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ORIGINAL RESEARCH

Prevalence, Predictors, Progression, and Prognosis of Hypertension Subtypes in the Framingham Heart Study

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BACKGROUND: The epidemiology of hypertension subtypes has not been well characterized in the recent era.

METHODS AND RESULTS: We delineated the prevalence, predictors, progression, and prognostic significance of hypertension subtypes in 8198 Framingham Heart Study participants (mean age, 46.5 years; 54% women). The prevalence of hypertension subtypes was as follows: nonhypertensive (systolic blood pressure [SBP] <140 mm Hg and diastolic blood pressure [DBP] <90 mm Hg), 79%; isolated systolic hypertension (ISH; SBP ≥140 mm Hg and DBP <90 mm Hg), 8%; isolated diastolic hypertension (SBP <140 mm Hg and DBP ≥90 mm Hg), 4%; and systolic-diastolic hypertension (SDH; SBP ≥140 mm Hg and DBP ≥90 mm Hg), 9%. The prevalence of ISH and SDH increased with age. Analysis of a subsample of nonhypertensive participants demonstrated that increasing age, female sex, higher heart rate, left ventricular mass, and greater left ventricular concentricity were predictors of incident ISH and SDH. Higher baseline DBP was associated with the risk of developing isolated diastolic hypertension and SDH, whereas higher SBP was associated with all 3 hypertension subtypes. On follow-up (median, 5.5 years), isolated diastolic hypertension often reverted to nonhypertensive BP (in 42% of participants) and ISH progressed to SDH (in 26% of participants), whereas SDH frequently transitioned to ISH (in 20% of participants). During follow-up (median, 14.6 years), 889 participants developed cardiovascular disease. Compared with the nonhypertensive group (referent), ISH (adjusted hazard ratio [HR], 1.57; 95% CI, 1.30–1.90) and SDH (HR, 1.66; 95% CI, 1.36–2.01) were associated with increased cardiovascular disease risk, whereas isolated diastolic hypertension was not (HR, 1.03; 95% CI, 0.68–1.57).

CONCLUSIONS: Hypertension subtypes vary in prevalence with age, are dynamic during short-term follow-up, and exhibit distinctive prognoses, underscoring the importance of blood pressure subphenotyping.

Key Words: blood pressure ■ cardiovascular disease ■ cohort studies ■ epidemiology ■ hypertension ■ prognosis

Hypertension is prevalent in nearly half of US adults and contributes to ≈96 000 deaths annually.[1] Despite the established benefits of blood pressure (BP) lowering on the risk of cardiovascular disease (CVD),[2] rates of hypertension control have been declining recently,[3] underscoring the importance of better management of hypertension to mitigate associated vascular risk.

A recent commentary[4] emphasized that subphenotyping hypertension may delineate pathophysiological subsets that could be targeted with greater precision, presumably resulting in better BP control. Yet, current guidelines[5,6] approach "essential" hypertension as a uniform condition rather than as a constellation of potentially heterogeneous subphenotypes that may vary in their prevalence, temporal course, and prognosis. A potential framework for subphenotyping hypertension leverages the differential elevations of systolic BP (SBP) versus diastolic BP (DBP). SBP rises and DBP falls with aging beyond the sixth decade of life, resulting in

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CLINICAL PERSPECTIVE

What Is New?

- Hypertension subtypes are dynamic during short-term follow-up, with less than half of participants with isolated diastolic hypertension and isolated systolic hypertension remaining in the same blood pressure category over a 5-year period.
- Isolated systolic hypertension and systolic-diastolic hypertension are the hypertension subtypes associated with increased cardiovascular risk, whereas isolated diastolic hypertension is not.

What Are the Clinical Implications?

- Hypertension subtypes might offer incremental prognostic information towards cardiovascular disease risk.
- Individuals with isolated systolic hypertension experienced the highest absolute risk of cardiovascular disease (relative to their nonhypertensive counterparts).
- Management of isolated systolic hypertension is critical to mitigate the elevated risk of cardiovascular disease associated with this hypertension subtype.

Nonstandard Abbreviations and Acronyms

DBP	diastolic blood pressure
FHS	Framingham Heart Study
FOS	Framingham Offspring Study
Gen 3	Third Generation Cohort
IDH	isolated diastolic hypertension
ISH	isolated systolic hypertension
JNC 7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
RWT	relative wall thickness
SBP	systolic blood pressure
SDH	systolic-diastolic hypertension

isolated systolic hypertension (ISH) when select thresholds of SBP are exceeded but DBP remains in the normal range.[7] The ISH phenotype has been attributed to arterial stiffening and is associated with most hypertension treatment failures in the elderly.[8,9] Additional hypertension subtypes are characterized by sole elevation of DBP (isolated diastolic hypertension [IDH]) or conjoint elevations of SBP and DBP (systolic-diastolic hypertension [SDH]).[10,11]

Information regarding the epidemiology of hypertension subtypes in the current era is limited, with previous reports using BP data gathered several decades ago.[10–12] Such contemporary data might be important given the rising burden of obesity and diabetes over the past 3 decades, increased awareness of and screening for high BP, and the changes over time in the BP thresholds defining hypertension among serial national guidelines. Accordingly, we characterized the prevalence, predictors, progression, and prognosis of hypertension subtypes in a large, ambulatory, community-based sample spanning a wide age range, which was followed up over the past 3 decades.

METHODS

All data and materials have been made publicly available at the National Heart, Lung, and Blood Institute data repository BioLINCC and can be accessed at https://biolincc.nhlbi.nih.gov/studies/framoffspring/.

Study Sample

The design and selection criteria of the FHS (Framingham Heart Study), FOS (Framingham Offspring Study), and Gen 3 (Third Generation Cohort) and the companion multiethnic Omni 1 and Omni 2 cohorts have been previously described.[13–15] There were 8810 FHS participants who attended FOS examination cycle 5 (1991–1995) and the first examination cycles of the Omni 1 (1994–1998), Gen 3 (2002–2005), and Omni 2 (2003–2005) cohorts; these examination cycles served as "baseline." Figure S1 and Data S1 detail the study sample derivation for different analyses. The institutional review board of the Boston University Medical Center approved the study protocol, and all study participants provided written informed consent.

Measurement of Clinical Covariates and Echocardiographic and Hemodynamic Traits

FHS participants underwent assessment of their medical history and a cardiovascular-focused physical examination at each examination cycle, including anthropometry and laboratory assays of vascular risk factors.[16,17] Participants also underwent routine transthoracic echocardiography (see Data S1[18–22]).

Measurement and Categorization of BP and Imputation for Antihypertensive Treatment

A physician measured BP twice in seated participants (who rested for at least 5 minutes) using a mercury-column sphygmomanometer, an appropriately-sized cuff, and a standardized protocol. The average of these

2 BP readings was used to categorize participants at their initial and follow-up evaluations.

We defined hypertension subtypes using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[23] as follows: nonhypertensive BP (untreated SBP <140 mm Hg and DBP <90 mm Hg), ISH (SBP ≥140 mm Hg and DBP <90 mm Hg), IDH (SBP <140 mm Hg and DBP ≥90 mm Hg), and SDH (SBP ≥140 mm Hg and DBP ≥90 mm Hg). We created the 4-level variable denoted "hypertension subtype" using the above definition. The JNC 7 BP thresholds were selected for our analyses because they represent treatment thresholds followed during our study period and enabled comparisons with previous reports.[11] For participants treated with antihypertensive medications, we imputed SBP/DBP based on the number of BP-lowering agents, drug class, and participants' race.[24,25] For each participant taking antihypertensive medications (N=1005; 12.3% of the total sample of 8198), we added values to the measured SBP and DBP that corresponded to the estimated weighted average effects of the medications on these 2 BP components.[25] The sum of the measured BP and the estimated treatment effect is referred to as the imputed BP of the participant.

We also performed sensitivity analyses restricted to participants who were not taking any antihypertensive medications to elucidate whether hypertension treatment impacted our results.

Definition of Outcome Events

All FHS participants undergo longitudinal surveillance for CVD events. Our primary outcome of interest was CVD as a composite of coronary heart disease (CHD; myocardial infarction, coronary insufficiency, and angina pectoris), stroke or transient ischemic attack, peripheral arterial disease (intermittent claudication), congestive heart failure, or CVD-related mortality. In secondary analyses, we also evaluated incident CHD as a separate outcome. A review panel of 3 physicians adjudicated all CVD events using a standardized protocol and criteria.[16]

Statistical Analysis

As noted above, primary analyses imputed SBP and DBP in participants treated with antihypertensive medications,[24,25] and were supplemented by sensitivity analyses restricted to untreated individuals. Analyses of prevalence and progression of hypertension subtypes were further stratified by median age (<46 years versus ≥46 years) and sex, given the known impact of age and sex on the relative prevalence of hypertension subtypes and their longitudinal BP progression.[7,11,12,17]

Prevalence of Hypertension Subtypes

At the baseline examinations, we assessed the prevalence of hypertension subtypes overall and in a subsample of individuals not taking antihypertensive medications. We also performed stratified analyses by median age and sex.

Clinical, Echocardiographic, and Hemodynamic Predictors of New-Onset Hypertension Subtypes

We evaluated predictors of hypertension subtypes on follow-up in a subsample of individuals who were nonhypertensive at baseline. First, we used multinomial logistic regression to relate clinical covariates (independent variables) to hypertension subtype (dependent variable; 4-level variable). Participants who were nonhypertensive at both the baseline and the follow-up examination served as the referent group for the outcome. We estimated the odds ratio (OR) of developing a specific hypertension subtype relative to staying in the referent nonhypertension group on follow-up. The clinical predictors evaluated included age, sex, body mass index, diabetes, smoking status, the ratio of serum total cholesterol to high-density lipoprotein cholesterol, triglycerides concentrations, and baseline SBP and DBP; these variables have been reported to be associated with the risk of developing elevated BP.[11,12] Models were adjusted for cohort type (FOS [referent] versus Gen 3 versus Omni 1 and Omni 2 cohorts).

Next, we used multinomial logistic regression to relate the echocardiographic and hemodynamic traits (separate analyses for each variable) to the incidence of hypertension subtype, adjusting for the statistically significant clinical correlates identified above and cohort type. The echocardiographic predictors evaluated included aortic root diameter, left atrial diameter, left ventricular (LV) mass indexed to body surface area, and relative wall thickness (RWT). We chose these echocardiographic variables because they reflect complementary aspects of proximal aortic stiffness (aortic root diameter), LV afterload (LV mass index), LV preload (left atrial diameter), and LV geometry (RWT), which have been related to hypertension incidence.[9,26–29] Hemodynamic predictors included resting heart rate, mean arterial pressure (calculated from SBP and DBP), stroke volume, cardiac output, and total peripheral resistance (see Data S1), which are variables reported to be associated with hypertension subtypes.[30–34]

Longitudinal Progression of Hypertension Subtypes

We cross-tabulated hypertension subtype at the baseline examination against hypertension subtype at the follow-up examination ≈5 years later. In these transition

matrices, participants could stay in the same hypertension subtype, progress to a different subtype, or revert to the nonhypertension group. We calculated the rates of change in hypertension subtype overall and stratified by median age and sex.

Relationship of Hypertension Subtypes to CVD and CHD Incidence

We related baseline hypertension subtype (predictor) to CVD incidence (outcome) over a follow-up period of 20 years after baseline. We used multivariable-adjusted Fine-Gray subdistribution hazards regression models[35] for comparing CVD risk among hypertension subtypes, adjusting for the competing risk of death, using the baseline nonhypertensive BP group as the referent (n=6460 observations). We verified that the assumption of proportionality of hazards held for all models. Models were adjusted for age, sex, body mass index, smoking, diabetes, total cholesterol to high-density lipoprotein cholesterol ratio, and cohort type.

In secondary analyses, we related the hypertension subtypes to incident CHD risk adjusting for covariates noted above; we did not analyze peripheral arterial disease, stroke/transient ischemic attack, or congestive heart failure as separate outcomes because the frequency of outcome events in select hypertension subtypes was <10, which precluded multivariable analyses.

A 2-sided value of $P<0.05$ was considered statistically significant for all models.

The authors (R.S. and V.X.) had full access to all of the data in the study and take responsibility for its integrity and the data analysis.

RESULTS

Baseline characteristics of the largest study sample are presented in Table 1. Our study sample was middle-aged (mean, 46.5 years; range, 19–82 years), and more than half (54%) were women. Characteristics of the subsample not taking antihypertensive medications are shown in Table S1. We observed similar trends in most characteristics among untreated individuals compared with the overall sample but a lower proportion of diabetes treatment among those with SDH.

Prevalence of Hypertension Subtypes by JNC 7

The majority of participants had nonhypertensive BP (79%). The most common hypertension subtypes were SDH (9%) and ISH (8%), with prevalences being similar in men and women except for IDH, which was more prevalent in men (Table S2).[23] The prevalence of ISH and SDH rose in the older age group (ie, >46 years) compared with the younger age group. A similar pattern was observed in analyses restricted to untreated individuals.

Antecedent Clinical, Echocardiographic, and Hemodynamic Predictors of New-Onset Hypertension Subtype

Predictors of new-onset hypertension subtypes are presented in Table 2. Baseline age was positively associated with new-onset ISH and SDH. Female sex, current smoking, and higher baseline SBP, but not baseline DBP, were significantly associated with incident ISH. Higher baseline SBP and DBP were associated with incident IDH and SDH. Omni 1 participants exhibited greater odds of developing IDH and SDH than their FOS counterparts (Table 2).

Aortic root diameter and left atrial diameter were not associated with any incident hypertension subtype. None of the echocardiographic traits were associated with IDH. Higher baseline RWT and LV mass index were associated with incident ISH and SDH (Table 2). Regarding hemodynamic predictors, a higher heart rate was associated with both ISH and SDH, whereas higher cardiac output was associated with greater odds of incident SDH. Higher mean arterial pressure and total peripheral resistance were associated with all incident hypertension subtypes (Table 2).

Analyses restricted to untreated participants revealed a similar pattern, but some weaker associations with all 3 sets of predictors were attenuated (Table S3).

Rates of Progression of Hypertension Subtypes

The nonhypertensive group at baseline had the highest proportion of individuals who remained in the same nonhypertensive category on follow-up (median, 5.5 years; range, 1.2–8.7 years), followed by those with SDH and ISH (Table 3). Participants with ISH rarely developed IDH on follow-up. Individuals with IDH were least likely to remain in the same category; they frequently reverted to nonhypertensive BP or SDH but rarely developed ISH. Individuals with SDH rarely developed IDH, but ≈20% developed ISH. Sensitivity analyses restricted to participants not taking antihypertensive medications revealed a pattern similar to the main analyses except that regression to the nonhypertension category was more common for all hypertension subtypes (Table 3, lower half).

Patterns of progression were similar in men and women (Table S4). In age-specific analyses, older participants (median age, ≥46 years) with nonhypertensive BP were more likely to progress to hypertension on follow-up than their younger counterparts (Table S4). Likewise, older individuals with IDH and ISH were more likely to develop SDH on follow-up. Sex- and age-stratified analyses of BP progression in participants

Table 1. Sample Characteristics by Hypertension Subtype at Baseline Examination

		Hypertension subtype		
Characteristics	Nonhypertensive BP (n=6483)	IDH (n=287)	ISH (n=663)	SDH (n=765)
Clinical features				
Age, y	44.5±11	44.9±8.7	59±9.8	52.9±10
Women, n (%)	3670 (57)	55 (21)	384 (56)	147 (40)
Cohort, n (%)				
FOS	2396 (37)	82 (28)	490 (74)	397 (52)
Gen 3	3445 (53)	172 (60)	110 (16)	272 (36)
Omni 1	330 (5)	16 (6)	44 (7)	57 (7)
Omni 2	312 (5)	17 (6)	19 (3)	39 (5)
BMI, kg/m^2	26.3±4.9	30.0±4.9	29.3±5.8	30.7±6.2
SBP, mm Hg*	115±12	132±6	152±12	159±16
DBP, mm Hg*	73±8	93±3	81±7	98±7
Hypertension medication, n (%)	192 (3)	83 (28.9)	216 (32.6)	514 (67.2)
Total cholesterol/HDL ratio	3.9±1.4	4.9±2.2	4.5±1.6	4.7±1.5
Triglycerides, mg/dL	96 (67–140)	145 (102–203)	135 (92–195)	142 (96–205)
Lipid-lowering medication, n (%)	262 (4)	39 (14)	71 (11)	99 (13)
Current smoking, n (%)	1097 (17)	47 (16)	99 (15)	98 (13)
Diabetes, n (%)	175 (2.7)	16 (5.6)	76 (11.5)	105 (13.7)
Diabetes treatment, n (%)	87 (1.3)	6 (2.1)	45 (6.8)	51 (6.7)
Echocardiographic features				
Aortic root diameter, cm	3.09±0.37	3.36±0.34	3.20±0.38	3.29±0.4
Left atrial diameter, cm	3.66±0.47	3.91±0.45	3.93±0.51	4.01±0.51
LV mass index (to body surface area), g/m^2	82±16	89±16	91±18	91±18
RWT	0.37±0.05	0.41±0.07	0.41±0.07	0.41±0.07
Hemodynamic features†				
Heart rate, beats per min	62±10	67±10	65±11	66±11
Stroke volume, mL per beat	72±15	76±15	74±17	76±16
Cardiac output, L/min	4.5±1.0	5.1±1.1	4.7±1.1	5±1.2
Mean arterial pressure, mm Hg	86±8	102±6	100±8	108±9
Total peripheral resistance, dynes/s per cm^{-5}	1634±501	1693±407	1796±487	1842±502

All Values are reported as mean±SD or median (quartile 1–quartile 3) unless otherwise stated. Blood pressure (BP) categories are defined per Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines. BMI indicates body mass index; FOS, Framingham Offspring Study; Gen 3, Framingham Third Generation; HDL, high-density lipoprotein; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; LV, left ventricular; RWT, relative wall thickness; and SDH, systolic diastolic hypertension.

*Systolic BP (SBP) and diastolic BP (DBP) values were imputed for patients taking medication.

†Hemodynamic features were derived in 5877 nonhypertensive, 256 IDH, 486 ISH, and 563 SDH patients.

not taking antihypertensive treatment revealed a similar pattern (data not shown).

Relations of Hypertension Subtype to CVD Incidence

Over a median follow-up of 14.6 years (range, 0.1–20 years), 889 participants (56% women) experienced a first CVD event. The age- and sex-adjusted probability of CVD by baseline hypertension subtype is presented in the Figure. Table 4 displays crude incidence rates of CVD and multivariable-adjusted hazard ratios and 95% CIs for incident CVD by hypertension subtype. IDH was the only hypertension subtype not significantly associated with CVD risk compared with the referent nonhypertensive group. Similar results were obtained in analyses of the subsample not taking antihypertensive medications (Table 4, lower half). In additional analyses relating hypertension subtypes to CHD incidence, we observed a pattern similar to that observed for CVD (Table S5).

Table 2. Predictors of New-Onset Hypertension Subtype Among Baseline Nonhypertensive BP

Covariate	Nonhypertensive BP	IDH		ISH		SDH	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Clinical correlates (n=5544)							
Age*	Referent	0.85 (0.67–1.08)	0.17	2.00 (1.69–2.37)	<0.0001†	1.33 (1.10–1.61)	0.0028†
Male sex	Referent	1.22 (0.81–1.82)	0.34	0.71 (0.54–0.93)	0.012	0.71 (0.53–0.96)	0.026
BMI*	Referent	1.12 (0.94–1.34)	0.19	1.10 (0.97–1.25)	0.12	1.16 (1.02–1.32)	0.026
Diabetes	Referent	0.88 (0.30–2.57)	0.82	1.40 (0.81–2.41)	0.23	1.26 (0.67–2.37)	0.47
Current smoking	Referent	0.86 (0.51–1.46)	0.58	1.42 (1.02–1.97)	0.035	1.06 (0.72–1.55)	0.77
Total cholesterol/HDL ratio*	Referent	0.95 (0.79–1.14)	0.58	1.03 (0.91–1.16)	0.61	1.12 (0.98–1.28)	0.10
Triglycerides*	Referent	1.08 (0.88–1.32)	0.48	1.03 (0.91–1.18)	0.62	0.97 (0.83–1.13)	0.66
SBP*	Referent	1.51 (1.14–1.99)	0.004	3.63 (3.00–4.40)	<0.0001†	2.93 (2.34–3.66)	<0.0001†
DBP*	Referent	2.73 (2.05–3.64)	<0.0001†	0.98 (0.83–1.15)	0.79	2.62 (2.10–3.25)	<0.0001†
Gen 3 vs FOS	Referent	1.11 (0.69–1.79)	0.66	0.80 (0.56–1.12)	0.19	0.79 (0.56–1.12)	0.18
Omni 1 vs FOS	Referent	4.42 (2.31–8.45)	<0.0001†	1.49 (0.90–2.47)	0.12	2.48 (1.49–4.14)	0.0005†
Omni 2 vs FOS	Referent	1.18 (0.49–2.82)	0.71	0.88 (0.43–1.79)	0.72	0.71 (0.33–1.55)	0.39
Echocardiographic correlates‡ (n=5000)							
Aortic root*	Referent	1.14 (0.90–1.44)	0.29	1.02 (0.86–1.21)	0.82	1.12 (0.93–1.34)	0.22
Left atrial diameter*	Referent	1.15 (0.90–1.46)	0.26	1.07 (0.91–1.27)	0.40	1.14 (0.95–1.37)	0.15
LV mass index*	Referent	0.95 (0.76–1.17)	0.62	1.27 (1.10–1.45)	0.001†	1.20 (1.03–1.41)	0.021
RWT*	Referent	1.08 (0.88–1.33)	0.44	1.27 (1.12–1.44)	0.0002†	1.27 (1.10–1.46)	0.001†
Hemodynamic correlates§ (n=4985)							
Heart rate*	Referent	1.17 (0.97–1.41)	0.10	1.17 (1.02–1.34)	0.026	1.23 (1.07–1.42)	0.0028†
Stroke volume*	Referent	0.90 (0.73–1.12)	0.34	1.04 (0.91–1.20)	0.56	1.02 (0.88–1.19)	0.79
Cardiac output*	Referent	1.05 (0.87–1.28)	0.61	1.12 (0.99–1.28)	0.07	1.16 (1.01–1.33)	0.032
MAP*	Referent	1.12 (1.09–1.15)	<0.0001†	1.11 (1.09–1.14)	<0.0001†	1.19 (1.16–1.22)	<0.0001†
Total peripheral resistance*	Referent	1.25 (1.05–1.49)	0.014	1.14 (1.02–1.28)	0.021	1.20 (1.07–1.36)	0.0028†

BP indicates blood pressure; DBP, diastolic blood pressure; FOS, Framingham Offspring Study; Gen 3, Framingham Third Generation; HDL, high-density lipoprotein cholesterol; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; LV, left ventricular; MAP, mean arterial pressure; RWT, relative wall thickness; SBP, systolic blood pressure; and SDH, systolic-diastolic hypertension.

*Odds ratios (ORs) are per 1-SD increment.

†*P* values are significant with Bonferroni correction (*P*<0.003).

‡ Models adjusted for clinical covariates significantly associated with ≥1 hypertension subtypes.

§ Models adjusted for age, sex, body mass index (BMI), smoking, and cohort.

Table 3. Unadjusted Incidence Rates of Progression to Different Hypertension Subtypes From the Baseline Examination to the Follow-Up Examination Using JNC 7 BP Thresholds

Baseline hypertension subtype	Hypertension subtype on follow-up			
	Nonhypertensive BP	IDH	ISH	SDH
Incidence rate in the overall sample, %				
Nonhypertensive BP (n=5544)	167.4 (87)	4.6 (2)	11.3 (6)	8.9 (5)
IDH (n=237)	79.7 (42)	31.9 (17)	11.2 (6)	66.1 (35)
ISH (n=593)	65.3 (28)	1.5 (1)	102.4 (45)	59.9 (26)
SDH (n=636)	32.4 (16)	14.9 (7)	41.2 (20)	117.7 (57)
Incidence rate in the subsample of individuals not taking antihypertensive medication (%)				
Nonhypertensive BP (n=5007)	177.2 (92)	2.6 (1)	8.6 (4)	3.4 (2)
IDH (n=105)	110.4 (58)	36.2 (19)	5.4 (3)	38 (20)
ISH (n=249)	101.6 (44)	1.9 (1)	110 (47)	18.6 (8)
SDH (n=106)	73 (36)	11.5 (6)	44.2 (22)	74.9 (37)

Incidence rates are reported per 1000 person-years; percentage is the proportion of individuals in a row transitioning from the baseline hypertension subtype to the follow-up hypertension subtype. Cells along the diagonal indicate individuals who remained in the same category on follow-up. Data reflect the pooled sample, including Framingham Offspring, Omni 1, Third Generation, and Omni 2 cohorts. BP indicates blood pressure; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; and SDH, systolic diastolic hypertension.

DISCUSSION

We investigated the prevalence of hypertension subtypes in a contemporary period spanning 3 decades. We evaluated their predictors and rates of progression in the short-term (median, 5.5 years) and prognostic significance on long-term follow-up (median, 15 years; maximum, 20 years) in relation to vascular risk.

Principal Findings

Our principal findings are 4-fold. First, in our large community-based sample, ISH and SDH (defined using JNC 7 guidelines[23]) were the most prevalent hypertension subtypes compared with IDH. Second, older age and heart rate, female sex, and greater LV mass and RWT were key predictors of future ISH and SDH. Higher systolic BP, mean arterial pressure, and total peripheral resistance were associated with increased risk of all hypertension subtypes. Higher diastolic BP predicted future IDH and SDH. Notably, non-White participants in the Omni 1 cohort demonstrated greater odds of new-onset IDH and SDH than their white FOS counterparts. Similar patterns of association were observed in analyses restricted to individuals not taking any antihypertensive medication, except that female sex, heart rate, and RWT were not associated with SDH incidence.

Third, hypertension subtypes were dynamic during short-term follow-up, with fewer than half of the participants with IDH and ISH remaining in the same BP category. IDH reverted to nonhypertensive BP in 42% of individuals, ISH progressed to SDH in ≈25%, whereas SDH transitioned to ISH in 20% of participants. Notably, IDH rarely progressed to ISH. Conversely, ISH rarely evolved into IDH. These patterns were consistent among both sexes. Rates of progression to hypertension or a different hypertension subtype were higher in older participants. A similar pattern was observed in individuals who were not treated with antihypertensive medications. Factors that determine the longitudinal stability versus progression of a particular hypertension subtype merit further study.

Last, individuals with ISH experienced the highest absolute and multivariable-adjusted relative risk of CVD on follow-up. IDH defined by JNC 7[23] was the only hypertension subtype not significantly associated with incident CVD. Sensitivity analyses of individuals not taking antihypertensive medications and of CHD as a separate outcome demonstrated a similar pattern.

Comparison With the Published Literature

Predictors of Hypertension Subtypes

In our investigation, higher antecedent SBP was associated with greater odds of developing all hypertension subtypes. In addition, higher baseline DBP was associated with greater odds of all hypertension subtypes, except for ISH. Prior observational studies emphasized the association between prehypertension, specifically higher baseline SBP, with incident hypertension.[36,37]

Epidemiologic studies have highlighted associations of ISH with older age and female sex, while IDH and SDH have been associated with higher body mass index.[7,8,11] In our investigation, body mass index was associated with SDH, older age was related to ISH and SDH, and female sex was associated with ISH and SDH.

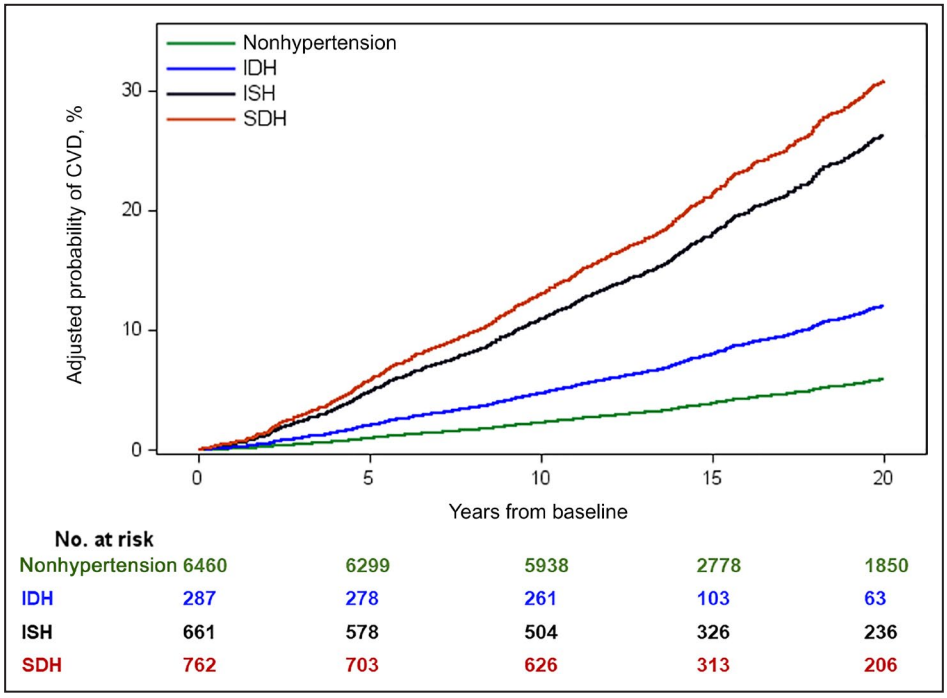

Figure. Age- and sex-adjusted probability of developing cardiovascular disease (CVD) on follow-up by baseline hypertension subtype defined using Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) blood pressure thresholds.
IDH indicates isolated diastolic hypertension; ISH, isolated systolic hypertension; and SDH, systolic diastolic hypertension.

We observed nearly 4-fold and >2-fold odds for developing IDH and SDH, respectively, among non-White participants in Omni 1 compared with White participants in FOS; this finding highlights potential racial/ethnic differences in developing hypertension subtypes. Previous reports have emphasized the increased prevalence of hypertension in non-White participants compared with White participants, partially attributed to environmental factors such as socioeconomic status and chronic neighborhood stressors.[38] Furthermore, increased proximal aortic stiffness and endothelial and microvascular dysfunction have been reported in Black and Hispanic participants compared with White participants.[39] Such differences in vascular function and

Table 4. Association of Hypertension Subtypes With the Incidence of CVD

Hypertension subtype	No. of events/No. at risk	Incidence rate per 1000 person-y	HR* (95% CI)	*P* value
Overall sample				
Nonhypertensive BP	483/6460	4.9	Referent	
IDH	26/287	6.2	1.03 (0.68–1.57)	0.88
ISH	195/661	20.7	1.57 (1.30–1.90)	<0.0001
SDH	185/762	17.0	1.66 (1.37–2.01)	<0.0001
Subsample of individuals not taking antihypertensive treatment				
Nonhypertensive BP	451/6270	4.7	Referent	
IDH	19/204	6.3	1.13 (0.68–1.87)	0.63
ISH	113/445	17.1	1.41 (1.12–1.78)	0.004
SDH	54/251	14.7	1.77 (1.29–2.41)	0.0003

Hypertension subtypes are defined per Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) blood pressure (BP) thresholds.

Models are adjusted for age, sex, body mass index, total cholesterol/high-density lipoprotein cholesterol ratio, smoking status, prevalent diabetes, and cohort type. CVD indicates cardiovascular disease; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; and SDH, systolic diastolic hypertension.

*Hazards ratios (HRs) are from Fine-Gray regression models that adjust for the competing risk of noncardiovascular death.

hemodynamics could contribute to the observed race-related differences in new-onset hypertension subtypes. Identifying the putative underlying mechanisms, including the potential role of social determinants of health, was beyond the scope of our investigation.

We observed that higher LV mass and greater RWT (concentricity) were key echocardiographic predictors of new-onset ISH and SDH. Prior observational studies have reported associations of LV mass/LV hypertrophy[26,27,40–42] and RWT[29] with incident hypertension, although these previous reports did not evaluate the incidence of hypertension subtypes. Prior reports have linked IDH pathogenetically to increased peripheral resistance,[33] ISH to increased arterial stiffness coupled with an elevated stroke volume and cardiac output,[31] and SDH to a hyperkinetic circulation (increased heart rate and stroke volume).[30,32] In the present investigation, we did not observe a unique hemodynamic signature for any hypertension subtype. Higher total peripheral resistance and mean arterial pressure were associated with all 3 hypertension subtypes, whereas higher heart rate was a key predictor of ISH and SDH.

CVD Outcomes Associated With Hypertension Subtypes

In the present investigation, both ISH and SDH were associated with a 50% to 60% increased risk of CVD, whereas IDH was not (compared with the referent group of nonhypertensive BP). Similar findings were observed for CHD incidence and when individuals without antihypertensive treatment were evaluated. The pathogenicity of IDH has also been questioned in some recent studies that used the 2017 American Heart Association/American College of Cardiology BP guidelines.[43,44] Yet, other reports that evaluated larger samples[44,45] and used the JNC 7 BP thresholds have noted a modest increase in CVD risk associated with IDH. The heterogeneity in results among different studies may reflect inherent differences in study samples and varying statistical power to observe modest associations compounded by potential challenges in accurately measuring DBP.[46]

Strengths and Limitations

We studied a large community-based sample of middle-aged adults with close monitoring of covariates and continuous surveillance for CVD. Yet, several limitations warrant consideration. First, we classified participants based on a single-occasion measure of BP, which may misclassify hypertension status. This is an unavoidable and inherent constraint in epidemiological studies. Second, we did not evaluate the role of arterial stiffness, LV diastolic function, and contemporary speckle tracking echocardiography in predicting the incidence of hypertension subtypes. Third, we did not correct for multiple statistical testing, although several observed associations would have survived Bonferroni correction (P value <0.003). Last, most of our participants were middle-aged White adults, limiting the generalizability of our results. Replication of our findings in large multiethnic samples is essential.

CONCLUSIONS

Our prospective study of a large community-based sample of middle-aged adults elucidated the dynamic nature of hypertension subtypes over the lifecourse within individuals. We observed that ISH and SDH are the hypertension subtypes associated with increased CVD risk, whereas IDH was not. Thus, hypertension subtypes might offer incremental prognostic information toward CVD risk. Additional studies are warranted to evaluate whether BP subphenotyping can inform clinical management and alter patient outcomes.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S5
Figure S1

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Supplemental Material

Data S1.

Supplemental Methods

Study sample derivation

There were 8,810 FHS participants (see **Figure S1** and **Data S1** for study sample derivation for different analyses**)** who attended FOS examination cycle 5 (1991-1995) and the first examination cycles of the Omni 1 (1994-1998), Gen3 (2002-2005), and Omni 2 (2003-2005) cohorts eligible for inclusion; these examination cycles served as 'baseline' for the present investigation. We excluded participants with prevalent CVD (n=504), unknown baseline hypertension status (n=26), or incomplete covariate data (n = 82), yielding a base sample of 8,198 participants for cross-sectional analyses (**Sample 1**). For analyses of longitudinal progression of HTN subtypes, we evaluated participants who attended their baseline examination and their next follow-up examination cycle, i.e., FOS examination cycle 6 (1995-1998) and examination cycle 2 for Omni 1 (1999-2001), Gen 3 (2008-2011), and Omni 2 (2009-2011) cohorts, resulting in a base sample of 7,010 participants for these prospective analyses (**Sample 2a**). Among the 7,010, we included 5,544 participants without baseline hypertension to examine longitudinal clinical correlates of HTN subtypes (**Sample 2b**) and 5,000 participants for longitudinal echocardiographic correlates of HTN subtypes (**Sample 2c**). Analyses of CVD incidence excluded 28 participants lost to follow-up for the analyses of CVD incidence after the baseline examination (**Sample 3**).

Definition of covariates

Participants were classified as having diabetes mellitus if their fasting blood glucose concentrations were ≥126 mg/dL or if they were treated with anti-diabetic medications. Current smoking was defined as regular cigarette smoking in the year before the baseline examination.

Measurement of Echocardiographic Traits

Routine two-dimensional transthoracic echocardiography (TTE) was performed at each examination cycle using a standardized protocol. All echocardiograms were digitized, and the digital images were read offline in a blinded fashion by an experienced cardiologist or a sonographer, with excellent reproducibility of the echocardiographic measurements.[18] M-mode measurements of thickness of the Left ventricular (LV) posterior wall (PW), interventricular septum (IVS) at end-diastole, and LV internal dimensions in end-systole and end-diastole (LVDD) were obtained from the average of ≥3 cardiac cycles, using the leading-edge-to-leading-edge convention, following American Society of Echocardiography (ASE) guidelines.[19] LV wall thickness (LVWT) was calculated by summing the end-diastolic thicknesses of the LVPW and IVS. Relative wall thickness (RWT) was subsequently calculated as LVWT/LVDD. Using the method by Devereux et al.,[20] LV mass (LVM) was calculated as follows: LVM = (0.8*(1.04(LVDD + IVS + PW)^3 - LVDD^3) + 0.6). In the present investigation, LVM is reported as indexed to body surface area (LVMI), calculated by the DuBois formula.[21] Per ASE guidelines, left atrial diameter (LAD) was measured via M-mode echocardiography using a leading-edge-to–leading-edge measurement of the maximal distance between the posterior aortic root wall and the posterior left atrial wall at end-systole.[19] Similarly, aortic root diameter was measured at the maximal distance between the anterior aortic root wall and the posterior aortic root wall at end-diastole by M-mode echocardiography using the leading-edge-to-leading-edge convention.

Stroke volume (ml/beat) was calculated using the Teicholz formula.[22] Cardiac output (Liters/minute) was estimated as stroke volume multiplied by the resting heart rate. Mean arterial pressure (MAP, mm Hg) was calculated as diastolic BP plus 1/3 pulse pressure (BP measured at the same FHS examination as the echocardiogram). Total peripheral resistance was calculated as the product of 80 x cardiac output x MAP.

Table S1. Sample characteristics by hypertension subtype at the baseline examination, excluding all individuals on antihypertensive medications.

		Hypertension subtype		
Characteristics	**Non-hypertensive BP** (n=6,291)	**IDH** (n=204)	**ISH** (n=447)	**SDH** (n=251)
Clinical Features				
Age, years	44.3 ± 11	43.4 ± 8.5	57.1 ± 9.8	49.4 ± 9.8
Women, n (%)	3564 (57)	35 (17)	250 (56)	94 (37)
Cohort, n (%)				
Offspring	2307 (37)	57 (28)	327 (73)	127 (51)
Third Generation	3363 (53)	127 (62)	85 (19)	106 (42)
Omni-1	319 (5)	9 (4)	26 (6)	10 (4)
Omni-2	302 (5)	11 (5)	9 (2)	8 (3)
Body mass index, kg/m^2	26.2 ± 4.8	29.8 ± 4.7	29.2 ± 6	30.9 ± 6.1
Systolic blood pressure, mm Hg	115 ± 12	131 ± 6	150 ± 11	153 ± 12
Diastolic blood pressure, mm Hg	73 ± 8	93 ± 3	80 ± 7	96 ± 5
Total cholesterol/HDL ratio	3.9 ± 1.4	5 ± 2.3	4.6 ± 1.6	4.6 ± 1.5
Triglycerides, mg/dL	96 (67, 139)	142 (102, 196)	137 (91, 200)	131 (89, 186)
Lipid-lowering treatment, n (%)	228 (4)	19 (9)	31 (7)	6 (2)
Current smoking, n (%)	1070 (17)	33 (16)	75 (17)	43 (17)
Diabetes mellitus, n (%)	157 (2.5)	10 (4.9)	42 (9.4)	19 (7.6)
Diabetes treatment, n (%)	76 (1.2)	4 (2)	18 (4)	2 (0.8)
Echocardiographic features				
Aortic root diameter, cm	3.08 ± 0.37	3.38 ± 0.33	3.21 ± 0.38	3.30 ± 0.38
Left atrial diameter, cm	3.65 ± 0.47	3.93 ± 0.45	3.91 ± 0.49	3.98 ± 0.47
Left ventricular mass index (to body surface area), g/m^2	82 ± 16	90 ± 16	91 ± 18	92 ± 17
Relative wall thickness	0.37 ± 0.05	0.40 ± 0.07	0.41 ± 0.07	0.41 ± 0.07
Hemodynamic Features*				
Heart rate, bpm	62 ± 10	68 ± 10	66 ± 11	69 ± 11
Stroke volume, ml/beat	72 ± 15	77 ± 15	74 ± 17	77 ± 16
Cardiac output, L/min	4.4 ± 1.0	5.2 ± 1	4.8 ± 1.1	5.3 ± 1.3
Mean Arterial Pressure, mm Hg	86 ± 8	105 ± 3	104 ± 6	115 ± 6
Total Peripheral resistance, $dynes/sec/cm^{-5}$	1636 ± 502	1704 ± 394	1827 ± 497	1832 ± 515

All values are reported as mean ± SD or median (Q1, Q3) unless stated otherwise. HTN subtypes are defined per JNC-7 guidelines. HDL, high-density lipoprotein; HTN, hypertension; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic-diastolic hypertension. *****Hemodynamic predictors were derived in 5715 non-hypertensive, 187 IDH, 339 ISH, and 193 SDH

Table S2. Baseline frequency and prevalence of hypertension subtypes by sex and median age (46 years) using JNC-7 guidelines in the overall sample and the subsample not on antihypertensive medications.

Hypertension Subtype (N=8,207)	Pooled	Men	Women	Age <Median	Age ≥Median
Overall sample, N (%)					
Non-HTN BP	6483 (79)	2813 (75)	3670 (82)	3562 (90)	2921 (69)
IDH	287 (4)	213 (6)	74 (2)	160 (4)	127 (3)
ISH	663 (8)	293 (8)	370 (8)	55 (1)	608 (14)
SDH	765 (9)	425 (11)	340 (8)	168 (4)	597 (14)
Subsample of individuals not on antihypertensive medications, N (%)					
Non-HTN BP	6291 (87)	2727 (84)	3564 (90)	3507 (93)	2784 (81)
IDH	204 (3)	169 (5)	35 (1)	128 (3)	76 (2)
ISH	447 (6)	197 (6)	250 (6)	48 (1)	399 (12)
SDH	251 (3)	157 (5)	94 (2)	80 (2)	171 (5)

All values reported as N (%).
BP, blood pressure; Non-HTN, non-hypertensive; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; JNC-7, Seventh Report of the Joint National Committee; SDH, systolic-diastolic hypertension.

Table S3. Predictors of new-onset hypertension subtype among participants with baseline non-hypertensive blood pressure.

Covariate	Non-HTN BP	IDH		ISH		SDH	
		Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Clinical Correlates (N=5007)							
Age†	Referent	0.66 (0.48-0.92)	**0.015**	2.05 (1.68-2.49)	***<.0001***	1.33 (0.99-1.80)	0.06
Male Sex	Referent	1.77 (0.99-3.17)	0.05	0.70 (0.51-0.96)	**0.027**	0.72 (0.45-1.17)	0.19
BMI†	Referent	1.14 (0.89-1.47)	0.30	1.02 (0.87-1.20)	0.80	1.17 (0.95-1.45)	0.14
Diabetes	Referent	0.47 (0.06-3.60)	0.46	1.10 (0.49-2.45)	0.81	0.27 (0.04-2.10)	0.21
Current Smoking	Referent	0.98 (0.49-1.97)	0.95	1.30 (0.89-1.92)	0.17	1.13 (0.62-2.05)	0.70
TChol/ HDL Ratio	Referent	0.95 (0.74-1.21)	0.68	1.00 (0.86-1.15)	0.95	1.03 (0.83-1.28)	0.79
Triglycerides†	Referent	1.10 (0.85-1.44)	0.47	1.03 (0.88-1.21)	0.70	1.05 (0.83-1.32)	0.71
Systolic BP†	Referent	1.34 (0.91-1.96)	0.14	3.15 (2.53-3.92)	***<.0001***	3.09 (2.17-4.41)	***<.0001***
Diastolic BP†	Referent	2.52 (1.72-3.70)	***<.0001***	1.07 (0.88-1.30)	0.51	2.63 (1.85-3.73)	***<.0001***
Gen 3 vs. FOS	Referent	0.74 (0.38-1.43)	0.37	0.63 (0.41-0.96)	**0.030**	1.13 (0.64-1.99)	0.67
Omni 1 vs. FOS	Referent	7.11 (3.28-15.43)	***<.0001***	1.48 (0.85-2.59)	0.17	4.78 (2.36-9.69)	***<.0001***
Omni 2 vs. FOS	Referent	0.95 (0.29-3.06)	0.93	0.58 (0.22-1.51)	0.27	0.63 (0.14-2.76)	0.54
Echocardiographic Correlates* (N=4552)							
Aortic root†	Referent	1.15 (0.83-1.58)	0.40	1.17 (0.96-1.42)	0.13	1.23 (0.93-1.65)	0.15
Left atrial diameter†	Referent	1.09 (0.78-1.52)	0.62	1.00 (0.82-1.22)	0.99	1.33 (0.99-1.78)	0.06
LV Mass index†	Referent	1.13 (0.85-1.51)	0.39	1.24 (1.06-1.46)	**0.009**	1.42 (1.11-1.81)	**0.005**
RWT†	Referent	1.19 (0.91-1.55)	0.21	1.26 (1.08-1.47)	***0.0025***	1.20 (0.95-1.50)	0.13
Hemodynamic Correlates (N=4539)**							
Heart rate†	Referent	1.23 (0.95-1.59)	0.12	1.15 (0.98-1.36)	0.09	1.17 (0.92-1.47)	0.20
Stroke volume†	Referent	0.90 (0.68-1.21)	0.50	1.08 (0.92-1.27)	0.35	1.21 (0.94-1.55)	0.14
Cardiac output†	Referent	1.10 (0.85-1.44)	0.46	1.13 (0.98-1.32)	0.10	1.31 (1.05-1.63)	**0.016**
MAP	Referent	1.14 (1.09-1.19)	***<.0001***	1.13 (1.11-1.16)	***<.0001***	1.25 (1.20-1.31)	***<.0001***
Total Peripheral resistance†	Referent	1.22 (0.96-1.56)	0.11	1.11 (0.97-1.26)	0.13	1.17 (0.95-1.44)	0.14

†Odds ratios are per 1 SD increment. ***** Models adjusted for age, sex, BMI, smoking, baseline SBP, baseline DBP, and cohort. **Models adjusted for age, sex, BMI, smoking, and cohort. *Italicized p-values are significant with Bonferroni correction (p<0.003).*

BMI, body mass index; BP, blood pressure; FOS, Framingham Offspring Study cohort; Gen 3, Framingham Third Generation cohort; HDL, high-density lipoprotein cholesterol; Non-HTN, non-hypertensive; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; LV, left ventricular; MAP, mean arterial pressure RWT, relative wall thickness; SDH, systolic-diastolic hypertension; TChol, total cholesterol

Table S4. Rates of progression to different hypertension subtypes from baseline to follow-up exam stratified by sex and median age.

Baseline hypertension subtype	Hypertension subtype on follow-up			
	Non-HTN BP	IDH	ISH	SDH
Men				
Non-HTN BP (n=2,416)	2054 (85)	83 (3)	143 (6)	136 (6)
IDH (n=178)	76 (43)	31 (17)	4 (2)	67 (38)
ISH (n=266)	70 (26)	4 (2)	111 (42)	81 (30)
SDH (n=356)	50 (14)	28 (8)	66 (19)	212 (60)
Women				
Non-HTN BP (n=3,128)	2772 (89)	51 (2)	184 (6)	121 (4)
IDH (n=59)	24 (41)	9 (15)	10 (17)	16 (27)
ISH (n=327)	99 (30)	0 (0)	154 (47)	74 (23)
SDH (n=280)	50 (18)	18 (6)	61 (22)	151 (54)
Age below median age (46 years)				
Non-HTN BP (n=2,968)	2743 (92)	86 (3)	53 (2)	86 (3)
IDH (n=126)	58 (46)	27 (21)	4 (3)	37 (29)
ISH (n=46)	22 (48)	1 (2)	16 (35)	7 (15)
SDH (n=132)	35 (27)	16 (12)	10 (8)	71 (54)
Age above median age (46 years)				
Non-HTN BP (n=2,576)	2083 (81)	48 (2)	274 (11)	171 (7)
IDH (n=111)	42 (38)	13 (12)	10 (9)	46 (41)
ISH (n=547)	147 (27)	3 (1)	249 (46)	148 (27)
SDH (n=504)	65 (13)	30 (6)	117 (23)	292 (58)

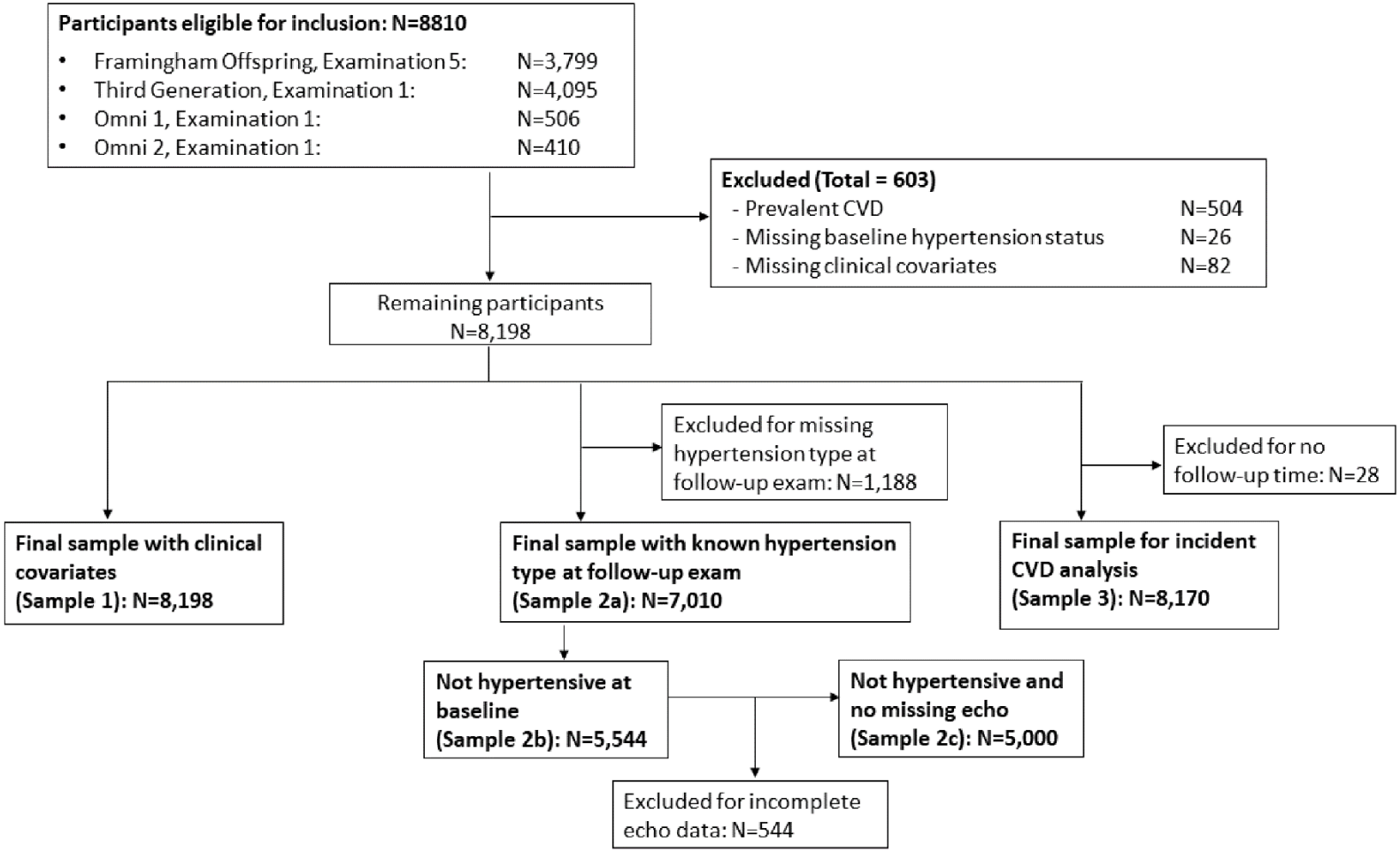
Values are reported as n (row %). Shaded cells indicate individuals who remained in the same category on follow-up.
Data reflect the pooled sample, including Offspring, Omni 1, Third Generation, and Omni 2 cohorts.
BP, blood pressure; non-HTN, non-hypertensive; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic-diastolic hypertension.

Table S5. Association of hypertension subtypes with the incidence of coronary heart disease.

Hypertension subtype	No. events/ No. at-risk	Incidence Rate per 1000 Person-years	Hazards Ratio* (95% CI)	P-value
Overall sample				
Non-HTN BP	171/6460	1.7	Referent	
IDH	13/287	3.0	1.44 (0.80-2.62)	0.23
ISH	95/661	9.3	2.24 (1.69-2.96)	<.0001
SDH	78/762	6.8	2.03 (1.50-2.76)	<.0001
Subsample of individuals not on antihypertensive medications				
Non-HTN BP	160/6270	1.6	Referent	
IDH	11/204	3.6	1.81 (0.94-3.48)	0.07
ISH	53/445	7.5	1.92 (1.36-2.72)	0.0002
SDH	19/251	4.9	1.69 (1.00-2.84)	0.049

*Hazards ratios are from Fine-Gray regression models that adjust for the competing risk of non-cardiovascular death.
Hypertension subtypes are defined per JNC-7 blood pressure thresholds.
Models are adjusted for age, sex, BMI, Tchol/HDL ratio, smoking status, prevalent diabetes, and cohort type.
BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; JNC-7, Seventh Report of the Joint National Committee; Non-HTN, non-hypertensive; SDH, systolic diastolic hypertension; Tchol, total cholesterol.

Figure S1. Flow diagram of the pooled study sample.



BP, blood pressure; CVD, cardiovascular disease.