Age-stratified association between isolated diastolic hypertension and carotid intima-media thickness: Results from the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) study

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This certifies that the master's thesis of

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GLOSSARY OF TERMS

BP: Blood pressure

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

PP: Pulse pressure

IDH: Isolated diastolic hypertension

ISH: Isolated systolic hypertension

SDH: Systolic diastolic hypertension

CVD: Cardiovascular disease

cIMT: Carotid intima-media thickness

BMI: Body mass index

TC: Total cholesterol

MI: Myocardial infarction

HF: Heart failure

OR: Odds ratio

HR: Hazard ratio

ACC/AHA: American College of Cardiology and American Heart Association

CMERC cohort study: Cardiovascular and Metabolic Diseases Etiology Research Center cohort study

ABSTRACT

Age-stratified association between isolated diastolic hypertension and carotid intima-media thickness: Results from the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) study

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(Directed by Professor Hyeon Chang Kim, M.D, Ph.D.)

Background:

There has been debate on benign outcomes and age-related results in people with isolated diastolic hypertension (IDH). Therefore, we aimed to evaluate the age-stratified association between IDH and increased carotid intima-media thickness (IMT) in a cross-sectional design.

Methods:

Cardiovascular and Metabolic Diseases Etiology Research center (CMERC) cohort baseline data was used. People with a medical history of myocardial infarction, heart failure, stroke, or cancer within 2 years were excluded. From the initial number of 8,097 aged 30 to 64 years (2,808 men and 5,289 women), (i) 1,324 participants who were taking antihypertensive medications, (ii) 13 participants who had missing values on examination of blood pressure and carotid IMT, and (iii) 1 additional person for missing the blood chemistry information were excluded. Finally, the study population included 6,759 individuals in the analysis (mean age at baseline, 50.46 ± 8.88 years; 2,234 men and 4,525 women). Blood pressure (BP) was categorized into 1) no hypertension, 2) IDH, 3) isolated systolic hypertension (ISH) and 4) systolic diastolic hypertension (SDH) according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline. Carotid IMT was scanned by B-mode ultrasonography and the 75 percentile of IMT was used to be considered increased IMT. Multiple logistic regression was used to investigate the association between IDH and the thickening of carotid IMT. We also conducted subgroup analyses by age group, ≥ 50 years and < 50 years.

Results:

In younger participants aged under 50, IDH was significantly associated with thickening of carotid IMT after adjusting for age, sex, body mass index, education, physical activity, smoking, diabetes, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering drug use, C-reactive protein, and study site (odds ratio: 1.57, 95% confidence interval: 1.10-2.26). But the association was not observed in those aged 50 years or older (odds ratio: 0.89, 95% confidence interval: 0.72-1.09). On the other hand, ISH and SDH were associated with the thickening of carotid IMT both in younger and older groups.

Conclusion:

In this cross-sectional study of Korean adults, IDH was associated with increased carotid IMT among individuals under 50 years of age, but not in those over 50. This finding suggests that IDH may not be a completely benign status and might be an initial step in providing evidence for early strategies appropriate for young adults with IDH.

Keywords: isolated diastolic hypertension; carotid intima-media thickness; atherosclerosis; cardiovascular disease;

Ⅰ. INTRODUCTION

It is well known that elevated blood pressure (BP) levels are associated with a higher risk of cardiovascular disease (CVD), cerebrovascular disease and coronary artery disease.[1,2] These BP levels include systolic blood pressure (SBP) or diastolic blood pressure (DBP). When these jump over the cutoff value, it is classified into isolated diastolic hypertension (IDH), isolated systolic hypertension (ISH), and systolic diastolic hypertension (SDH), and these constitute hypertension subtype.

There have been released several hypertension guidelines to diagnose and manage people with high blood pressure. The cutoff value of BP is 140/90 mmHg in the seventh report of the Joint National Committee (JNC7)[3], and the 2018 European Society of Cardiology and European Society of Hypertension Task Force (ESC/ESH). [4] Contrary to the above guidelines, new strict guidelines which define the cutoff as 130/80 mmHg were published in 2017, named as American College of Cardiology/American Heart Association (ACC/AHA).[5] IDH by ACC/AHA definition was a DBP ≥ 80 mmHg with an SBP < 130 mmHg, which is lower than 10 mmHg than previous guidelines. Accordingly, the number of adults in the US newly eligible for a diagnosis of IDH was approximately 12 million individuals[6], and the prevalence of IDH was 6.1% compared with 1.4% when the JNC/ESC definitions were used.[7] Researchers have been careful in applying the ACC/AHA definition of IDH as more people were targeted for the treatment of hypertension.

According to the 2017 ACC/AHA guideline, if either SBP or DBP exceeds the threshold, IDH (DBP exceeds), ISH (SBP exceeds), or SDH (both exceed) were diagnosed, and antihypertensive treatment is recommended. Because these three BPs do not share the same risk of CVD and should be treated with different levels of evidence for antihypertensive medications. However, the guideline doesn't distinguish between IDH, ISH, or SDH when giving treatment recommendations. Therefore, it is necessary to evaluate the association between IDH and CVD events.

There have been inconsistent reports on IDH by the 2017 ACC/AHA definition, different from traditional BP definitions, JNC7, and 2018 ESC/ESH. Several studies suggested that IDH by the 2017 ACC/AHA definition was not significantly associated with CVD risk consisting of coronary events, stroke, heart failure, and cardiovascular death compared to normotension.[6,8,9] However, contrary to the previous results, participants with IDH had a significantly positive association with the risk of CVD. Based on a nationwide epidemiological database, Japan Medical Data Center (JMDC), the statistically significant association between IDH by 2017 ACC/AHA guideline and incident CVD including myocardial infarction (MI), angina pectoris, and stroke was observed.[10] A study involving participants from

Kaiser Permanente Northern California (KPNC) reported the burden of IDH was associated with the composite outcome among individuals who did not have a burden of ISH, regardless of BP thresholds. The composite outcome events included MI, ischemic stroke, or hemorrhagic stroke.[7] Furthermore, age-dependent associations between IDH and CVD were presented in some studies, which was not associated with increased cardiovascular risk or low risk in older people but was a significant risk factor for CVD in young adults.[11-13] Young adults aged 20-39 years with IDH (2017 ACC/AHA definition) had a higher risk of CVD than normotension.[14] In a large prospective cohort study of the UK population[11], the effects of IDH on CVD and CVD death were stronger in younger adults aged < 60 years and null in older adults aged ≥ 60 years.

If there is a fundamental causal link between IDH by the 2017 ACC/AHA definition and CVD, it could be expected to find clear evidence of subclinical atherosclerosis in affected persons. To our knowledge, there are few studies regarding the age-stratified association between IDH and subclinical atherosclerosis. Therefore, this study aimed to investigate the age-stratified association between IDH defined by the 2017 ACC/AHA and carotid intima-media thickness (IMT), which is considered a sensitive marker for subclinical atherosclerosis, in a cross-sectional design.

II. MATERIALS AND METHODS

1. Data collection and participants

This study used the baseline data from the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) cohort study. The CMERC cohort study enrolled community-dwelling, middle-aged adults (aged 30-64 years) with the aim of discovering novel risk factors and developing prevention strategies for cardiovascular and metabolic diseases between 2013 and 2018. The data was collected at 2 research centers at the Yonsei University College of Medicine (YUCM) in Seoul, Korea, and at the Ajou University School of Medicine (AUSM) in Suwon, Korea. Participants fit the following criteria: 1) had lived in their current residence at the time of their enrollment for at least 8 months without plans to move out within the following 2 years, 2) were able to convey their own opinions regarding study participation, 3) no medical history of severe diseases (myocardial infarction, heart failure, stroke, cancer) within 2 years, 4) were not participating in any clinical trials, and 5) not pregnant. Further details of the CMERC study protocol and procedures have been published elsewhere.[15,16]

Figure 1 shows a flow chart for selecting the study population. From the initial number of 8,097 (mean age at baseline, 51.42 ± 8.70 years; 2,808 men and 5,289 women), we excluded 1,324 participants who were taking antihypertensive medications, 13 participants due to missing values on examination of blood pressure and carotid IMT, and 1 participant for missing the blood chemistry information. Finally, we included 6,759 participants in the analysis (mean age at baseline, 50.46 ± 8.88 years; 2,234 men and 4,525 women).

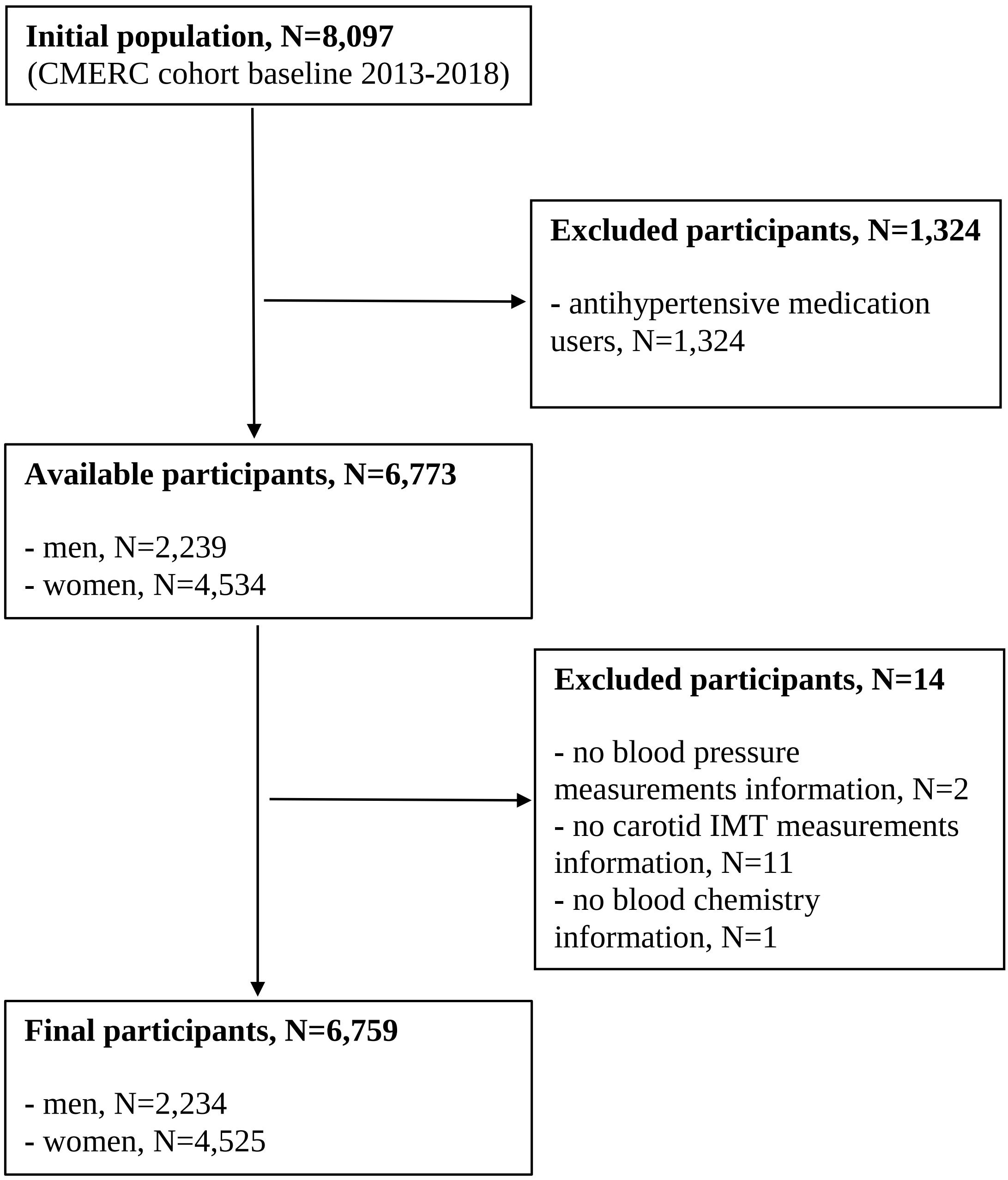


Figure 1. Flow diagram of the study population

2. Measurement

(1) Blood pressure measurement and classification of hypertension subtypes

Blood pressure was measured using an automated oscillometric device (HEM-7080, Omron Health, Matsusaka, Japan) with the standard protocol at both research clinics. Before an examination, participants took at least 5 minutes of rest in a seated position and maintained a comfortable status during all measurements. Trained research staff conducted BP measurements three times at 2-minute intervals, and the average value of the second and third measurements was used for analysis. When the mean value of systolic blood pressure is ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg, or using antihypertensive drugs with consideration of cardiovascular risk estimation, it is defined as hypertension by 2017 ACC/AHA guidelines.[5] Hypertension is classified into subtypes of isolated diastolic hypertension (IDH), isolated systolic hypertension (ISH), and systolic diastolic hypertension (SDH) depending on which blood pressure (systolic or diastolic or both) jumped over the cutoff value. Participants were categorized into 4 mutually exclusive groups: 1) no hypertension (including elevated): SBP < 130 mmHg and DBP < 80 mmHg; 2) IDH: SBP < 130 mmHg and DBP ≥ 80 mmHg; 3) ISH: SBP ≥ 130 mmHg and DBP < 80 mmHg; 4) SDH: SBP ≥ 130 mmHg and DBP ≥ 80 mmHg, according to 2017 ACC/AHA guidelines.

(2) Assessment of carotid IMT

Carotid arteries were examined using different ultrasonography machines at two research clinics, the YUCM clinic (Accuvix XG, Samsung Medison, Seoul, Korea) and the AUSM clinic (Logiq S8 ECG module, GE Healthcare, Chalfont St. Giles, UK) by trained operators based on a predefined study protocol.[16] Quality control was performed by standardizing the examination including the participant's position during the test and the measurement site.[15] Carotid IMT was scanned at the 1-cm segment of the common carotid arteries proximal to the bulb region, at the time of the R-wave on the electrocardiogram. IMT was computed in mean or max measurements using the dedicated software. IMT thickening was defined as the max carotid IMT of the left and right sides equal to or greater than the cutoff value. The cutoff value was set to the 75 percentile of the max carotid IMT measured on both sides, for more than 75 percentile is considered high and indicative of increased cardiovascular risk by the American Society of Echography.[17] Using max measurements in main analyses, the criterion was 0.857mm.

(3) Covariates

In the baseline assessment, demographic information, socio-economic status, medical/medication history, and lifestyle factors (smoking, drinking, physical activity) have been collected by trained interviewers using a general questionnaire with a standardized protocol. Educational background was grouped based on the education curriculum in Korea (high school or below, college or above). Physical activity was assessed using the Korean version of the International Physical Activity Questionnaire (IPAQ) – a short form obtaining the last 7 days of activities, which were divided into three groups (low, moderate, and high). The reliability and validity of the Korean version of the IPAQ short form were proven.[18] Smoking status was classified into "never", "past", and "current". Diagnosis of diabetes was classified as "no", and "yes". Usage of lipid-lowering drugs at baseline was categorized into "no", and "yes". Body mass index (BMI) was calculated as the ratio of weight (kg) divided by the square of the standing height (m^2). Body weight was measured to the nearest 0.1 kg using a DB-150 digital scale (CAS, Seongnam, Korea), and height was measured to the nearest 0.1 cm using a DS-102 stadiometer (Jenix, Seoul, Korea).

Blood samples were obtained after 8-hour fasting. Lipid profile, such as total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-c), was measured enzymatically, and C-reactive protein (CRP) was evaluated by the turbidimetric method (ADIVA 1800 AutoAnalyzer; Siemens Medical Sol.).

3. Statistical analysis

(1) Main analyses

Baseline characteristics were presented in mean and standard deviation or median and interquartile range for continuous variables, and in frequency and percent for categorical variables. Analysis of variance, Kruskal-Wallis, and chi-square test were used to compare differences between categories of blood pressure.

The associations between hypertension subtypes and carotid IMT thickening were estimated by multiple logistic regression models. These are adjusted for age, sex, body mass index, education, physical activity, smoking, diabetes, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering drug use, C-reactive protein, and study cite. Age was categorized into 30-49 years and 50-64 years and more specifically, it was stratified by 10-year units based on previous studies reporting blood pressure changes in aging[7,19] and our data characteristics whose representative age is near 50 (median age is 52). With this criterion, age-stratified analyses were conducted to evaluate the age-related associations between hypertension subtypes and carotid IMT thickening. We tested for effect modification of age using an interaction term in the analyzed models.

(2) Sensitivity analyses

We performed additional analyses to identify the robustness of our results. (1) By including participants taking antihypertensive medications, comparisons of drug inclusion with drug exclusion data were conducted (N=1,324). (2) By applying different measurements on carotid IMT whose thickness was measured in mean value, associations between hypertension subtypes and carotid IMT were assessed. The mean was calculated from both right and left IMT mean measurements. (3) By using different percentiles whose cutoffs were 80 and 90 percentiles and applying age- and sex-specific cutoffs, we ran the same analyses.[20,21]

All tests were conducted using the SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and the statistical significance was a 2-tailed p-value of less than 0.05.

(3) Ethical approval

All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of Severance Hospital at YUCM (Institutional Review Board number: 4-2013-0661) and of Ajou University Hospital at AUSM (AJIRB-BMR-SUR-13-272).

III. RESULTS

1. Characteristics of the study population

The general characteristics of the study population are presented in Table 1. In the hypertension subtypes, the IDH group had a higher DBP than the ISH group, but lower than the SDH group. The youngest group is IDH (51.0 [44.0-57.0] years), and the oldest group is ISH (58.0 [54.0-62.0] years). An increase in carotid IMT had the highest percentage in the ISH group (46.9%) and decreased sequentially toward SDH (39.4%), IDH (24.6%), and no hypertension group (20.5%). This pattern was the same when carotid IMT was continuous. All of the blood pressures, carotid IMT, and biochemical variables were significantly different by hypertension subtypes. Systolic and diastolic blood pressure distribution of participants by age was presented in Figure 2 via two scatter plots. For those aged under 50, the distribution is mainly on the upper left, and for those over 50 years old, the distribution is mainly on the lower right. This is because DBP increases until the age of 50 and then decreases after that.[7] Figure 3 shows the prevalence of hypertension subtypes by age. In all ages, the highest prevalence was in the no hypertension group, and the lowest prevalence was in the ISH group. IDH was higher than SDH in the 30s and 40s, and an opposite pattern was observed in the 50s and 60s. This trend supported that IDH was common in young adults aged less than 50 years.

Population characteristics according to age groups (<50 years, ≥50 years) were provided in (Appendix 1). Among the 6,759 participants, Individuals over 50 years were 4,093 (60.56%). The older group had thicker carotid arteries and higher BPs, and the differences were statistically significant. There was no significant difference in body mass index and HDL cholesterol between the two age groups.

Table 1. Baseline characteristics of participants (n= 6,759) according to hypertension subtypes

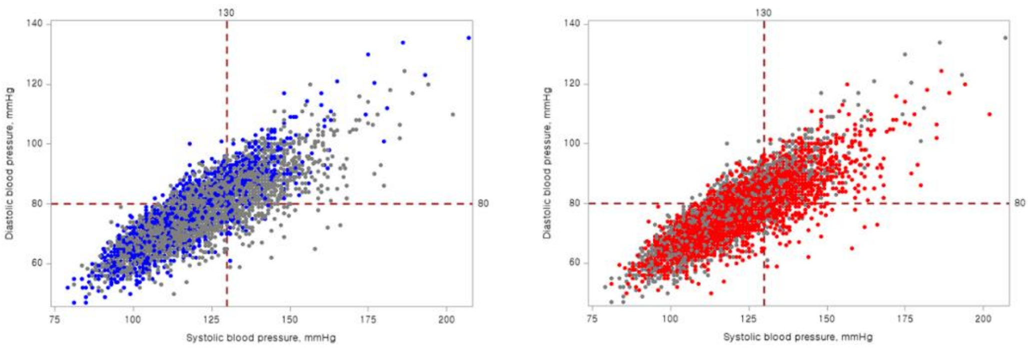
Variables	No hypertension (n= 4,455)	IDH (n= 961)	ISH (n= 192)	SDH (n= 1,151)	p-value
cIMT, mm	0.765 ± 0.139	0.783 ± 0.136	0.882 ± 0.187	0.839 ± 0.155	<.0001
Age-adjusted cIMT, mm	0.768 ± 0.002	0.787 ± 0.004	0.844 ± 0.009	0.829 ± 0.004	<.0001
cIMT, %					
≥ 75p (0.857mm)	913 (20.5)	236 (24.6)	90 (46.9)	453 (39.4)	<.0001
SBP, mmHg	110.1 ± 8.9	122.7 ± 4.6	135.4 ± 6.0	141.1 ± 10.5	<.0001
DBP, mmHg	69.9 ± 5.8	83.8 ± 3.4	75.4 ± 3.8	90.3 ± 7.6	<.0001
Pulse pressure, mmHg	40.2 ± 6.3	38.9 ± 4.7	60.0 ± 7.4	50.9 ± 8.5	<.0001
Age, year	52.0 [43.0-57.0]	51.0 [44.0-57.0]	58.0 [54.0-62.0]	54 [47.0-58.0]	<.0001
Body mass index, kg/m^2	23.3 ± 2.8	24.6 ± 3.1	24.7 ± 3.2	25.2 ± 3.1	<.0001
Fasting glucose, mg/dL	89.0 [83.0-96.0]	92.0 [85.0-100.0]	95.5 [87.0-104.0]	94.0 [87.0-103.0]	<.0001
Total cholesterol, mg/dL	195 ± 34.2	199.2 ± 34.0	204 ± 37.3	203.7 ± 33.9	<.0001
HDL cholesterol, mg/dL	57.8 ± 14.1	54.2 ± 14.1	54.9 ± 14.0	53.9 ± 14.0	<.0001
CRP, mg/L	0.5 [0.3-1.0]	0.6 [0.4-1.4]	0.6 [0.4-1.1]	0.7 [0.4-1.4]	<.0001
Gender, %					
Men	1,074 (24.1)	483 (50.3)	58 (30.2)	619 (53.8)	<.0001
Women	3,381 (75.9)	478 (49.7)	134 (69.8)	532 (46.2)	
Education, %					
Low	2,434 (54.6)	514 (53.5)	140 (72.9)	698 (60.6)	<.0001
High	2,021 (45.4)	446 (46.5)	52 (27.1)	453 (39.4)	
Household income(year), %					
Low	1,008 (22.6)	201 (20.9)	60 (31.3)	262 (22.8)	0.1791
Low-Middle	1,213 (27.2)	260 (27.1)	42 (21.9)	318 (27.6)	
High-Middle	1,073 (24.1)	224 (23.3)	41 (21.4)	270 (23.5)	
High	1,161 (26.1)	276 (28.7)	49 (25.5)	301 (26.2)	
Physical activity(mvpa), %					
Low	2,320 (52.1)	465 (48.4)	97 (50.5)	574 (49.9)	0.4068
Middle	590 (13.2)	143 (14.9)	27 (14.1)	152 (13.2)	
High	1,545 (34.7)	353 (36.7)	68 (35.4)	425 (36.9)	
Smoking status, %					
Never	3,419 (76.8)	556 (57.9)	143 (74.5)	632 (54.9)	<.0001
Former	547 (12.3)	217 (22.6)	27 (14.1)	307 (26.7)	
Current	489 (11.0)	188 (19.6)	22 (11.5)	212 (18.4)	
Diabetes, %					
No	4,291 (96.3)	924 (96.2)	169 (88.0)	1,099 (95.5)	<.0001
Yes	164 (3.7)	37 (3.9)	23 (12.0)	52 (4.5)	
Use of lipid-lowering drugs, %					
No	4,146 (93.1)	889 (92.5)	178 (92.7)	1,075 (93.4)	0.8774
Yes	309 (6.9)	72 (7.5)	14 (7.3)	76 (6.6)	

Values are presented as mean ± standard deviation, median [interquartile range], or numbers (%).

SBP, systolic blood pressure; DBP, diastolic blood pressure; cIMT, carotid intima-media thickness; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension; CRP, C-reactive protein; HDL, high-density lipoprotein; mvpa, moderate to vigorous physical activity.

Figure 2. Distribution of systolic and diastolic blood pressure by age group

(A) **(B)**



Scatter plots show the distribution between systolic and diastolic blood pressures. Dashed lines indicate cutoffs of 130 mmHg for systolic blood pressure and 80 mmHg for diastolic blood pressure. (A) presents the distribution of participants aged <50 in blue dots. (B) presents the distribution of those aged ≥50 in red dots. And the grey dots indicate the opposite age group, such as the distribution of those aged ≥50 in (A), and the distribution of those aged <50 in (B).

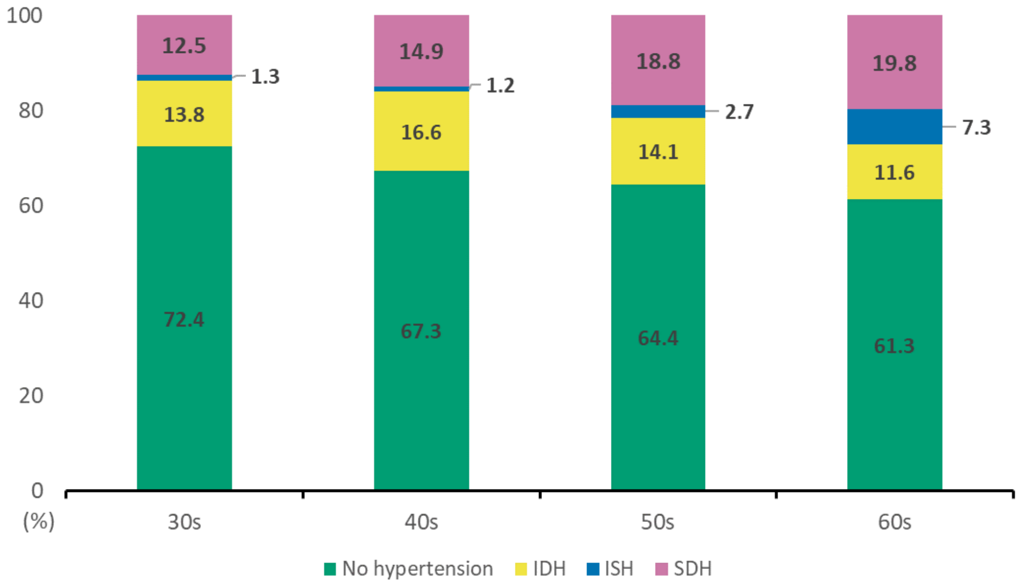


Figure 3. Prevalence of hypertension subtype by age stratum

2. Association of hypertension subtypes with carotid IMT by age

Table 2 shows the association between hypertension subtype and increased carotid IMT. The association between IDH and carotid IMT was shown differently with age. In younger participants aged <50, IDH was significantly associated with an increased IMT (OR=1.57 [1.10 - 2.26]). However, OR for the IDH group was 0.89 (95% CI, 0.72 - 1.09) in older individuals aged ≥50. The IDH group had a weaker association than the other two groups, ISH and SDH, in all cases. Based on the age stratification, there was evidence of effect modification on age only in the IDH group (P-interaction: 0.0027). According to the 10-year age stratum, the associations between hypertension subtype and carotid IMT were evaluated in Table 3. Similar trends were observed by age as in Table 2. Two younger age groups, ranging from 30 to 39 and 40 to 49, showed that IDH had a thick carotid IMT, though there was no statistical significance. The ORs were 1.94 (0.91-4.13) in 30 to 39 and 1.52 (1.00-2.29) in 40 to 49. In the two older age groups, 50 to 59 and 60 to 64, ORs were less than 1.0 and the results were not significant. In 50 to 59, the OR was 0.97 (0.76-1.24) and in 60 to 64 was 0.70 (0.47-1.06). Except for the 40 to 49 age group, ORs for ISH were highest in all age groups.

The associations of hypertension subtype with carotid IMT including a medication group were presented in (Appendix 2). Among the 1,324 participants who were taking antihypertensive medications, most of them belonged to the older group (1,176 people, 89.09%). Participants aged <50 with IDH were positively related to the thickening of IMT and the relationship was significant. Also, we conducted identical analyses using different carotid IMT measurements (mean) (Appendix 3). Persons aged <50 years in the IDH group showed a higher carotid IMT compared to the no hypertension group, but the association was not significant in the multivariate-adjusted model. Applying different percentile cutoffs for IMT, we reran the analyses in the multivariate model (Appendix 4). The cutoff value was 0.882 mm in the 80 percentile, and the trends were similar to those in table 2. But in the 90 percentile, whose cutoff value was 0.972 mm, individuals aged under 50 with IDH were not associated with thickening of IMT. (Appendix 5) showed the association between hypertension subtype and IMT by using sex- and age-specific cutoffs. In the multivariate model, participants aged <50 with IDH had a higher carotid IMT, regardless of sex, and the findings were not significant. However, participants aged over 50 years showed the opposite direction of association according to sex.

Table 2. Age-stratified analyses of the association between hypertension subtype and carotid IMT

Blood pressure categories	No. of people	No. (%) of increased IMT		Carotid intima-media thickness for more than 75p (0.857mm) vs less than 75p: Crude model		Age-adjusted model		Multivariate model[ab]	
				OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Total (N=6,759)									
No hypertension	4,455	913	(20.5)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	961	236	(24.6)	1.26	(1.07 - 1.49)	1.34	(1.13 - 1.59)	1.03	(0.86 - 1.24)
ISH	192	90	(46.9)	3.42	(2.56 - 4.59)	2.21	(1.62 - 3.02)	1.89	(1.37 - 2.60)
SDH	1,151	453	(39.4)	2.52	(2.19 - 2.89)	2.36	(2.04 - 2.74)	1.77	(1.51 - 2.07)
Aged <50 (N=2,666)									
No hypertension	1,851	121	(6.5)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	411	62	(15.1)	2.54	(1.83 - 3.52)	2.41	(1.73 - 3.36)	1.57	(1.10 - 2.26)
ISH	33	6	(18.2)	3.18	(1.29 - 7.84)	3.72	(1.47 - 9.41)	2.35	(0.87 - 6.30)
SDH	371	78	(21.0)	3.81	(2.79 - 5.19)	3.56	(2.60 - 4.89)	2.10	(1.48 - 2.98)
Aged ≥50 (N=4,093)									
No hypertension	2,604	792	(30.4)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	550	174	(31.6)	1.06	(0.87 - 1.29)	1.10	(0.90 - 1.35)	0.89	(0.72 - 1.09)
ISH	159	84	(52.8)	2.56	(1.86 - 3.54)	2.06	(1.48 - 2.86)	1.91	(1.35 - 2.68)
SDH	780	375	(48.1)	2.12	(1.80 - 2.49)	2.12	(1.79 - 2.50)	1.70	(1.43 - 2.03)

OR is calculated from multiple logistic regression models in the age stratification, using the max of both right and left IMT max measurements.
IMT, intima-media thickness; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension;

[a]Adjusted for age, sex, body mass index, education, physical activity, smoking, diabetes, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering drug use, C-reactive protein, and study site.

[b]P-interaction between each hypertension subtype and age group in the full model. IDH: 0.0027; ISH: 0.7204; SDH: 0.1534;

Table 3. Age-stratified analyses of the association between hypertension subtype and carotid IMT by 10-year age stratification

Blood pressure categories	No. of people	No. (%) of increased IMT		Carotid intima-media thickness for more than 75p (0.857mm) vs less than 75p					
				Crude model		Age-adjusted model		Multivariate model*	
				OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age									
30-39 (N=1,103)									
No hypertension	799	23	(2.9)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	152	14	(9.2)	3.42	(1.72 - 6.82)	3.37	(1.69 - 6.72)	1.94	(0.91 - 4.13)
ISH	14	3	(21.4)	9.20	(2.40 - 35.22)	10.02	(2.57 - 39.09)	5.32	(1.17 - 24.21)
SDH	138	16	(11.6)	4.43	(2.27 - 8.61)	4.38	(2.25 - 8.53)	1.83	(0.85 - 3.96)
40-49 (N=1,563)									
No hypertension	1,052	98	(9.3)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	259	48	(18.5)	2.22	(1.52 - 3.23)	2.21	(1.51 - 3.23)	1.52	(1.00 - 2.29)
ISH	19	3	(15.8)	1.83	(0.52 - 6.37)	2.11	(0.60 - 7.44)	1.32	(0.35 - 5.00)
SDH	233	62	(26.6)	3.53	(2.47 - 5.05)	3.35	(2.33 - 4.81)	2.15	(1.44 - 3.20)
50-59 (N=3,018)									
No hypertension	1,945	503	(25.9)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	425	123	(28.9)	1.17	(0.93 - 1.47)	1.20	(0.94 - 1.51)	0.97	(0.76 - 1.24)
ISH	81	41	(50.6)	2.94	(1.88 - 4.60)	2.55	(1.62 - 4.01)	2.43	(1.52 - 3.89)
SDH	567	266	(46.9)	2.53	(2.09 - 3.08)	2.55	(2.10 - 3.11)	2.06	(1.67 - 2.54)
60-64 (N=1,075)									
No hypertension	659	289	(43.9)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	125	51	(40.8)	0.88	(0.60 - 1.30)	0.90	(0.61 - 1.33)	0.70	(0.47 - 1.06)
ISH	78	43	(55.1)	1.57	(0.98 - 2.52)	1.53	(0.95 - 2.46)	1.46	(0.89 - 2.39)
SDH	213	109	(51.2)	1.34	(0.99 - 1.83)	1.33	(0.98 - 1.81)	1.09	(0.78 - 1.51)

*Adjusted for age, sex, body mass index, education, physical activity, smoking, diabetes, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering drug use, C-reactive protein, and study site.
OR is calculated from multiple logistic regression models in the age stratification, using the max of both right and left IMT max measurements.
IMT, intima-media thickness; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension;

Ⅳ. DISCUSSION

1. Summary of findings

Our study investigated the association between IDH and carotid IMT and the age-stratified association between IDH and carotid IMT in healthy Korean population data. The association between IDH and carotid IMT was observed differently with age. IDH was significantly associated with the thickening of carotid IMT among participants aged less than 50. However, the association was not identified in those aged 50 years or older.

2. Comparison with previous studies

In this present study of the general population aged 30-64 years, IDH was not clearly associated with an increased carotid IMT, but an age-related association was found. Some studies investigated the association of IDH with CVD risk.[6,8,9] In the UK Biobank, 89,126 participants with systolic BP below 130 mmHg (mean age 53 years, 34% male, without CVD) were included.[9] No significant associations were found in both overall and age-stratified analyses. In total, the hazard ratio (HR) for CVD risk was 1.00 (95% CI, 0.92-1.10) in IDH by ACC/AHA definition. The associations in subgroups based on the median age of 55 years or older and under were assessed similarly (P-interaction > 0.1). Comparable findings were reported in some studies. Using Atherosclerosis Risk in Communities (ARIC) study with 8,703 participants, HR for incident ASCVD was 1.06 (95% CI, 0.89-1.26). After stratifying by median age of 55 years in this study, HR for less than 55 years was 1.11 (0.85-1.44) and for above 55 years was 1.03 (0.81-1.30).[6] A study included 9,590 people from National Health and Nutrition Examination Survey (NHANES), and HR for CV mortality was 1.17 (95% CI, 0.87-1.56).[6] Evaluating 13,263 participants in Give Us a Clue to Cancer and Heart Disease (CLUE) II, HR for CV death was 1.02 (95% CI, 0.92-1.14).[6] A study using 24-hour ambulatory BP measurements included 11,135 whose median age was 54.7 years and supported previous results. The HR for CV events was 1.14 (95% CI, 0.94-1.40). Age-related associations were also identified with an HR for aged under 50 years was 2.87 (1.72-4.80) and for aged 50 years or over was 0.98 (0.78-1.23).[8] In a study including 1.3 million adults, whose median age was 53 years, the burden of IDH by ACC/AHA definition predicted a composite outcome event defined as the first episode of MI, ischemic stroke, and hemorrhagic stroke.[7] The HR per unit increase in z score was 1.52 (1.03-2.23). A study including 1,746,493 Japanese with mean age of 42.9 ± 10.7 years showed positive associations of stage 1 and 2 IDH of ACC/AHA definition with subsequent CV events including MI, angina pectoris, and stroke.[10] The HR for stage 1 IDH was 1.17 (1.13-1.20) and for stage 2 IDH was 1.28 (1.17-1.41). A study in Finland analyzing 1,924 individuals whose mean age was 55.7 ± 2.4 also reported that the relative hazard for CV events was significantly higher in individuals with IDH defined by home BP, SBP less than 135 mmHg and DBP at least 85.[22] The HR was 1.94 (1.06-3.57). In line with previous studies, among 6,424,090 Korean young adults aged 20-39 years, participants with IDH were likely to have higher CVD risks. The HR for stage 1 IDH was 1.32 (1.28-1.36) and for stage 2 IDH was 1.82 (1.75-1.89).[14] There were other studies presenting age-specific associations of IDH with CVD risk.[11-13]

In addition to CVD outcomes, there have been studies exploring the association with subclinical atherosclerosis. In a study conducted in France, researchers studied 1,605 healthy adults aged 18 years or older, free of acute and/or chronic diseases, and evaluated the associations between hypertension subtypes and markers of target organ damage including cIMT.[23] Hypertension was categorized in 130/80 cutoff and BP was measured by 24-hour ambulatory BP monitoring. IDH was not significantly associated with an increase more than the median value of cIMT (OR, 1.27; 95% CI, 0.79-2.06) compared to normotension as reference. A study using coronary artery calcium score as a subclinical marker examined 4,057 people aged 45 to 84 without clinical CVD at baseline in the Multi-Ethnic Study of Atherosclerosis (MESA).[24] There was a lack of significance on the association between the 2017 ACC/AHA definition of IDH and coronary artery calcification over 0 (OR, 0.92; 95% CI, 0.70-1.22). According to a study conducted in US predicting age of conversion to CAC score of more than 0, in an average case, it was only after the age of 70 that the score exceeded 100 corresponding to low risk.[25] A study from Korea Initiatives on Coronary Artery Calcification (KOICA) registry evaluated 86,165 asymptomatic adults. The results showed that the prevalence and severity of CAC differed, higher in US than in Korean adults.[26] Thus, it was not suitable to apply the CAC score to our healthy population data.

Contrary to two previous studies, a multiethnic study was conducted with 14,618 participants aged 35 years over excluding previous cardiovascular events, such as MI, stroke, and heart failure in 3 ethnicities, Han, Uygur and Kazakh. Using the maximal carotid IMT, OR for IMT thickening defined as 1.0 mm ≤ cIMT ≤ 1.5 mm was 1.402 (95% CI, 1.201-1.632).[27] In Korea, researchers examined the relationship of IDH with the presence of coronary plaque defined as ≥ 1mm with 4,666 participants not on antihypertensive medications (mean age 52.6 ± 7.3 years, 71.0% was men).[28] There were positive associations of stage 1 and stage 2 IDH, which had a cutoff value at least 80 and 90 mmHg, with the prevalence of coronary plaque (OR, 1.40; 95% CI, 1.15-1.70; OR, 1.50; 95% CI, 1.16-1.93), respectively.

In age-stratified analyses, although inconsistent results were reported as above, there seems to be a pattern that positive associations in the younger age, and no or weak associations in the elder group.[29] Unlike other BP phenotypes such as ISH and SDH, IDH has a relatively low prevalence and is predominantly distributed even in young or middle-aged people.[7,12] Because of the low prevalence of IDH, the numbers of outcome events were small, and if it is divided into subgroups, the number will become even smaller. From this point of view, the previous null observations may have been underpowered to detect the association of IDH with CVD risk.[24] Therefore, a study acquiring a relatively large number of events in subgroup analyses might support our age-related findings.[12]

Among these studies mentioned above, we have one more to consider. Because it is difficult to measure DBP accurately[30], once overestimating the actual DBP, people whose true intra-arterial pressure is within normal limit might be misclassified as having IDH. Particularly among older adults, who have brachial artery gradually stiffening, accurate BP measurements may be difficult.

This raised concerns about so-called pseudo-hypertension, a false diagnosis of hypertension.[31] Consequently, if there are some erroneous overestimated readings in IDH cases, the CVD risk associated with IDH among the elderly might be underestimated, and this misclassification tends to occur when BP measurements were conducted at a single visit rather than 24-hour rigorous monitoring.[8] Therefore, it is not clear whether IDH by ACC/AHA guidelines had an adverse effect[8], and it is important to clarify this open question given that IDH has clinical implications for millions of adults.[24]

About 83% of persons with baseline IDH developed new-onset SDH during the following 10 years of follow-up.[32] Among participants with stage 1 IDH or ISH, the incidence rates and hazard ratios for CVD events were higher in participants whose BP category changed into stage 1 SDH or stage 2 hypertension in the next 2 to 9 years, compared to those who stayed in the same BP group.[14]

In this respect, it might be inferred that IDH is not an entirely benign status[32], though there is an unclear association between IDH and CVD risk. And adults <50 years with IDH showed a higher carotid IMT. Although the absolute risk for CVD is low, early intervention in young individuals with IDH is important in that it may reduce the lifetime risk of CVD.[33] Consequently, this study would be an initial step in providing evidence for early strategies appropriate for young adults with IDH.[33]

3. Possible mechanisms

Hypertension acts on CV events through different age-related hemodynamic routes. Aging plays an important role in affecting the relation of BP indexes, such as SBP, DBP, and PP, to coronary heart disease (CHD) risk. DBP is a stronger predictor of CHD risk than SBP or PP in patients aged under 50 years. In people over 50 years of age, similar predictive power between BP indices or a shift to SBP and PP is observed, in terms of predicting CHD risk.[19,34] Young adults with hypertension aged under 50 have increased peripheral resistance and decreased peripheral pulse wave amplification, which is recorded in the brachial artery. This may partially offset the peripheral rise in SBP not influencing the rise in DBP, accordingly, peripheral DBP has a greater influence than SBP in young individuals.[19] On the other hand, persons over 50 years have increased central arterial stiffness and early wave reflection. This structural degeneration and wave reflection induces a higher brachial artery SBP and a lower DBP.[10] Previous studies reporting an age-dependent association of IDH with CVD risk support the mechanism described above.[8,11-13] The Rotterdam elderly study involving people aged 50 years or older provided an association between an increased carotid IMT and systolic hypertension.[35] A study including 129 healthy men suggested that carotid SBP increases progressively with aging, reaching a level comparable to brachial SBP, and is significantly related to carotid wall hypertrophy.[36] Although the underlying mechanism is not clear[36], the predominance of SBP with advancing age may show that there is an age-dependent association of IDH and carotid IMT, an independent predictor of CVD.

4. Strengths and Limitations

The strengths of the present study include an apparently healthy population, a predefined protocol, and various confounders. Since we examined a general population without clinical CVD or other severe diseases, IDH which is not a strong risk factor can be properly assessed in a relatively healthy population. Also, the CMERC cohort study strictly followed a standardized protocol to deal with possible measurement errors. Furthermore, this study investigated various categories of variables, thus a number of potential confounders were treated in our analyses. Studies examining the age-related association of IDH and carotid IMT are scarce globally. Therefore, our results might give a clue of evidence for the age-stratified association of IDH with carotid IMT among Korean adults.

Several limitations should be considered when interpreting the findings of this study. First, BP measurements were conducted in a manner of single office BP. The 2021 US Preventive Services Task Force (USPSTF) evaluated the accuracy of office BP measurement (OBPM) in a single visit compared with the reference standard, ambulatory BP measurement (ABPM). When using single-visit OBPM alone, numerous participants with true hypertension are missed.[37] For the diagnosis and management of hypertension, it is essential to measure BP accurately. In this respect, the BP measurements of CMERC were not enough to function as a screen for the presence of white-coat hypertension. Second, although we included risk factors for subclinical atherosclerosis there might be possible residual confounding. Other drugs that affect BP, such as hormone treatment, and steroids may be considerations since our study had 857 (12.7%) women individuals aged over 50 years with hypertension.[38] We also may consider inflammation factors, sodium intake, and psychological health.[39,40] Finally, since this study had a cross-sectional design, temporal causality between IDH and thickening of carotid IMT could not be drawn.

V. CONCLUSIONS

This study evaluated the association between IDH and increased carotid IMT and conducted age-stratified analyses among Korean adults. We found that IDH was associated with increased carotid IMT in young individuals under 50 years of age, but not in those over 50. This finding suggests that IDH may not be a completely harmless status and might be an initial step in presenting evidence for early strategies appropriate for young adults with IDH.

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Appendix 1. Baseline characteristics of participants (n= 6,759) according to age group

Variables	Age <50 (n= 2,666)		Age ≥50 (n= 4,093)		P-value
cIMT, mm	0.694 ± 0.120		0.802 ± 0.192		<.0001
cIMT, %					
≥ 75p (0.857mm)	267	(10.0)	1425	(34.8)	<.0001
SBP, mmHg	115.3 ± 14.0		119.5 ± 15.1		<.0001
DBP, mmHg	74.9 ± 10.5		75.87 ± 9.78		0.0001
Pulse pressure, mmHg	40.4 ± 6.9		43.7 ± 8.9		<.0001
Age, year	42.0 [36.0-46.0]		56.0 [53.0-60.0]		<.0001
Body mass index, kg/m^2	23.8 ± 3.3		23.9 ± 2.7		0.5159
Fasting glucose, mg/dL	89.0 [83.0-95.0]		92.0 [86.0-100.0]		<.0001
Total Cholesterol, mg/dL	190.1 ± 32.4		202.1 ± 34.9		<.0001
HDL Cholesterol, mg/dL	56.4 ± 14.3		56.6 ± 14.1		0.5789
hs CRP, mg/L	0.5 [0.3-1.1]		0.6 [0.3-1.1]		<.0001
Sex, %					
Men	1,009	(37.9)	1,225	(29.9)	<.0001
Women	1,657	(62.2)	2,868	(70.1)	
Education, %					
Low	1,039	(39.0)	2,747	(67.1)	<.0001
High	1,626	(61.0)	1,346	(32.9)	
Household income(year), %					
Low	577	(21.6)	954	(23.3)	<.0001
Low-Middle	821	(30.8)	1,012	(24.7)	
High-Middle	646	(24.2)	962	(23.5)	
High	622	(23.3)	1,165	(28.5)	
Physical activity(mvpa), %					
Low	1,392	(52.2)	2,064	(50.4)	0.0004
Middle	398	(14.9)	514	(12.6)	
High	876	(32.9)	1,515	(37.0)	
Smoking status, %					
Never	1,708	(64.1)	3,042	(74.3)	<.0001
Former	401	(15.0)	697	(17.0)	
Current	557	(20.9)	354	(8.7)	
Diabetes, %					
No	2,615	(98.1)	3,868	(94.5)	<.0001
Yes	51	(1.9)	225	(5.5)	
Use of lipid-lowering drugs, %					
No	2,613	(98.0)	3,675	(89.8)	<.0001
Yes	53	(2.0)	418	(10.2)	

Values are presented as mean ± standard deviation, median [interquartile range], or numbers (%).

cIMT, carotid intima-media thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs CRP, high sensitivity C-reactive protein; HDL, high density lipoprotein; mvpa, moderate to vigorous physical activity.

Appendix 2. Age-stratified analyses of the association between hypertension subtype and carotid IMT including treated participants

Blood pressure categories	No. of people	No. (%) of increased IMT		Carotid intima-media thickness for more than 75p (0.88mm) vs less than 75p							
				Crude model		Age-adjusted model		except for drugs model[a]		Multivariate model[b]	
				OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Total (N=8,079)											
No hypertension	5,050	1,056	(20.9)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
IDH	1,186	287	(24.2)	1.21	(1.04 - 1.40)	1.26	(1.08 - 1.48)	1.01	(0.86 - 1.19)	1.00	(0.85 - 1.18)
ISH	296	149	(50.3)	3.83	(3.02 - 4.86)	2.50	(1.95 - 3.21)	2.17	(1.68 - 2.81)	2.14	(1.65 - 2.77)
SDH	1,547	576	(37.2)	2.24	(1.98 - 2.54)	2.07	(1.81 - 2.35)	1.60	(1.39 - 1.83)	1.58	(1.37 - 1.81)
Aged <50 (N=2,810)											
No hypertension	1,898	120	(6.3)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
IDH	442	61	(13.8)	2.37	(1.71 - 3.29)	2.20	(1.58 - 3.07)	1.45	(1.01 - 2.08)	1.44	(1.00 - 2.06)
ISH	39	8	(20.5)	3.83	(1.72 - 8.50)	4.24	(1.86 - 9.68)	2.65	(1.10 - 6.36)	2.50	(1.03 - 6.03)
SDH	431	80	(18.6)	3.38	(2.49 - 4.58)	3.04	(2.23 - 4.15)	1.77	(1.25 - 2.49)	1.69	(1.19 - 2.39)
Aged ≥50 (N=5,269)											
No hypertension	3,152	936	(29.7)	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
IDH	744	226	(30.4)	1.03	(0.87 - 1.23)	1.09	(0.91 - 1.30)	0.91	(0.75 - 1.09)	0.90	(0.75 - 1.08)
ISH	257	141	(54.9)	2.88	(2.22 - 3.72)	2.38	(1.83 - 3.09)	2.20	(1.67 - 2.88)	2.17	(1.65 - 2.84)
SDH	1,116	496	(44.4)	1.89	(1.65 - 2.18)	1.90	(1.65 - 2.19)	1.55	(1.33 - 1.80)	1.54	(1.32 - 1.79)

[a] An adjustment was conducted except for antihypertensive medications from the multivariate model.

[b] Adjusted for age, sex, body mass index, education, physical activity, smoking, diabetes, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering drug use, C-reactive protein, study site, and antihypertensive drugs.

OR is calculated from multiple logistic regression models in the age stratification, using the max of both right and left IMT max measurements.

HTN, hypertension; IMT, intima-media thickness; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension;

Appendix 3. Age-stratified analyses of the association between hypertension subtype and carotid IMT applying a different measurement (mean) of IMT

Blood pressure categories	Carotid intima-media thickness for more than 75p (0.69mm) vs less than 75p								
	No. of people	No. (%) of increased IMT		Crude model		Age-adjusted model		Multivariate model*	
				OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Total (N=6,759)									
No hypertension	4,455	919	(20.6)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	961	223	(23.2)	1.16	(0.98 - 1.37)	1.23	(1.03 - 1.47)	0.95	(0.79 - 1.15)
ISH	192	95	(49.5)	3.77	(2.81 - 5.05)	2.36	(1.72 - 3.25)	2.15	(1.55 - 3.00)
SDH	1,151	453	(39.4)	2.50	(2.17 - 2.87)	2.36	(2.03 - 2.74)	1.80	(1.54 - 2.12)
Aged <50 (N=2,666)									
No hypertension	1,851	105	(5.7)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	411	50	(12.2)	2.30	(1.61 - 3.29)	2.17	(1.51 - 3.11)	1.45	(0.98 - 2.17)
ISH	33	6	(18.2)	3.70	(1.49 - 9.15)	4.57	(1.78 - 11.71)	3.64	(1.32 - 10.07)
SDH	371	68	(18.3)	3.73	(2.69 - 5.18)	3.45	(2.46 - 4.83)	2.23	(1.53 - 3.27)
Aged ≥50 (N=4,093)									
No hypertension	2,604	814	(31.3)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	550	173	(31.5)	1.01	(0.83 - 1.23)	1.05	(0.86 - 1.29)	0.82	(0.67 - 1.02)
ISH	159	89	(56.0)	2.80	(2.02 - 3.86)	2.21	(1.58 - 3.07)	2.15	(1.52 - 3.03)
SDH	780	385	(49.4)	2.14	(1.82 - 2.52)	2.15	(1.82 - 2.54)	1.69	(1.41 - 2.02)

* Adjusted for age, sex, body mass index, education, physical activity, smoking, diabetes, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering drug use, C-reactive protein, and study site.

OR is calculated from multiple logistic regression models in the age stratification.

IMT, intima-media thickness; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension;

Appendix 4. Age-stratified analyses of the association between hypertension subtype and carotid IMT using different cutoffs of IMT

Blood pressure categories	No. of people	Carotid intima-media thickness for more than cutoff vs less than cutoff							
		80p (0.882 mm)				90p (0.972 mm)			
		No. (%) of increased IMT		OR	(95% CI)	No. (%) of increased IMT		OR	(95% CI)
Total (N=6,759)									
No hypertension	4,455	726	(16.3)	1.00	Ref	341	(7.7)	1.00	Ref
IDH	961	179	(18.6)	0.94	(0.77 - 1.15)	73	(7.6)	0.76	(0.58 - 1.01)
ISH	192	79	(41.1)	1.96	(1.41 - 2.73)	46	(24.0)	1.90	(1.30 - 2.78)
SDH	1,151	370	(32.1)	1.67	(1.42 - 1.98)	216	(18.8)	1.84	(1.50 - 2.25)
Aged <50 (N=2,666)									
No hypertension	1,851	78	(4.2)	1.00	Ref	36	(1.9)	1.00	Ref
IDH	411	44	(10.7)	1.77	(1.16 - 2.71)	11	(2.7)	0.67	(0.32 - 1.42)
ISH	33	6	(18.2)	4.47	(1.63 - 12.23)	3	(9.1)	2.56	(0.64 - 10.29)
SDH	371	56	(15.1)	2.37	(1.57 - 3.56)	22	(5.9)	1.44	(0.78 - 2.63)
Aged ≥50 (N=4,093)									
No hypertension	2,604	648	(24.9)	1.00	Ref	305	(11.7)	1.00	Ref
IDH	550	135	(24.5)	0.80	(0.64 - 1.00)	62	(11.3)	0.77	(0.57 - 1.04)
ISH	159	73	(45.9)	1.86	(1.32 - 2.64)	43	(27.0)	1.95	(1.32 - 2.89)
SDH	780	314	(40.3)	1.58	(1.31 - 1.90)	194	(24.9)	1.89	(1.52 - 2.35)

Adjusted for age, sex, body mass index, education, physical activity, smoking, diabetes, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering drug use, C-reactive protein, and study site.

OR is calculated from multiple logistic regression models in the age stratification, using the max of both right and left IMT max measurements.
IMT, intima-media thickness; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension;

Appendix 5. Sex- and age- specific analyses of the association between hypertension subtype and carotid IMT

Blood pressure categories	No. of people	No. (%) of increased IMT		Carotid intima-media thickness for more than 75p vs less than 75p: Crude model OR	(95% CI)	Age-adjusted model OR	(95% CI)	Multivariate model* OR	(95% CI)
Aged <50									
Men (0.8 mm)†									
No hypertension	481	111	(23.1)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	248	75	(30.2)	1.45	(1.02 - 2.04)	1.26	(0.88 - 1.80)	1.17	(0.80 - 1.70)
ISH	25	11	(44.0)	2.62	(1.16 - 5.94)	3.18	(1.35 - 7.49)	1.99	(0.78 - 5.09)
SDH	255	74	(29.0)	1.36	(0.97 - 1.92)	1.27	(0.89 - 1.82)	1.03	(0.70 - 1.51)
Women (0.76 mm)†									
No hypertension	1,370	298	(21.8)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	163	54	(33.1)	1.78	(1.26 - 2.53)	1.64	(1.14 - 2.36)	1.34	(0.91 - 1.96)
ISH	8	3	(37.5)	2.16	(0.51 - 9.08)	1.94	(0.43 - 8.76)	1.97	(0.42 - 9.23)
SDH	116	70	(60.3)	5.47	(3.69 - 8.11)	4.01	(2.66 - 6.03)	3.05	(2.00 - 4.67)
Aged ≥50									
Men (0.96 mm)†									
No hypertension	593	127	(21.4)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	235	58	(24.7)	1.20	(0.84 - 1.72)	1.34	(0.93 - 1.93)	1.15	(0.78 - 1.68)
ISH	33	14	(42.4)	2.71	(1.32 - 5.55)	2.17	(1.04 - 4.50)	1.60	(0.74 - 3.48)
SDH	364	124	(34.1)	1.90	(1.42 - 2.54)	2.02	(1.50 - 2.72)	1.91	(1.38 - 2.64)
Women (0.88 mm)†									
No hypertension	2,011	513	(25.5)	1.00	Ref	1.00	Ref	1.00	Ref
IDH	315	69	(21.9)	0.82	(0.62 - 1.09)	0.84	(0.63 - 1.12)	0.77	(0.57 - 1.03)
ISH	126	59	(46.8)	2.57	(1.79 - 3.70)	2.06	(1.42 - 2.99)	1.89	(1.29 - 2.77)
SDH	416	160	(38.5)	1.83	(1.46 - 2.28)	1.79	(1.43 - 2.24)	1.57	(1.25 - 1.99)

* Adjusted for age, sex, body mass index, education, physical activity, smoking, diabetes, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering drug use, C-reactive protein, and study site.

OR is calculated from multiple logistic regression models in the age stratification, using the max of both right and left IMT max measurements.

IMT, intima-media thickness; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension;

†Sex and age-specific cutoffs were applied.

ABSTRACT(KOREAN)

고립성 이완기 고혈압과 경동맥 내중막 두께 사이의 연령 층화 연관성

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배경 및 목적:

고립성 이완기 고혈압 환자들에서 양성 결과와 연령 특이적인 결과에 관한 논쟁이 있어왔다. 따라서 우리는 단면 연구 디자인에서 고립성 이완기 고혈압과 경동맥 내중막 두께 사이의 연령 특이적인 연관성을 확인하고자 한다.

연구 방법:

심혈관 대사질환 원인 연구 센터의 코호트 기반조사 데이터를 사용하였다. 2년 이내 심근경색, 심부전, 뇌졸중 또는 암이 있던 사람들은 제외하였다. 30-64세의 초기인원 8,097명 (2,808명의 남성과 5,289명의 여성)으로부터 (ⅰ) 고혈압약 복용자 1,324명, (ⅱ) 혈압 및 경동맥 내중막 두께에서 결측값을 보이는 대상자 13명, (iii) 혈액 화학적 변수에서 결측값을 보이는 1명을 추가로 제외하였다. 최종적으로 6,759명을 분석에 포함하였다 (베이스라인 평균 연령, 50.46 ± 8.88세; 2,234명의 남성과 4,525명의 여성). 혈압은 2017 미국심장협회/심장학회 가이드라인에 따라 1) 고혈압 아님, 2) 고립성 확장기 고혈압, 3) 고립성 수축기 고혈압, 4) 수축기 이완기 고혈압으로 분류되었다. 경동맥 내중막 두께는 B-모드 초음파로 측정되었으며 상위 75 퍼센트에 해당하는 두께를 증가된 내중막 두께로 정의하였다. 다중로지스틱 회귀분석을 사용하여 고립성 이완기 고혈압과 경동맥 내중막 두께 사이의 연관성을 조사하였다. 또한 연령에 따라 50세 이상 및 50세 미만으로 하위그룹 분석을 시행하였다.

연구 결과:

50세 미만의 대상자에서 고립성 이완기 고혈압은 나이, 성별, 체질량지수, 교육수준, 신체활동, 흡연, 당뇨병 진단여부, 총콜레스테롤, 고밀도지단백 콜레스테롤, 지질강하제 사용여부, C-반응성 단백질 및 연구 장소를 보정하였을 때 경동맥 내중막 두께가 두꺼워지는 것과 유의한 연관성이 있었다 (오즈비: 1.57, 95% 신뢰구간: 1.10-2.26). 그러나 50세 이상의 대상자에서는 연관성이 관찰되지 않았다 (오즈비: 0.89, 95% 신뢰구간: 0.72-1.09). 한편, 고립성 수축기 고혈압과 수축기 이완기 고혈압은 젊은 그룹과 나이 든 그룹 모두에서 경동맥 내중막 두께의 증가와 관련이 있었다.

결론 및 고찰:

한국 성인에 관한 본 단면연구에서, 고립성 이완기 고혈압은 50세 미만의 대상자에서 경동맥 내중막 두께의 증가와 연관성이 있었으나, 50세 이상의 대상자에서는 관련성이 없었다. 이 결과는 고립성 이완기 고혈압이 완전히 양성 상태가 아닐 수 있고, 고립성 이완기 고혈압이 있는 젊은 성인에게 적합한 초기 전략에 대한 증거를 제공하는 초기 단계가 될 수 있음을 시사한다.

핵심어: 고립성 이완기 고혈압; 경동맥 내중막 두께; 죽상 동맥 경화증; 심혈관질환