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Editorial

Risk Factor of Cardiovascular Disease Among Older Individuals

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In spite of the increase in the attribute of metabolic disorders to the incidence of cardiovascular disease (CVD), hypertension remains the most important risk factor in Japanese people[1, 2]. Hypertension accounted for more than one-third of stroke incidence in the mostly middle-aged participants of the Japan Public Health Center-based prospective (JPHC) Study[3]. It is an established risk factor of stroke in much older individuals too[4, 5]. In the Suita Study, the cumulative lifetime risk of stroke at the age of 75 years was 11.8% and 13.1% for hypertensive men and women, respectively; the risk lowers to 5.5% and 5.3% for men and women without hypertension, respectively[6]. Furthermore, it was reported in this issue of the *Journal of Atherosclerosis and Thrombosis* that hypertension was the only risk factor significantly associated with stroke incidence in individuals aged ≥75 years (old-old) and 60−74 years (young-old) in the Ohasama Study[7]. These results from the observational studies[8-16] together with findings of previous intervention studies[17-20] confirm the appropriateness of the current hypertension guidelines for the management of hypertension for older individuals in Japan[21] (**Table 1**).

Evidence from observational studies generally requires careful interpretation. It is judicious to use some kind of checklist when making a causal judgment[22]. For example, diabetes was positively associated with stroke incidence in the young-old participants, but the association was not found in the old-old participants in the Ohasama Study. The authors raised a possibility of selection (bias) for this unexpected finding, i.e., those who survived to be old-old might have a resistance to the effect of diabetes on the cardiovascular system. Apart from this authors' idea, we can discuss the issue again using the checklist (**Table 2**).

Confounding refers to a situation where the association between two variables (causal- and outcome-assumed variables) arises (becomes stronger) or diminishes (becomes weaker) under the existence of a confounding variable that is associated with both the variables. We cannot expect that all the confounding variables are always measured. A confounding variable is not a mediator; but is a factor that is generated by the causal variable and pathophysiologically affects the outcome variable by definition. In the study, nutritional condition and body habitus might have been the confounding variables if they had been related to both diabetes and stroke incidence[23, 24]. Another possible confounding factor is health service usage. If blood pressure of those with diabetes had been managed more carefully than those without or if they had received more preventive measures, such as aspirin, this could have confounded the association.

We present a possible scenario of reverse causation here. The subjects who were likely to develop stroke in future could have been less likely to have, be aware of, or report diabetes at baseline. With that being said, this scenario would have hardly happened.

Measurement sometimes causes misclassification. It occurs in both causal and outcome variables. In the study, diabetes was self-reported. In general, the validity of self-report at baseline is not influenced by the outcome in prospective studies. Thus, this kind of misclassification is usually called non-differential misclassification and is likely to lead to attenuation of the association toward null. An example of differential misclassification related to self-report is recall bias. Differential misclassification of the outcome variable occurs if surveillance or case definition is influenced by baseline variables. In such instances, the association between the causal and outcome variables appears stronger or weaker than in reality. In the study, the association between diabetes and stroke incidence was null (not inverse) in the old-old individuals. Inaccurate self-report on diabetes status may partly explain

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Table 1. Recent (published in 2013 or later) epidemiological findings of blood pressure's association with cardiovascular disease in the older individuals

Study name, year published	Singapore Chinese Health Study, 2016[8]	Costa Rican CRELES study, 2016[10]	Northern Manhattan Study (US), 2016[9]	Taipei City Geriatric Health Examination Database, 2015[11]	Strobe-Compliant Study (China), 2015[12]
Baseline year	1993-1998	2004-2006	1993-2001	2006	2004-2006
Follow-up, years	max: 10	mean: 5.1	median: 13	max: 4	median: 4.8
Age range or mean age, years	48-85, 63.0 ± 7.8	60-, 76 ± 10.2	60-, 72 ± 8	65-, 73.0	60-, 69.5 ± 7.0
Sample size	30,692 (n of age ≥ 60 = 19,110)	2,346	1,750	77,389	5,006
Inclusion criteria related to histories	none	those without stroke, heart disease or cancer	those without stroke, DM, and CKD	none	those with HT
Women (%)	55.7%	52.7%*	63.0%	49.2%	51.4%
Baseline SBP/DBP, mmHg	SBP: < 100: 2.9% 110-119: 20.1%, 120-139: 35.4%, 140-159: 26.4%, 160-179: 11.1%, ≥ 180: 4.1%	SBP: 140-159: 31%*, ≥ 160: 21.7%*; DBP < 70: 17.6%*, ≥ 90: 22.0%*	SBP: < 140: 43%, 140-149: 20%, ≥ 150: 37%	Men: SBP: 135.0 ± 19.0/ DBP: 76.4 ± 11.5, Women: SBP: 135.7 ± 20.1/ DBP: 75.8 ± 11.4	SBP: 162.5 ± 21.3/ DBP: 91.7 ± 12.9
Outcome	CVD mortality	CVD mortality	Stroke incidence	CVD mortality	CVD mortality, CHD and stroke incidence
Reference BP category	SBP 120-139	SBP < 140	SBP < 140	SBP < 120 and DBP < 80	SBP < 130 DBP 85-89
BP categories significantly associated with increased outcome	SBP ≥ 180; SBP < 100 in those with CVD history	SBP ≥ 160	SBP 140-149	SBP ≥ 160 DBP ≥ 100	SBP ≥ 160 DBP ≥ 100

CRELES indicates Costa Rican Longevity and Healthy Aging Study; US, United States; DM, diabetes mellitus; CKD, chronic kidney disease; HT, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; CHD, coronary heart disease; BP, blood pressure. *: The percentages are based on the number of total participants interviewed at baseline. Those of the analyzed sample were not available.

that finding. The authors mentioned the possibility as a study limitation that the validity of self-report on diabetes decreased as the age of the subjects increased.

Finally, can we generalize the present findings? Characterization of the studied participants was simple but comprehensive in the article. The baseline survey was conducted in 1998. The study excluded those with a history of stroke while included those with histories of heart and kidney diseases. Confounding variables, such as height and weight, and medical histories were obtained via self-reporting. This information raises the possibilities of residual confounding of health statuses at baseline and unmeasured confounding of other lifestyle factors, such as diet. However, the participation rate was satisfactory. Approximately 90% of the population agreed to participate in the study, and 80% of the population was actually analyzed. Therefore, the present findings would be generalizable to another geriatric population, like Ohasama, in spite of the possibility of residual and unmeasured confounding.

Conflict of Interest

None.

References

1) Sugiyama D, Okamura T, Watanabe M, Higashiyama A, Okuda N, Nakamura Y, Hozawa A, Kita Y, Kadota A, Murakami Y, Miyamatsu N, Ohkubo T, Hayakawa T, Miyamoto Y, Miura K, Okayama A, Ueshima H and Group NDR: Risk of hypercholesterolemia for cardiovascular disease and the population attributable fraction in a 24-year Japanese cohort study. J Atheroscler Thromb, 2015; 22: 95-107
2) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi

(Cont Table 1)

Study name, year published	Kangwha cohort study (Korea), 2015[13]	REGARDS study (US), 2014[14]	TGLS Study (Iran), 2014[15]	LSUHLS (US), 2013[16]
Baseline year	1985	2003-2007	1999-2001	1999-2009
Follow-up, years	max: 23.8	median: 4.5	median: 10	mean: 6.0
Age range or mean age, years	55-, 66.7 ± 8.0	55-, 79.3 ± 3.7 [for those aged ≥ 75]	60-, 65.8	30-94
Sample size	6,294 (n of age ≥ 65 = 3,387)	9,787 (n of age ≥ 75 = 1,839)	1,845	30,154
Inclusion criteria related to histories		those taking antihypertensive medications	those without CVD	DM patients without a history of CHD or stroke
Women (%)	57.2%	63.1% [for those aged ≥ 75]	49.6%	64%
Baseline SBP/DBP, mmHg	SBP: 148.5 ± 31.7 [for total sample]	Isolated Systolic Hypertension, 25.7% [for those aged ≥ 75]	SBP: 136.0/DBP: 80.1	SBP: 145/DBP: 80
Outcome	CVD mortality	CVD incidence	CVD incidence	CHD incidence
Reference BP category	SBP: 100-119	SBP < 120	SBP < 120 and DBP < 80	SBP: 130-139 and DBP: 80-89
BP categories significantly associated with increased outcome	SBP ≥ 180 (in those aged ≥ 65)	SBP ≥ 150 (in those aged ≥ 75)	SBP ≥ 140, DBP ≥ 90 or on antihypertensive medications (in those aged ≥ 60)	< 110/65 (in those aged 60-94)

REGARDS indicates REasons for Geographic and Racial Differences in Stroke; TLGS, Tehran Lipid and Glucose Study; LSUHLS, Louisiana State University Hospital−Based Longitudinal Study. For the other abbreviations, please see the first page of Table 1.

Table 2. Checklist for interpreting epidemiological studies

Confounding
Reverse causation
Measurement
Generalizability

S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M and Yokote K: Diabetes mellitus. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan--2012 version. J Atheroscler Thromb, 2014; 21: 93-98

3) Yatsuya H, Iso H, Yamagishi K, Kokubo Y, Saito I, Suzuki K, Sawada N, Inoue M and Tsugane S: Development of a point-based prediction model for the incidence of total stroke: Japan public health center study. Stroke, 2013; 44: 1295-1302
4) Fujiyoshi A, Ohkubo T, Miura K, Murakami Y, Nagasawa SY, Okamura T, Ueshima H and Observational Cohorts in Japan Research G: Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women. Hypertens Res, 2012; 35: 947-953
5) Lewington S, Clarke R, Qizilbash N, Peto R, Collins R and Prospective Studies C: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet, 2002; 360: 1903-1913
6) Turin TC, Okamura T, Afzal AR, Rumana N, Watanabe M, Higashiyama A, Nakao Y, Nakai M, Takegami M, Nishimura K, Kokubo Y, Okayama A and Miyamoto Y: Hypertension and lifetime risk of stroke. J Hypertens, 2016; 34: 116-122
7) Murakami K, Asayama K, Satoh M, Inoue R, Tsubota-Utsugi M, Hosaka M, Matsuda A, Nomura K, Murakami T, Kikuya M, Metoki H, Imai Y and Ohkubo T: Risk Factors for Stroke among Young-Old and Old-Old Community-Dwelling Adults in Japan: the Ohasama Study. J Atheroscler Thromb, 2017; 24: 290-300
8) Koh AS, Talaei M, Pan A, Wang R, Yuan JM and Koh WP: Systolic blood pressure and cardiovascular mortality in middle-aged and elderly adults - The Singapore Chinese Health Study. Int J Cardiol, 2016; 219: 404-409
9) Dong C, Della-Morte D, Rundek T, Wright CB, Elkind

MS and Sacco RL: Evidence to Maintain the Systolic Blood Pressure Treatment Threshold at 140 mm Hg for Stroke Prevention: The Northern Manhattan Study. Hypertension, 2016; 67: 520-526
10) Rosero-Bixby L, Coto-Yglesias F and Dow WH: Pulse blood pressure and cardiovascular mortality in a population-based cohort of elderly Costa Ricans. J Hum Hypertens, 2016; 30: 555-562
11) Wu CY, Hu HY, Chou YJ, Huang N, Chou YC and Li CP: High Blood Pressure and All-Cause and Cardiovascular Disease Mortalities in Community-Dwelling Older Adults. Medicine (Baltimore), 2015; 94: e2160
12) Zheng L, Li J, Sun Z, Zhang X, Hu D and Sun Y: Relationship of Blood Pressure With Mortality and Cardiovascular Events Among Hypertensive Patients aged >/=60 years in Rural Areas of China: A Strobe-Compliant Study. Medicine (Baltimore), 2015; 94: e1551
13) Yi SW, Hong S and Ohrr H: Low systolic blood pressure and mortality from all-cause and vascular diseases among the rural elderly in Korea; Kangwha cohort study. Medicine (Baltimore), 2015; 94: e245
14) Banach M, Bromfield S, Howard G, Howard VJ, Zanchetti A, Aronow WS, Ahmed A, Safford MM and Muntner P: Association of systolic blood pressure levels with cardiovascular events and all-cause mortality among older adults taking antihypertensive medication. Int J Cardiol, 2014; 176: 219-226
15) Mohebi R, Mohebi A, Ghanbarian A, Momenan A, Azizi F and Hadaegh F: Is systolic blood pressure below 150 mm Hg an appropriate goal for primary prevention of cardiovascular events among elderly population? J Am Soc Hypertens, 2014; 8: 491-497
16) Zhao W, Katzmarzyk PT, Horswell R, Wang Y, Li W, Johnson J, Heymsfield SB, Cefalu WT, Ryan DH and Hu G: Aggressive blood pressure control increases coronary heart disease risk among diabetic patients. Diabetes Care, 2013; 36: 3287-3296
17) Wei Y, Jin Z, Shen G, Zhao X, Yang W, Zhong Y and Wang J: Effects of intensive antihypertensive treatment on Chinese hypertensive patients older than 70 years. J Clin Hypertens (Greenwich), 2013; 15: 420-427
18) Zhang Y, Zhang X, Liu L, Zanchetti A and Group FS: Is a systolic blood pressure target <140 mmHg indicated in all hypertensives? Subgroup analyses of findings from the randomized FEVER trial. Eur Heart J, 2011; 32: 1500-1508
19) Bangalore S, Gong Y, Cooper-DeHoff RM, Pepine CJ and Messerli FH: 2014 Eighth Joint National Committee panel recommendation for blood pressure targets revisited: results from the INVEST study. J Am Coll Cardiol, 2014; 64: 784-793
20) Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT, Jr., Pajewski NM and Group SR: Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. JAMA, 2016; 315: 2673-2682
21) Chapter 8. Hypertension in the elderly. Hypertens Res, 2014; 37: 325-332
22) Hu F: Interpreting epidemiologic evidence and causal inference in obesity research. In: Obesity Epidemiology, pp38-52, Oxford University Press, New York, 2008
23) Noda H, Iso H, Irie F, Sairenchi T, Ohtaka E, Doi M, Izumi Y and Ohta H: Low-density lipoprotein cholesterol concentrations and death due to intraparenchymal hemorrhage: the Ibaraki Prefectural Health Study. Circulation, 2009; 119: 2136-2145
24) Kroll ME, Green J, Beral V, Sudlow CL, Brown A, Kirichek O, Price A, Yang TO, Reeves GK and Million Women Study C: Adiposity and ischemic and hemorrhagic stroke: Prospective study in women and meta-analysis. Neurology, 2016;