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EARLY-ONSET HYPERTENSION

Clinical characteristics and relation to adverse outcomes

Karri Suvila

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SARJA – SER. D OSA – TOM. 1567 | MEDICA – ODONTOLOGICA | TURKU 2021

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To my loved ones

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ABSTRACT

Established hypertension is a well-known risk factor for cardiovascular disease and dementia. However, limited evidence exists on the relation between the age of hypertension onset and adverse events. The aim of this thesis was to study the impact of early-onset hypertension on end-organ damage and cognitive function in midlife. Additional aims were to examine risk factors for early-onset hypertension and the feasibility of different methods for detecting hypertension onset age.

This thesis is based on the Coronary Artery Risk Development in Young Adults (CARDIA), which is a biracial prospective follow-up study. The CARDIA study was initiated in 1985–1986 and included a sample of 5115 American young adults. The study participants underwent up to 30 years of follow-up with regularly conducted follow-up exams. We also included a separate study sample from the Health 2000 survey, a population-based study carried out in 2000–2001 that examined 8028 Finns. Both study samples collected either objective or self-reported data on the participants' age of hypertension onset as well as an assessment of adverse outcomes.

In the CARDIA study sample, we observed that an early age of hypertension onset was most robustly associated with echocardiographic left ventricular hypertrophy (LVH), diastolic dysfunction, and coronary calcification in midlife. Additionally, early-onset hypertension in these individuals was related to midlife cognitive impairment. In contrast, late-onset hypertension was not associated with these adverse outcomes. Self-reported hypertension onset age was not related to electrocardiographic LVH in the Health 2000 study sample. However, self-reported early-onset hypertension was associated with end-organ damage in the CARDIA participants. We also identified African American ethnicity, diabetes, and obesity as the most potent correlates of early-onset hypertension.

In conclusion, early-onset hypertension, but not late-onset hypertension, is associated with having end-organ damage by midlife. Our findings demonstrate the importance of assessing the age of hypertension onset, even by patients' self-report, in order to feasibly assess the lifetime burden of hypertension and to improve risk stratification of individuals with hypertension in clinical practice.

KEYWORDS: hypertension, age of onset, risk factors, end-organ damage, cognitive function, epidemiology

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Verenpainetauti on merkittävä dementian sekä sydän- ja verisuonisairauksien riskitekijä. Aiempia tutkimuksia verenpainetaudin puhkeamisiän merkityksestä haittatapahtumien kehittymiselle on kuitenkin vähän. Tämän väitöskirjatutkimuksen tavoitteena oli tutkia varhain puhkeavan verenpainetaudin vaikutusta pääte-elinvaurioihin sekä kognitiiviseen suorituskykyyn keski-iässä. Lisäksi selvitimme varhain puhkeavalle verenpainetaudille altistavia tekijöitä sekä eri menetelmien soveltuvuutta verenpainetaudin puhkeamisiän arvioimiseksi.

Tutkimusaineistona käytettiin ensisijaisesti yhdysvaltalaista prospektiivista CARDIA-seurantatutkimusta, johon osallistui 5115 nuorta amerikkalaista miestä ja naista vuosina 1985–1986. Tutkimushenkilöt ovat osallistuneet 30 vuoden ajan säännöllisesti suoritettuihin seurantatutkimuksiin. Toinen tutkimusväestö koostui 8028 väestörekisteristä satunnaisotannalla valitusta suomalaisesta, jotka osallistuivat Terveys 2000-tutkimukseen vuosina 2000–2001. Molempien tutkimusotoksien osallistujilta määritettiin verenpainetaudin puhkeamisikä joko objektiivisesti tai itseilmoitettuna sekä mitattiin verenpainetaudin pääte-elintapahtumia.

Ensimmäisessä tutkimusaineistossa varhaisella iällä puhjennut verenpainetauti oli voimakkaimmin yhteydessä vasemman kammion hypertrofiaan, sydämen diastoliseen toimintahäiriöön sekä sepelvaltimoiden kalkkeutumiseen keski-iässä. Varhainen verenpainetauti altisti myös kognitiivisten toimintojen heikentymiselle. Myöhäinen verenpainetauti ei ollut yhteydessä vastaaviin haittatapahtumiin. Myös itseilmoitettu varhain puhjennut verenpainetauti oli yhteydessä pääte-elinvaurioihin ensimmäisessä tutkimusotoksessa, mutta ei elektrokardiografisesti määritettyyn vasemman kammion hypertrofiaan toisessa tutkimusotoksessa. Afroamerikkalainen syntyperä, diabetes ja ylipaino olivat riskitekijöitä varhaiselle verenpainetaudille.

Löydökset osoittavat, että erityisesti varhain puhkeava verenpainetauti altistaa verenpainetaudin pääte-elinvaurioille jo keski-iässä. Verenpainetaudin alkamisiän määrittäminen osana verenpainetaudin hoitoa voisi edesauttaa lääkäreitä huomioimaan korkean verenpaineen elinikäistä vaikutusta elimistöön ja mahdollisesti edistää näiden potilaiden tulevien haittatapahtumien ennaltaehkäisyä.

AVAINSANAT: verenpainetauti, puhkeamisikä, riskitekijät, pääte-elinvaurio, kognitiivinen suorituskyky, epidemiologia

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Abbreviations

ARIC	Atherosclerosis Risk in Communities
AUC	Area under curve
AWMV	Abnormal white matter volume
BMI	Body mass index
BP	Blood pressure
CAC	Coronary artery calcification
CARDIA	Coronary Artery Risk Development in Young Adults
CI	Confidence interval
CIMT	Carotid intima-media thickness
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DSST	Digit Symbol Substitution test
ECG-LVH	Electrocardiographic left ventricular hypertrophy
ECHO-LVH	Echocardiographic left ventricular hypertrophy
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EVA	Early vascular aging
FLAIR	Fluid-attenuated inversion recovery
GMV	Grey matter volume
HDL	High-density lipoprotein
HMOD	Hypertension-mediated organ damage
HR	Hazard ratio
ICV	Intracranial volume
LLM	Lipid-lowering medication
LVDD	Left ventricular diastolic dysfunction
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMI	Left ventricular mass index
MAP	Mean arterial pressure
MOCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging

OR	Odds ratio
PP	Pulse pressure
PWV	Pulse wave velocity
RAAS	Renin-angiotensin-aldosterone system
RAVLT	Rey Auditory Verbal Learning test
RR	Risk ratio
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
TBV	Total brain volume
UACR	Urine albumin-to-creatinine ratio
WMFA	White matter fractional anisotropy
WMV	White matter volume

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Suvila K, McCabe EL, Lehtonen AO, Ebinger JE, Lima JAC, Cheng S, Niiranen TJ. Early Onset Hypertension Is Associated With Hypertensive End-Organ Damage Already by MidLife. *Hypertension*, 2019; 74(8): 305–312.

II Suvila K, McCabe EL, Lima JAC, Aittokallio J, Yano Y, Cheng S, Niiranen TJ. Self-reported Age of Hypertension Onset and Hypertension-Mediated Organ Damage in Middle-Aged Individuals. *American Journal of Hypertension*, 2020; 33(7): 644–651.

III Lehtonen AO*, Suvila K*, Jula AM, Niiranen TJ. Association between self-reported hypertension onset age and electrocardiographic left ventricular hypertrophy. *Journal of Human Hypertension*, 2021; 35(5): 479–482.

IV Suvila K, Lima JAC, Yano Y, Tan ZS, Cheng S, Niiranen TJ. Early but Not Late Onset Hypertension is Related to Midlife Cognitive Function. *Hypertension*, 2021; 77(3): 972–979.

V Suvila K, Lima JAC, Cheng S, Niiranen TJ. Clinical Correlates of Early-Onset Hypertension. *Submitted.*

* Equal contribution

1 Introduction

High blood pressure (BP) remains the most common modifiable risk factor for cardiovascular disease (CVD) morbidity and mortality worldwide. Furthermore, these harmful effects extend beyond CVD as elevated BP also contributes to the development of chronic kidney disease and dementia, while increasing the risk of adverse events (1,2). Therefore, chronically elevated BP, i.e. hypertension, represents a major global public health problem. There are worldwide increasing trends in the number of individuals with high BP, one can speak of a global burden of hypertension (3,4). Over 1 billion people in all parts of the world have been estimated to have high BP which means that over 30% of the world's population would be diagnosed as having hypertension (5,6). On the national level, hypertension represents an even more important threat for public health, as recent data from NCD Risk Factor Collaboration has reported that Finland has the highest prevalence of hypertension of 12 high-income countries (7).

Findings from observational studies have long indicated that hypertension is already evident even in the very early stages of life (8,9). In fact, numerous investigators have examined the relationship between the presence of hypertension during different stages of life and the subsequent risk for various health problems. Hence, the current chronological age of an individual has been established as an important contributing factor for hypertension-related complications. However, to date, little evidence exists on whether hypertension that manifests early in life has a different impact from hypertension originating in late-life. Already in the 1970s, early onset of hypertension was observed among those community residents who consumed drinking water with a higher level of nitrates (10). Surprisingly, there are rather few previous studies that have focused on assessing the role of early-onset hypertension or age of hypertension onset for diagnostic or predictive purposes in individuals with hypertension. More evidence about this topic could have important clinical implications for those younger hypertensive adults in the community, as hypertension can be particularly detrimental in these individuals who still often remain undiagnosed and untreated (11,12).

Chronic diseases call for very different management and treatment approaches when compared to acute health problems. Previous studies have suggested that the

chronicity of hypertension and its effects can be evaluated with a variety of methods, i.e. to elucidate the long-term exposure to high BP (13–15). However, the clinical applicability of these methods has remained unclear and thus accounting for the chronicity of hypertension in screening and treating hypertensive individuals is rarely, if ever, conducted. Prior evidence suggests that age of disease onset impacts on the risk of adverse outcomes in the context of other chronic diseases, such as diabetes and obesity (16–18). Findings from these studies have demonstrated that generally an early disease onset predicts a worse disease prognosis in comparison to a late onset. Chronic diseases such as diabetes, obesity and hypertension share similar features regarding their prognostic value with respect to adverse events and treatment strategies in everyday clinical practice. Thus, it is presumable that the onset age of hypertension could likewise become incorporated as a part of an individual's overall risk-assessment. However, the current international hypertension treatment guidelines do not yet recommend assessing the age of onset in the strategy of management of hypertension (19,20). Similarly, the recently updated national Finnish guidelines for high BP care also fail to take into account the hypertension onset age as part of the disease management strategies (21). Clearly, it would be advantageous to gather more evidence on the impact of the hypertension onset age, and particularly early-onset hypertension.

The aim of this thesis was to investigate the relation between early age of hypertension onset and adverse outcomes, in contrast to late hypertension onset age. This study examined the association of early-onset hypertension with hypertension-mediated organ damage (HMOD) and cognitive function in midlife. An additional aim was to study the feasibility of assessing the age of hypertension according to the individual's self-report in contrast to objective measurement methods. Furthermore, this study provides evidence on the clinical correlates of early-onset hypertension. Based on these findings, a framework is presented for incorporating the age of hypertension onset assessment into hypertension management in clinical practice.

2 Review of the Literature

2.1 Age-related changes in blood pressure

2.1.1 Blood pressure tracking over age

BP is a constantly fluctuating physiological measure that depends on the co-operation of various body regulatory systems and stimulus signals. BP refers to the pressure experienced in the large arteries which is applied by the systemic circulating blood volume. A complex BP regulatory system is required to maintain a sufficient and stable BP level to ensure adequate perfusion of human tissues and organs. However, an excessively high BP for long durations is known be harmful for the human body and to cause various health problems. In brief, the vascular anatomy along with various vascular, tissue and neurohumoral factors contribute to the regulation of BP. BP is commonly expressed as two measures: the systolic blood pressure (SBP) which is the highest pressure during one heartbeat, and diastolic blood pressure (DBP) which represents the lowest pressure in-between heartbeats. Moreover, mean arterial pressure (MAP) is calculated as the mean between SBP and DBP, whereas pulse pressure (PP) stands for the difference between SBP and DBP.

BP is known to be highly age-dependent as BP tends to rise with age (22,23). In fact, the overall lifetime risk of developing hypertension has been reported to be as high as 90% (24). The BP progression by age follows similar patterns in the general population. Common trends for normal lifetime BP progression may be distinguished at a population level; these have been well-documented (25,26). On average, SBP consistently rises over the life course, whereas DBP reaches a peak around middle age after which it gradually declines. This difference is caused by the decreased elasticity and increased stiffness of the large arteries, leading to increased BP during the systole, and decreased BP during the diastole (27). PP tends to increase with age in a similar manner to SBP but with an accelerating velocity later in life, whereas MAP reaches a plateau level and often decreases after midlife. In late-life, SBP and DBP begin to decrease more than a decade prior to death, with the steepest decrease being observed in the last 2 years of life (28). Moreover, the steepest yearly decreases have been seen in individuals with hypertension, late-life weight loss, heart failure and dementia. The BP progression patterns also vary by sex, as the overall

mean BP levels tend to be higher in men (26,29). Nevertheless, the overall BP trends over age are relatively in parallel in men and women and the sex-specific differences attenuate with advancing age (Figure 1). However, a recent study has suggested that BP trajectories vary markedly by sex over the entire life course (30). In that study, BP was demonstrated to increase more steeply with age in women than in men, starting already in the early stages of life. The age- and sex-related BP trends share similar patterns globally, as the tendency for BP to increase by age has been observed in citizens from virtually all nations (3,4).

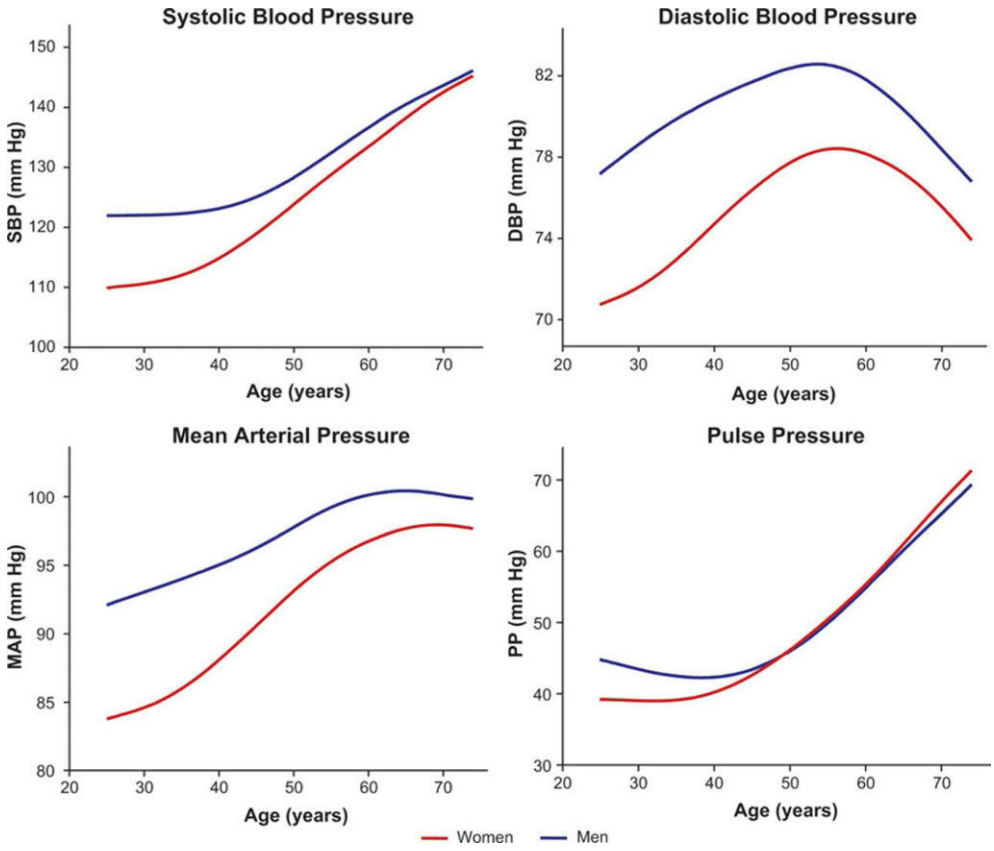

Figure 1. Blood pressure measures with increasing age in men and women. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. Reproduced from Hypertension (Cheng et al., 2012) with permission of Wolters Kluwer Health, Inc.

Several longitudinal studies in different population cohorts have conducted BP tracking throughout the life course. Elevated BP already from childhood has been demonstrated to correlate with the measured BP values in adults (9,31–33). A meta-analysis including data from 50 cohort studies reported average correlation

coefficients for BP tracking from childhood to adulthood of 0.38 for SBP and 0.28 for DBP (34). Similar findings were reported in another meta-analysis examining 29 studies (35). Additionally, sex, baseline age, and follow-up length were identified as significant predictors of BP tracking. Thus, these BP patterns appear to extend from adulthood to late-life (22,36). Previous findings suggest that repeated BP measurements already in the early stages of life are beneficial in predicting elevated BP levels later in life. Despite the common patterns on BP progression at the population level, population heterogeneity and between-individual related risk factors have been related to a shift in BP trajectories.

2.1.2 Primary vs. secondary hypertension

Hypertension is defined as persistently raised BP based on currently approved BP measurement methods and diagnostic thresholds. Hypertension is generally further classified as either primary or secondary hypertension based on the disease etiology. Primary hypertension, also referred to as essential hypertension, is defined as high BP in which secondary causes are not present; this is by far the more common form of hypertension. In fact, primary hypertension has been estimated to account for at least 90% of all hypertension cases (37–39). For decades now, primary hypertension has been suggested to originate already from early childhood (8). The development of primary hypertension is usually a result of multiple causes including genetic and lifestyle factors. For instance, important etiological factors include obesity, unsatisfactory diet, and a sedentary lifestyle (37). Individuals with primary hypertension often experience a clustering of other risk factors for CVD, such as insulin resistance, dyslipidemias, and the metabolic syndrome. Furthermore, primary hypertension has been identified as a heritable trait, which is often assessed by determining the potential parental history of hypertension (40). The pathophysiology of primary hypertension has been related to vascular aging, mediated by endothelial dysfunction and oxidative stress (41). Individuals with primary hypertension also seem to experience a reduced availability of nitric oxide with evidence of vascular remodeling at an earlier age than their normotensive counterparts (42). Other contributing mechanisms include alterations in hormonal mechanisms such as the renin-angiotensin-aldosterone system (RAAS) and in the activity of the autonomic nervous system (43). Over time, established hypertension promotes the development of various types of HMODs, gradually shifting from asymptomatic to symptomatic conditions, which finally lead to end-stage diseases and possibly death (44).

Secondary hypertension accounts for approximately 5 to 10% of all hypertensive cases in the community. The most frequent causes of secondary hypertension are primary hyperaldosteronism, renal parenchymal diseases, renal artery stenosis, and obstructive sleep apnea (38,39). Other less common causes include

pheochromocytoma, Cushing's syndrome, thyroid disease and coarctation of the aorta. Heritability studies in children have suggested that secondary hypertension is related to only a few genes, whereas primary hypertension is likely caused by an additive, polygenic effect (45). Secondary hypertension has been reported to be more common among younger individuals, and the current guidelines recommend screening for secondary hypertension causes in individuals with an early age of hypertension onset (19,20). However, one study demonstrated that primary hypertension was still the predominant form of hypertension in children already after 6 years of age (46). In that study, 43% of children aged 0 to 19 years had primary hypertension, with the remaining 57% suffering from secondary hypertension. Compared to children with secondary hypertension, those with primary hypertension were more likely to be older, had a lower prevalence of preterm birth and to have family history of hypertension. Furthermore, the prevalence of secondary hypertension has also been reported to increase with advancing age and with coexisting atherosclerosis (47). A recent meta-analysis investigating 31 studies reported increased odds ratios (OR) of 2.58 (95% CI, 1.93–3.45) for stroke, 1,77 (95% CI, 1.10–2.83) for coronary artery disease and 2.05 (95% CI 1.11–3.78) for heart failure in patients with primary hyperaldosteronism, when compared to patients with primary hypertension (48). Nevertheless, the risk of cardiovascular events varies considerably depending on the secondary cause of hypertension and primary hyperaldosteronism accounts for less than 10% of all secondary hypertension cases (38). Even though the underlying cause of secondary hypertension may be treatable, many of these individuals still carry a high residual lifetime risk of developing hypertension even after treating the diagnosed secondary cause (38,39). However, these previous studies have not distinguished between the onset age of hypertension, and thereby the prevalence of secondary hypertension among individuals with early-onset hypertension is unknown. All in all, irrespective of its etiology, established hypertension calls for medical intervention to prevent hypertensive complications.

2.1.3 Determinants of population blood pressure changes

Increasing population growth and aging populations have resulted in a marked shift of population BP trends, i.e. there is now a continuously increasing global burden of high BP. However, previous evidence suggests that distinct subgroups who share similar patterns of BP trajectories over age may be identified in the general population (49). Besides age and sex, ethnicity and genetic factors are important predictors of hypertension. (50,51). Particularly African American ethnicity and having a family history of hypertension increase the risk for developing hypertension. BP progression patterns also seem to have a genetic predisposition as familial hypertension history has been demonstrated to predict the risk that an individual will have higher BP levels

(52,53). However, lifestyle-related factors account for the majority of the global BP burden. The most important modifiable risk factors for high BP include obesity, smoking, alcohol use, physical inactivity, and an unhealthy diet such as one with an excessive salt intake (50). There are some more disputed contributing factors e.g. other health disorders, sleep quality, stress, environmental hazards, and early life factors such as birth weight. However, the factors predicting population changes in BP trajectories differ somewhat from the overall risk factors for high BP.

Male sex and older age have been demonstrated to predict all BP measures in tracking of BP, whereas female sex seems to merely predict SBP (26,54). A higher resting heart rate has also been associated with all BP tracking measures. Socioeconomic status has likewise been suggested as an independent predictor of BP progression at least in women (55). Similarly, a higher body mass index (BMI) has consistently been shown to predict a higher late-life BP, particularly SBP (26,54,56). Additional predisposing factors related to a shift into the higher BP trajectories in these studies included smoking, dyslipidemia, impaired glucose regulation and decreased kidney function. Chronic kidney disease is a particularly important cause of hypertension among older individuals (57). Similar findings about the BP progression predictors have been reported also among individuals in early adulthood (29). Conversely, individuals categorized in the "normative BP trajectories" subgroup are more likely have a lower BMI in midlife but also a higher birth weight (49,53). Some studies have also suggested that a high level of serum uric acid predicts the progression of late-life high BP (56,58).

Overall, previous findings suggest that distinct determinants related to BP changes throughout the life course can be distinguished from the general population (Table 1). These findings provide tools with which one can identify individuals at high risk for hypertension and further to address the importance of lifestyle interventions in the management of high BP. Nonetheless, the population-based BP determinants seem to explain only a relatively small proportion of the age-related BP patterns at the individual level (49). Therefore, a more individualized approach is called for to predict future high BP.

Table 1. Determinants of blood pressure tracking.

Sex	Smoking
Age	Dyslipidemias
BMI	Impaired glucose regulation
Resting heart rate	Decreased kidney function
Socioeconomic status	Birth weight
High serum uric acid level	Family history of hypertension

2.1.4 Association between arterial stiffness and blood pressure

Arterial stiffening is described as a gradual change in the vascular structure and function which leads to decreased compliance and elasticity of the arteries. This vascular process is highly age-related, as older age itself promotes arterial stiffening and this phenomenon is further modulated by the presence of arteriosclerosis. The pathophysiology and mechanisms related to arterial stiffening are complex and involve several factors such as structural components of the vessel wall, vasoactive mediators, and neurohumoral factors (Figure 2) (59). Arterial stiffness in the large arteries maintains the optimal perfusion of the human organs. However, increased early large artery stiffness leads to a reduced adaptability to cope with the cardiac output, which is observed as increased PP, and ultimately results in a higher number of CVD outcomes (60). Various invasive and non-invasive methods have been previously presented to measure arterial stiffness (61). Surrogate measures such as pulse wave velocity (PWV), changes in pulse wave reflections and PP have been used to evaluate arterial stiffness. PP and aortic PWV gradually increase with advancing age, while the travel time of the reflected pressure wave decreases, which represents the normal vascular aging (62). This form of arterial aging is commonly argued to be the most important pathophysiological mechanism explaining the BP changes occurring in an individual's lifetime. Early vascular aging (EVA) on the other hand represents a pathological process of premature arterial aging, consequently leading to accelerated BP progression patterns (63). However, inconsistent evidence exists on the relationships between the hemodynamic correlates of BP progression over the life course.

Elevated BP in childhood and early adulthood have been demonstrated to predict increased arterial stiffness later in life (64–66). Conversely, arterial stiffness has been shown to independently predict subsequent increases in longitudinal BP patterns (67–69). Moreover, findings from the Framingham Heart Study suggest that it is the forward pressure wave amplitude, rather than wave reflection, which is the predominant hemodynamic correlate of PP over the whole life course and particularly in late-life (70,71). The Framingham Heart Study was initiated already in the 1948 to uncover CVD risk factors, and to this date the still ongoing study has included more than 15 000 individuals from three generations (72). A meta-analysis including 64 studies that assessed the impact of wave reflection changes on BP patterns over age also found that a shift in wave reflection timing did not significantly contribute to age-related BP changes (73). Indeed, the commonly accepted gold standard for assessing arterial stiffness is the measurement of the carotid-femoral PWV. The current ESC/ESH hypertension guidelines also approve measuring PP in elderly individuals as an alternative method (19). The guidelines suggest measured carotid-femoral PWV > 10 m/s or PP in the elderly ≥ 60 mmHg

as a method to detect arterial stiffening. These findings are in line with the previous evidence indicating that PWV is an important CVD risk factor (74). This meta-analysis which examined a total of 17 studies reported a pooled risk ratio (RR) of 2.02 (95% confidence interval (CI), 1.68–2.42) for CVD mortality, and 1.90 (95% CI, 1.61–2.24) for all-cause mortality in individuals with high aortic PWV, compared to those with low aortic PWV.

To sum up, the current evidence proposes a two-way association between hemodynamic determinants, vascular remodeling, and the corresponding BP (75). PWV and PP are likely to explain a major proportion of changes in the life course BP patterns, whereas changes in wave reflection and vascular resistance are believed to act as secondary factors. Prior findings also suggest that the longitudinal trajectories of arterial stiffness, measured as PWV and BP, follow very similar patterns (76,77). However, this relationship seems to fade later in life, at least in men. Nevertheless, current evidence suggests that arterial stiffness and elevated BP interact with each other in a bidirectional manner throughout the individual's lifespan.

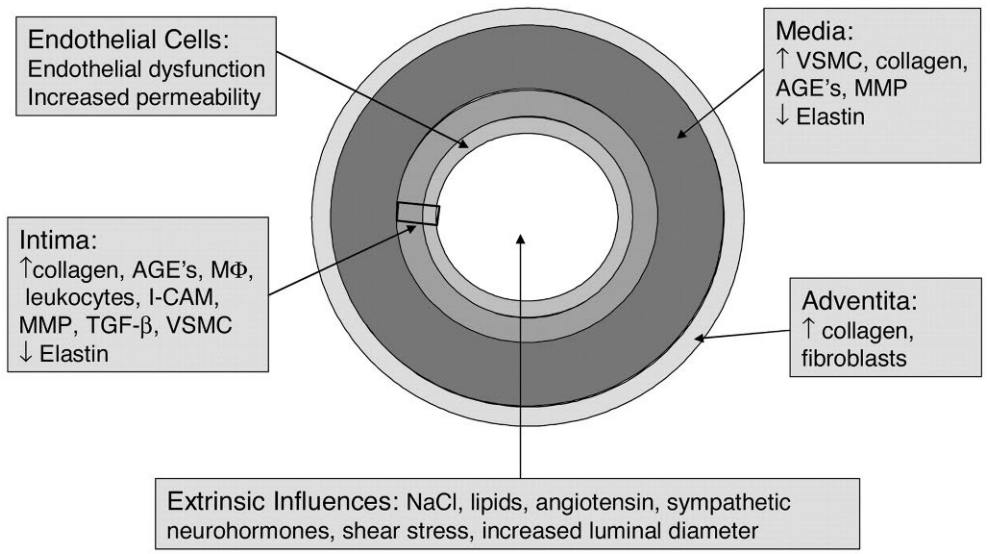

Figure 2. Mechanisms of arterial stiffness. Reproduced from Arteriosclerosis, Thrombosis, and Vascular Biology (Zieman et al., 2005) with permission of Wolters Kluwer Health, Inc.

2.2 Hypertension at any age and risk of adverse outcomes

2.2.1 Association between blood pressure and organ damage

High BP is a generally known risk factor for the development of target organ damage, commonly referred to as hypertension-mediated organ damage (HMOD). Numerous studies to date have examined the relation between elevated BP and HMOD. Different surrogate measures have been used to assess the presence of HMOD. The current hypertension guidelines recommend assessing electrocardiographic left ventricular hypertrophy (ECG-LVH), and albuminuria as the most basic HMOD screening methods (19,20). Other more elaborate methods to determine the presence of HMOD include assessments of echocardiographic left ventricular hypertrophy (ECHO-LVH) and diastolic dysfunction, carotid intima-media thickness (CIMT), coronary artery calcification (CAC) score, PWV, ankle-brachial index, hypertensive retinopathy, brain imaging and cognitive function tests.

A higher BP level has been associated with a higher risk of virtually all HMODs at all ages. Hypertension adversely impacts on the cardiac structure and function, and thus LVH is the most commonly measured marker of altered cardiac structure (78). Elevated BP has been associated with an increased risk of ECHO-LVH, measured as an increased left ventricular mass (LVM) and left ventricular mass index (LVMI) (79). Similar relations have also been reported with ECG-LVH as the outcome measure (80). ECG-LVH has generally been demonstrated as specific but insensitive in detecting anatomic LVH or ECHO-LVH, with moderate correlation between ECG-LVH and ECHO-LVH (81). A meta-analysis concluded that both prehypertension (SBP between 120 and 139 or DBP between 80 and 89 mmHg) and established hypertension (SBP/DBP ≥140/90) were associated with increased LVMI and the prevalence of ECHO-LVH (82). In that study, prehypertension was associated with an OR of 2.09 (95% CI, 1.50–3.00) for concentric LVH and OR of 1.65 (95% CI, 1.40–1.90) for eccentric LVH.

In addition to the cardiac effects, a higher BP in early life has been related to an increased risk of higher CIMT in adulthood (83). Similarly, findings from the Coronary Artery Risk Development in Young Adults (CARDIA) study have reported odds of 1.3 (95% CI, 1.1–1.5) per each 10 mmHg increase in SBP for having an increased CAC score (84). High BP has also been linked to impaired kidney function, measured as the presence of albuminuria or diagnosed kidney disease (85,86), with hypertension being related to an OR of 1.57 (95% CI, 1.17–2.12) for developing new-onset kidney disease in middle-aged individuals. Moreover, a large study investigating over 2.5 million adolescents reported that hypertension was

associated with an adjusted hazard ratio (HR) of 1.98 (95% CI, 1.42–2.77) for having end-stage renal disease in late-life (87).

Overall, it is evident that high BP increases the risk of developing HMOD. Previous evidence also suggests that the relation between elevated BP and HMOD can be determined by using different BP measurement methods and that individuals with established hypertension seem to experience a clustering of several HMODs (88,89). Interestingly, findings from isolated population studies suggest that the development of subclinical CVD could be avoided by lowering the common modern era risk factors, including reducing BP (90). What is more, evidence from clinical trials has demonstrated that previously established LVH and microalbuminuria is reversible with antihypertensive treatment i.e. by lowering BP (91,92). Nevertheless, as established HMOD has been shown to increase the risk of overt CVD by several-fold in individuals with hypertension (93–96), current evidence supports the importance of recognizing high BP at any age as an important CVD risk factor.

2.2.2 Association between blood pressure and cardiovascular outcomes

Along with HMOD, subclinical CVD and cognition, high BP levels have also been associated with increased risk of various hard CVD outcomes. Elevated BP is continuously and causally related to the incidence of serious cardiovascular events, such as heart failure, myocardial infarction, stroke, and sudden death (97,98). A large study revealed a robust trend between increasing BP and the risk for 12 different CVD outcomes (97). In that study, individuals with hypertension had an overall lifetime CVD risk of 63.3% and developed CVD approximately 5 years earlier than individuals without hypertension. In middle-aged individuals, new-onset hypertension was reported to increase the subsequent likelihood of future cardiovascular event considerably in comparison to a non-cardiovascular death (99). A meta-analysis examining over 4 million young adults from 17 studies reported a progressive association between higher BP category and an increased risk of future cardiovascular events (100). In that study, grade 2 hypertension (SBP ≥160 or DBP ≥100 mmHg) was associated with an RR of 3.15 (95% CI, 2.31–4.29) and a risk difference of 4.24 (95% CI, 2.58–6.48 per 1000 person years) for a composite of all cardiovascular events. The results were similar for stroke and coronary heart disease. However, even a much lower BP level may be harmful as an elevated BP starting already around 120/70 mmHg has been shown to increase the future risk of cardiovascular outcomes in all age groups (101,102). Moreover, this detected risk increased exponentially with increasing age and BP level.

High BP is an important risk factor for cardiovascular events throughout an individual's lifetime, although increasing chronological age also increases the risk

for CVD outcomes and modifies the relationship between BP and CVD (103). Data from 1.3 million adults have indicated that both SBP and DBP independently predict cardiovascular outcomes; here systolic hypertension was related to a standardized HR of 1.18 (95% CI, 1.17–1.18) and diastolic hypertension to a standardized HR of 1.06 (95% CI, 1.06–1.07) for having a myocardial infarction or stroke (104). Nonetheless, this association with CVD also differed depending on the BP measure. Current evidence suggests that the best BP measure to predict coronary heart disease shifts gradually from DBP to SBP and eventually to PP with advancing age (105). A number of studies have also reported a J-curve shaped relationship between BP and CVD outcomes (104,106). For instance, in patients with stable coronary artery disease, an SBP under 120 mmHg was associated with an increased HR of 1.56 (95% CI, 1.36–1.81) for a composite CVD outcome (107). The corresponding observed HR for DBP under 60 mmHg in that study was 2.01 (95%, 1.50–2.70). On the other hand, every 10 mmHg reduction in SBP among hypertensive patients has been shown to reduce the risk for CVD events and all-cause mortality (108). All in all, data from epidemiological studies have suggested lower BP thresholds for hypertension and lower BP treatment goals for a long time, whereas the official hypertension guidelines have only recently adopted even lower target BP levels (20). Nonetheless, these findings together suggest that both too low DBP and excessively high DBP increase the risk for CVD events and thus highlight the importance of maintaining the optimal BP level throughout the individual's lifetime.

2.2.3 Association between blood pressure and cognition

Hypertension not only damages peripheral organs, but brain injuries have also been distinguished as an end-organ damage. In fact, BP has been related not only to impaired cognitive function, but also to structural brain changes and development of subsequent dementia (109–111). Cognitive function is commonly assessed with various neuropsychological tests (112–115), and a number of studies have assessed the relationship between hypertension and cognition (116,117). However, aging also gradually harms the brain and leads to similar cerebral changes. Therefore it is evident that age itself is one of the most important risk factors for cognitive decline and dementia (118,119). Consequently, a highly age-dependent relationship has been demonstrated between BP and cognition, as the risk for altered cognitive function also increases with advancing age, irrespective of the presence of hypertension (120,121). Conflicting evidence exists on the relationships between BP, age, and cognition as the findings have remained somewhat inconclusive. Nevertheless, it is crucial to specify the current age at the time when BP was measured, and cognitive function assessed. There is moderately strong evidence indicating that high BP in midlife is associated with impaired cognitive function in late-life (122,123).

Additionally, some studies have also suggested that elevated BP present already in the young adulthood would lead to poorer cognitive function already by midlife (124,125). In fact, a meta-analysis by Ou et al. including data from 136 studies concluded that the association between BP and cognition was stronger with high BP in midlife than in late-life (126). In that study, midlife hypertension was associated with an increased RR of 1.55 (95% CI, 1.19–2.03) for worse global cognitive function. In the light of the previous studies, even a reversed association has been suggested, as individuals with a better cognitive performance in early life have been demonstrated to be less likely to develop hypertension later in life (127). This raises questions about the causal relationship between BP and cognition, although there is convincing evidence that BP is the causative factor for a deterioration in cognitive function (128).

Over time, elevated BP also causes damage to the brain, leading to structural and functional changes. The brain structure is often evaluated by using brain imaging techniques, such as cerebral magnetic resonance imaging (MRI). All in all, while there is more evidence on the relationship between BP and age with cognitive capacity and dementia, less evidence has accumulated considering the structural brain changes as the outcome measure. High BP in midlife has been related to smaller brain volumes and increased white matter hyperintensity volumes later in life (129). In addition to white matter alterations, some studies have identified high BP as a risk factor also for cerebral microbleeds (130). Cerebral microbleeds are hypothesized to represent an early imaging biomarker for hemorrhagic brain lesions which in turn have been associated with cognitive decline and dementia (131). What is more, most previous studies involving middle-aged individuals have reported merely worse performance in cognitive tests, even though findings from the Framingham Heart Study identified BP-related brain changes already among young adults (111). However, considering the high age-dependency of the cognition measures, no definite data yet exists about the correlation between the functional and structural brain alterations.

Results from a 15-year longitudinal study published already in 1996 indicated that previously measured high BP levels increased the risk of dementia later in life (110). Since then, numerous studies have assessed the relation between BP and dementia. Moderately strong evidence suggests that high BP in midlife is associated with the development of dementia in late-life (132). Less convincing evidence supports the assumption that high BP present not until later in life is related to clinical dementia (133,134). The meta-analysis by Out et al. reported that hypertension in midlife was related to an increased RR of 1.20 (95% CI, 1.06–1.35) for having dementia (126). Increasing SBP was observed to linearly increase the risk of all-cause dementia. In contrast, a U-shaped relationship was observed between DBP and Alzheimer's disease, implying that a DBP value between 90 and 100 mmHg would

be the optimal BP level in the elderly. However, it has also been reported that low BP, particularly in late-life, is related to the risk of having dementia (135). Patients with dementia also tend to have lower BP levels compared to those without dementia, and the decline in BP is apparent already a few years prior to the dementia diagnosis (136). Researchers have hypothesized that the new-onset hypertensive BP levels detected in late-life might merely represent a physiological adaptation to ensure enough cerebral perfusion. Therefore, the optimal BP levels during different time points in life that are required to preserve cognition have remained unknown. All in all, most previous studies have measured BP at a single time-point either prior to or simultaneously with the outcome assessment. It is evident that longitudinal measures are necessary if one wishes to clarify the impact of lifetime BP as a predictor of cognition.

2.3 Longitudinal blood pressure patterns and risk of adverse outcomes

2.3.1 Measuring long-term exposure to high blood pressure

Even though BP in general has been established as a risk factor for adverse events, less evidence exists on the impact of long-term BP exposure on hazardous effects. In recent years, several studies have suggested that the use of longitudinal BP data provides incremental prognostic value over single-occasion BP measurements at various time-points. These studies have utilized different methods to quantify the long-term lifetime exposure to high BP. Lauer et al. introduced a method already in 1991 to calculate the mean SBP from all collected BP measurements over a 30-year time-period to examine how it related to future LVM (13). This method to compute the average BP over any time period has thereafter been commonly referred as time-averaged BP. Antecedent BP, as in the average BP measured before a study baseline, represents virtually the same phenomenon as time-averaged BP. Since then, some investigators have devised another method to assess the cumulative exposure to high BP over time, described as the cumulative BP (14). Similarly to time-averaged BP, the average BP over time is calculated to determine the cumulative BP, while simultaneously considering the exposure time between BP measurements. The most commonly used formula to compute cumulative BP in follow-up studies has been presented as: $[(BP^1 + BP^2)/2 \times years^{1\text{-}2}] + [(BP^2 + BP^3)/2 \times years^{2\text{-}3}] + [(BP^3 + BP^n)/2 \times years^{3\text{-}n}]$ where BP^1, BP^2, BP^3 and BP^n indicate measured BP at each examination until examination n, and where years1-2, years2-3, and years3-n indicate the time between consecutive examinations until examination n, and where n represents the total number of examinations throughout the study (14). An assessment of BP trajectories has been introduced as an even more advanced method to describe the

longitudinal BP patterns at a population level (15). Long-term BP trajectories recognize subgroups of individuals who share similar longitudinal BP change patterns. These computational processes utilize latent class models and consider both the starting levels, along with the slope and cumulative exposure of the individuals BP throughout the lifetime by using group-based trajectory modeling (137).

Overall, a total of three different methods including time-averaged BP, cumulative BP and BP trajectories have been utilized in previous studies to assess the long-term exposure to high BP. Nonetheless, the principle of all these BP indices is essentially the same as they aim to measure the area under curve (AUC) effect of BP over time while applying different approaches. A less studied method is assessment of the individual's age of hypertension onset, indicating the age when the criteria for hypertension is met for the first time. A graphic demonstration of these methods measuring the longitudinal BP exposure over the life course is presented in Figure 3 (138). Time-averaged BP represents the most simple method, whereas implementation of BP trajectories serves as a more advanced, yet complex method which is also dependent on the user-specific parameters of the shape and number of trajectories. Cumulative BP on the other hand captures both the intensity and the duration of elevated BP levels during the life course. It is evident that all these BP indices also require documentation of a large number of BP readings throughout a lifetime.

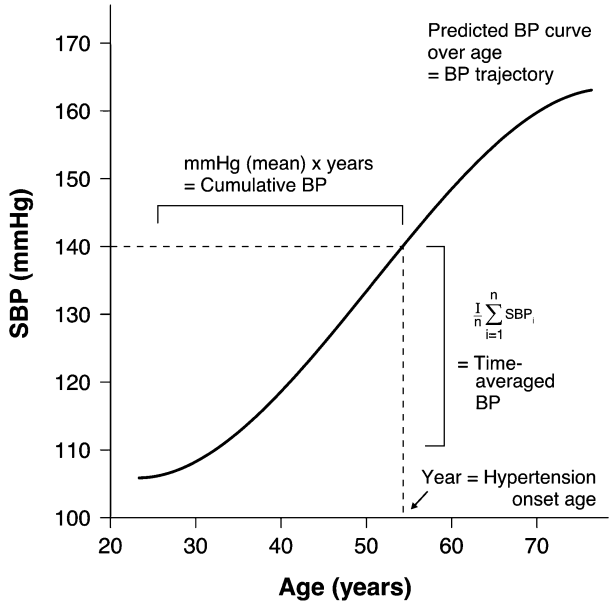

Figure 3. Graphic demonstration of different methods used for assessing overall long-term exposure to high blood pressure by using systolic blood pressure as an example measure. SBP, systolic blood pressure; BP, blood pressure. Reproduced from Annals of Medicine (Nuotio & Suvila et al., 2020) with permission of Taylor & Francis Group.

2.3.2 Long-term blood pressure exposure and organ damage

The first findings on the impact of long-term BP exposure concerned the risk for developing HMOD, more precisely as the risk of having LVH (13). In that study, Lauer et al. found that a time-averaged SBP over a 30 year period was a better predictor of LVH compared to current SBP. Here, a 20-mmHg increase in time-averaged BP was related to an increased OR of 3.20 for men and an OR of 3.27 for women. No CIs were reported, yet the results were stated as being statistically significant ($p<0.05$ for both). Results from the Framingham Heart Study indicated that a higher average antecedent SBP was also associated with increased odds of carotid artery stenosis in the elderly (139). However, in a study conducted by Olesen et al., a 5-year antecedent BP was not consistently associated with HMOD among 1910 study participants (140). Here, antecedent BP did not improve the prediction of any of the measured HMODs (including increased PWV, increased urine albumin-to-creatinine ratio (UACR), or LVH) among other traditional risk factors. Unfortunately, the study sample was relatively small and the follow-up time for BP measurements was short.

In 2014, findings from the Bogalusa Heart Study suggested that also a higher cumulative BP burden, measured as the AUC effect of BP from childhood to adulthood, was related to the appearance of LVH (141). The Bogalusa Heart Study is a longitudinal, biracial population study which was conducted to investigate the early life risk factors for CVD (142). Comparable results were later reported from the same cohort after an extended follow-up time to further assess the impact of life-course cumulative BP on LVH progression (143). In that study, a higher total AUC of cumulative SBP was associated with an increased odds of 1.34 (95% CI, 1.08–1.67), and 1.38 (95% CI, 1.03–1.84), for incident LVH and eccentric cardiac hypertrophy, respectively. Similar findings from the Bogalusa Heart study reported that the long-term cumulative BP from childhood to adulthood was associated with impaired cardiac function, measured as LVMI, E/A ratio and E/e′ ratio (144). Higher cumulative SBP starting from young adulthood in CARDIA study participants has likewise been associated with developing both left ventricular systolic and diastolic dysfunction by middle age (145). Moreover, here the results were comparable also for cumulative DBP. A *post hoc* analysis from the CARDIA study revealed that cumulative BP during 30 years of follow-up was associated with echocardiographic left atrial remodeling and subclinical dysfunction (146). Left atrial structural remodeling refers to the changes in the size and function of the left atrium which predict CVD outcomes such as atrial fibrillation (147). In that study, the correlations were stronger for cumulative SBP than for cumulative DBP. Higher cumulative SBP levels among 3789 non-diabetic multiethnic adults were demonstrated to consistently associate also with elevated odds of persistently higher UACR during a

median follow-up time of 9 years (14). Comparable findings were also later observed from the CARDIA study data (148). In that study, individuals with higher cumulative SBP (cumulative SBP ≥2500 mmHg over 20 years) had significantly higher geometric means of UACR compared to those with lower cumulative SBP values (cumulative SBP <2500 mmHg).

Findings from the Bogalusa Heart Study suggested that higher level-independent linear slopes of SBP trajectories in adolescence were associated with an increased odds between 1.29 and 1.46 in all high trajectory categories ($p<0.01$ for all) for having echocardiographic ECHO-LVH in adulthood (149). Hao et al. on the other hand demonstrated in a sample of 683 individuals that those subjects in the highest BP trajectory group from childhood to adulthood had both increased LVMI and CIMT compared to the lowest trajectory group (150). Additionally, results from the CARDIA study have indicated that BP trajectories from young adulthood also have an impact on the risk for elevated midlife CAC (151). Here five distinct BP trajectories were distinguished and, in comparison to the low-stable BP trajectory group, all four groups with higher BP trajectories had systematically greater odds of having a high CAC-score. A Chinese study investigating 2430 individuals studied the impact of BP trajectories from childhood to adulthood on subsequent midlife renal function (152). The authors identified 4 different BP trajectories and found that the odds of higher UACR linearly increased across all the higher BP trajectories groups when compared with the low and stable BP trajectory group. Similar results were reported from the CARDIA study with a 10-year follow-up period by using declines in the estimated glomerular filtration rate as the outcome measure (153). In that study, every 10 mmHg increase in SBP slope during follow-up was related to a decrease of 0.52 (95% CI, 0.03–1.02) in the glomerular filtration rate per year. The findings were comparable for shifts in the slope of DBP.

2.3.3 Long-term blood pressure exposure and cardiovascular outcomes

In addition to target organ damage, time-averaged BP has also been related to a higher risk of future CVD events as compared to current BP. In 2001, results from the Framingham Heart Study data indicated that both recent (1 to 9 years before baseline) and remote (10 to 19 years before baseline) time-averaged BP markedly contributed to the subsequent ischemic stroke risk (154). These findings were later extended to predicting incident heart failure, CVD and any future CVD event in the same cohort (155–157). For example, Vasan et al. demonstrated that every 1-standard deviation (SD) increment in current SBP, recent time-averaged SBP and remote time-averaged SBP were associated with adjusted HRs of 1.35 (95% CI, 1.08–1.68), 1.83 (95% CI, 1.31–2.54), and 1.97 (95% CI, 1.45–2.67) for any CVD

event among 80-year-old men, respectively (155). The associations observed were however attenuated in the younger age groups. Similarly, a higher time-averaged BP over 5 years prior to baseline was related to excess CVD mortality in a Japanese study population of 46 484 subjects (158). These findings were further confirmed in a large study based on electronic health record data with over 80 000 participants (159). In concordance with other previous studies, Ayala Solares et al. concluded that time-averaged BP was related to a higher risk of incident CVD event than a single-occasion BP. Another recent study involving 1910 middle-aged individuals detected an association between 5-year antecedent SBP levels and subsequent any major adverse cardiovascular event (140). However in that study, antecedent SBP did not markedly improve the risk prediction among other conventional CVD risk factors.

Along with time-averaged BP, Ayala Solares et al. have also studied the impact of cumulative BP on future CVD events (159). Here, each 20-mmHg x year increment in cumulative BP was related to a multivariable-adjusted HR of 1.32 for an incident CVD event ($p<0.05$). In a large study cohort including over 50 000 middle-aged Chinese individuals, both higher cumulative SBP and cumulative DBP were observed to associate with increased risk for stroke, cerebrovascular events, and all-cause mortality (160). However, the study sample included mostly men, the HRs were relatively low overall and the associations with myocardial infraction were non-significant. Pooled data from three major cohort studies examining 11 767 middle-aged individuals suggested that cumulative SBP from 5 to 10 years prior to outcome assessment improved the risk prediction of future atherosclerotic CVD events (161). In that report, addition of cumulative SBP to risk prediction models resulted in a marginally improved 10-year net reclassification index at an even rate by 0.04 (95% CI, 0.02–0.06) for men, and 0.03 (95% CI, 0.01–0.06) for women.

A study from 2012 followed over 60 000 individuals for a mean follow-up of 14 years to evaluate the impact of baseline BP levels and changes in BP over time on their lifetime risk of CVD (162). In that study, participants whose BP increased in midlife had a higher remaining lifetime risk for CVD, whereas individuals with decreases in BP had a lower CVD risk. Similar results were later reported from the ARIC study, where the CVD incidence was observed to gradually increase across the 14 identified patterns for BP trajectories: 6 patterns for SBP, 3 patterns for DBP, and 5 patterns for MAP (163). Findings from the Rotterdam Study suggested that BP trajectories from midlife to late-life were also related to risk of stroke (164). Here, four SBP trajectories were identified among 6745 participants aged between 55 and 106 years, and the increasing SBP trajectories were associated with a higher risk of stroke, whereas the risk increases for all-cause death were less consistent. These results were later confirmed in a large prospective Chinese study of almost 80 000 individuals (165). In that study, those SBP trajectories with an increasing tendency

were consistently associated with a greater risk of stroke and the highest SBP trajectory group had increased adjusted HRs of 12.4 (95% CI, 5.95–26.0) and 5.07 (95% CI, 3.77–6.82) for intracerebral hemorrhage and cerebral infarction, respectively, in comparison to the stable normotensive group. Two studies have also examined the relations between BP trajectories and the mortality risk. Findings from two extinction cohorts investigating only men indicated that the 10-year BP trajectories were strong predictors of CVD mortality and all-cause mortality, although in the end, the average mean BP was the strongest predictor for the other cohort (15). A Chinese study including almost 30 000 participants and with a 30-year follow-up time later demonstrated that BP trajectories were related to an increased risk of all-cause, CVD and stroke mortality (166). For instance, individuals who experienced a shift from prehypertension to hypertension during the follow-up had an increased HR of 1.36 (95% CI, 1.23–1.51) for all-cause mortality, compared to those with stable normotension. All in all, current evidence consistently suggests that long-term BP measures are superior in predicting adverse CVD outcomes compared to single-occasion BP.

2.3.4 Long-term blood pressure exposure and cognition

The impact of long-term BP exposure has also been studied in relation with cognition. Studies which have assessed the impact of time-averaged BP have mainly used structural brain alterations as the outcome measures. Findings from the Atherosclerosis Risk in Communities (ARIC) study indicated that time-averaged SBP predicted white-matter hyperintensity progression better than single-occasion SBP (167). For example, a 20-mmHg increase in time-averaged BP was related to OR of 1.93 (95% CI, 1.47–2.53) for a greater progression in white-matter hyperintensities. Goldstein et al. later reported similar findings, although that study had a relatively short follow-up time of 5 years (168). Another study utilizing a 28-year average MAP assessment also reported similar results (169). Consistently elevated or a rising SBP, defined as the hypertension status at the beginning and at the end of follow-up, has also been demonstrated to associate with smaller brain volumes (121). In one study including elderly individuals who were followed until death with a mean follow-up of 8 years, higher time-averaged BP, but also a faster decline in SBP in late-life was related to an increased odds of incident brain infarcts (170). However, in that study no consistent relation was detected with late-life BP and Alzheimer's disease pathology.

Studies on cumulative BP on the other hand have focused on the cognitive function measures. Results from the CARDIA study have suggested that cumulative BP exposure in early life would be associated with worse cognitive function and poorer gait already by midlife (171,172). Here, standardized linear regression models

were utilized for both cumulative BP and cognitive function measures. In brief, higher cumulative SBP values were observed to relate with slower walking speed and smaller step length, along with poorer cognitive performance in memory, executive function and global cognition ($p<0.005$ for all) (172). These findings were later replicated using data from The Young Finns Study (124). Comparable results have also been reported from a Chinese study, in which higher cumulative SBP was associated with cognitive impairment as defined by a low Mini-Mental State Examination score among middle-aged and elderly individuals (173). According to a recent large study including pooled data from 5 different cohorts, higher cumulative BP was related to cognitive decline particularly in African Americans (174). The authors of that study speculated that the higher cumulative BP levels in African American individuals could account for the racial differences in the rate of the cognitive decline. Additionally, Jenkins et al. found that higher cumulative BP was also associated with morphological alterations in the thalamus and the basal ganglia in CARDIA study participants (175).

A simplified method to examine the effect of BP trajectories on cognitive function was introduced already in the 1990s (176). Here, individuals were categorized into three BP tracking subgroups according to measured BP levels in midlife and late-life, and the subjects in the high tracking group were found to have the worst cognitive capacity. Subsequently, only a few studies have examined the relation between adequately computed BP trajectories and various cognitive outcomes over the life course. BP trajectories have also been related to the presence of autopsy-confirmed microinfarcts (177). In that study, subjects with subcortical microinfarcts experienced a steeper decline of both SBP and DBP in late-life before death. However, here the participants were followed-up only just prior to death, and no mean follow-up time was reported. Findings from the Honolulu-Asia Aging Study in 2009 demonstrated that, when compared with those men without dementia, men who developed dementia had similar patterns of increasing SBP from middle age to late-life, after which their SBP steeply declined (178). Similar results were reported from a study sample including middle-aged Swedish women who were followed consistently for up to 37 years (179). According to recent data from the ARIC study, participants with sustained midlife and late-life hypertension had an HR of 1.49 (95% CI, 1.06–2.08) for increased dementia risk in the future compared to those with sustained normotension (180). In that study, the corresponding HR for individuals with midlife hypertension followed by late-life hypotension was 1.62 (95% CI, 1.11–2.37). In conclusion, prior studies have used very different methods to assess the long-term exposure to high BP, and majority of these studies have not considered the impact of hypertension onset age on adverse events.

2.4 Age of hypertension onset

2.4.1 Definitions of hypertension onset age and early-onset hypertension

Rather few previous epidemiological and clinical studies have investigated age of hypertension onset. Additionally, these studies have used varying approaches to define the age at which the criteria for hypertension would be met for the first time. Three different methods have been used to derive age of onset, including self-report, medical records and serial BP measurements with the majority of prior clinical studies utilizing self-reported information to define the hypertension onset age (181–185). When utilizing self-report, the onset age is based on the individuals' recall on when they initially received a hypertension diagnosis or started antihypertensive treatment. The use of self-reported information is a common method in both epidemiological studies, and cross-sectional studies, but also in clinical practice where longitudinal BP data are often not available. Occasionally, information from previously documented BP readings or from medical records have also been utilized to define hypertension onset age in some cross-sectional observational studies (181,182). Even though self-reported or medical record-based information is often easily available, these are likely to represent mainly the age of the hypertension diagnosis rather than the actual onset age. Additionally, the self-reported hypertension onset age is also dependent on the currently applied definition of hypertension, which has changed several times over the past decades.

In most epidemiological studies, such as the Framingham Heart Study, the age of hypertension onset age has been determined objectively from previously detected serial BP measurements (181,186–188). These studies have incorporated data from periodically repeated BP measurements at standard intervals from visit to visit, enabling as reliable as possible an assessment of the true age of hypertension onset. Hypertension has been defined as SBP/DBP ≥140/90 or the use of antihypertensive agents in most of these prior studies. This is consistent with commonly used hypertension criteria, although recently updated American guidelines suggest that even lower BP thresholds should be applied (19,20). Moreover, in most cases the criteria for hypertension were required to be met on at least two consecutively attended follow-up visits in order to represent a lasting BP change and to reduce any temporary fluctuations in the actual BP (186–188). Some studies have determined hypertension onset as a high BP value or antihypertensive medication use on only one occasion (181).

As well as the varying methods to define the age of hypertension onset, different age thresholds for early-onset hypertension have also been applied. Most previous studies have focused on an early hypertension onset age as a distinct hypertension

subtype, usually referred to as either ”early-onset hypertension” or ”young-onset hypertension” (187,189). Despite the literal terminology, most studies have involved mainly adult individuals regardless of the etiology of the hypertension, considering that childhood onset hypertension often involves different determinants (190). Early-onset hypertension has been defined as a hypertension onset age at or under 55 years of age in the majority of recent studies (181,186–188). However, also many other age thresholds have been used, including <35 years, <40 years and <50 years (182,189,191). In general, the study sample age range has influenced the applied definitions, as the majority of these studies have categorized the study participants into multiple 10-year age of onset subgroups in order to achieve relatively similar subgroup sizes. For example, the 2018 European Society of Hypertension (ESH)/ The European Society of Cardiology (ESC) guidelines suggest that there should be an age threshold of under 40 years for defining an early age of hypertension onset (19). The British hypertension guidelines on the other hand recommend different treatment approaches for patients under and over 55 years of age (192). However, no uniform criteria are yet available which would help to define early-onset hypertension or age of hypertension onset.

2.4.2 Correlates of early-onset hypertension

Very limited evidence exists about the clinical characteristics related to early-onset hypertension. Two small studies have identified common characteristics among individuals with early-onset hypertension. The first study sample included 82 mainly male Taiwanese patients who developed hypertension prior to 40 years of age (189). In that trial, the patient characteristics differed by sex, as women were more likely to have higher uric acid levels, whereas men had higher BMI. Both men and women with early-onset hypertension had higher serum triglyceride levels than the control subjects. Another study examining under 30-year old Japanese university students identified only nine individuals with early-onset primary hypertension among almost 17 000 screened individuals (193). All nine of these patients were male, and most had a family history of antihypertensive medication use. The authors concluded that the risk factors for having early-onset hypertension in that study included genetic background, male sex, and high BMI. Both of these studies included only individuals with primary hypertension. Another study observed an inverse relationship between BMI and age of hypertension onset particularly in men and individuals with diabetes (194). Additionally, a recent study proposed a framework to provide optimal investigation and screening strategies for defining secondary hypertension in individuals with early-onset hypertension (195). In that work, the authors provided age, sex, race, and BMI specific BP thresholds for individuals with

early-onset hypertension as well as when these individuals should be investigated for secondary causes of hypertension.

There are some findings that suggest that high BP related pregnancy complications might be associated with the hypertension onset age (184). In that study, Heida et al found that women who experienced a hypertensive disorder of pregnancy self-reported having a hypertension diagnosis 7.7 years earlier compared to women who experienced no complications during pregnancy. More recently, a large prospective cohort study including 18 133 individuals without hypertension assessed the potential social and behavioral factors related to an earlier onset of hypertension (196). During 3.5 years of follow-up, lower education, neighborhood poverty, being widowed, smoking and low physical activity were associated with new-onset hypertension. However, here the follow-up time was short, the participants were already in their mid-forties, and the effect of age of hypertension onset between individuals was not considered.

Altogether, there is rather limited prior evidence about the risk factors for early-onset hypertension. A summary of the potential suggested contributing factors is presented in Table 2. Other potential contributors for early-onset hypertension might include various social and behavioral factors, as well as pregnancy complications. However, previous studies have not investigated these potential risk factors across hypertension onset age subgroups over a long follow-up time. It may be important to consider different BP thresholds for these individuals when screening for causes for secondary hypertension. Nevertheless, no consensus exists about the correlates of early-onset hypertension.

Table 2. Potential contributing factors for developing early-onset hypertension.

Male sex	High BMI
Ethnicity	Diabetes
Family history of hypertension	High triglyceride level
Social and behavioral factors	Pregnancy complications

2.4.3 Heritability of early-onset hypertension

Development of hypertension has been established to include both environmental and genetic factors. Genome-wide association studies have identified numerous gene loci and single nucleotide polymorphisms associated with BP phenotypes (197,198). However, the heritability estimates of hypertension vary greatly in different populations and the environmental factors are generally considered to account for majority of the global burden of hypertension (199,200). Genomic studies have demonstrated that early-onset hypertension has a considerably stronger genetic

component than late-onset hypertension. In fact, the published studies have mainly focused on determining the genetic predisposition of early-onset hypertension, rather than onset at later ages. Studies in varying populations have aimed to discover the genetic factors which could explain the underlying cause for an early age of hypertension onset (201–206). While several studies have proposed a link between early-onset hypertension and various single nucleotide polymorphisms, to date they have been unsuccessful in consistently detecting these associations in different study populations. Nonetheless, there is some evidence suggesting that different genetic variants and polymorphisms related to the RAAS may be associated with early-onset hypertension (201–204). Other potential suggested susceptibility loci for early-onset hypertension have been located in chromosomes 2, 4, 6, 14, and 18 (185,205–209).

In addition, various individual genes, along with gene clusters, have been suggested to be differentially expressed among subjects with early-onset hypertension (206–211). As well as trials which have only included individuals with early-onset hypertension, a single study found that age of hypertension onset was more closely related to certain previously identified BP slope genes than single-occasion BP (212). Here, the authors concluded that diverse BP trait measures could be useful in identifying distinct genes related to these traits. Even though there is limited evidence on these potential trait-related genes, one study has indicated that genetic variation in the human SORBS1 would be associated with the hypertension onset age (213). Moreover, the genetics of early-onset hypertension seems to vary extensively in individuals from different ethnic and geographic backgrounds (201,205,206). The majority of the genomic data associated with early-onset hypertension has been reported in Taiwanese populations, whereas other ethnicities have remained less widely evaluated. Thus, the genetic etiology of early-onset hypertension still remains unclear.

The heritability of hypertension onset age has also been investigated in population-based studies. In the Johns Hopkins Precursor Study, early age of parental hypertension onset in both parents was related to a 6.2-fold higher risk that their offspring would have hypertension (181). However, here the study sample included only white men who had attended medical school. Similar findings were later reported from the Framingham Heart Study in which early-onset hypertension in both parents was associated with 3.4-fold odds of hypertension in the offspring (187). The cumulative hypertension incidence by parental hypertension onset age in that study is illustrated in Figure 4. Conversely, late parental hypertension onset age in both parents was not related hypertension in their offspring in the Framingham Heart Study; in the Johns Hopkins Precursor study, the observed risk was markedly lower than for early-onset parental hypertension. Furthermore, in a study sample of 3608 participants of the Framingham Heart Study third generation cohort, early-onset hypertension in grandparents was likewise a potent predictor of hypertension

in the grandchildren even after accounting for parental hypertension (188). In that study, an increase of one parent with early-onset hypertension was associated with odds OR of 2.10 (95% CI, 1.67–2.64) for having hypertension, whereas a 1-grandparent increase with early-onset hypertension was associated with OR of 1.33 (95% CI, 1.13–1.56) for having hypertension. Thus, these findings suggest that there is a considerable familial predisposition of early-onset hypertension, and this effect might even cross generations.

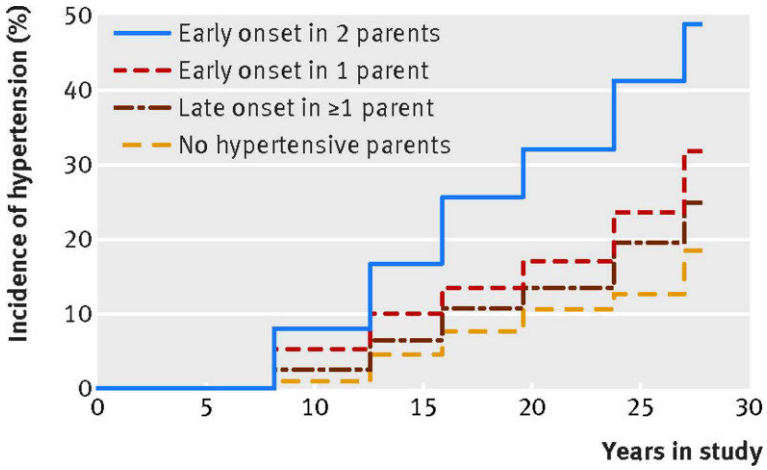

Figure 4. Cumulative incidence of hypertension during follow-up in the Framingham Heart Study according to parental age at onset of hypertension. Reproduced from BMJ (Niiranen et al., 2017) with permission of BMJ Publishing Group Limited.

2.4.4 Hypertension onset age and cardiovascular disease

A few previous studies have assessed the relationship between hypertension onset age and the disease risk. However, to date no previous studies have directly investigated the association between hypertension onset age and HMODs. Three prior studies have examined the relationship between age of hypertension onset and CVD outcomes (Table 3). The first of these studies was published already in the 1980s by Buck et al.; these authors suggested that the prognosis of hypertension varied according to the age of hypertension onset (191). In that study, 10 313 primary care patients were categorized into groups according to their age at hypertension diagnosis. After 5 years of follow-up, individuals with hypertension onset between 40 and 49 years of age had a markedly higher risk of CVD events when compared to those with a hypertension onset after 49 years of age. However, in that study, hypertension was diagnosed only based on DBP. Moreover, CIs for the results were not reported and the results were unadjusted for conventional CVD risk factors, including serum glucose and cholesterol levels.

Similar results were later reported from the Framingham Heart Study data (187) where the study participants were followed-up for up to 60 years and hypertension onset age was defined as BP ≥140/90 mmHg or antihypertensive medication use on two consecutive follow-up visits. Unlike in the report of Buck et al., in the Framingham Heart Study, the analyses were adjusted for several other CVD risk factors. An increasing linear trend in odds of CVD mortality was observed with decreasing hypertension onset age ($p<0.001$ in the adjusted models).

These findings were recently confirmed from a large prospective study cohort which initially included over 100 000 Chinese individuals (214). Wang et al. investigated the relation between hypertension onset age and CVD outcomes for the first time in a time-to-event cohort study setting. That study examined 19 887 new-onset hypertension cases and the same number of age- and sex-matched controls without hypertension. However, the mean follow-up time in that study was only 6.5 years. Consistent with previous studies, the authors reported that individuals with an early age of hypertension onset (onset <45 years of age) had the highest risk for CVD events compared to other age of onset groups. Additionally, similar results were observed in that study also when all-cause mortality was applied as the outcome measure, as individuals with hypertension onset age <45 and ≥65 years had increased HR of 2.59 (95% CI, 1.32–5.07), and HR of 1.29 (95% CI, 1.11–1.51) for all-cause mortality, respectively.

Overall, the highest CVD outcome risk has been consistently observed in the earliest age of hypertension onset group across all these studies. The underlying mechanisms of how early hypertension onset age promotes a poorer prognosis of CVD, and possibly other diseases, is still unknown. However, the numbers of studies in this domain are still very limited.

Table 3. Studies on hypertension onset age and association with cardiovascular disease outcomes.

Author (Year)	N	Outcome	Hypertension onset age	Estimate (95% CI)
Buck et al. (1987)	10 313	CVD event*	60–65 years	OR:1.2 (N/A)
			50–59 years	OR: 1.8 (N/A)
			40–49 years	OR: 5.2 (N/A)
			No HTN	Reference
Niiranen et al. (2017)	3614	CVD death	≥65 years	OR: 1.47 (1.16–1.87)
			55-64 years	OR: 1.86 (1.48–2.34)
			45-54 years	OR: 2.10 (1.67–2.63)
			<45 years	OR: 2.19 (1.77–2.70)
			No HTN	Reference
Niiranen et al. (2017)	3614	CHD death	≥65 years	OR: 1.36 (0.98–1.87)
			55-64 years	OR: 1.71 (1.26–2.32)
			45-54 years	OR: 2.18 (1.64–2.90)
			<45 years	OR: 2.26 (1.75–2.93)
			No HTN	Reference
Wang et al. (2020)	39 774	CVD event†	≥65 years	HR: 1.33 (1.04–1.69)
			55-64 years	HR: 1.42 (1.12–1.79)
			45-54 years	HR: 1.62 (1.24–2.12)
			<45 years	HR: 2.26 (1.19–4.30)
			No HTN	Reference

CVD, cardiovascular disease; CHD, coronary heart disease; N/A, not available; HTN, hypertension; OR, odds ratio; CI, confidence interval.*Stroke, myocardial infraction, heart failure or renal failure. †Stroke, or myocardial infarction.

2.4.5 Hypertension onset age and cognition

Only two prior studies have assessed the impact of hypertension onset age on cognition. Both these studies have used incident dementia as the outcome measure, and thereby the potential relation with cognitive test performance or structural brain alterations has remained unknown. The study of Gilsanz et al. investigated the relation between age of hypertension onset and dementia in a sample of 5646 individuals (182). Compared to those without hypertension, mid-adulthood hypertension onset in women was associated with an HR of 1.68 (95% CI, 1.20–2.34) for having dementia later in life during a mean follow-up time of 15.3 years.

However, hypertension onset in mid-adulthood was not related to the dementia risk in men, and the association with early adulthood hypertension onset remained non-significant for both sexes. Unfortunately, the results were not adjusted for many other potential contributors for cognitive decline such as sedentary time and alcohol use. Interestingly, findings from *The 90+ Study* suggested that onset of hypertension after 80 years is related to a lower risk of dementia compared to those without the presence of hypertension (183). In that study, hypertension onset ≥90 years and between 80 to 89 years was associated with HR of 0.37 (95% CI, 0.19–0.73), and 0.58 (95% CI, 0.34–0.98), for developing all-cause dementia, respectively. Nevertheless, this study was performed in a highly selected cohort including only 559 elderly participants and the mean follow-up period was only 2.8 years. All in all, the evidence about the relation between hypertension onset age and cognition is limited and restricted to only dementia-related outcomes.

2.5 Summary of the literature review

BP progression over the life course follows specific patterns, yet considerable heterogeneity exists between individuals. The underlying mechanisms behind physiological and pathological BP changes during the lifetime are complex, while arterial stiffness acts as one important contributing factor. The majority of the global burden of hypertension arises from idiopathic origins, although secondary causes for hypertension should be investigated in younger individuals with new-onset hypertension.

There is extensive previous evidence about the undisputed impact of high BP on HMOD and CVD outcomes irrespective of age. Yet, the relationship between BP and cognition seems to be more age-dependent and lower BP might not always be desirable. Nevertheless, the presence of hypertension at any age is a commonly distinguished risk factor for various adverse events. Moreover, SBP that chronically exceeds over 120 mmHg has been demonstrated to precede the onset of hypertension regardless of age (215). However, a very limited number of individuals are able to maintain the optimal BP level throughout the life course. To date, most prior studies have focused on assessing the impact of "present" BP values, providing information only as a snapshot of time.

The increasing amount of epidemiological studies in recent years have utilized various longitudinal BP measures in relation to hypertension-related complications. Evidence from these studies consistently suggests that accounting for the long-term burden of high BP improves the overall risk prediction in hypertensive individuals. However, the clinical applicability of these BP indices has remained poor and thus their clinical significance has remained unknown. Thus, more feasible approaches are called for if these are to be incorporated into clinical practice. Growing interest

and accumulating evidence of assessing the long-term exposure to high BP may result in updated clinical guidelines in the future.

A limited number of published studies have investigated the role of early-onset hypertension or the age of hypertension onset in hypertensive individuals. No standard definition yet exists for early-onset hypertension, and methods to define age of hypertension onset have been inconsistent. Nonetheless, early-onset hypertension might have a distinct etiology, possibly related to arterial stiffness and endothelial dysfunction (216,217). Even though early-onset hypertension has been established as a highly heritable trait, other potential risk factors for early hypertension onset age have remained unresolved. At present, very limited evidence exists on the relationship between the age of hypertension onset and the risk of adverse outcomes. Most of the few published studies have mainly focused on CVD-related outcomes. However, there is prior evidence that early-onset prehypertension without progression to hypertension does not increase the odds of CVD death (186). This may advocate the importance of preventative measures to avoid the development of early-onset hypertension. Moreover, the relevance of using different methods to assess the age of hypertension has not been clarified.

So far, there are no studies which have assessed the impact of early hypertension onset age on having HMOD or midlife cognitive function. Data about the clinical correlates of early-onset hypertension also remain inconclusive. Furthermore, no studies have evaluated the agreement between objectively defined and self-reported hypertension onset age or examined the association between self-reported age of hypertension onset age and HMOD.

3 Aims

This thesis was designed to examine the potential correlates of early-onset hypertension and the risks of adverse events related to early hypertension onset age. We also aimed to evaluate the differences between assessing age of hypertension onset age using objective methods in comparison with self-report.

The specific aims of this study were:

1. To study the association between objectively defined early-onset hypertension and prevalence of HMODs. (Study I)

2. To determine the relation between self-reported early hypertension onset age and HMODs. Additionally, we aimed to assess the agreement between self-reported and objectively defined hypertension onset age. (Study II)

3. To study the association between self-reported hypertension onset age and the prevalence of ECG-LVH. (Study III)

4. To determine the relation between objectively defined early-onset hypertension and cognition. (Study IV)

5. To detect common clinical characteristics among individuals with early-onset hypertension. (Study V)

4 Materials and Methods

4.1 Study populations

4.1.1 Coronary Artery Risk Development in Young Adults

The CARDIA study is a prospective cohort study that began in 1985. A detailed description of the CARDIA study has been published previously (218). The initial aim of the CARDIA study was to examine the development and determinants of CVD. In brief, the CARDIA study involved 5115 individuals aged 18–30 years from four study centers across the United States in Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. The study participants were selected to attain approximately same number of individuals in subgroups of race (black and white), sex (men and women) and education (high school graduation or less and more than high school education). All participants gave informed consent to participate in the study. The study was approved by the local institutional committees in each of the participating centers. All materials and data of the CARDIA study are publicly available at the National Institutes of Health's Biologic Specimen and Data Repository Information Coordinating Center and can be accessed at: https://biolincc.nhlbi.nih.gov/studies/cardia/.

4.1.2 Health 2000 survey

The Health 2000 survey is a nationwide survey which was carried out between 2000 and 2001 in Finland. Details of the survey methods and protocols have been published previously (219). The aim of the Health 2000 survey was to study the major public health problems among the Finnish adults as well as their causes and treatment possibilities. The Health 2000 survey included 8028 individuals (aged 30 years and over, 55% women) who were invited to participate in the study after being randomly drawn from the population register. Written informed consent to participate in the study was received from all participants. The Health 2000 survey study protocol was conducted according to the Declaration of Helsinki and was approved by the ethical committees of the local hospital district.

4.2 Flow of studies

4.2.1 Coronary Artery Risk Development in Young Adults

The CARDIA study participants attended up to nine follow-up examinations between years 1985–1986 and 2015–2016. The flow of Studies I to II and IV to V have been illustrated in Figure 5. During each follow-up visit, the participants underwent a thorough health examination including self-administered questionnaires, physical examination, and blood tests. For this study, we included participants with HMOD measurements from the Year 25 examination and participants with measurements of cognition from the Year 30 examination. We considered midlife as the participants age range from the Year 25 examination to the Year 30 examination (from 43 to 60 years of age).

Study I

We considered participants who attended the Year 25 examination (n=3499) for this study. After excluding individuals with any missing covariate or HMOD data at Year 25 examination (n=819), the final Study I sample consisted of 2680 participants.

Study II

Similarly, we included participants from the Year 25 examination with the same exclusion criteria than in Study I. We additionally excluded those without information about self-reported age of hypertension onset (n=41), resulting into a final Study II sample of 2649.

Study IV

The study sample consisted of participants who attended the Year 30 examination. We excluded the subjects with any missing cognitive function test measures or covariate data (n=412). The final study IV sample thereby included 2946 participants. Additionally, brain MRI measurements were available for 599 of these participants.

Study V

We included individuals from the CARDA Year 30 examination after excluding those with any missing data on demographic characteristics or lifestyle related factors (n=222), resulting into final Study V sample of 3136 participants.

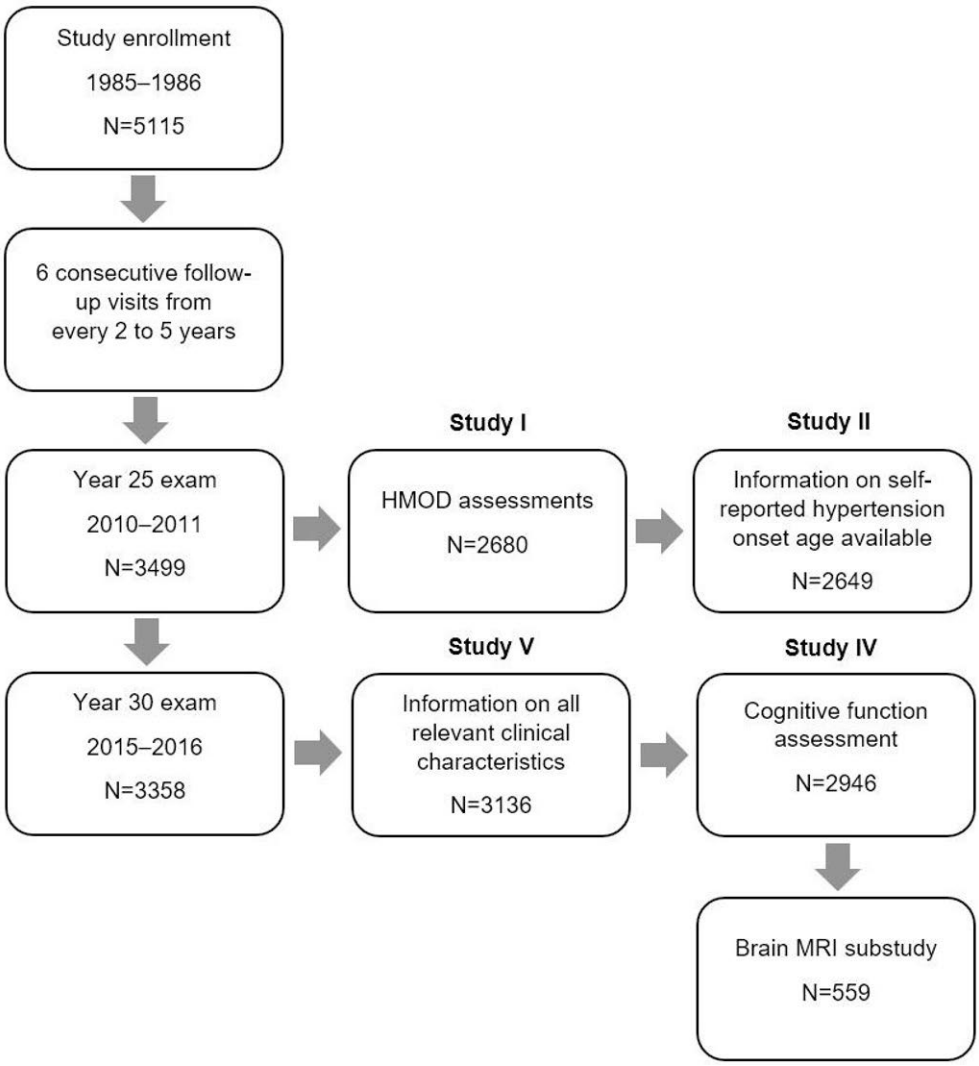

Figure 5. Flow chart illustrating the examined participants of the CARDIA study and sample selection for studies I, II, IV and V.

4.2.2 Health 2000 survey

In the initial health interview of the Health 2000 Survey, information was gathered by centrally trained interviewers about the participant's demographic characteristics, use of medications, state of health, and diagnosed illnesses (219). Participants attended a health examination from 1 to 6 weeks later performed by centrally trained nurses and physicians. There was a 79% participation rate for attending both the home health interview and the health examination (n=6354, 55% women).

Study III

For the study sample, we included participants aged ≥50 years (n=3404) so that all study participants could be categorized to all possible ages of hypertension onset categories. We also excluded individuals with atrial fibrillation (Minnesota code 8.3), paced rhythm (Minnesota code 6.8), ventricular conduction defect (Minnesota code 7), Wolf-Parkinson-White electrocardiogram pattern (Minnesota code 6.4), or missing covariate data, resulting in a final Study III sample of 2864 participants.

4.3 Clinical examinations and questionnaires

4.3.1 Coronary Artery Risk Development in Young Adults Study

BP was measured between the baseline and year 15 examination using a random zero mercury sphygmomanometer. BP was measured three times at each follow-up visit by centrally trained and certified personnel (218). The BP measurements were carried out in duplicate for quality control and no distinct differences were observed between the centers in technician-specific single-point histograms. From the Year 20 examination onwards, BP was measured with a validated Omron model HEM907XL oscillometric monitor (220). BP was measured by trained technicians three times from the right arm with the participant in the sitting position after 5 minutes of quiet rest. We corrected the differences between oscillometric and auscultatory measurements by calibrating the oscillometric values to the corresponding sphygmomanometer values. Calibrated SBP was computed as: measured Omron SBP*0.96+3.74 and calibrated DBP as follows: measured Omron DBP*0.97+1.30 (221). The current BP values were computed as means of the second and third measurements at each follow-up visit. Weight and height were measured with all participants in light clothing. Self-administered questionnaires were carried out at all follow-up visits to collect information about the participants' demographic characteristics, smoking status, amount of alcohol intake (average ethanol consumption per day), completed years of education, history of pre-eclampsia or high BP during pregnancy in women, and the use of any medications, including antihypertensive and antihyperglycemic agents. Sedentary behavior time was assessed with the CARDIA Sedentary Behaviour Questionnaire (222). We calculated the average sedentary time (hours/day) from the overall weekly sedentary behaviour time.

4.3.2 Health 2000 survey

Medical history (including diagnosed coronary heart disease, heart failure and previous stroke), smoking status and the use of antihypertensive medication or hormone replacement therapy was self-reported during the health interview (219). BP was measured by the trained personnel at the health examination two times from the right arm after a 10 minutes rest from all participants using a standardized mercury sphygmomanometer (Mercuro 300; Speidel & Keller, Jungingen, Germany). BP was measured by listening to the Korotkoff sounds, while SBP was recorded as the appearance of the first Korotkoff sounds, and DBP was recorded as the fifth phase of the Korotkoff sounds. SBP and DBP values were defined as means of the two measurements. Height and weight were also measured from all participants.

4.4 Biochemical analyses

All participants from both study populations provided fasting blood samples, which were analyzed according to standard enzymatic procedures to measure serum glucose, total cholesterol, and high-density lipoprotein (HDL-cholesterol) (219,223). Diabetes was defined in all studies as serum fasting glucose ≥7 mmol/l or the use of antidiabetic agents.

The CARDIA study participants additionally provided single, untimed spot urine samples at the Year 25 examination. The samples were centrally analyzed to quantify urinary albumin and creatinine levels according to the standard procedures as previously described (224). We defined albuminuria as UACR >30 mg/g (>3 mg/mmol) (225).

4.5 Hypertension onset age assessment

Studies I, IV and V

Age of hypertension onset was defined objectively based on all available BP measurements during the follow-up until outcome assessment. We defined objectively determined hypertension onset as BP ≥140/90 mmHg or use of any antihypertensive medication on two consecutively attended follow-up examinations. This definition was used aiming to demonstrate a lasting change in BP and to reduce the effect of variability between single elevated BP measurements. Age of hypertension onset was defined as the age in the first examination on which the hypertension criteria were met to be consistent with previous studies (181,187). Participants were categorized into four groups according to their hypertension onset

age as: <35 years, 35–44 years, ≥45 years, or no established hypertension. Early-onset hypertension was defined as hypertension onset <35 years of age and late-onset hypertension as ≥45 years of age.

Study II

Objectively defined hypertension onset age was determined similarly as in Studies I, IV and V. Additionally, an alternative definition for objectively defined hypertension onset age was used as BP ≥140/90 mmHg or antihypertensive medication use at only one follow-up visit. We also determined the participants' self-reported hypertension onset age from replies to the following Year 25 examination self-administered questionnaire questions: "Has a doctor or nurse ever said that you have high BP or hypertension?" and "At what age were you first told about this?". Subgroups were formed and defined using the same age categories as in Studies I, IV and V.

Study III

In Study III hypertension onset age was self-reported by the subjects at the health interview as the year when hypertension had been diagnosed by a physician for the first time. We divided the participants into categories according to age of hypertension onset as <40 years, 40–49 years, ≥50 years, or no hypertension. Early-onset hypertension was defined as hypertension onset <40 years of age and late-onset hypertension as ≥50 years of age.

4.6 Measurements of adverse outcomes

4.6.1 Echocardiography

Echocardiographic measurements were performed for participants attending the Year 25 examination of the CARDIA study. Experienced echocardiographic sonographers centrally analyzed all acquired echocardiograms. A 2-dimensionally guided M-mode and Doppler echocardiography was performed at all study centers according to a standardized study protocol. Pulse wave doppler recordings of the peak velocity flow in both early and late diastole as well as LVM were calculated from all acquired echocardiograms. Further technical details of the echocardiographic protocols and measurements have been published elsewhere (226). We computed the LVMI as LVM divided by the body surface area (0.007184 x weight $[kg]^{0.425}$ x height $[cm]^{0.725}$). We defined left ventricle diastolic dysfunction as a ratio between peak velocity flow in early and late diastole of over 2.0 or under

0.8 according to standard recommendations (227). Similarly, LVH was defined in men as LVMI >115 g/m^2 and in women as LVMI >95 g/m^2 (227).

4.6.2 Electrocardiography

For the Health 2000 Survey participants, standard 12-lead electrocardiograms were recorded at the health examination according to standard procedures using a MAC 5000 recorder (Marquette Hellige, Freiburg, Germany, and Milwaukee, Wisconsin, USA). The recordings were centrally analyzed with the Magellan software program (Marquette Electronics Inc., Milwaukee, Wisconsin, USA). The electrocardiogram measurements were also checked manually by centrally trained nurses, supervised by a clinical physiologist, and corrected if necessary. Minnesota coding was carried out for all electrocardiograms by two cardiologists, who were blinded to clinical status. In case of disagreement, the final coding was decided through mutual consensus. ECG-LVH was defined by the voltage criteria of Sokolow-Lyon (SV1+RV5/V6 ≥3.5 mV) and Cornell (SV3+RaVL >2.8 mV for men and >2.0 mV for women) (228). Additional alternative criterion was used according to the Minnesota ECG-LVH coding (Minnesota codes 3.1 and 3.3).

4.6.3 Coronary artery calcification

Cardiac multidetector computed tomography was used in the Year 25 examination of the CARDIA study to measure the amount of calcified coronary artery plaque. Obtained images were analyzed centrally and an Agatston score was computed to quantify the highest detected density of calcification in the coronary arteries. The protocols for CAC imaging and Agatston score calculation have been previously described in detail (229,230). The presence of CAC was defined as Agatston score ≥100 in accordance with previous studies (231).

4.6.4 Cognitive function tests

Centrally trained and certified study technicians carried out four distinct cognitive function tests for the participants in the Year 30 examination of the CARDIA study. Further details of the test protocols have been previously reported (232). The Rey Auditory Verbal Learning test (RAVLT) was used to assess verbal memory capacity (114). The long-delay free recall test score was counted as the number of words recalled. The Stroop test was utilized to evaluate the participants' executive function properties (233). The Stroop test involves three subtests, each of which is individually scored as the sum of time in seconds used to complete the test and the number of errors occurred. We used the computed interference scores (subtest three

score subtracted by the subtest two score). The Digit Symbol Substitution test (DSST) was used to measure the psychomotor speed (113). The DSST score was calculated as the number of correctly substituted symbols by the time-limit. The Montreal Cognitive Assessment (MoCA) test was used as a more comprehensive method to assess global cognitive function and as a tool to screen for mild cognitive impairment (115). The MoCA test covers multiple components of the cognitive domain including orientation, memory, attention, visuospatial abilities, language, and executive function. Higher scores in each test represent better cognitive performance, except for the Stroop test where a higher interference score indicates worse performance.

All test scores were also converted to standardized z-scores for easier interpretation between the tests according to the following formula: z = (score – mean)/ SD. For the Stroop test, we used inversed z-scores to attain uniform interpretation of the results across all tests. To further assess global cognitive function, we calculated a composite cognitive score as the average z-score from RAVLT, DSST and Stroop test as previously demonstrated (232).

4.6.5 Brain MRI protocol and measures

The brain MRI substudy was carried out during the Year 30 examination of the CARDIA study concurrently with the cognitive function tests. Neuroimaging was performed in three CARDIA study cites (Birmingham, Oakland, and Minneapolis) using the axial plane on 3T scanners. A Philips 3T Achieva/2.6.3.6 platform was used in Birmingham and a Siemens 3T Tim Trio/VB 15 platform was used in Oakland and Minneapolis. Further technical and methodological details of the imaging protocol have been previously described (234–236). In general, standard quality control protocols were adhered to for all the devices and the structural brain images were obtained using 3D T1 and T2 sequences. An automated multispectral computer algorithm was utilized to assess areas of white matter, grey matter, and cerebrospinal fluid. The regions of interests were detected after corrections, the images were visually checked for quality control, and finally quantitatively analyzed.

Total brain volume (TBV) was computed as the sum of white matter volume (WMV) and grey matter volume (GMV). Total intracranial volume (ICV) was calculated as the sum of TBV and cerebrospinal fluid volume. Additionally, the images were analyzed for the amount of abnormal white matter volume (AWMV) from the sagittal 3D fluid-attenuated inversion recovery (FLAIR) T1 and T2 sequences, and white matter fractional anisotropy (WMFA) by using diffusion tensor imaging. AWMV represents the damaged white matter tissue due to abnormalities such as inflammation, ischemia, or demyelination. WMFA is expressed as a value from 0 to 1, where 0 represents isotropy and 1 represents anisotropy. A higher

WMFA value represents a higher micro-structural integrity of the white matter tracts, whereas a lower WMFA is associated with aging and neurogenerative disorders (237). All brain-related measurements were standardized to z-scores likewise the cognitive test scores.

4.7 Statistical analyses

We performed all analyses with SAS software version 9.4 (SAS Institute, Cary, NC, USA). We assessed normal distribution visually and with Saphiro-Wilks test when necessary. We used Levene's test for verifying equality of variances. BMI was calculated as weight (kg)/(height (cm))^2 in all studies. UACR values were log-transformed for all analyses due to their skewed distribution. The amount of alcohol intake was standardized to z-score as above to obtain normal distribution. We considered a two-tailed P-value under 0.05 as statistically significant. In all studies, we used one-way analysis of variance for continuous variables and a chi-squared test for categorical variables to examine the differences between hypertension onset age subgroups.

Study I

We examined the CARDIA Year 25 examination participants' characteristics and prevalence of HMODs in the whole sample and by age of hypertension onset categories. We used a two-sample t-test for the continuous variables and the χ^2 test for categorical variables to compare the baseline characteristics between the study sample and the excluded participants. We used a case-control study design (measured HMOD versus no HMOD) to examine the association of hypertension onset age with HMODs. Participants with no hypertension were considered as the reference group. We used both univariable and multivariable logistic regression models in the analyses. Multivariable analyses were adjusted for conventional HMOD risk factors, i.e. sex, age, race, smoking, BMI, diabetes, total cholesterol, HDL-cholesterol, present SBP and use of any antihypertensive medication. We also assessed the linear trend between hypertension onset age and HMOD by including the strata as a continuous variable in the models. Additionally, we used a multinomial logistic regression model to assess the relation between hypertension onset age and the sum of HMODs (0, 1 and 2 or more).

Study II

We compared participants' characteristics and established HMODs in subgroups according to self-reported age of hypertension onset and in the whole sample at

CARDIA year 25 examination. We examined the association between self-reported age of hypertension onset and HMODs using a case (presence of HMOD) versus control (no presence of HMOD) study design with those without self-reported hypertension as the reference group. The relation between self-reported hypertension onset age and HMOD was assessed with univariable and multivariable logistic regression models. We used the same covariates for the multivariable analyses than in Study I. We also performed a trend test for ORs by hypertension onset age subgroups. We used the standard SAS software version 9.4 settings to calculate and construct the weighted kappa coefficients for the agreement analyses between self-reported and objectively defined hypertension onset age. To further assess the agreement between these methods, we also used an alternative definition for objectively defined age of hypertension onset as high BP or use of antihypertensive medication on only one check-up. We calculated the cumulative incidence of hypertension onset by age based on objectively defined and self-reported onset age.

Study III

We examined the participants' characteristics and prevalence of ECG-LVH in the whole sample and by self-reported hypertension onset age subgroups. We used univariable and multivariable logistic regression models to examine the association between age of hypertension onset categories and ECG-LVH with participants who did not report having hypertension as the reference group. We adjusted the models for sex, age, BMI, diabetes, smoking, heart rate, non-HDL-cholesterol, use of antihypertensive medication, present SBP, coronary heart disease and heart failure. We compared the differences across ORs for all ECG-LVH criterion between hypertension onset age <40 years and ≥50 years with a *z* test.

Study IV

We compared the characteristics and measures of cognitive function of the CARDIA year 30 examination participants by hypertension onset categories and in the whole sample. We compared the baseline characteristics between the excluded participants and the study sample with chi-squared test for categorical variables and two-sample t-tests for the continuous variables. Due to skewed distribution, alcohol intake was standardized to z-score in the analyses. We used univariable and multivariable linear regression models to assess the association of hypertension onset age with cognitive function test scores and brain MRI measures. Participants who did not develop hypertension were used as the reference group. The minimally adjusted model was adjusted for sex, race, age, and education. The fully adjusted model was further adjusted for BMI, smoking, diabetes, sedentary time, alcohol intake, current SBP

and use of antihypertensive medication. The adjusted models which included brain-related measures as the outcome variable were additionally adjusted for total ICV.

Study V

We performed a trend test across age of hypertension onset categories with a linear regression model for continuous variables and the Cochran-Armitage test for trends of the categorical variables in the CARDIA Year 30 examination participants. We used a multinomial logistic regression model to examine the relation between hypertension onset age categories and the participants' clinical characteristics. We assessed all characteristics simultaneously in the model with hypertension onset age category being the dependent variable. Individuals without hypertension were used as the reference group. We used linear regression to examine for a trend in ORs across the dependent variable categories. The characteristics included in the model were sex (man or woman), race (African American or white), smoking (smoker or non-smoker), diabetes mellitus (diabetes or no diabetes), lipid-lowering medication (LLM) (using or not using), BMI (kg/m^2, 1-SD increase), education (years, 1-SD increase), alcohol intake (ml/day, 1-SD increase), sedentary time (hours/day, 1-SD increase), total serum cholesterol (mmol/l, 1-SD increase), and HDL-cholesterol (mmol/l, 1-SD increase). We standardized the continuous variables into z-scores.

5 Results

5.1 Clinical correlates of early-onset hypertension (V)

The sample characteristics of the CARDIA participants from the year 30 examination are presented in Table 4. The Study V sample included 3136 participants (mean age 55±4, 57% women, 47% African Americans). During 30 years of follow-up, 27.9 % of the participants had experienced an objectively defined onset of hypertension, and 3.7% had early-onset hypertension (onset <35 years of age). In the early age of hypertension onset group, 47.0% were men, 77.8% were African American, 20.5% smoked, 35.0% had diabetes mellitus, and 41.0% were taking LLM. The hypertension onset age subgroups statistically significantly differed from each other over race, current smoking, having diabetes, BMI, current BP, use of antihypertensive medication or LLM, sedentary time, cholesterol levels, and education years ($p<0.01$; Table 4). The results remained significant for race, smoking, diabetes, use of LLM, sedentary time, BMI, total serum cholesterol and education years while testing for a trend across the four categories towards earlier hypertension onset ($p<0.01$ for trend for all).

In the multivariable multinomial logistic regression model, individuals who were African American, had diabetes, had 1-SD higher BMI, or used LLM had an increased odds of 3.70 (95% CI, 2.28–6.02), 2.86 (95% CI, 1.80–4.54), 1.47 (95% CI, 1.20–1.80), and 3.46 (95% CI, 2.24–5.35), for having early-onset hypertension compared to those who did not develop hypertension, respectively. The corresponding odds for these four traits were 3.24 (95% CI, 2.39–4.39), 2.14 (95% CI, 1.54–2.98), 1.74 (95% CI, 1.52–1.99), and 3.74 (95% CI, 2.79–5.03) for hypertension onset between 35 and 44 years of age, and 1.94 (95% CI, 1.52–2.47), 1.99 (95% CI, 1.48–2.69), 1.48 (95% CI, 1.32–1.67), and 3.65 (95% CI, 2.84–4.69) for hypertension onset ≥45 years of age, respectively. In African American and diabetic individuals, the odds also increased linearly across the subgroups towards an earlier hypertension onset age ($p<0.05$ for both). Conversely, smoking was only related to an increased odds of hypertension onset at ≥ 45 years of age ($p<0.05$), whereas a higher education was borderline statistically significantly associated with a decreased odds of developing hypertension between 35 and 44 years of age

(p=0.05). Male sex, sedentary time, amount of alcohol intake, total cholesterol, and HDL-cholesterol were not statistically significantly associated with the age of hypertension onset (p>0.11 for all). The cumulative incidence of hypertension onset by age according to race, diabetes status, BMI, and education level is illustrated in Figure 6. The hypertension incidence was always higher among individuals who were African American, diabetic, had higher BMI or had lower education. The differences in incidence patterns between the groups commenced already prior to 30 years of age.

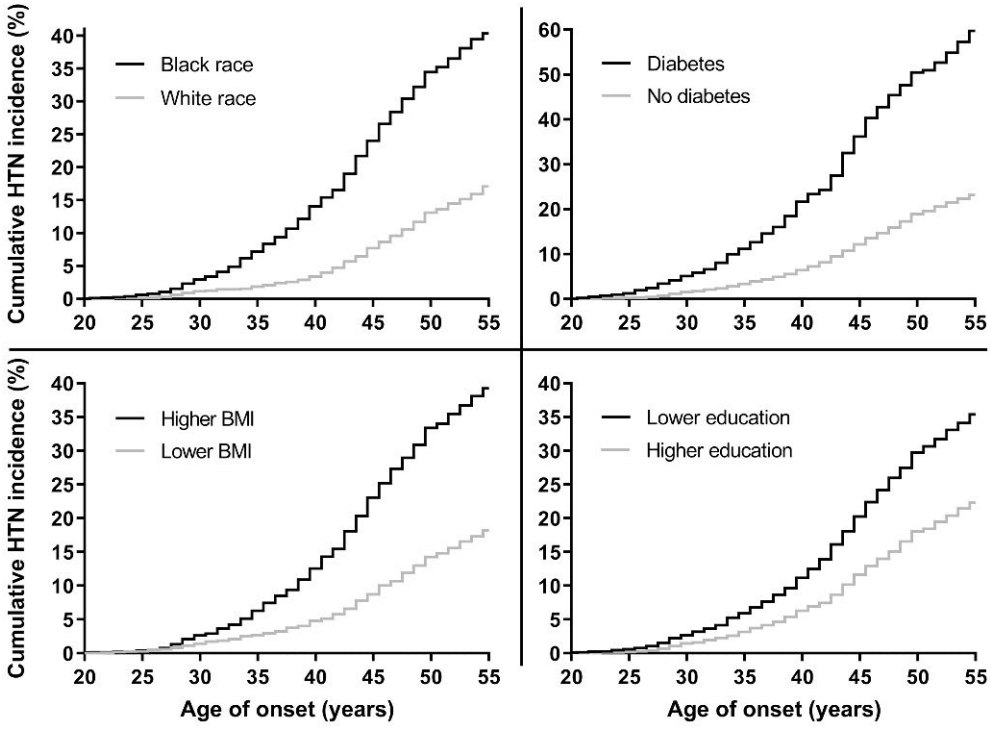

Figure 6. Cumulative hypertension incidence in the CARDIA study by age of onset according to race, diabetes status, BMI, and education level. Higher BMI was defined as BMI >30 and lower BMI as BMI ≤30. Lower education was defined as <15 education years and higher education was defined as ≥15 education years. N=3136. HTN, hypertension.

Table 4. Characteristics of the CARDIA study sample according to objectively defined hypertension onset age.

	Age of Hypertension Onset					
Characteristic	All	<35 years	35–44 years	≥45 years	No hypertension	P-value*
N	3136	117	309	450	2260	-
Women (%)	1789 (57)	62 (53)	180 (58)	258 (57)	1289 (57)	0.80
Age (years)	55.1 (3.6)	55.1 (3.5)	54.3 (3.7)	56.6 (2.9)	54.9 (3.6)	<0.001
African American race (%)	1465 (47)	91 (78)	227 (73)	273 (61)	874 (39)	<0.001
Smokers (%)	451 (14)	24 (21)	46 (15)	87 (19)	294 (13)	<0.01
Diabetes (%)	412 (13)	41 (35)	93 (30)	112 (25)	166 (7.4)	<0.001
BMI (kg/m^2)	30.4 (6.8)	33.5 (7.4)	34.6 (7.2)	32.8 (6.9)	29.2 (6.2)	<0.001
Total cholesterol (mmol/l)	5.0 (1)	4.7 (1.0)	4.7 (1.0)	4.8 (1.0)	5.1 (0.9)	<0.001
HDL-cholesterol, (mmol/l)	1.6 (0.5)	1.5 (0.6)	1.4 (0.5)	1.5 (0.5)	1.6 (0.5)	<0.001
SBP (mmHg)	119 (15)	125 (19)	126 (18)	125 (16)	116 (13)	<0.001
DBP (mmHg)	72 (10)	76 (12)	77 (11)	76 (11)	71 (9.7)	<0.001
Antihypertensive medication use (%)	1019 (32)	109 (93)	284 (92)	395 (88)	231 (10)	<0.001
Lipid lowering medication use (%)	623 (20)	48 (41)	125 (40)	174 (39)	276 (12)	<0.001
Education (years)	14.9 (1.9)	14.2 (1.9)	14.3 (1.9)	14.5 (1.9)	15.0 (1.9)	<0.001
Sedentary time (h)	7.5 (4.1)	9.1 (4.4)	8.6 (4.4)	8.0 (4.4)	7.2 (4.0)	<0.001

Characteristics drawn from the CARDIA year 30 examination. Data presented as N (percentage) or as mean (SD). h, hours in a week. *P-value for any differences between hypertension onset age groups.

5.2 Agreement between self-reported and objectively determined hypertension onset age (II)

The sample of Study II consisted of 2649 participants (mean age 50±4 years, 57% women). The characteristics of the Study II participants are presented in Article II, Table 1. When hypertension onset age was based on self-report, the proportion of women in the early-onset hypertension group increased. At the CARDIA Year 25 examination, 31.4% (n=831) of the individuals' self-reported onset of hypertension

based on a previously made hypertension diagnosis. The overall hypertension incidence by the Year 25 examination according to the objective definition was 35.3% (n=935) when hypertension onset was based on only 1 examination, and 17.9% (n=475) based on the hypertension criteria needed to be met in 2 consecutive examinations. The overall cumulative hypertension incidence based on objectively defined and self-reported onset age is illustrated in Article II, Figure 1.

The comparison between hypertension onset age categories based on self-reported and objective definition is shown in Table 5. When the objective hypertension diagnosis was based on 2 examinations, self-reported hypertension had good sensitivity (95%) but lower specificity (83%). Conversely, when only 1 examination was required for the objective diagnosis, the sensitivity for self-reported hypertension was poorer (79%), while the specificity was better (95%). The overall agreement for hypertension onset age between the subgroups according to self-reported and objective definition based on 2 examinations was 78%, with the kappa coefficient of 0.48 (95% CI, 0.44–0.51), thus indicating moderate agreement. In contrast, the overall agreement for hypertension onset age between self-reported and objective definition based on only 1 examination was 79%, with a kappa coefficient of 0.66 (95% CI, 0.63–0.68), indicating a substantial agreement. In individuals not using antihypertensive medication, the agreement was only slightly lower (Article II, Online Supplementary Data).

Table 5. Comparison between individuals in hypertension onset age subgroups based on objective definitions and self-report.

		Objectively defined HTN onset age							
		Diagnosis based on 1 examination				Diagnosis based on 2 consecutive examinations			
		<35 years, n	35–44 years, n	≥45 years, n	No HTN, n	<35 years, n	35–44 years, n	≥45 years, n	No HTN, n
Self-reported hypertension onset age	<35 years, n	88	65	23	18	65	67	12	50
	35–44 years, n	40	150	84	23	20	133	41	103
	≥45 years, n	21	48	224	47	5	41	67	227
	No HTN, n	42	36	114	1626	3	8	13	1794

Data presented as n (number of individuals) according to CARDIA year 25 examination. N=2649. HTN, hypertension.

5.3 Association between objectively defined age of hypertension onset and organ damage (I)

The characteristics of the Study I participants are shown in Article I, Table 1. Briefly, the sample for Study I consisted of 2680 individuals (mean age 50 years, 57% women). The prevalence of measured HMODs in subgroups by objectively defined hypertension onset age are shown in Table 6. Furthermore, the mean values of HMOD measures by age of hypertension onset are shown in Article I, Table 2. Overall, the prevalence of all measured HMODs consistently increased with decreasing hypertension onset age. The groups statistically significantly differed from each other for all measured HMODs ($p<0.01$ for all). Individuals in the objectively defined early-onset hypertension group had the highest prevalence of ECHO-LVH, left ventricular diastolic dysfunction (LVDD), coronary calcification, and albuminuria (Table 6). The bivariate correlations between HMODs are presented in Table 7. Additionally, individuals in the early hypertension onset age subgroup had the highest proportion of 1 or more damaged organs (59.5%), and also the highest proportion of multiple damaged organs (24.5%) (Figure 7). Participants without hypertension had the lowest prevalence of any single HMOD (23.7%), and two or more HMODs (4.6%).

Table 6. Prevalence of HMODs at CARDIA year 25 examination according to objectively defined hypertension onset age.

	Objectively defined HTN onset age					
	<35 years	35–44 years	≥45 years	No HTN	All	P-value
N	94	251	136	2199	2680	-
Echo-LVH (%)	35.1	29.1	23.5	13.9	16.6	<0.001
LVDD (%)	16.0	12.4	11.8	8.1	8.9	<0.01
Coronary calcification (%)	23.4	15.9	20.6	6.6	8.8	<0.001
Albuminuria (%)	14.9	14.3	7.4	4.8	6.2	<0.001

HTN, hypertension; ECHO-LVH, echocardiographic left ventricular hypertrophy; LVDD, left ventricular diastolic dysfunction.

Table 7. Bivariate correlations between HMODs at CARDIA year 25 examination.

	ECHO-LVH	LVDD	Coronary calcification	Albuminuria
ECHO-LVH	-	0.047	0.085	0.082
LVDD	0.047	-	0.005	0.072
Coronary calcification	0.085	0.005	-	0.063
Albuminuria	0.082	0.072	0.063	-

Correlations were computed using Pearson correlation coefficient. ECHO-LVH, echocardiographic left ventricular hypertrophy; LVDD, left ventricular diastolic dysfunction. N= 2680.

The results from the unadjusted and multivariable adjusted logistic regression models are shown in Article I, Table 3. Overall, objectively defined early-onset hypertension was most strongly associated with HMODs in all models. Compared to participants without hypertension, early-onset hypertension was related to increased unadjusted ORs of 3.35 (95% CI, 2.16–5.20), 2.17 (95% CI, 1.22–3.85), 4.33 (95% CI, 2.61–7.18), and 3.49 (95% CI, 1.91–6.36) for ECHO-LVH, LVDD, coronary calcification and albuminuria, respectively. In the final multivariable adjusted models, the corresponding odds remained significant for ECHO-LVH, LVDD, and coronary calcification ($p<0.05$ for all), but not for albuminuria ($p=0.75$) (Table 8). Late-onset hypertension was not associated with any of the measured HMODs after appropriate statistical adjustments ($p>0.05$ for all). The results remained largely the same when the adjustments were based on the baseline examination covariates (Article I, Online Supplementary Data). We also observed a linear trend in odds of HMODs by decreasing age of hypertension onset in the unadjusted models ($p<0.005$ for trend in all). However, the trend test results were non-significant in the multivariable adjusted models ($p>0.11$ for trend in all). Participants in the objectively defined early-onset hypertension group also had the highest odds of simultaneously having 2 or more HMODs than any other hypertension onset age group (Figure 7).

Table 8. Adjusted odds of HMOD according to hypertension onset age at CARDIA year 25 examination.

	ECHO-LVH	LVDD	Coronary calcification	Albuminuria
Hypertension onset age	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
<35 years	2.29 (1.36–3.86)	2.06 (1.04–4.05)	2.94 (1.57–5.49)	1.12 (0.55–2.29)
35–44 years	1.67 (1.12–2.48)	1.59 (0.93–2.73)	1.83 (1.10–3.05)	1.25 (0.74–2.09)
≥45 years	1.23 (0.74–2.03)	1.44 (0.75–2.79)	1.41 (0.79–2.52)	0.62 (0.29–1.34)
No hypertension	1.00	1.00	1.00	1.00

Model is adjusted for age, sex, race, BMI, diabetes, total cholesterol, HDL-cholesterol, smoking, use of antihypertensive medication, and systolic blood pressure. ECHO-LVH, echocardiographic left ventricular hypertrophy; LVDD, left ventricular diastolic dysfunction.

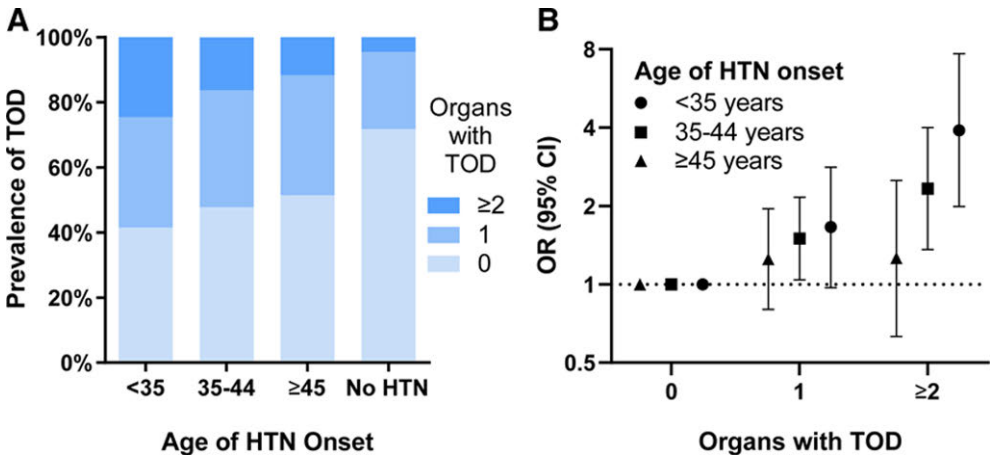

Figure 7. Proportion of individuals with 0, 1 or ≥2 types of organ damage according to hypertension onset age (A). Adjusted odds of having 0, 1 or ≥2 damaged organs by hypertension onset age (B). HTN, hypertension; OR, odds ratio; CI, confidence interval; TOD, target end-organ damage. Reproduced from Hypertension with permission of Wolters Kluwer Health, Inc. (Study I).

5.4 Association between objectively defined age of hypertension onset and cognition (IV)

The sample of Study IV consisted of 2946 participants (mean age 55±4, 57% women). The Study IV sample characteristics are displayed in Article IV, Table 1. Mean cognitive function test scores in the Study IV sample by objectively defined hypertension onset age are presented in Table 9. Participants with early-onset hypertension had the lowest mean scores in DSST, RAVLT and MoCA, and consistently also the highest mean score in the Stroop test ($p<0.001$ for all). Additionally, individuals in the early hypertension onset age group had the lowest mean level of brain volumes as detected by MRI (Table 10). The amount of AWMV and WMFA did not statistically significantly differ between the groups ($p\geq0.05$ for both) (Article IV, Online Supplementary Data).

Table 9. Mean cognitive function test scores at CARDIA Year 30 examination in subgroups by objectively defined hypertension onset age.

	Objectively defined HTN onset age					
	<35 years	35–44 years	≥45 years	No HTN	All	P-value
N	112	277	426	2131	2946	-
DSST, symbols	58 (18)	64 (17)	63 (16)	70 (16)	68 (17)	<0.001
RAVLT, words	6.9 (3.2)	7.5 (3.4)	7.7 (3.4)	8.9 (3.4)	8.5 (3.4)	<0.001
Stroop test, score	28 (14)	25 (13)	25 (14)	21 (11)	23 (12)	<0.001
Composite cognition, z-score	-0.5 (0.8)	-0.2 (0.8)	-0.2 (0.8)	0.1 (0.7)	0.0 (0.7)	<0.001
MoCA, score	21 (3.9)	23 (3.9)	23 (4.1)	24 (3.7)	24 (3.9)	<0.001

Data presented as mean (SD). Htn, hypertension; RAVLT, Rey Auditory Verbal Learning test; DSST, Digit Symbol Substitution test; MoCA, Montreal Cognitive Assessment.

Table 10. Mean brain volumes at CARDIA Year 30 examination in subgroups by objectively defined hypertension onset age.

	Objectively defined HTN onset age					
	<35 years	35–44 years	≥45 years	No HTN	All	P-value
N	18	41	78	462	599	-
ICV, cm^3	1250 (165)	1340 (154)	1360 (151)	1390 (151)	1380 (154)	<0.001
WMV, cm^3	485 (63)	518 (60)	521 (64)	533 (64)	529 (65)	<0.01
GMV, cm^3	576 (54)	612 (66)	620 (60)	639 (64)	633 (64)	<0.001
TBV, cm^3	1060 (108)	1130 (121)	1140 (118)	1170 (123)	1160 (123)	<0.001

Data presented as mean (SD). Htn, hypertension; ICV, intracranial volume; WMV, white matter volume; GMV, grey matter volume; TBV, total brain volume.

The associations between objectively defined hypertension onset age and cognitive function are shown in Article IV, Table 3. In the unadjusted model, participants with early-onset hypertension had β± standard error (SE) of 0.57±0.09, 0.71±0.09, 0.50±0.09, 0.60±0.07, and 0.81±0.09 lower standardized scores for RAVLT, DSST, Stroop test, composite cognition, and MoCA ($p<0.001$ for all), compared to normotensive participants. The associations remained significant in the fully adjusted model for all cognitive function tests ($p<0.05$), except for the RAVLT ($p=0.22$) (Table 11). The hypertension onset between 35–44 years or over 44 years of age was not statistically significantly associated with cognitive test performance after final covariate adjustments ($p>0.05$ for all). The relations between objectively defined hypertension onset age and global cognitive function scores are presented in

Figure 8. Overall, only early-onset hypertension was related to both a lower standardized composite cognitive score and a lower MoCA score in the final adjusted models ($p<0.05$ for both). We also observed a linear trend in the fully adjusted models between a decreasing hypertension onset age and lower global cognitive function scores ($p<0.01$ for trend in both). Additionally, objectively defined early-onset hypertension was related to standardized z-scores (β±SE) of 0.76±0.24, 0.97±0.23, and 0.90±0.24 for lower WMV, GMW and TBV in the unadjusted analyses ($p< 0.01$ for all) (Article IV, Online Supplementary Data). However, after appropriate model adjustments, hypertension onset age was no longer statistically significantly associated with the structural brain alterations ($p<0.05$ for all).

Table 11. Adjusted associations between hypertension onset age and cognitive test performance at CARDIA year 30 examination.

	DSST	RAVLT	Stroop test	MoCA
Hypertension onset age	(β±SE)	(β±SE)	(β±SE)	(β±SE)
<35 years	-0.24±0.09†	-0.12±0.09	-0.22±0.10‡	-0.27±0.09†
35–44 years	-0.03±0.07	-0.07±0.07	-0.08±0.07	-0.06±0.07
≥45 years	-0.07±0.06	-0.03±0.06	-0.11±0.07	0.04±0.06
No hypertension	Ref.	Ref.	Ref.	Ref.

Model is adjusted for age, sex, race, education, diabetes, BMI, smoking, alcohol intake, sedentary time, use of antihypertensive medication, and systolic blood pressure. †p<0.01, ‡p<0.05. RAVLT, Rey Auditory Verbal Learning test; DSST, Digit Symbol Substitution test; MoCA, Montreal Cognitive Assessment; Ref, reference.

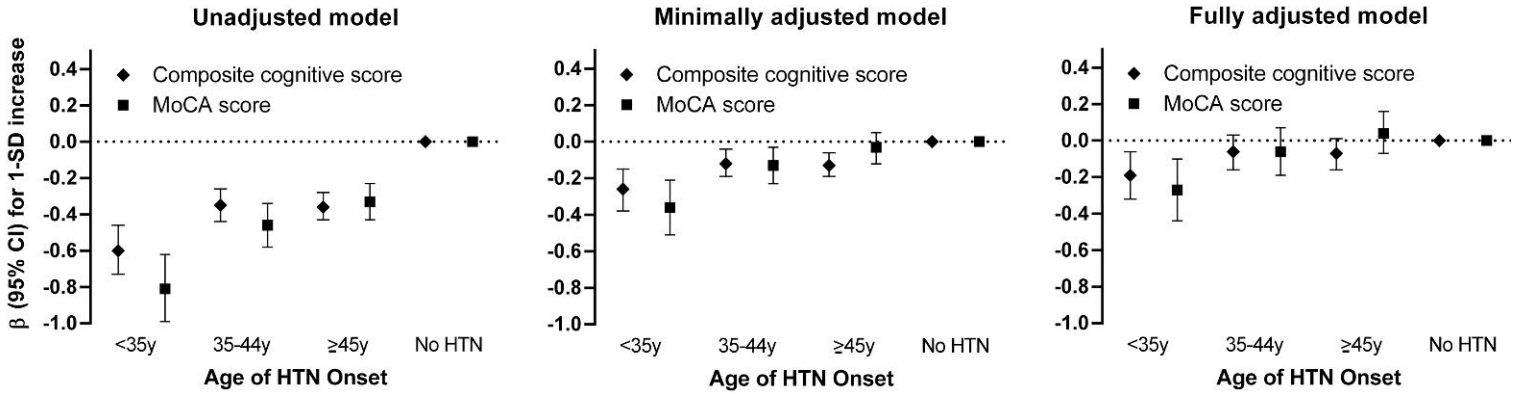

Figure 8. Associations between hypertension onset age and 1-SD increase in mean global cognitive function scores. Minimally adjusted model is adjusted for age, sex, race, and education. Fully adjusted model is adjusted for age, sex, race, education, diabetes, BMI, smoking, alcohol intake, sedentary time, use of antihypertensive medication and systolic blood pressure. HTN, hypertension; y, year; MoCA, Montreal Cognitive Assessment. Reproduced from Hypertension with permission of Wolters Kluwer Health, Inc. (Study IV).

5.5 Association between self-reported age of hypertension onset and organ damage (II and III)

In the Study II sample, we also assessed the relation between self-reported hypertension onset age and presence of HMODs. In the Study II sample, 194 (7.3%) individuals had self-reported early-onset hypertension. Overall, the associations between self-reported hypertension onset age and HMODs were similar when compared to the objectively defined hypertension onset age (Article II, Table 3). Individuals with self-reported hypertension onset <35 years of age had an increased unadjusted odds of 3.54 (95% CI, 2.55–4.92), 2.14 (95% CI, 1.39–3.29), 4.15 (95% CI, 2.79–6.19), and 4.05 (95% CI, 2.50–6.54) for having ECHO-LVH, LVDD, coronary calcification and albuminuria when compared to individuals who did not report having hypertension ($p<0.001$ for all). In the final multivariable logistic regression models, early-onset hypertension was associated with ECHO-LVH, LVDD and coronary calcification ($p<0.01$ for all) (Figure 9). The self-reported hypertension onset age was not related to the presence of albuminuria in the fully adjusted models ($p>0.05$ for groups). Instead, the self-reported hypertension onset age ≥45 years was associated with having LVDD in the final adjusted model ($p<0.05$). Furthermore, the odds for albuminuria with late-onset hypertension were lower than with early-onset hypertension (Figure 9). Self-reported late-onset hypertension was not associated with ECHO-LVH, coronary calcification or albuminuria ($p>0.05$ for all).

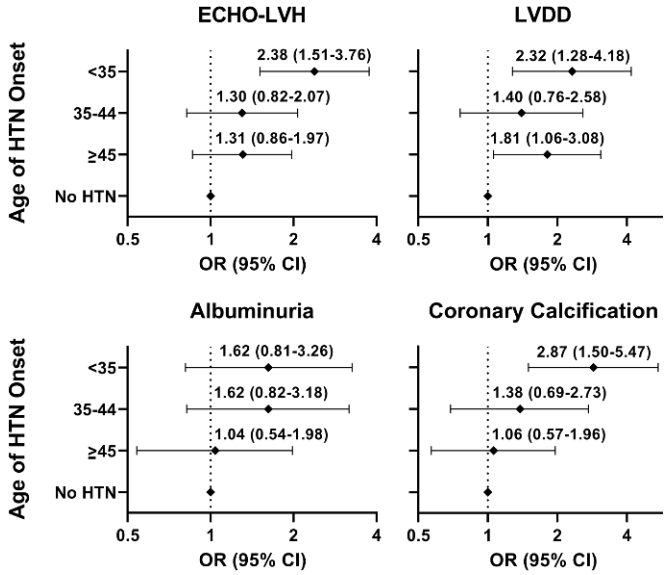

Figure 9. Odds of HMODs according to self-reported hypertension onset age at CARDIA Year 25 examination. Model is adjusted for age, sex, race, diabetes, BMI, total cholesterol, HDL-cholesterol, smoking, use of antihypertensive medication and systolic blood pressure. HTN, hypertension; OR, odds ratio; CI, confidence interval, ECHO-LVH, echocardiographic left ventricular hypertrophy; LVDD, left ventricular diastolic dysfunction.

Additionally, we evaluated the association between self-reported hypertension onset age and HMOD in another sample in Study III. The sample of Study III consisted of 2864 individuals from the Health 2000 survey (mean age 63±10, 57% women). The detailed characteristics of Study III sample are presented in Article III, Table 1. Briefly, 40% (n=1158) of the study III participants self-reported having hypertension and 6.0% (n=172) had self-reported early-onset hypertension (onset <40 years of age). Here, the prevalence of ECG-LVH was statistically significantly higher in those with the self-reported hypertension onset at any age in comparison to those who did not report having hypertension ($p<0.001$ for Cornell voltage, Sokolow-Lyon voltage, and Minnesota criteria) (Article III, Table 1). However, there were no statistically significant differences in ECG-LVH prevalence between the age of hypertension onset subgroups ($p\geq0.47$ for all). In the multivariable adjusted models, the self-reported hypertension onset at any age was associated with increased odds of ECG-LVH when compared to individuals without self-reported hypertension ($p<0.001$ for Sokolow-Lyon and Minnesota criteria). Participants with self-reported early-onset hypertension had multivariable adjusted ORs of 2.10 (95%, CI 1.19–3.72), 1.17 (95%, CI 0.66–2.08), and 2.22 (95%, CI 1.40–3.52) for ECG-LVH by Sokolow-Lyon, Cornell, and Minnesota criteria, respectively ($p<0.05$ for Sokolow-Lyon and Minnesota criteria). In contrast, there were no significant differences in ORs for ECG-LVH according to the self-reported hypertension onset age and thus the odds for ECG-LVH were similar to the values in individuals with late-onset hypertension (Figure 10).

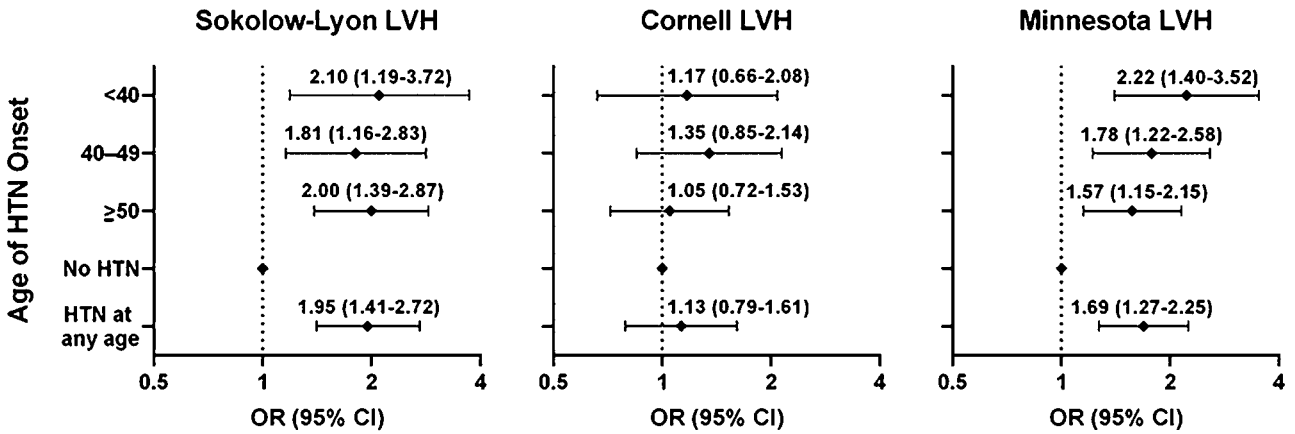

Figure 10. Odds of ECG-LVH according to self-reported hypertension onset age in Health 2000 survey. Model is adjusted for age, sex, BMI, smoking, diabetes, non-HDL-cholesterol, heart rate, heart failure, coronary heart disease, use of antihypertensive medication and systolic blood pressure. HTN, hypertension; LVH, left ventricular hypertrophy, OR, odds ratio; CI, confidence interval.

6 Discussion

6.1 Clinical correlates of early-onset hypertension (V)

In Study V, we observed that African American race, diabetes mellitus, higher BMI, and LLM were associated with having early-onset hypertension. In African Americans and diabetic individuals, the odds for earlier hypertension onset also linearly increased in all of the age of onset categories. A similar trend was also observed for lower education, however this did not reach statistical significance. Our findings are in line with previous two studies which demonstrated that individuals with an early-onset hypertension onset were more likely to be obese (189,193). In contrast to these studies, we did not observe a statistically significant association between an early hypertension onset age and male sex. However, these two studies had very small sample sizes and included only Asian individuals. In this study, we identified African American race, and diabetes as additional potential risk factors for developing early-onset hypertension in this large biracial cohort with individuals of varying ages of hypertension onset. Similar racial differences in hypertension incidence patterns by age have also previously been reported from the CARDIA study (238). In that previous report, approximately 75% of African American men and women had developed hypertension by 55 years of age. However, in that study, hypertension was defined using a lower BP threshold of ≥130/80 mmHg, and the diagnosis was based on a single visit. Even though in that study African Americans had a higher risk of developing hypertension, the HRs were not reported separately for early-onset hypertension. It is likely that if a lower BP threshold had been used in our study, as recommended by the current AHA/ACC guidelines, the overall prevalence of hypertension had been higher. In accordance with prior evidence (195), our findings emphasize the need for applying different diagnostic and management strategies when investigating secondary causes among African American individuals with early-onset hypertension. However, in this study the etiology of hypertension was not known. Overall, compared to primary hypertension, secondary hypertension is still much less common among these individuals given the high burden of primary hypertension (37,38). Nevertheless,

race appears to be one of the most prominent contributors to the risk of early-onset hypertension onset.

A genetic predisposition is a notable and previously established risk factor for early-onset hypertension. The heritability of hypertension can also be estimated at least to some extent by determining the family history of hypertension (187,206). Previous studies have suggested that the pathophysiology of hypertension among African Americans involves the interaction between environmental factors, genetic background, comorbid conditions and psychosocial components (239,240). Genetic determinants are indeed important as genetic studies have identified distinct genes, such as those involved in RAAS activation, associated with hypertension particularly in African Americans (241,242). Similar findings have been reported also among other individuals of African descent, however on the other hand the prevalence of hypertension also seems to vary greatly between populations (242,243). It might be possible that genetic predisposition accounts for the development of early-onset hypertension in African American individuals, although these individuals might also merely experience accumulation of risk factors for having early-onset hypertension. However, there is yet very limited evidence on the impact of social, behavioral, and pregnancy-related factors (184,196). Our findings expand the previous knowledge by proposing diabetes to be a potential risk factor for early-onset hypertension. Interestingly, findings from one study suggested that a familial history of hypertension and obesity could promote the onset of primary hypertension already in childhood (190). These findings suggest that potential risk factors of early-onset hypertension might be distinguished very early in life, thereby enabling the implementation of even earlier intervention strategies for preventing hypertension and consequently its complications. This is particularly important as our findings suggest that individuals with early-onset hypertension seem to experience a clustering of CVD risk factors and increased prevalence of LLM use, which might imply that these individuals are also more likely to have dyslipidemias.

Even though diabetes, a high value of BMI and African American race have been previously distinguished as risk factors for developing hypertension at any age (50,51), these features seem to associate particularly robustly with having early-onset hypertension. Especially African American ethnicity and diabetes were related with a trend towards an earlier onset of hypertension. Considering that particularly early-onset hypertension increases the risk for subsequent CVD and all-cause mortality (187,191,214), identifying these high-risk individuals already prior to the manifestation of actual hypertension could improve their long-term disease prognosis. Indeed, early-onset hypertension could in part further explain the social and ethnic disparities in CVD morbidity and mortality (3,4). Our findings suggest that intensive screening protocols for hypertension should be focused on African American individuals in the community already in the early stages of life, even prior

to adulthood. Moreover, early prevention and treatment strategies should be applied to those individuals with other comorbidities, particularly those with diabetes and obesity, in order to avoid the development of early-onset hypertension.

6.2 Agreement between self-reported and objectively determined hypertension onset age (II)

Results from Study II revealed that the overall diagnostic agreement between self-reported and objectively defined age of hypertension onset was satisfactory, varying from moderate to substantial agreement depending on the criteria for the objectively reported onset of hypertension. Self-reported hypertension onset at any age also had rather high sensitivity and specificity. Previous reports have suggested that the specificity of the overall presence of hypertension by self-report is over 90%, although the sensitivity on self-reported hypertension is generally much lower and ranges from around 50% to over 80%, depending on the study (244–246). However, we are not aware of any other previous investigations which had directly assessed the agreement between different methods to determine the onset age of hypertension. Given that the agreement was higher when objective hypertension onset age was defined by hypertension criteria met at 1 examination rather than 2 consecutive examinations, this is likely to represent the hypertension diagnosis made during the follow-up for the CARDIA study participants. Requirement of 2 examinations for the objective diagnosis presumably leads to a lower agreement as the participants have probably been diagnosed based on 1 follow-up visit and some may have achieved normotension by the next follow-up visit without antihypertensive medication. Compared to the general population, the CARDIA study participants have also undergone rather many routinely conducted health examinations and are presumably more aware of their state of health along with diagnosed chronic diseases. In that respect, these individuals are also likely to have improved recall of the age at which hypertension diagnosis was set for them. This improved accuracy in self-rated health might therefore depict the impact of conducting routine health counseling during young adulthood (247,248). Moreover, the age of hypertension onset here is likely to very closely represent the actual onset of hypertension in these individuals considering the short time-intervals between the follow-up examinations. Thereby, the maximum delay between age of hypertension onset and age at hypertension diagnosis in CARDIA study is only 5 years. For most hypertensive individuals in the community, the lag time is however likely to be longer in everyday clinical practice.

The agreement between these methods is also highly dependent on the definition and methods utilized to determine the objectively defined hypertension onset age. In

fact, the BP thresholds to define hypertension have changed considerably during the past few decades, as guidelines have gradually recommended the adoption of lower thresholds for hypertension. If a lower BP threshold for objective hypertension onset had been used in our study, this would presumably have led to increased sensitivity and decreased specificity of self-reported hypertension. Moreover, modern methods for improved diagnostic accuracy for hypertension have been introduced and applied for use in clinical practice, such as home BP and ambulatory BP monitoring (249,250). Therefore, it is evident that the correlation between self-reported and objectively defined age of hypertension onset will always be dependent on the diagnostic accuracy, along with the patient-clinician interaction and the efficiency of provided patient education. Nevertheless, clinical practice in the field of medicine invariably involves some diagnostic inaccuracies and uncertainties in all measurement methods (251). Additionally, despite some limitations regarding precision, self-reported information on the individual's state of health is commonly used in both epidemiological research and in clinical practice mostly due to its easy availability and good feasibility (252). In that respect, assessing the age of hypertension onset from the patient's self-report could represent a valuable alternative method in situations where objective BP data are not available.

6.3 Association between objectively defined age of hypertension onset and organ damage (I)

In Study I, we observed that objectively defined early age of hypertension onset is associated with an increased odds of ECHO-LVH, LVDD, and coronary calcification. Late hypertension onset age on the other hand was not associated with any of the measured HMODs. However, the age of hypertension onset was not associated with albuminuria. Additionally, the prevalence and odds for multiple HMODs were highest among individuals with early-onset hypertension. Even though the odds of HMODs generally gradually increased according to the earlier age of hypertension onset subgroup, the trend test across age groups remained non-significant in the multivariable-adjusted models.

Even though the presence of hypertension in general is a commonly known risk factor for development of HMOD, no prior studies have investigated the impact of hypertension onset age on HMODs. A few previous studies have demonstrated that early hypertension onset age is a prominent risk factor for subsequent hard CVD outcomes, including CVD death (187,191,214). Findings from this study indicate that these individuals with early-onset hypertension are also at high risk of having HMODs in midlife. The presence of HMOD has been demonstrated to substantially increase the risk of overt CVD in these hypertensive individuals (93–96). Particularly the presence of LVH and CAC has been identified as strong predictors

of overt coronary heart disease and major hard cardiovascular events in those previous studies. Therefore, the pathophysiological mechanisms behind early hypertension onset age could act via first causing impaired function of various organs, initially leading to coronary heart disease and eventually to CVD death. Our findings suggest that the factors underlying early-onset hypertension may act particularly by impairing the function of cardiac effects and promoting coronary calcification, rather than inducing notable renal-related complications. Moreover, the impact on cardiac effects seems to differ by sex as men with early-onset hypertension tend to experience an increase in LVM, whereas early-onset hypertension in women associates more prominently with altered diastolic function (253).

Several previous studies have demonstrated that long-term exposure to elevated BP during an individual's life course predicts subsequent HMOD and CVD outcomes (13–15,161). Unfortunately, these previous studies have used various methods to evaluate the overall exposure to BP during the individual's lifetime e.g. by utilizing different BP indices, including time-averaged BP, cumulative BP, and BP trajectories, although all these parameters are based on objective BP data. Although repeatedly measured and documented BP data spanning over decades provides good prognostic information about the future CVD risk, these kinds of data are unlikely to be available for most patients in everyday clinical practice. Nevertheless, age of hypertension onset is likely to represent the overall lifetime exposure to high BP similarly to other long-term BP indices. The overall hypertension exposure time is another potential contributing factor for this phenomenon. In fact, this continuous effect of high BP experienced by the cardiovascular system throughout decades appears to carry an even higher CVD risk when compared to high BP detected on single occasions. This might be partly explained by the dose-response effect for the number of years with high BP on the lifetime risk of CVD. All in all, these findings advocate the need for more efficient treatment strategies for younger hypertensive patients, who still frequently remain undetected and undertreated (11,12). Moreover, these results highlight the importance of achieving and maintaining good hypertension control throughout the individual's lifetime.

Besides solely experiencing a higher longitudinal BP burden, other mechanisms causing accelerated HMOD development should also be considered. One possible pathophysiological mechanism accounting for the increased risk of CVD outcomes could be mediated through induced EVA. Prior studies have demonstrated the increased hypertension heritability and distinct genomic background of early-onset hypertension (181,188,207,209). Interestingly, arterial stiffness has also been suggested to have a strong genetic predisposition (254). Thereby, the potential impact of EVA on early-onset hypertension could offer a possible pathway

explaining the heritability aspect of early-onset hypertension, a proposal that warrants further investigations.

6.4 Association between objectively defined age of hypertension onset and cognition (IV)

In Study IV, we demonstrated that objectively defined early hypertension onset age was associated with impaired cognitive function, but not with smaller brain volumes, in midlife. The association was significant for the global cognitive function and this association remained regardless of the current BP when the cognitive status was assessed. In contrast, a late hypertension onset age was not related to worse cognitive function as compared to those without hypertension. These findings suggest that the impact of hypertension onset age extends beyond CVD related outcomes and may be linked with an increased risk of subsequent dementia in later life (113,115,172). This observed cognitive decline in midlife may precede mild cognitive impairment and eventually lead to late-life clinical dementia. Therefore these results could well suggest that deaths due to dementia may account for part of the non-CVD mortality leading to increased risk for all-cause mortality in individuals with early age of hypertension onset (214). Should that be the case, it is evident that a clarification of the mechanisms related to early-onset hypertension and cognitive function could be extremely beneficial in the context of public health challenges in this era of a global aging population and an accumulating burden of dementia (119,255).

Our findings are in line with the two previous studies (182,183), suggesting that hypertension onset during early-and mid-adulthood increases the risk for cognitive impairment in midlife and subsequent late-life dementia (112,114,115). Conversely, it might be possible that very late hypertension onset age onset could even be protective against dementia. However, evidence in this study field is still very limited and the published studies have included individuals of very different ages. Indeed, several studies have demonstrated a highly age-dependent relationship between BP exposure and cognitive outcome assessment (120,122,126,171). These findings are likely explained by the normal pathophysiological changes experienced in aging, indicating that a high BP throughout the majority of an individual's lifetime is detrimental for her/his cognition. However, a BP increase in late-life could arise from the physiological and necessary compensatory mechanisms to ensure sufficient blood flow to the brain through stiffened arteries caused by normal vascular aging (62). Consequently, a high BP in the elderly has also been observed to prevent dementia (134,135,256). Similarly to previously described risk for CVD, the cumulative effects of long-term BP exposure during the life course is therefore presumably an important contributor also for cognitive decline (172,173,180). All in all, assessing the age of hypertension onset along with current BP in hypertensive

individuals could improve the risk-stratification of cognitive impairment by representing the lifetime hypertension chronicity. This could result in diminishing unnecessarily strict BP control in old age patients.

Contrary to the observed effect on cognitive function, we did not detect an association between hypertension onset age and structural brain changes, such as decreased brain volumes, in midlife. However, the majority of the age-related differences in brain volumes as quantified with MRI have been suggested to occur gradually and only after 50 years of age (257). Therefore, the potential harms of early-onset hypertension on major structural brain changes might only be evident in older study populations. Yet, it is possible that cerebral microbleeds had been evident already among these younger individuals with early-onset hypertension, however this data was not available in our study. These findings could indicate that hypertension, and its age of onset, initially impacts on cognitive function in younger individuals, which might eventually later be detected as neuroanatomical changes in the elderly (258,259). However, these initial effects on cognition might be detectable by using more advanced brain imaging techniques which also capture the functional brain properties (260). Nevertheless, assessing the age of hypertension onset could aid in distinguishing the individuals at a high-risk for impaired cognitive function, and thereby improve the treatment strategies in hypertensive individuals. Nonetheless, it evident that assessing the hypertension onset age by self-report in individuals with potentially decreased cognitive capacity might lack precision and reliability. Thus, objective ways to define the age of hypertension onset may be preferable methods when assessing the risk that an individual will suffer a cognitive decline.

6.5 Association between self-reported age of hypertension onset and organ damage (II and III)

Based on the results of Study II and Study III, the association between self-reported hypertension onset age and presence of HMODs seems inconsistent. Here, we observed that self-reported early-onset hypertension was more strongly related to an increased odds of ECHO-LVH, LVDD, and coronary calcification among the CARDIA study participants, as compared to self-reported late-onset hypertension. These associations between self-reported hypertension onset age and HMODs seem to be comparable with those obtained using objectively defined hypertension onset age. However, the difference in odds of HMODSs between early- and late-onset hypertension was not as robust when defined by self-report, supporting the agreement analyses, indicating that self-reported hypertension onset age does have satisfactory sensitivity but lacks some sensitivity in determining the actual onset age

of hypertension. Furthermore, in our other distinct population study sample, the self-reported hypertension onset age was not associated with ECG-LVH more strongly than the overall onset of hypertension at any age. These differences might be caused by several factors. First, previous data suggests that ECG-LVH lacks sensitivity in detecting anatomical LVH (261), and therefore echocardiographic LVH is presumably a more accurate method for distinguishing the actual presence of LVH (262). Second, the study populations differ from each other as the CARDIA study involved both African American and white US citizens, whereas the Health 2000 survey examined only white Finns. Third, the Study III sample included slightly older individuals compared to those in Study II. Fourth, the study designs were markedly distinct considering the cross-sectional study nature of the Health 2000 survey and in comparison, the prospective design of the CARDIA cohort study including up to 30 years of follow-up. Thereby, no clear conclusions can yet be made based on these two study findings and further investigations are needed.

Although no previous evidence exists on the relations between self-reported hypertension onset age and CVD, previous studies have successfully used self-report as a method to determine the hypertension onset age in the context of other research areas (182–184). In the everyday clinical setting, physicians might struggle with gaining access to previous medical records and gathering information from previously obtained objective measures of health. Thus, assessing the age of hypertension onset could still be convenient for clinicians treating hypertensive patients without access to longitudinal BP data. Despite the potentially linear association between age of hypertension onset and adverse outcomes, defining early-onset hypertension by a specific age-threshold could be useful in describing a more precise risk estimate also for physicians. Novel methods to improve risk assessment in these individuals with LVH could have important clinical implications, as BP treatment induced regression of echocardiographic LVH and ECG-LVH has been demonstrated to improve the prognosis of CVD (263,264). However, the clinical applicability of self-reported hypertension is likely to depend on the individual's ability to recall his/her previous state of health and hypertension diagnosis, which might cause notable between-individual variation. Given that hypertension is a symptomless disease, distinguishing between age of hypertension onset and age at hypertension diagnosis is likely to be unachievable. Nevertheless, an assessment of self-reported hypertension onset age could represent a feasible supplemental method to be implemented in everyday clinical practice in order to optimize the risk-stratification of hypertensive individuals.

6.6 Strengths and limitations of the study

The strengths of this study include a large, multiethnic, and socially diverse CARDIA study cohort. Additionally, participants joining this prospective study were in their early adulthood during study enrollment and have undergone up to 30 years of follow-up with 9 regularly conducted follow-up examinations. The participation rate at Year 30 examination was approximately 65.7% of the initial cohort. However, the brain MRI substudy in Study IV included fewer individuals (17.8% of Year 30 examination participants). Additionally, assessment of other brain MRI measures, such as white matter hyperintensities, could have provided more information about the impact of hypertension onset age on cognition. Given the observational nature of the CARDIA study, we applied a case-control study setting which has some limitations in the level of evidence provided. The CARDIA study participants BP levels and antihypertensive medication use were serially documented throughout the follow-up, allowing a precise estimation of hypertension onset age since only a few individuals had developed hypertension before the study was initiated. However, we were unable to consider the intensity of antihypertensive treatment, or the effect of different antihypertensive medication use throughout the follow-up. Even though we did not observe an association between early-onset hypertension and albuminuria, this might have been due to the use of RAAS inhibitors which might have prevented development of albuminuria. Additionally, considering the follow-up study design and lack of elderly participants in the CARDIA study, our results may not be generalizable to the entire social population.

Self-administered questionnaires were used to collect information on self-reported age of hypertension onset from the participants. Therefore, we had no information on the initial source of the self-reported hypertension and distinguishing between the timing of hypertension onset and hypertension diagnosis was not possible. We drew all sample characteristics from the same examination during outcome assessment, although use of baseline covariates could have enabled a more longitudinal study analyses. We also included participants from another cross-sectional study consisting of slightly older Finns, who were randomly drawn from the general community population register. Even though no objective BP measurement data were available and ECG-LVH was the only available assessed HMOD, this distinct study sample did allow us to evaluate the extent of this phenomenon in another population. Due to these epidemiologic study designs, we were able to determine associations, which do not necessarily imply a causal effect. Nevertheless, we have provided novel insights about the feasibility of both objectively and self-reported hypertension onset age.

6.7 Clinical implications

In clinical practice, making an assessment of age of hypertension onset instead of paying attention to only current BP levels, could offer considerable advantages for evaluating the chronic stage of hypertension. The clinical feasibility of previously introduced BP indices to assess long-term BP exposure have remained poor given the requirement of having access to numerous previously documented BP measurements and the complexity of the proposed calculation methods. Compared to these other longitudinal BP indices, age of hypertension onset offers a simplified constant two-digit attribute which could be documented into patient records to evaluate the patient's cumulative lifetime BP burden. This information describing the hypertension chronicity could be easily considered in the clinical risk stratification methods and it could be a feasible alternative for considering the patient's theoretical BP load. Consequently, improved prediction of future CVD and other adverse outcomes, might be achieved. Moreover, this method provides a more individualized and patient centered approach for management and treatment of hypertension, which could in turn improve the patient's motivation to treatment. The reversibility of HMODs also emphasizes the window of opportunity to optimize antihypertensive treatment in these individuals. Better consideration for each patient's individual values may in turn motivate him/her to undertake the necessary lifestyle changes and possibly even improve his/her adherence to treatment.

Overall, the age of hypertension onset could act as a patient-specific assessment with good applicability for health care professionals while engaging patients to actively participate in decision-making of their own state of health. By incorporating patient values and preferences in the management of hypertension, a more patient centered care could be offered. For clinicians, practical and time-efficient methods are crucial in order to provide the most beneficial impact for the entire community. Considering the pragmatic approach of this method, it might have important clinical implications especially for primary care physicians. Additionally, as hypertension onset age improves the estimation of hypertension heritability, information of the patient's parents should also be determined to simultaneously assess the risk of hypertension in his/her offspring. Given that physicians might struggle with access to patients previously obtained objective BP data from different health care providers or even access to older medical records, many physicians may need to rely on self-reported information about hypertension onset age. However, preliminary results indicate that this could also be a sufficiently satisfactory source of information. Therefore, it is recommended that clinicians should document the age of hypertension onset for their newly diagnosed hypertensive patients.

6.8 Future prospects

Findings from this study describe the potential predisposing factors and risks of adverse outcomes related to early-onset hypertension. However, there are only a few studies which have considered the age of hypertension onset in their analyses. Thus, more research is needed to investigate this phenomenon in both similar and different study populations with even longer follow-up times extending over the entire lifespan. Moreover, these results should also be replicated in other studies in order to further address whether the applied study design would have an effect on the findings, which would therefore impact the potential clinical feasibility of assessing hypertension onset age. Additionally, the current evidence so far is mostly based on observational studies as ways of providing evidence about the harms and prognosis of early-onset hypertension. Therefore, interventional study designs and settings will be necessary to clarify the potential causal relationship and to decrease the potential risk of research bias. Randomized clinical trials could be carried out to examine the potential effect of different therapeutic interventions, including antihypertensive treatment strategies, depending on the subject's age of hypertension onset.

To date, no universal definition for early-onset hypertension exists and likewise there is no clear consensus about the BP thresholds to define the onset of hypertension. Evaluating the pros and cons of different BP thresholds and age of onset definitions could further improve our understanding of this phenomenon. Similarly, the underlying mechanisms causing early-onset hypertension, such as the potential impact of EVA, demand more focus. With accumulating evidence, new improved risk prediction models for hypertensive individuals could possibly be implemented into clinical practice. In the future, the assessment of hypertension onset age could potentially be added to the clinical guidelines for the management of hypertension. Different treatment and management strategies for hypertension may be called for according to both the current chronological age of the patient and their age of hypertension onset. Therefore, hypertensive individuals could be assigned to different BP target and risk levels depending on their current age and their hypertension onset age. Given its genetic underpinnings, in the future, early-onset hypertension might even be considered as a distinct hypertension subtype.

7 Summary/Conclusions

In this thesis we aimed to elucidate the correlates of early-onset hypertension and the role of early hypertension onset age in relation with an individual having end-organ damage in midlife. In addition, we assessed the feasibility of different methods to assess age of hypertension onset and also discussed the potential clinical significance of these findings.

We identified African American ethnicity, diabetes, and obesity as potential risk factors for developing early-onset hypertension. Individuals with early hypertension onset age seem to experience a clustering of commonly distinguished CVD risk factors. Unfortunately, no standard definition for early-onset hypertension yet exists. Nevertheless, targeted screening strategies may be called for these individuals at high risk for having early-onset hypertension.

Furthermore, we observed that early-onset hypertension is associated with increased odds of having LVH, LVDD and coronary calcification by midlife. Similarly, an early age of hypertension onset was related to impaired midlife cognitive function. In contrast, late-onset hypertension was not associated with the aforementioned outcomes. Overall, hypertension that begins in early life appears to be more detrimental compared to hypertension that initially appears only later in life. Interestingly, the impact of the hypertension onset age on adverse events seems to be noteworthy irrespective of the present BP level during the outcome assessment. It is presumable that the long-term lifetime exposure to high BP is a major factor contributing to adverse events in later life. The age of hypertension onset is likely to represent the individual's cumulative lifetime burden of high BP in a similar manner as several other previously introduced longitudinal BP measures. However, the assessment of hypertension onset age could possibly provide an even more advantageous method for incorporation into clinical practice due to its simplicity and feasibility.

Our findings also suggest that the age of hypertension onset could also be assessed rather reliably by using self-reported information. Even though objective measures are probably the most optimal and precise way to define hypertension onset, self-reported hypertension onset age could serve as a practical and pragmatic approach and one which could be applied in clinical practice to assess the chronicity

of hypertension. In addition, evaluating the age of hypertension onset could simultaneously be used to estimate hypertension heritability in these individuals, and their offspring. It seems that the most optimal method to define the age of hypertension onset still remains to be determined. Nevertheless, the assessment of the hypertension onset age, even if this information is obtained by patients' self-report, could feasibly improve the risk assessment of hypertensive individuals particularly in primary health care. This could aid in distinguishing the high-risk individuals in need for enhanced hypertension treatment strategies from those who are less likely to benefit from antihypertensive therapy.

Given its distinct features and established genetic underpinnings, in the future, early-onset hypertension may potentially even be considered as a distinct hypertension entity. The potential underlying mechanism of early-onset hypertension may be related to accelerated vascular aging, leading to various adverse events. An appreciation of this phenomenon could lead to the discovery of novel tools for diagnostic purposes and potential targets for therapeutic interventions. However, more research will be required on this topic and the overall level of evidence on the impact of early-onset hypertension is still limited. Nonetheless, the current evidence suggests that individuals with established hypertension already at a very young age might need more rigorous actions to achieve hypertension control in order to improve the long-term lifetime prognosis of hypertension.

In conclusion, findings from this thesis further emphasize the importance of assessing the age of hypertension in individuals with hypertension in clinical practice. Therefore, physicians should be aware of the age at which their patients initially became hypertensive, rather than simply being satisfied with diagnosing the presence or absence of hypertension. Future studies will be needed to clarify the impact of this phenomenon in different study settings and populations.

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References

1. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet. 2018; 392:2052–2090.
2. Forouzanfar MH, Afshin A, Alexander LT, Biryukov S, Brauer M, Cercy K, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388:1659–1724.
3. Zhou B, Bentham J, Di Cesare M, Bixby H, Danaei G, Cowan MJ, et al. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2017; 389:37–55.
4. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115mmHg, 1990-2015. JAMA. 2017; 317:165–182.
5. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control. Circulation. 2016; 134:441–450.
6. Beaney T, Schutte AE, Tomaszewski M, Ariti C, Burrell LM, Castillo RR, et al. May Measurement Month 2017: an analysis of blood pressure screening results worldwide. Lancet Glob Heal. 2018; 6:e736–e743.
7. Zhou B, Danaei G, Stevens GA, Bixby H, Taddei C, Carrillo-Larco RM, et al. 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; 394:639–651.
8. Berenson GS, Wattigney WA, Bao W, Nicklas TA, Jiang X, Rush JA. Epidemiology of early primary hypertension and implications for prevention. The Bogalusa Heart Study. J Hum Hypertens. 1994; 8:303–311.
9. Bao W, Threefoot SA, Srinivasan SR, Berenson GS. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: The Bogalusa heart study. Am J Hypertens. 1995; 8:657–665.
10. Malberg JW, Savage EP, Osteryoung J. Nitrates in drinking water and the early onset of hypertension. Environ Pollut. 1978; 15:155–160.
11. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013; 310:959–968.
12. Sivén SS, Niiranen TJ, Aromaa A, Koskinen S, Jula AM. Social, lifestyle and demographic inequalities in hypertension care. Scand J Public Health. 2015; 43:246–253.
13. Lauer MS, Anderson KM, Levy D. Influence of contemporary versus 30-year blood pressure levels on left ventricular mass and geometry: The Framingham Heart Study. J Am Coll Cardiol. 1991; 18:1287–1294.

14. Zemaitis P, Liu K, Jacobs DR, Cushman M, Durazo-Arvizu R, Shoham D, et al. Cumulative systolic BP and changes in urine albuminto-creatinine ratios in nondiabetic participants of the multi-ethnic study of atherosclerosis. Clin J Am Soc Nephrol. 2015; 9:1922–1929.
15. Tielemans SMAJ, Geleijnse JM, Menotti A, Boshuizen HC, Soedamah-Muthu SS, Jacobs DR, et al. Ten-year blood pressure trajectories, cardiovascular mortality, and life years lost in 2 extinction cohorts: the Minnesota Business and Professional Men Study and the Zutphen Study. J Am Heart Assoc. 2015; 4:e001378.
16. Rawshani A, Sattar N, Franzén S, Rawshani A, Hattersley AT, Svensson AM, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet. 2018; 392:477–486.
17. Al-Saeed AH, Constantino MI, Molyneaux L, D'Souza M, Limacher-Gisler F, Luo C, et al. An inverse relationship between age of type 2 diabetes onset and complication risk and mortality: The impact of youth-onset type 2 diabetes. Diabetes Care. 2016; 39:823–829.
18. Luo J, Hodge A, Hendryx M, Byles JE. Age of obesity onset, cumulative obesity exposure over early adulthood and risk of type 2 diabetes. Diabetologia. 2020; 63:519–527.
19. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for themanagement of arterial hypertension. Eur Heart J. 2018; 39:3021–3104.
20. Whelton PK, Carey RM, Aronow WS, Casey DE, 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. J Am Coll Cardiol. 2018; 71:e127–e248.
21. Helsinki Blood Pressure. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Hypertension Society.Helsinki: The Finnish Medical Society Duodecim, 2020 (Referred November 20, 2020). [Internet]. Available from: www.käypähoito.fi
22. Ference BA, Julius S, Mahajan N, Levy PD, Williams KA, Flack JM. Clinical effect of naturally random allocation to lower systolic blood pressure beginning before the development of hypertension. Hypertension. 2014; 63:1182–1188.
23. Gurven M, Blackwell AD, Rodríguez DE, Stieglitz J, Kaplan H. Does blood pressure inevitably rise with age?: Longitudinal evidence among forager-horticulturalists. Hypertension. 2012; 60:25–33.
24. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA. 2002; 287:1003–1010.
25. Franklin SS, Gustin IV W, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure: The Framingham Heart Study. Circulation. 1997; 96:308–315.
26. Cheng S, Xanthakis V, Sullivan LM, Vasan RS. Blood pressure tracking over the adult life course: Patterns and correlates in the Framingham Heart Study. Hypertension. 2012; 60:1393–1399.
27. Brzezinski WA. Clinical Methods: The History, Physical, and Laboratory Examinations; Blood pressure. 3rd ed. Boston: Butterworths. 1990. ISBN-10: 0-409-90077-X.
28. Delgado J, Bowman K, Ble A, Masoli J, Han Y, Henley W, et al. Blood pressure trajectories in the 20 years before death. JAMA Intern Med. 2018; 178:93–99.
29. Sylvestre MP, Kâ K, Dugas EN, Zappitelli M, O'Loughlin J. Sex-specific trajectories of systolic and diastolic blood pressure in youth. J Hypertens. 2017; 35:1416–1423.
30. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, Cheng S. Sex Differences in Blood Pressure Trajectories over the Life Course. JAMA Cardiol. 2020; 5:255–262.
31. Juhola J, Magnussen CG, Viikari JSA, Kähönen M, Hutri-Kähönen N, Jula A, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: The cardiovascular risk in young Finns study. J Pediatr. 2011; 159:584–590.

32. Oikonen M, Nuotio J, Magnussen CG, Viikari JSA, Taittonen L, Laitinen T, et al. Repeated Blood Pressure Measurements in Childhood in Prediction of Hypertension in Adulthood. Hypertension. 2016; 67:41–47.
33. Lauer RM, Lauer RM, Clarke WR, Mahoney LT, Witt J. Childhood predictors for high adult blood pressure: The Muscatine study. Pediatrics. 1993; 40:23–40.
34. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: A systematic review and meta-regression analysis. Circulation. 2008; 117:3171–3180.
35. Toschke AM, Kohl L, Mansmann U, Von Kries R. Meta-analysis of blood pressure tracking from childhood to adulthood and implications for the design of intervention trials. Acta Paediatr. 2010; 99:24–29.
36. Wills AK, Lawlor DA, Matthews FE, Sayer AA, Bakra E, Ben-Shlomo Y, et al. Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. PLoS Med. 2011; 8:e1000440.
37. Carretero OA, Oparil S. Essential hypertension. Part I: Definition and etiology. Circulation. 2000; 101:329–335.
38. Rimoldi SF, Scherrer U, Messerli FH. Secondary arterial hypertension: When, who, and how to screen?. Eur Heart J. 2014; 35:1245–1254.
39. Acelajado MC, Calhoun DA. Resistant Hypertension, Secondary Hypertension, and Hypertensive Crises: Diagnostic Evaluation and Treatment. Cardiol Clin. 2010; 28:639–654.
40. Friedman GD, Selby J V, Quesenberry CP, Armstrong MA, Klatsky AL. Precursors of essential hypertension: Body weight, alcohol and salt use, and parental history of hypertension. Prev Med (Baltim). 1988; 17:387–402.
41. Bruno RM, Masi S, Taddei M, Taddei S, Virdis A. Essential Hypertension and Functional Microvascular Ageing. High Blood Press Cardiovasc Prev. 2018; 25:35–40.
42. Bruno RM, Duranti E, Ippolito C, Segnani C, Bernardini N, Di Candio G, et al. Different Impact of Essential Hypertension on Structural and Functional Age-Related Vascular Changes. Hypertension. 2017; 69:71–78.
43. Saxena T, Ali AO, Saxena M. Pathophysiology of essential hypertension: an update. Expert Rev Cardiovasc Ther. 2018; 16:879–887.
44. Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet. 2007; 370:591–603.
45. Robinson RF, Batisky DL, Hayes JR, Nahata MC, Mahan JD. Significance of heritability in primary and secondary pediatric hypertension. Am J Hypertens. 2005; 18:917–921.
46. Gupta-Malhotra M, Banker A, Shete S, Hashmi SS, Tyson JE, Barratt MS, et al. Essential hypertension vs. secondary hypertension among children. Am J Hypertens. 2015; 28:73–80.
47. Anderson GH, Blakeman N, Streeten DHP. The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. J Hypertens. 1994; 12:609–615.
48. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: A systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2018; 6:41–50.
49. Wills AK, Lawlor DA, Muniz-Terrera G, Matthews F, Cooper R, Ghosh AK, et al. Population heterogeneity in trajectories of midlife blood pressure. Epidemiology. 2012; 23:203–211.
50. National High Blood Pressure Education Program. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. N Y State J Med. 2004; 1–104.
51. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019; 139:e56–e528.
52. Burke V, Beilin LJ, Dunbar D. Tracking of blood pressure in Australian children. J Hypertens. 2001; 19:1185–1192.

53. Theodore RF, Broadbent J, Nagin D, Ambler A, Hogan S, Ramrakha S, et al. Childhood to Early-Midlife Systolic Blood Pressure Trajectories: Early-Life Predictors, Effect Modifiers, and Adult Cardiovascular Outcomes. Hypertension. 2015; 66:1108–1115.
54. Franklin SS, Pio JR, Wong ND, Larson MG, Leip EP, Vasan RS, et al. Predictors of new-onset diastolic and systolic hypertension: The Framingham Heart Study. Circulation. 2005; 111:1121–1127.
55. Conen D, Glynn RJ, Ridker PM, Buring JE, Albert MA. Socioeconomic status, blood pressure progression, and incident hypertension in a prospective cohort of female health professionals. Eur Heart J. 2009; 30:1378–1384.
56. Huang Y, Dai M, Deng Z, Huang X, Li H, Bai Y, et al. Clustering of risk factors and the risk of new-onset hypertension defined by the 2017 ACC/AHA Hypertension Guideline. J Hum Hypertens. 2020; 34:372–377.
57. Grams ME, Chow EKH, Segev DL, Coresh J. Lifetime Incidence of CKD stages 3-5 in the United States. Am J Kidney Dis. 2013; 62:245–252.
58. Sundström J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension. 2005; 45:28–33.
59. Shirwany NA, Zou MH. Arterial stiffness: A brief review. Acta Pharmacol Sin. 2010; 31:1267–1276.
60. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, et al. Arterial stiffness and cardiovascular events: The Framingham Heart Study. Circulation. 2010; 121:505–511.
61. Mackenzie IS, Wilkinson IB, Cockcroft JR. Assessment of arterial stiffness in clinical practice. QJM - Int J Med. 2002; 95:67–74.
62. Safar ME. Arterial aging-hemodynamic changes and therapeutic options. Nat. Rev. Cardiol. 2010; 7:442–449.
63. Nilsson PM. Early vascular aging (EVA): consequences and prevention. Vasc. Health Risk Manag. 2008; 4:547–552.
64. Juonala M, Järvisalo MJ, Mäki-Torkko N, Kähönen M, Viikari JSA, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: The cardiovascular risk in young finns study. Circulation. 2005; 112:1486–1493.
65. Li S, Chen W, Srinivasan SR, Berenson GS. Childhood Blood Pressure as a Predictor of Arterial Stiffness in Young Adults: The Bogalusa Heart Study. Hypertension. 2004; 43:541–546.
66. Ferreira I, Van De Laar RJ, Prins MH, Twisk JW, Stehouwer CD. Carotid stiffness in young adults: A life-course analysis of its early determinants: The Amsterdam growth and health longitudinal study. Hypertension. 2012; 59:54–61.
67. Takase H, Dohi Y, Toriyama T, Okado T, Tanaka S, Sonoda H, et al. Brachial-ankle pulse wave velocity predicts increase in blood pressure and onset of hypertension. Am J Hypertens. 2011; 24:667–673.
68. Najjar SS, S cuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, et al. Pulse Wave Velocity Is an Independent Predictor of the Longitudinal Increase in Systolic Blood Pressure and of Incident Hypertension in the Baltimore Longitudinal Study of Aging. J Am Coll Cardiol. 2008; 51:1377–1383.
69. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA. 2012; 308:875–881.
70. Mitchell GF, Mitchell GF, Wang N, Palmisano JN, Larson MG, Hamburg NM, Vita JA, et al. Hemodynamic correlates of blood pressure across the adult age spectrum: Noninvasive evaluation in the Framingham Heart Study. Circulation. 2010; 122:1379–1386.
71. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: The Framingham Heart Study. Hypertension. 2004; 43:1239–1245.

72. Andersson C, Johnson AD, Benjamin EJ, Levy D, Vasan RS. 70-year legacy of the Framingham Heart Study. Nat. Rev. Cardiol. 2019; 16:687–698.
73. Baksi AJ, Treibel TA, Davies JE, Hadjiloizou N, Foale RA, Parker KH, et al. A Meta-Analysis of the Mechanism of Blood Pressure Change With Aging. J Am Coll Cardiol. 2009; 54:2087–2092.
74. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness. A Systematic Review and Meta-Analysis. J Am Coll Cardiol. 2010; 55:1318–1327.
75. Mitchell GF. Arterial stiffness and hypertension: Chicken or egg? Hypertension. 2014; 64:210–214.
76. AlGhatrif M, Strait JB, Morrell CH, Canepa M, Wright J, Elango P, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: The Baltimore longitudinal study of aging. Hypertension. 2013; 62:934–941.
77. Scuteri A, Morrell CH, Orrù M, Strait JB, Tarasov K V, Ferreli LAP, et al. Longitudinal perspective on the conundrum of central arterial stiffness, blood pressure, and aging. Hypertension. 2014; 64:1219–1227.
78. Santos M, Shah AM. Alterations in cardiac structure and function in hypertension. Curr. Hypertens. Rep. 2014; 16:1–10.
79. Cuspidi C, Facchetti R, Bombelli M, Tadic M, Sala C, Grassi G, et al. High normal blood pressure and left ventricular hypertrophy echocardiographic findings from the PAMELA population. Hypertension. 2019; 73:612–619.
80. Ueda H, Miyawaki M, Hiraoka H. High-normal blood pressure is associated with new-onset electrocardiographic left ventricular hypertrophy. J Hum Hypertens. 2015; 29:9–13.
81. Reichek N, Devereux RB. Left ventricular hypertrophy: Relationship of anatomic, echocardiographic and electrocardiographic findings. Circulation. 1981; 63:1391–1398.
82. Cuspidi C, Sala C, Tadic M, Gherbesi E, Facchetti R, Grassi G, et al. High-normal blood pressure and abnormal left ventricular geometric patterns: A meta-analysis. J Hypertens. 2019; 37:1312–1319.
83. Juhola J, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, et al. Combined effects of child and adult elevated blood pressure on subclinical atherosclerosis: The international childhood cardiovascular cohort consortium. Circulation. 2013; 128:217–224.
84. Loria CM, Liu K, Lewis CE, Hulley SB, Sidney S, Schreiner PJ, et al. Early Adult Risk Factor Levels and Subsequent Coronary Artery Calcification. The CARDIA Study. J Am Coll Cardiol. 2007; 49:2013–2020.
85. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PWF, Levy D. Predictors of New-Onset Kidney Disease in a Community-Based Population. JAMA. 2004; 291:844–850.
86. Pontremoli R, Ravera M, Bezante GP, Viazzi F, Nicolella C, Berruti V, et al. Left ventricular geometry and function in patients with essential hypertension and microalbuminuria. J Hypertens. 1999; 17:993–1000.
87. Leiba A, Fishman B, Twig G, Gilad D, Derazne E, Shamiss A, et al. Association of Adolescent Hypertension with Future End-stage Renal Disease. JAMA Intern Med. 2019; 179:517–523.
88. Wachtell K, Palmieri V, Olsen MH, Bella JN, Aalto T, Dahlöf B, et al. Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE study. Losartan Intervention for Endpoint Reduction. Am Heart J. 2002; 143:319–326.
89. Bliziotis IA, Destounis A, Stergiou GS. Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: A systematic review and meta-analysis. J. Hypertens. 2012; 30:1289–1299.
90. Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. Lancet. 2017; 389:1730–1739.

91. Schmieder RE. Reversal of Left Ventricular Hypertrophy in Essential Hypertension. JAMA. 1996; 275:1507–1513.
92. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of Microalbuminuria in Type 1 Diabetes. N Engl J Med. 2003; 348:2285–2293.
93. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ, J et al. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. JAMA. 2003; 289:194–202.
94. Viazzi F, Leoncini G, Conti N, Tomolillo C, Giachero G, Vercelli M, et al. Combined effect of albuminuria and estimated glomerular filtration rate on cardiovascular events and all-cause mortality in uncomplicated hypertensive patients. J Hypertens. 2010; 28:848–855.
95. Madhavan M V, Tarigopula M, Mintz GS, Maehara A, Stone GW, Généreux P. Coronary artery calcification: Pathogenesis and prognostic implications. J Am Coll Cardiol. 2014; 63:1703–1714.
96. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic Implications of Echocardiographically Determined Left Ventricular Mass in the Framingham Heart Study. N Engl J Med. 1990; 322:1561–1566.
97. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet. 2014; 383:1899–1911.
98. Redon J, Tellez-Plaza M, Orozco-Beltran D, Gil-Guillen V, Pita Fernandez S, Navarro-Pérez J, et al. Impact of hypertension on mortality and cardiovascular disease burden in patients with cardiovascular risk factors from a general practice setting: The ESCARVAL-risk study. J Hypertens. 2016; 34:1075–1083.
99. Lloyd-Jones DM, Leip EP, Larson MG, Vasan RS, Levy D. Novel approach to examining first cardiovascular events after hypertension onset. Hypertension. 2005; 45:39–45.
100. Luo D, Cheng Y, Zhang H, Ba M, Chen P, Li H, et al. Association between high blood pressure and long term cardiovascular events in young adults: Systematic review and meta-analysis. BMJ. 2020; 370:3222.
101. Li Y, Thijs L, Zhang Z-Y, Asayama K, Hansen TW, Boggia J, et al. Opposing Age-Related Trends in Absolute and Relative Risk of Adverse Health Outcomes Associated With Out-of-Office Blood Pressure. Hypertension. 2019;74:1333–1342.
102. Egan BM, Stevens-Fabry S. Prehypertension—prevalence, health risks, and management strategies. Nat Rev Cardiol. 2015; 12:289–300.
103. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, et al. Lifetime risks of cardiovascular disease. N Engl J Med. 2012; 366:321–329.
104. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, et al. Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes. N Engl J Med. 2019; 381:243–251.
105. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, et al. Does the relation of blood pressure to coronary heart disease risk change with aging?: The Framingham Heart Study. Circulation. 2001; 103:1245–1249.
106. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP. J-shaped relationship between blood pressure and mortality in hypertensive patients: New insights from a meta-analysis of individual-patient data. Ann Intern Med. 2002; 136:438–448.
107. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet. 2016; 388:2142–2152.
108. 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; 387:957–967.
109. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: A 20-year follow-up of 999 men. Hypertension. 1998; 31:780–786.

110. 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; 347:1141–1145.
111. Maillard P, Seshadri S, Beiser A, Himali JJ, Au R, Fletcher E, et al. Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: A cross-sectional study. Lancet Neurol. 2012; 11:1039–1047.
112. Jacobs DM, Sano M, Dooneief G, Marder K, Bell KL, Stern Y. Neuropsychological detection and characterization of preclinical Alzheimer's disease. Neurology. 1995; 45:957–962.
113. Wechsler D. Manual for the Wechsler Adult Intelligence Scale, Revised. J Psycheduc Assess. 1983;1:309–319.
114. Rosenberg SJ, Ryan JJ, Prifitera A. Rey auditory-verbal learning test performance of patients with and without memory impairment. J Clin Psychol. 1984; 40:785–787.
115. Nasreddine ZS, hillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53:695–699.
116. Birns J, Kalra L. Cognitive function and hypertension. J Hum Hypertens. 2009; 23:86–96.
117. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. Nat. Rev. Cardiol. 2010; 7:686–698.
118. Singh-Manoux A, K ivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of onset of cognitive decline: Results from Whitehall II prospective cohort study. BMJ. 2012; 344:d7622.
119. Nichols E, Szoeke CEI, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019; 18:88–106.
120. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005; 4:487–499.
121. Power MC, Schneider ALC, Wruck L, Griswold M, Coker LH, Alonso A, et al. Life-course blood pressure in relation to brain volumes. Alzheimer's Dement. 2016; 12:890–899.
122. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The Association Between Midlife Blood Pressure Levels and Late-Life Cognitive Function: The Honolulu-Asia Aging Study. JAMA. 1995; 274:1846–1851.
123. Gottesman RF, Schneider ALC, Albert M, Alonso A, Bandeen-Roche K, Coker L, et al. Midlife hypertension and 20-year cognitive change: The atherosclerosis risk in communities neurocognitive study. JAMA Neurol. 2014; 71:1218–1227.
124. Rovio SP, P Pahkala K, Nevalainen J, Juonala M, Salo P, Kähönen M, et al. Cardiovascular Risk Factors From Childhood and Midlife Cognitive Performance: The Young Finns Study. J Am Coll Cardiol. 2017; 69:2279–2289.
125. Lamballais S, S ajjad A, Leening MJG, Gaillard R, Franco OH, Mattace-Raso FUS, et al. Association of blood pressure and arterial stiffness with cognition in 2 population-based child and adult cohorts. J Am Heart Assoc. 2018; 7: e009847.
126. Ou YN, Tan CC, Shen XN, Xu W, Hou XH, Dong Q, et al. Blood pressure and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 209 prospective studies. Hypertension. 2020; 76:217–225.
127. Altschul DM, Wraw C, Der G, Gale CR, Deary IJ. Hypertension Development by Midlife and the Roles of Premorbid Cognitive Function, Sex, and Their Interaction. Hypertension. 2019; 73:812–819.
128. Sun D, Thomas EA, Launer LJ, Sidney S, Yaffe K, Fornage M. Association of blood pressure with cognitive function at midlife: A Mendelian randomization study. BMC Med Genomics. 2020; 13:121.
129. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience

substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. Lancet Neurol. 2019; 18:942–952.
130. Poels MMF, Vernooij MW, Ikram MA, Hofman A, Krestin GP, Van Der Lugt A, et al. Prevalence and risk factors of cerebral microbleeds: An update of the Rotterdam scan study. Stroke. 2010; 41:103–106.
131. Akoudad S, Wolters FJ, Viswanathan A, De Bruijn RF, Van Der Lugt A, Hofman A, et al. Association of cerebral microbleeds with cognitive decline and dementia. JAMA Neurol. 2016; 73:934–943.
132. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: Longitudinal, population based study. BMJ. 2001; 322:1447–1451.
133. McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, et al. Blood pressure from mid-to late life and risk of incident dementia. Neurology. 2017; 89:2447–2454.
134. Li G, Rhew IC, Shofer JB, Kukull WA, Breitner JCS, Peskind E, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: A community-based prospective cohort study. J Am Geriatr Soc. 2007; 55:1161–1167.
135. Guo Z, Viitanen M, Fratiglioni L, Winblad B. Low blood pressure and dementia in elderly people: The Kungsholmen project. BMJ. 1996; 312:805–808.
136. Qiu C, Von Strauss E, Winblad B, Fratiglioni L. Decline in blood pressure over time and risk of dementia: A longitudinal study from the Kungsholmen project. Stroke. 2004; 35:1810–1815.
137. Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure for estimating them. Sociol Methods Res. 2007; 35:542–571.
138. Nuotio J, Suvila K, Cheng S, Langén V, Niiranen T. Longitudinal blood pressure patterns and cardiovascular disease risk. Ann Med. 2020; 52:43–54.
139. Wilson PWF, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, et al. Cumulative Effects of High Cholesterol Levels, High Blood Pressure, and Cigarette Smoking on Carotid Stenosis. N Engl J Med. 1997; 337:516–522.
140. Olesen TB, Pareek M, Stidsen J V, Blicher MK, Rasmussen S, Vishram-Nielsen JKK, et al. Association between antecedent blood pressure, hypertension-mediated organ damage and cardiovascular outcome. Blood Press. 2020; 29:232–240.
141. Lai CC, Sun D, Cen R, Wang J, Li S, Fernandez-Alonso C, et al. Impact of long-term burden of excessive adiposity and elevated blood pressure from childhood on adulthood left ventricular remodeling patterns: The Bogalusa heart study. J Am Coll Cardiol. 2014; 64:1580–1587.
142. Berenson GS. Bogalusa Heart Study: A long-term community study of a rural biracial (Black/White) population. Am J Med Sci. 2001; 322:267-274.
143. Yan Y, Li S, Guo Y, Fernandez C, Bazzano L, He J, et al. Life-Course Cumulative Burden of Body Mass Index and Blood Pressure on Progression of Left Ventricular Mass and Geometry in Midlife: The Bogalusa Heart Study. Circ Res. 2020; 126:633–643.
144. Liu Y, Yan Y, Jiang T, Li S, Guo Y, Fernandez C, et al. Impact of Long-Term Burden of Body Mass Index and Blood Pressure From Childhood on Adult Left Ventricular Structure and Function. J Am Heart Assoc. 2020; 9:e016405.
145. Kishi S, Teixido-Tura G, Ning H, Venkatesh BA, Wu C, Almeida A, et al. Cumulative blood pressure in early adulthood and cardiac dysfunction in middle age: The CARDIA study. J Am Coll Cardiol. 2015; 65:2679–2687.
146. Vasconcellos HD, Moreira HT, Ciuffo L, Nwabuo CC, Yared GS, Ambale-Venkatesh B, et al. Cumulative blood pressure from early adulthood to middle age is associated with left atrial remodelling and subclinical dysfunction assessed by three-dimensional echocardiography: A prospective post hoc analysis from the Coronary Artery Risk Development in Young Adults Study. Eur Heart J Cardiovasc Imaging. 2018; 19:977–984.
147. Hoit BD. Left atrial size and function: Role in prognosis. J Am Coll Cardiol. 2014; 63:493–505.

148. Kramer H, Colangelo L, Lewis CE, Jacobs DR, Pletcher M, Bibbins-Domingo K, et al. Cumulative exposure to systolic blood pressure during young adulthood through midlife and the urine albumin-to-creatinine ratio at midlife. Am J Hypertens. 2017; 30:502–509.
149. Zhang T, Li S, Bazzano L, He J, Whelton P, Chen W. Trajectories of childhood blood pressure and adult left ventricular hypertrophy: The bogalusa heart study. Hypertension. 2018; 72:93–101.
150. Hao G, Wang X, Treiber FA, Harshfield G, Kapuku G, Su S. Blood pressure trajectories from childhood to young adulthood associated with cardiovascular risk. Hypertension. 2017; 69:435–442.
151. Allen NB, Siddique J, Wilkins JT, Shay C, Lewis CE, Goff DC, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. JAMA. 2014; 311:490–497.
152. Zheng W, Mu J, Chu C, Hu J, Yan Y, Ma Q, et al. Association of blood pressure trajectories in early life with subclinical renal damage in middle age. J Am Soc Nephrol. 2018; 29:2835–2846.
153. Ku E, Vittinghoff E, Jacobs DR, Lewis CE, Allen NB, Bibbins-Domingo K, et al. Changes in Blood Pressure During Young Adulthood and Subsequent Kidney Function Decline: Findings From the Coronary Artery Risk Development in Young Adulthood (CARDIA) Study. Am J Kidney Dis. 2018; 72:243–250.
154. Seshadri S, Wolf PA, Beiser A, Vasan RS, Wilson PWF, Kase CS, et al. Elevated midlife blood pressure increases stroke risk in elderly persons: The Framingham Study. Arch Intern Med. 2001; 161:2343–2350.
155. Vasan RS, Massaro JM, Wilson PWFF, Seshadri S, Wolf PA, Levy D, et al. Antecedent blood pressure and risk of cardiovascular disease: The Framingham Heart Study. Circulation. 2002; 105:48–53.
156. Lee DS, Massaro JM, Wang TJ, Kannel WB, Benjamin EJ, Kenchaiah S, et al. Antecedent blood pressure, body mass index, and the risk of incident heart failure in later life. Hypertension. 2007; 50:869–876.
157. Bonifonte A, Ayer T, Veledar E, Clark A, Wilson PWF. Antecedent blood pressure as a predictor of cardiovascular disease. J Am Soc Hypertens. 2015; 9:690-696.e1.
158. Sasai H, Sairenchi T, Irie F, Otaka E, Iso H, Tanaka K, et al. Long-term exposure to elevated blood pressure and mortality from cardiovascular disease in a Japanese population: The Ibaraki prefectural health study. Hypertens Res. 2011; 34:139–144.
159. Ayala Solares JR, Canoy D, Raimondi FED, Zhu Y, Hassaine A, Salimi-Khorshidi G, et al. Long-Term Exposure to Elevated Systolic Blood Pressure in Predicting Incident Cardiovascular Disease: Evidence From Large-Scale Routine Electronic Health Records. J Am Heart Assoc. 2019; 8:e012129.
160. Wang YX, Song L, Xing AJ, Gao M, Zhao HY, Li CH, et al. Predictive Value of Cumulative Blood Pressure for All-Cause Mortality and Cardiovascular Events. Sci Rep. 2017; 7:41969.
161. Pool LR, Ning H, Wilkins J, Lloyd-Jones DM, Allen NB. Use of Long-term Cumulative Blood Pressure in Cardiovascular Risk Prediction Models. JAMA Cardiol. 2018; 3:1096–1100.
162. Allen N, Berry JD, Ning H, Van Horn L, Dyer A, Lloyd-Jones DM. Impact of blood pressure and blood pressure change during middle age on the remaining lifetime risk for cardiovascular disease: The cardiovascular lifetime risk pooling project. Circulation. 2012; 125:37–44.
163. Petruski-Ivleva N, Viera AJ, Shimbo D, Muntner P, Avery CL, Schneider ALC, et al. Longitudinal patterns of change in systolic blood pressure and incidence of cardiovascular disease: The atherosclerosis risk in communities study. Hypertension. 2016; 67:1150–1156.
164. Portegies MLP, Mirza SS, Verlinden VJA, Hofman A, Koudstaal PJ, Swanson SA, et al. Mid-to late-life trajectories of blood pressure and the risk of stroke: The Rotterdam study. Hypertension. 2016; 67:1126–1132.
165. Li W, Jin C, Vaidya A, Wu Y, Rexrode K, Zheng X, et al. Blood Pressure Trajectories and the Risk of Intracerebral Hemorrhage and Cerebral Infarction: A Prospective Study. Hypertension. 2017; 70:508–514.

166. Fan JH, Wang JB, Wang SM, Abnet CC, Qiao YL, Taylor PR. Longitudinal change in blood pressure is associated with cardiovascular disease mortality in a Chinese cohort. Heart. 2018; 104:1764–1771.
167. Gottesman RF, Coresh J, Catellier DJ, Sharrett AR, Rose KM, Coker LH, et al. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis risk in communities (ARIC) study. Stroke. 2010; 41:3–8.
168. Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and the brain: A 5-year follow-up. Neurology. 2005; 64:1846–1852.
169. Allan CL, Zsoldos E, Filippini N, Sexton CE, Topiwala A, Valkanova V, et al. Lifetime hypertension as a predictor of brain structure in older adults: Cohort study with a 28-year follow-up. Br J Psychiatry. 2015; 206:308–315.
170. Arvanitakis Z, Capuano AW, Lamar M, Shah RC, Barnes LL, Bennett DA, et al. Late-life blood pressure association with cerebrovascular and Alzheimer disease pathology. Neurology. 2018; 91:e517–e525.
171. Yaffe K, V Vittinghoff E, Pletcher MJ, Hoang TD, Launer LJ, Whitmer R, et al. Early adult to midlife cardiovascular risk factors and cognitive function. Circulation. 2014; 129:1560–1567.
172. 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; 141:712–724.
173. Liu J, Huang Y, Chen G, Liu X, Wang Z, Cao Y, et al. Cumulative systolic blood pressure exposure in relation to cognitive function in middle-aged and elderly adults: A prospective, population-based study. Medicine (Baltimore). 2016; 95:e5514.
174. Levine DA, Gross AL, Briceño EM, Tilton N, Kabeto MU, Hingtgen SM, et al. Association between Blood Pressure and Later-Life Cognition among Black and White Individuals. JAMA Neurol. 2020; 77:810–819.
175. Jenkins LM, Garner CR, Kurian S, Higgins JP, Parrish TB, Sedaghat S, et al. Cumulative blood pressure exposure, basal ganglia, and thalamic morphology in midlife. Hypertension. 2020; 75:1289–1295.
176. Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. Stroke. 1998; 29:2334–2340.
177. Graff-Radford J, Raman MR, Rabinstein AA, Przybelski SA, Lesnick TG, Boeve BF, et al. Association between microinfarcts and blood pressure trajectories. JAMA Neurol. 2018; 75:212–218.
178. Stewart R, Xue QL, Masaki K, Petrovitch H, Ross GW, White LR, et al. Change in blood pressure and incident dementia: A 32-year prospective study. Hypertension. 2009; 54:233–240.
179. Joas E, Bäckman K, Gustafson D, Östling S, Waern M, Guo X, et al. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. Hypertension. 2012; 59:796–801.
180. Walker KA, S Sharrett AR, Wu A, Schneider ALC, Albert M, Lutsey PL, et al. Association of midlife to late-life blood pressure patterns with incident dementia. JAMA. 2019; 322:535–545.
181. Wang N-YY, Young JH, Meoni LA, Ford DE, Erlinger TP, Klag MJ. Blood Pressure Change and Risk of Hypertension Associated With Parental Hypertension: The Johns Hopkins Precursors Study. Arch Intern Med. 2008; 168:643–648.
182. Gilsanz P, Mayeda ER, Glymour MM, Quesenberry CP, Mungas DM, DeCarli C, et al. Female sex, early-onset hypertension, and risk of dementia. Neurology. 2017; 89:1886–1893.
183. Corrada MM, Hayden KM, Paganini-Hill A, Bullain SS, DeMoss J, Aguirre C, et al. Age of onset of hypertension and risk of dementia in the oldest-old: The 90+ Study. Alzheimer's Dement. 2017; 13:103–110.
184. Heida KY, Franx A, Van Rijn BB, Eijkemans MJC, Boer JMA, Verschuren MWM, et al. Earlier Age of Onset of Chronic Hypertension and Type 2 Diabetes Mellitus After a Hypertensive Disorder of Pregnancy or Gestational Diabetes Mellitus. Hypertension. 2015; 66:1116–1122.

185. Wilk JB, Djousse L, Arnett DK, Hunt SC, Province MA, Heiss G, et al. Genome-wide linkage analyses for age at diagnosis of hypertension and early-onset hypertension in the HyperGEN study. Am J Hypertens. 2004; 17:839–844.
186. Niiranen TJ, Larson MG, McCabe EL, Xanthakis V, Vasan RS, Cheng S. Prognosis of prehypertension without progression to hypertension. Circulation. 2017; 136:1262–1264.
187. Niiranen TJ, McCabe EL, Larson MG, Henglin M, Lakdawala NK, Vasan RS, et al. Heritability and risks associated with early onset hypertension: multigenerational, prospective analysis in the Framingham Heart Study. BMJ. 2017; 357:j1949.
188. Niiranen TJ, McCabe EL, Larson MG, Henglin M, Lakdawala NK, Vasan RS, et al. Risk for hypertension crosses generations in the community: a multi-generational cohort study. Eur Heart J. 2017; 38:2300–2308.
189. Chen JW, Wu SY, Pan WH. Clinical characteristics of young-onset hypertension - Implications for different genders. Int J Cardiol. 2004; 96:65–71.
190. Gupta-Malhotra M, Shete S, Barratt MS, Milewicz D, Hashmi SS. Epidemiology of Childhood Onset Essential Hypertension. J Hum Hypertens. 2018; 32:808–813.
191. Buck C, Baker P, Bass M, Donner A. The prognosis of hypertension according to age at onset. Hypertension. 1987; 9:204–208.
192. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B. Management of hypertension: Summary of NICE guidance. BMJ. 2011; 343:d4891–d4891.
193. Ejima Y, Hasegawa Y, Sanada S, Miyama N, Hatano R, Arata T, et al. Characteristics of young-onset hypertension identified by targeted screening performed at a university health check-up. Hypertens Res. 2006; 29:261–267.
194. Channanath AM, Farran B, Behbehani K, Thanaraj TA. Association between body mass index and onset of hypertension in men and women with and without diabetes: A cross-sectional study using national health data from the State of Kuwait in the Arabian Peninsula. BMJ Open. 2015; 5:7043.
195. Thompson P, Logan I, Tomson C, Sheerin N, Ellam T. Obesity, Sex, Race, and Early Onset Hypertension: Implications for a Refined Investigation Strategy. Hypertension. 2020; 76:859–865.
196. Pantell MS, Prather AA, Downing JM, Gordon NP, Adler NE. Association of Social and Behavioral Risk Factors With Earlier Onset of Adult Hypertension and Diabetes. JAMA Netw open. 2019; 2:e193933.
197. Padmanabhan S, Aman A, Dominiczak AF. Genomics of hypertension. Pharmacol Res. 2017; 121:219–229.
198. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B, et al. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. Nat Genet. 2017; 49:403–415.
199. Shih PAB, O'Connor DT. Hereditary determinants of human hypertension: Strategies in the setting of genetic complexity. Hypertension. 2008; 51:1456–1464.
200. Kolifarhood G, Daneshpour M, Hadaegh F, Sabour S, Mozafar Saadati H, Akbar Haghdoust A, et al. Heritability of blood pressure traits in diverse populations: a systematic review and meta-analysis. J Hum Hypertens. 2019; 33:775–785.
201. Porto PI, García SI, Dieuzeide G, González C, Pirola CJ. Renin-angiotensin-aldosterone system loci and multilocus interactions in young-onset essential hypertension. Clin Exp Hypertens. 2003; 25:117–130.
202. Shahin DS, Irshaid YM, Saleh AA. The A1166C polymorphism of the AT1R gene is associated with an early onset of hypertension and high waist circumference in Jordanian males attending the Jordan University Hospital. Clin Exp Hypertens. 2014; 36:333–339.
203. Schmidt S, Sharma AM, Oliver Z, Beige J, Walla-Friedel M, Ganten D, et al. Association of M235T variant of the angiotensinogen gene with familial hypertension of early onset. Nephrol Dial Transplant. 1995; 10:1145–1148.

204. Pan WH, Chen JW, Fann C, Jou YS, Wu SY. Linkage analysis with candidate genes: The Taiwan young-onset hypertension genetic study. Hum Genet. 2000; 107:210–215.
205. von Wowern F, Bengtsson K, Lindgren CM, Orho-Melander M, Fyhrquist F, Lindblad U, et al. A genome wide scan for early onset primary hypertension in Scandinavians. Hum Mol Genet. 2003; 12:2077–2081.
206. Chiang KM, Yang HC, Liang YJ, Chen JHJW, Hwang SM, Ho HY, et al. A three-stage genome-wide association study combining multilocus test and gene expression analysis for young-onset hypertension in Taiwan Han Chinese. Am J Hypertens. 2014; 27:819–827.
207. Yang HC, Liang YJ, Wu YL, Chung CM, Chiang KM, Ho HY, et al. Genome-wide association study of young-onset hypertension in the Han Chinese population of Taiwan. PLoS One. 2009; 4:e5459.
208. Chiang KM, Yang HC, Pan WH. A two-stage whole-genome gene expression association study of young-onset hypertension in han Chinese population of Taiwan. Sci Rep. 2018; 8:1800.
209. Lynn KS, Lu CH, Yang HY, Hsu WL, Pan WH. Construction of gene clusters resembling genetic causal mechanisms for common complex disease with an application to young-onset hypertension. BMC Genomics. 2013; 14:497.
210. Leu HB, Chung CM, Lin SJ, Chiang KM, Yang HC, Ho HY, et al. Association of circadian genes with diurnal blood pressure changes and non-dipper essential hypertension: A genetic association with young-onset hypertension. Hypertens Res. 2015; 38:155–162.
211. Scholl UI, Stölting G, Nelson-Williams C, Vichot AA, Choi M, Loring E, et al. Recurrent gain of function mutation in calcium channel CACNA1H causes early-onset hypertension with primary aldosteronism. Elife. 2015; 4:e06315.
212. Daw EW, Liu X, Wu C-C. Age-of-onset of hypertension vs. a single measurement of systolic blood pressure in a combined linkage and segregation analysis. BMC Genet. 2003; 4:S80.
213. Chang T-JJ, Wang W-CC, Hsiung CA, He C-TT, Lin M-WW, Sheu WH-HH, et al. Genetic Variation in the Human SORBS1 Gene is Associated With Blood Pressure Regulation and Age at Onset of Hypertension. Medicine (Baltimore). 2016; 95:e2970.
214. Wang C, Yuan Y, Zheng M, Pan A, Wang M, Zhao M, et al. Association of Age of Onset of Hypertension With Cardiovascular Diseases and Mortality. J Am Coll Cardiol. 2020; 75:2921–2930.
215. Niiranen TJ, Henglin M, Claggett B, Muggeo VMR, Mccabe E, Jain M, et al. Trajectories of blood pressure elevation preceding hypertension onset an analysis of the Framingham Heart Study original cohort. JAMA Cardiol. 2018; 3:427–431.
216. Gökaslan S, Özer Gökaslan Ç, Demirel E, Çelik S. Role of aortic stiffness and inflammation in the etiology of young-onset hypertension. Turkish J Med Sci. 2019; 49:1748–1753.
217. Gokaslan S, Ozer Gokaslan C, Celik S. The role of endothelial dysfunction and inflammation in young-onset hypertension. Ital J Med. 2020; 14:151–155.
218. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR, et al. Cardia: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988; 41:1105–1116.
219. Heistaro S. Methodology report: The Health 2000 Survey. Helsinki. National Public Health Institute. 2008;1–248.
220. Ostchega Y, Nwankwo T, Sorlie PD, Wolz M, Zipf G. Assessing the validity of the omron HEM-907XL oscillometric blood pressure measurement device in a national survey environment. J Clin Hypertens. 2010; 12:22–28.
221. Jacobs DR, Yatsuya H, Hearst MO, Thyagarajan B, Kalhan R, Rosenberg S, et al. Rate of decline of forced vital capacity predicts future arterial hypertension: The Coronary Artery Risk Development in Young Adults Study. Hypertension. 2012; 59:219–225.
222. Gibbs BB, King WC, Davis KK, Rickman AD, Rogers RJ, Wahed A, et al. Objective vs. self-report sedentary behavior in overweight and obese young adults. J Phys Act Heal. 2015; 12:1551–1557.

223. Kim C, Siscovick DS, Sidney S, Lewis CE, Kiefe CI, Koepsell TD. Oral Contraceptive Use and Association With Glucose , Insulin , and Diabetes in young adult women: The CARDIA Study. Diabetes Care. 2002; 25:1027–1032.
224. Murtaugh MA, Jacobs Jr. DR, Yu X, Gross MD, Steffes M. Correlates of urinary albumin excretion in young adult blacks and whites: the Coronary Artery Risk Development in Young Adults Study. Am J Epidemiol. 2003; 158:676–686.
225. Gerstein HC, Mann JFE, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001; 286:421–426.
226. Armstrong AC, Ricketts EP, Cox C, Adler P, Arynchyn A, Liu K, et al. Quality Control and Reproducibility in M-Mode, Two-Dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year 25 Examination Experience. Echocardiography. 2015; 32:1233–1240.
227. Lang RM, Badano LP, Victor MA, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28:1-39.e14.
228. Schillaci G, Battista F, Pucci G. A review of the role of electrocardiography in the diagnosis of left ventricular hypertrophy in hypertension. J. Electrocardiol. 2012; 45:617–623.
229. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR, et al. Calcified Coronary Artery Plaque Measurement with Cardiac CT in Population-based Studies: Standardized Protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) Study. Radiology. 2005; 234:35–43.
230. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990; 15:827–832.
231. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008; 358:1336–1345.
232. Mcevoy CT, Hoang T, Sidney S, Steffen LM, Jacobs DR, Shikany JM, et al. Dietary patterns during adulthood and cognitive performance in midlife: The CARDIA study. Neurology. 2019; 92:E1589–E1599.
233. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935; 18:643–662.
234. Launer LJ, Lewis CE, Schreiner PJ, Sidney S, Battapady H, Jacobs DR, et al. Vascular factors and multiple measures of early brain health: CARDIA brain MRI study. PLoS One. 2015; 10:e0122138.
235. Dougherty RJ, Moonen J, Yaffe K, Sidney S, Davatzikos C, Habes M, et al. Smoking mediates the relationship between SES and brain volume: The CARDIA study. PLoS One. 2020; 15:e0239548.
236. Goldszal AF, Davatzikos C, Pham DL, Yan MXH, Bryan RN, Resnick SM. An image-processing system for qualitative and quantitative volumetric analysis of brain images. J Comput Assist Tomogr. 1998; 22:827–837.
237. Kochunov P, Thompson PM, Lancaster JL, Bartzokis G, Smith S, Coyle T, et al. Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: Tract-based spatial statistics study of aging. Neuroimage. 2007; 35:478–487.
238. Justin Thomas S, Booth JN, Dai C, Li X, Allen N, Calhoun D, et al. Cumulative incidence of hypertension by 55 years of age in blacks and whites: The cardia study. J Am Heart Assoc. 2018; 7:e007988.
239. Maraboto C, Ferdinand KC. Update on hypertension in African-Americans. Prog Cardiovasc Dis. 2020; 63:33–39.
240. Nesbitt S, Victor RG. Pathogenesis of hypertension in African Americans. Congest Heart Fail. 2004; 10:24–29.

241. Adeyemo A, Gerry N, Chen G, Herbert A, Doumatey A, Huang H, et al. A genome-wide association study of hypertension and blood pressure in African Americans. PLoS Genet. 2009; 5:1000564.
242. Zilbermint M, Hannah-Shmouni F, Stratakis CA. Genetics of hypertension in African Americans and others of African descent. Int J Mol Sci. 2019; 20:1081.
243. Cooper RS, Zhu X. Racial differences and the genetics of hypertension. Curr Hypertens Rep. 2001; 3:19–24.
244. Gonçalves VSS, Andrade KRC, Carvalho KMB, Silva MT, Pereira MG, Galvao TF, et al. Accuracy of self-reported hypertension: A systematic review and meta-analysis. J Hypertens. 2018; 36:970–978.
245. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J Clin Epidemiol. 2004; 57:1096–1103.
246. Goldman N, Lin IF, Weinstein M, Lin YH. Evaluating the quality of self-reports of hypertension and diabetes. J Clin Epidemiol. 2003; 56:148–154.
247. Siren R, Eriksson JG, Vanhanen H. Observed changes in cardiovascular risk factors among high-risk middle-aged men who received lifestyle counselling: a 5-year follow-up. Scand J Prim Health Care. 2016; 34:336–342.
248. Siren R, Eriksson JG, Peltonen M, Vanhanen H. Impact of health counselling on cardiovascular disease risk in middle aged men: Influence of socioeconomic status. PLoS One. 2014; 9:e88959.
249. Ntineri A, Niiranen TJ, McManus RJ, Lindroos A, Jula A, Schwartz C, Kollias A, Andreadis EA, et al. Ambulatory versus home blood pressure monitoring: Frequency and determinants of blood pressure difference and diagnostic disagreement. J Hypertens. 2019; 37:1974–1981.
250. Lindroos AS, Johansson JK, Puukka PJ, Kantola I, Salomaa V, Juhanoja EP, S et al. The association between home vs. Ambulatory night-time blood pressure and end-organ damage in the general population. J Hypertens. 2016; 34:1730–1737.
251. Bhise V, Rajan SS, Sittig DF, Morgan RO, Chaudhary P, Singh H. Defining and Measuring Diagnostic Uncertainty in Medicine: A Systematic Review. J Gen Intern Med. 2018; 33:103–115.
252. Haapanen N, Miilunpalo S, Pasanen M, Oja P, Vuori I. Agreement between questionnaire data and medical records of chronic diseases in middle-aged and elderly Finnish men and women. Am J Epidemiol. 1997; 145:762–769.
253. Niiranen TJ, Suvila K, Suppogu N, Ebinger JE, Lima JAC, Bairey Merz CN, et al. Sex Differences in the Cardiac Effects of Early-Onset Hypertension. Hypertension. 2019; 74:e52–e53.
254. Lacolley P, Challande P, Osborne-Pellegrin M, Regnault V. Genetics and pathophysiology of arterial stiffness. Cardiovasc Res. 2009; 81:637–648.
255. Vos T, Abajobir AA, Abbafati C, Abbas KM, Abate KH, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017; 390:1211–1259.
256. Kritz-Silverstein D, Laughlin GA, McEvoy LK, Barrett-Connor E. Sex and Age Differences in the Association of Blood Pressure and Hypertension with Cognitive Function in the Elderly: The Rancho Bernardo Study. J Prev Alzheimer's Dis. 2017; 4:165–173.
257. DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the Framingham Heart Study: Establishing what is normal. Neurobiol Aging. 2005; 26:491–510.
258. Oschwald J, Guye S, Liem F, Rast P, Willis S, Röcke C, et al. Brain structure and cognitive ability in healthy aging: A review on longitudinal correlated change. Rev Neurosci. 2019; 31:1–57.
259. Waldstein SR. Hypertension and neuropsychological function: A lifespan perspective. Exp Aging Res. 1995; 21:321–352.
260. Habib M, Mak E, Gabel S, Su L, Williams G, Waldman A, et al. Functional neuroimaging findings in healthy middle-aged adults at risk of Alzheimer's disease. Ageing Res Rev. 2017; 36:88–104.

261. Levy D, Labib SB, Anderson KM, Christiansen JC, Kannel WB, Castelli WP. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. Circulation. 1990; 81:815–820.
262. Woythaler JN, Singer SL, Kwan OL, Meltzer RS, Reubner B, Bommer W, et al. Accuracy of echocardiography versus electrocardiography in detecting left ventricular hypertrophy: Comparison with postmortem mass measurements. J Am Coll Cardiol. 1983; 2:305–311.
263. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, et al. Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study. Circulation. 2003; 108:684–690.
264. Devereux RB, Wachtell K, Gerdts E, Boman K, Nieminen MS, Papademetriou V, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA. 2004; 292:2350–2356.

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