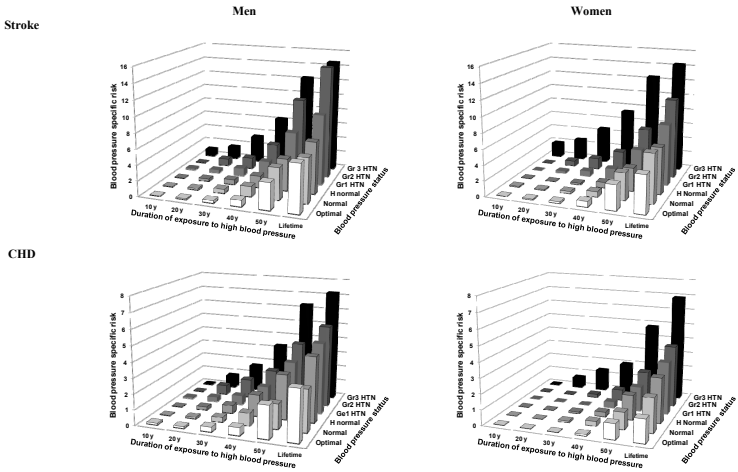
Long-term consequences of hypertension

Epidemiology of hypertension and adverse cardiovascular outcomes

Epidemiological studies have proven beyond doubt that high BP is associated with adverse cardiovascular outcomes [19]. A study in more than one million adults from 61 observational cohorts determined that each increase in SBP of 20 mmHg, or in DBP of 10 mmHg, was associated with a doubling of the risk of death from ischaemic heart disease and more than doubling of the risk of stroke death, for an individual in middle age (40–69 years) [20]. Another large study in 107,737 individuals participating in observational cohorts in Japan calculated the lifetime risk of death from coronary heart disease or stroke that was attributable to hypertension [21]. The lifetime risks of these adverse outcomes for an individual aged 35 years increased with increasing categories of BP both in men and women, with the excess risk increasing sharply at longer durations of exposure to high BP (Figure 3). This study is important because it stresses the long-term nature of the vascular risk associated with hypertension: for example, the BP-specific risk estimate for stroke death associated with Grade 2 hypertension (160–179/100–109 mmHg, see Table 1) increased from 0.0 at 10 years to 14.5 for men and 10.3 for women across a lifetime.

Calculation of the population-attributable risk (PAR) for a given risk factor allows an estimation of the proportion of cases of a given outcome that were due to the effects of that risk factor. A study in 1,244 community-dwelling subjects in Spain, of whom 35% had hypertension, calculated

Figure 3 Risks of death from stroke or coronary heart disease (CHD) associated with different levels of blood pressure at 35 years of age [21].



"GR1 HTN" refers to Grade 1 hypertension (see Table 1 for other definitions). "H Normal" = "high normal". Drawn from data presented in reference [21].

the PAR for cardiovascular disease associated with hypertension [22]. The 13-year risks (95% confidence interval [CI]) of cardiovascular disease associated with hypertension were 1.89 (1.63 to 2.18) in men and 1.71 (1.4 to 2.09) in women, with PARs of 33.1% and 33.8%, respectively.

High BP is associated with a number of other adverse clinical outcomes besides coronary heart disease and stroke, as described below.

Heart failure: The relationship between BP and outcomes in people with heart failure is complex, higher SBP is associated with improved prognosis once heart failure is established. However, hypertension has been described as the predominant risk factor for future heart failure [23]. Conversely, most people with heart failure have a history of hypertension [24]. The observational study described above demonstrated a PAR for heart failure associated with hypertension of 57% in men and 69% in women [22]. Data from the Framingham Heart Study in the USA found that hypertension accounted for 39% of cases of heart failure in men and 59% of cases in women [25].

Chronic kidney disease (CKD): Renal dysfunction is usually associated with the development of hypertension [26]. Elevated SBP

was the strongest risk factor for renal death among those studied in a meta-analysis of 35 studies incorporating >500,000 subjects; each increase in SBP of 19 mmHg was associated with an increase in the risk of renal death of >80% [27]. A systematic review of studies that enrolled a total of more than 2 million subjects found that hypertension (SBP >140 mmHg vs <120 mmHg) was associated with a relative risk of incident CKD or end-stage renal disease (ESRD) of 1.56 (95% CI, 1.39 to 1.75) in women and 2.06 (95% CI, 1.64 to 2.60) in men [28]. Analysis of a health insurance population in the USA found that the risk of ESRD increased in line with increasing severity of hypertension, but that even modest increases in BP to 120–129/80–84 mmHg (vs <120/80 mmHg) were associated with a significantly increased risk of ESRD [29].

Cognitive decline: The results of several observational studies have confirmed associations between arterial hypertension, especially in midlife, and cognitive impairment or dementia later in life [30–32]. Moreover, the results of the CARDIA study (Coronary Artery Risk Development in Young Adults), a community-based cohort of young individuals followed over 30 years, suggested that not only hypertension but also higher cumulative systolic BP levels were associated with lower cognitive performance in the executive, memory and global domains, and higher cumulative diastolic BP was associated with lower cognitive performance in the memory domain, in midlife [33]. Notably, the results of meta-analyses of fourteen randomised clinical trials (96,158 participants) have documented that BP lowering with antihypertensive agents, compared with the control group, was associated with a significantly lower risk of incident dementia or cognitive impairment [34].

Other adverse clinical outcomes: Epidemiological studies have demonstrated significant associations between high BP and a range of other adverse clinical outcomes, including cardiomyopathy, atrial fibrillation, erectile dysfunction, and peripheral arterial disease [19].

Proven outcome benefits from antihypertensive therapy

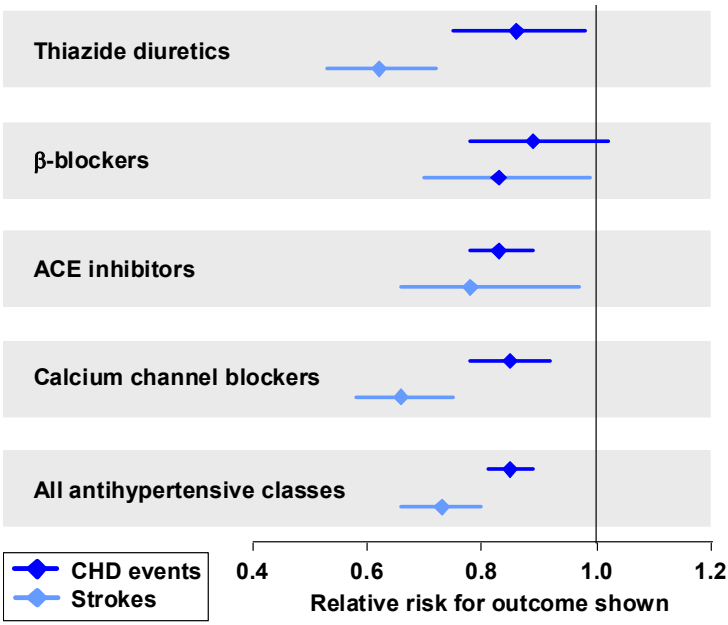
Randomised evaluations of antihypertensive therapies have been conducted, and these provide another source of evidence relating to the association between high BP and adverse clinical outcomes. Many clinical trials of this type have been conducted, and this section will consider large systematic reviews and meta-analyses in this area. In general, the significant reductions in the risk of adverse cardiovascular outcomes within pooled randomised trial populations was consistent with the magnitude of benefit expected from epidemiological studies of the excess risk of these outcomes associated with high BP, and the main results of three principal meta-analyses are summarised below [35–37].

Law et al demonstrated significant benefit for antihypertensive therapy on cardiovascular outcomes (relative risks vs control groups of 0.84 [95% CI, 0.81 to 0.88] for coronary heart disease events and 0.70 [95% CI, 0.65 to 0.76] for stroke) [37]. Importantly, similar benefits were seen whether or not patients had a history of cardiovascular disease. This analysis also demonstrated that the effects of different classes of antihypertensive therapies on coronary heart disease outcomes was broadly similar, apart from a modest additional efficacy of calcium channel blockers for preventing strokes (Figure 4).

Bundy et al compared outcomes between randomised treatment groups that achieved different levels of SBP, compared with an achievement of 120–124 mmHg [35]. The hazard ratios (95% CI) for major cardiovascular disease events in this group were 0.71 (0.60 to 0.83) versus mean achieved SBP of 130–134 mmHg, 0.58 (0.48 to 0.72) versus mean achieved SBP of 140–144 mmHg, 0.46 (0.34 to 0.63) versus mean achieved SBP of 150–154 mmHg, and 0.36 (0.26 to 0.51) versus mean achieved SBP of 160 mmHg. Comparable reductions in the risk of all-cause mortality were seen that also increased in line with the differences in achieved SBP.

In the meta-analysis from **Ettehad et al** [36], each 10 mmHg reduction in SBP associated with antihypertensive therapy was associated with reduced relative risks (95% CI) of coronary heart disease

Figure 4 Effects of different classes of antihypertensive agents on clinical cardiovascular outcomes from a large meta-analysis of randomised trials in populations with hypertension [37].



Relative risks are for antihypertensive drug classes versus placebo or control. Excludes trials of β-blockers in patients with a history of coronary heart disease (CHD). Angiotensin receptor blockers are omitted as only 4 trials were included in the original meta-analysis, with 378 CHD events (relative risk 0.86 [95% CI, 0.53 to 1.40]) and 0 stroke events.
Drawn from data presented in reference [37]. ACE: angiotensin converting enzyme.

(0.83 [0.78 to 0.88]), stroke (0.73 [0.68 to 0.77]), heart failure (0.72 [0.67 to 0.78]) and all-cause mortality (0.87 [0.84 to 0.91]) [36].

Thus, evidence from randomised trials of BP lowering agents adds to the evidence from observational studies on the relationship between high BP and an increased risk of adverse cardiovascular outcomes.

Conclusions

Hypertension is a common condition, occurring in about one-quarter of individuals worldwide, with a markedly higher prevalence in some countries. The severe burden of morbidity and premature mortality imposed by high BP is proven beyond doubt, and a large database of clinical trials and meta-analyses has confirmed that reducing BP delivers statistically and clinically significant reductions in the risk of cardiovascular events. As a result, pharmacological antihypertensive therapy is firmly established as evidence-based care for hypertension. The following chapter considers the place of each class of currently available antihypertensive agents in the management of hypertension.

References

1 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.

2 Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115. https://doi.org/10.1161/hyp.0000000000000065.

3 National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management: NICE guideline [NG136]. 2019. Available from: https://www.nice.org.uk/guidance/ng136. Accessed May 2022.

4 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398:957–80. https://doi.org/10.1016/s0140-6736(21)01330-1.

5 Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16:223–37. https://doi.org/10.1038/s41581-019-0244-2.

6 NCD Risk Factor Collaboration (NCD-RisC). Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. Lancet. 2019;394:639–51. https://doi.org/10.1016/s0140-6736(19)31145-6.

7 Katsimardou A, Imprialos K, Stavropoulos K, Sachinidis A, Doumas M, Athyros V. Hypertension in metabolic syndrome: novel insights. Curr Hypertens Rev. 2020;16:12–8. https://doi.org/10.2174/1573402115666190415161813.

8 Center for Disease Control and Prevention (CDC). The facts, stats, and impacts of diabetes. 2022. Available from: https://www.cdc.gov/diabetes/library/spotlights/diabetes-facts-stats.html Accessed June 2022.

9 Salameh AB, Hyassat D, Suhail A, Makahleh Z, Khader Y, El-Khateeb M, et al. The prevalence of hypertension and its progression among patients with type 2 diabetes in Jordan. Ann Med Surg (Lond). 2022;73:103162. https://doi.org/10.1016/j.amsu.2021.103162.

10 Akalu Y, Belsti Y. Hypertension and its associated factors among type 2 diabetes mellitus patients at Debre Tabor General Hospital, Northwest Ethiopia. Diabetes Metab Syndr Obes. 2020;13:1621–31. https://doi.org/10.2147/dmso.S254537.
11 Sreedevi A, Krishnapillai V, Menon VB, Mathew MM, Nair RR, Pillai GS, et al. Uncontrolled blood pressure and associated factors among persons with diabetes: a community based study from Kerala, India. Front Public Health. 2021;9:778235. https://doi.org/10.3389/fpubh.2021.778235.
12 Colosia AD, Palencia R, Khan S. Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. Diabetes Metab Syndr Obes. 2013;6:327–38. https://doi.org/10.2147/dmso.S51325.
13 Aronow WS. Association of obesity with hypertension. Ann Transl Med. 2017;5:350. https://doi.org/10.21037/atm.2017.06.69.
14 Atiim GA, Elliott SJ. The global epidemiologic transition: noncommunicable diseases and emerging health risk of allergic disease in Sub-Saharan Africa. Health Educ Behav. 2016;43:37s–55s. https://doi.org/10.1177/1090198115606918.
15 Ciccacci F, Orlando S, Majid N, Marazzi C. Epidemiological transition and double burden of diseases in low-income countries: the case of Mozambique. Pan Afr Med J. 2020;37:49. https://doi.org/10.11604/pamj.2020.37.49.23310.
16 Mendoza W, Miranda JJ. Global shifts in cardiovascular disease, the epidemiologic transition, and other contributing factors: toward a new practice of global health cardiology. Cardiol Clin. 2017;35:1–12. https://doi.org/10.1016/j.ccl.2016.08.004.
17 Juma K JP, Shumba C, Otieno P, Asiki G. Non-communicable diseases and urbanization in African cities: a narrative review. In: Public Health in Developing Countries: Challenges and Opportunities. Anugwom EE and Awofeso Ns: Anugwom EE and Awofeso N. Published by: Intech Open Publishing. 2019.
18 Gupta R, Xavier D. Hypertension: the most important non communicable disease risk factor in India. Indian Heart J. 2018;70:565–72. https://doi.org/10.1016/j.ihj.2018.02.003.
19 Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. Hypertension. 2020;75:285-92. https://doi.org/10.1161/hypertensionaha.119.14240.
20 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–13. https://doi.org/10.1016/s0140-6736(02)11911-8.
21 Satoh M, Ohkubo T, Asayama K, Murakami Y, Sugiyama D, Yamada M, et al. Lifetime risk of stroke and coronary heart disease deaths according to blood pressure level: EPOCH-JAPAN (Evidence for Cardiovascular Prevention from Observational Cohorts in Japan). Hypertension. 2019;73:52–9. https://doi.org/10.1161/hypertensionaha.118.11635.
22 Ruiz-Hernandez A, Tellez-Plaza M, Dominguez-Lucas A, Pichler G, Martin-Escudero JC, Martinez-Garcia F, et al. Population attributable risk for cardiovascular disease associated with hypertension: results from the Hortega follow-up study. Journal of Hypertension. 2018;36:e27. https://doi.org/10.1097/01.hjh.0000539035.92296.a3.
23 Tackling G, Borhade MB. Hypertensive heart disease. In: StatPearls. Published by: Treasure Island (FL): StatPearls Publishing. 2021.
24 Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. JACC Heart Fail. 2017;5:543–51. https://doi.org/10.1016/j.jchf.2017.04.012.
25 Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996;275:1557–62. https://doi.org/10.1001/jama.1996.03530440037034.
26 Taddei S, Bruno RM, Masi S, Solini A. Epidemiology and pathophysiology of hypertension. In: The ESC Textbook of Cardiovascular Medicine (online edition). Third edn. Camm AJ, Lüscher TF, Maurer G, Serruys PW (eds). Oxford; ESC Family 2018 [cited 27 July 2022]. Available from: https://academic.oup.com/esc/book/35489/chapter-abstract/312428514?redirectedFrom=fulltext.

27 O'Seaghdha CM, Perkovic V, Lam TH, McGinn S, Barzi F, Gu DF, et al. Blood pressure is a major risk factor for renal death: an analysis of 560 352 participants from the Asia-Pacific region. Hypertension. 2009;54:509–15. https://doi.org/10.1161/hypertensionaha.108.128413.
28 Weldegiorgis M, Woodward M. The impact of hypertension on chronic kidney disease and end-stage renal disease is greater in men than women: a systematic review and meta-analysis. BMC Nephrol. 2020;21:506. https://doi.org/10.1186/s12882-020-02151-7.
29 Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med. 2005;165:923–8. https://doi.org/10.1001/archinte.165.8.923.
30 Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005;64:277–81. https://doi.org/10.1212/01.Wnl.0000149519.47454.F2.
31 Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000;21:49–55. https://doi.org/10.1016/s0197-4580(00)00096-8.
32 Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-year longitudinal study of blood pressure and dementia. Lancet. 1996;347:1141–5. https://doi.org/10.1016/s0140-6736(96)90608-x.
33 Mahinrad S, Kurian S, Garner CR, Sedaghat S, Nemeth AJ, Moscufo N, et al. Cumulative blood pressure exposure during young adulthood and mobility and cognitive function in midlife. Circulation. 2020;141:712–24. https://doi.org/10.1161/circulationaha.119.042502.
34 Hughes D, Judge C, Murphy R, Loughlin E, Costello M, Whiteley W, et al. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. JAMA. 2020;323:1934–44. https://doi.org/10.1001/jama.2020.4249.
35 Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol. 2017;2:775–81. https://doi.org/10.1001/jamacardio.2017.1421.
36 Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957–67. https://doi.org/10.1016/s0140-6736(15)01225-8.
37 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665. https://doi.org/10.1136/bmj.b1665.