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 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).

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...
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.

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Table 1.

| Study name, year published | Kangwha cohort study (Korea), 2015 | REGARDS study (US), 2014 | TGLS Study (Iran), 2014 | LSUHLS (US), 2013 |
|---------------------------|---------------------------------|--------------------------|------------------------|-------------------|
| 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 [for those aged ≥75] | 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 BP/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 |
|-------------|-------------------|-------------|------------------|

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