Weight Change and Cardiovascular Mortality – Methodological Challenges –

Hiroshi Yatsuya, MD, PhD; Frank B. Hu, MD, PhD

In this issue of the Journal, Chou et al present their careful analysis of the relationship between weight change since age 20 and subsequent risk of cardiovascular disease (CVD) mortality. Their study included 1,756 deaths from CVD (408 ischemic heart disease (IHD); 357 ischemic stroke; 198 hemorrhagic stroke; 235 stroke of unknown subtype; 558 unspecified CVD) among 41,364 Japanese men and women aged 40–79 at baseline in the Ohsaki Cohort Study followed from 1995 to 2008.¹

Article p679

Those who gained weight were younger, lighter at age 20 and heavier at baseline (see Table 1). Baseline prevalences of diabetes and current smoking were higher in those who lost weight. In this cohort, less than 10% of individuals lost ≥ 10 kg weight. On average, in both men and women, those who lost ≥ 10 kg weight were overweight at age 20 (body mass index (BMI) ≥ 25 kg/m²). In their analysis adjusted for age at baseline, weight at age 20 and other potentially confounding variables, ≥ 10 kg weight gain was associated with 50% increased risk of CVD mortality compared with those with stable weight (± 4.9 kg) in women, but such an association was not observed in men. In contrast, ≥ 10 kg weight gain compared with stable weight was significantly inversely related to IHD mortality in men.

The observed positive association between weight gain and CVD mortality is consistent with several previous studies. For example, in the Nurses' Health Study,² there was a dose-response relationship between the amount of weight gained and the incidence of coronary artery disease (CAD) during 20 years of follow-up. However, the lack of an association between weight gain and CVD mortality in men is puzzling because a positive association between weight gain and CAD incidence in men has been previously shown.³ The reasons for the observed sex difference is unclear, but might be related to differences in baseline weight and body fat distribution between men and women.

The lack of a consistent association between weight gain and stroke mortality in men may reflect a temporal change in the relationship between body weight and hypertension, a major CVD risk factor. A previous study reported that hypertension without being overweight used to constitute the majority of hypertension cases in men in rural communities in Japan in the

1960s, but it decreased significantly by the 1980s, resulting in increases in the proportion of hypertension cases among the overweight.⁴ Thus, a correlation between BMI and diastolic blood pressure was not present in the 1960s in rural men aged 40–49 years; however, it emerged in the 1970s and became stronger in the 1980s. Because blood pressure is the strongest risk factor for the development of stroke,⁵ the association of body weight with stroke mortality would not be revealed in a cohort that consisted of participants born between 1915 and 1945. Further investigations are warranted in other cohort studies to examine the role of weight gain in stroke mortality.

In both men and women, losing ≥ 10 kg since age 20 was associated with increased CVD mortality. The increased CVD mortality related to weight loss was observed in younger (40–59 at baseline) or never smoking individuals in both sexes, but these results were not statistically significant because of the small number of deaths in the subgroups. However, there exist important methodological and practical limitations in these analyses. First, the outcome was mortality, not incidence. A certain risk factor could become a prognostic factor for better outcome after disease occurrence because the development of the disease may have led to changes in exposure. Thus, mortality associations could not directly be used for preventive strategies. In addition, a number of cohort studies have shown that weight loss is associated with increased mortality.⁶ Although cases of prevalent CVD or history of cancer and death occurring 3 years from baseline were excluded, some existing or preclinical conditions could be present for several years before their clinical manifestations, leading to reverse causation.⁶

Second, weight was recorded at only 2 time-points. The present investigation examined the association of net weight change occurring over a long period of time, up to 60 years, with CVD mortality. Those in the lost-weight categories might have gained more weight at some time during adulthood. Although stratified analysis by baseline age at 60 years did not suggest any effect modification, obtaining information on attained weight at age 40 and additional analyses of weight change until mid-life may provide more useful results.

Third, the history of intentionality of the weight loss was not assessed. As the maintenance of intentionally lost weight is difficult in those with excess weight,⁷ weight loss observed largely reflects unintentional weight loss. Previous studies have shown that unintentional weight loss but not intentional

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received January 16, 2013; accepted January 16, 2013; released online February 5, 2013

Department of Public Health, Fujita Health University School of Medicine, Toyoake (H.Y.), Japan; Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA (F.B.H.), USA

Mailing address: Hiroshi Yatsuya, Professor, MD, PhD, Department of Public Health, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake 470-1192, Japan. E-mail: yatsuya@gmail.com

ISSN-1346-9843 doi:10.1253/circj.CJ-13-0049

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

weight loss is associated with increased mortality.⁸

The present study indicates that long-term weight gain is likely to be a CVD risk factor, especially in women. However, the results of long-term weight loss and mortality are difficult to interpret because of serious methodological challenges, especially reverse causation. Nonetheless, a large body of literature has clearly demonstrated that maintaining a healthy weight over the life course confers many health benefits, including reduced risk of developing hypertension, diabetes, CVD, and other chronic diseases.⁶

References

1. Chou WT, Kakizaki M, Tomata Y, Nagai M, Sugawara Y, Kuriyama S, et al. Impact of weight change since age 20 and cardiovascular disease mortality risk: The Ohsaki Cohort Study. *Circ J* 2013; **77**: 679–686.
2. Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, et al. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation* 2006; **113**: 499–506.
3. Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, et al. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol* 1995; **141**: 1117–1127.
4. Komachi Y. Recent trend in the research of hypertension in Japan. Characteristics of hypertension in Japan. *Nippon Naika Gakkai Zasshi* 1988; **77**: 1802–1805 (in Japanese).
5. Saito I. Epidemiological evidence of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease in Japan. *Circ J* 2012; **76**: 1066–1073.
6. Hu FB. Obesity epidemiology. Oxford University Press, 2008.
7. Yatsuya H, Jeffery RW, Langer SL, Mitchell N, Flood AP, Welsh EM, et al. Changes in C-reactive protein during weight loss and the association with changes in anthropometric variables in men and women: LIFE Study. *Int J Obes (Lond)* 2011; **35**: 684–691.
8. Wannamethee SG, Shaper AG, Lennon L. Reasons for intentional weight loss, unintentional weight loss, and mortality in older men. *Arch Intern Med* 2005; **165**: 1035–1040.