

Chapter 7

Obesity and Diabetes Mellitus as Risk Factors for Cardiovascular Disease in the Elderly



Hirofumi Ohnishi and Shigeyuki Saitoh

Abstract In recent years, the prevalence of obesity has been increasing in older people with aging of the population. Obesity is the most important risk factor for several lifestyle-related diseases including type 2 diabetes, hypertension, and cardiovascular disease in the elderly population as well as in the middle-aged population. However, the impact of obesity on incidence of lifestyle-related diseases and all-cause or cardiovascular disease (CVD) mortality is weaker in the elderly population than in the younger population. It is also known that the relationship between waist circumference and CVD mortality in men aged ≤ 65 years is U-shaped. Consideration of the different effects of obesity on lifestyle-related diseases in elderly and non-elderly people may be important for the prevention of lifestyle-related diseases.

The epidemic of diabetes mellitus in the elderly is an important global problem as well as obesity. Elderly patients with type 2 diabetes are more likely than middle-aged patients to have diabetic microangiopathy and macroangiopathy, and poorly controlled diabetes is one of the strong risk factors for CVD or all-cause death in the elderly population as well as in the middle-aged population. However, several studies have shown that there is a J-curve phenomenon in the relationship between HbA1c and CVD events or all-cause mortality in elderly patients with type 2 diabetes. Intensive control of diabetes mellitus causes severe hypoglycemia, and severe hypoglycemia may increase CVD events in the elderly individuals with diabetes mellitus. We have to achieve both maintenance of a good control level of blood glucose to avoid long-term complications and minimization of hypoglycemia and hypoglycemia-associated morbidity and mortality.

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7.1 Obesity in the Elderly and Lifestyle-Related Diseases or Cardiovascular Disease

In recent years, the prevalence of obesity in older people has increased with aging of the population in developed countries. In the United States, more than 30% of men and women aged 60 years or over are obese as defined by a body mass index (BMI) of 30 kg/m² or more [1]. In Japan, the National Health and Nutrition Survey in 2015 showed that the prevalences of obesity defined as a BMI of 25 kg/m² or more were 28% and 25% in men and women aged 60 years or over, respectively. Although the cutoff points of BMI are different in Asian and Western countries, an epidemic of obesity is an important and common global problem.

Obesity is the most important risk factor for several lifestyle-related diseases in the elderly population as well as in the middle-aged population. In fact, BMI and waist circumference have been shown to be strongly associated with the prevalences and incidences of type 2 diabetes, hypertension, and dyslipidemia [2–4]. Moreover, obesity is recognized as a risk factor for cardiovascular disease (CVD) and all-cause death. However, the impact of obesity on the incidences of lifestyle-related diseases and all-cause or CVD mortality is less in the older population than in the younger population.

We have reported the effect of abdominal obesity (AO) on new onset of type 2 diabetes in a general Japanese elderly population compared with that in a non-elderly population [5]. We have been carrying out a cohort study in two towns in Hokkaido, called “The Tanno-Sobetsu study”, for more than 40 years and have reported risk factors for various lifestyle-related diseases and cardiovascular disease [3, 4, 6]. The participants in the study were 827 people aged 29–84 years who underwent medical examinations in 1994 and subsequently in either 2003 or 2004, after the exclusion of individuals with type 2 diabetes at baseline. The participants were divided into two groups according to waist circumference at baseline using the Japanese cutoff points: an AO group (waist circumferences of 85 cm or more for men and 90 cm or more for women) and a non-AO group. The percentages of individuals with new onset of type 2 diabetes recorded in either in 2003 or 2004 were compared between these two groups, and the odds ratio (OR) of AO for new onset of type 2 diabetes was calculated separately for elderly (≥ 65 years of age) and non-elderly (< 65 years of age) participants using multiple logistic regression analysis. The percentage of non-elderly participants with new onset of type 2 diabetes was significantly higher in the AO group than in the non-AO group (16.9% vs. 5.4%), but there was no statistically significant difference between the elderly participants in the two groups (12.7% vs. 7.1%). Multiple logistic regression analysis showed that there was a significant relationship between AO and NODM (OR, 2.68; 95% confidence interval (CI), 1.05–6.90) in the non-elderly subjects but not in the elderly subjects (OR, 0.67; 95% CI, 0.16–2.84). Consideration of the dif-

Table 7.1 Comparisons of odds ratios of the existence of abdominal obesity for new onset of type 2 diabetes in non-elderly and elderly individuals [5]

	Model 1	Model 2	Model 3
Non-elderly (<65 years)	3.67 (95% CI, 1.67–8.27)	3.72 (95% CI, 1.59–8.67)	2.68 (95% CI, 1.05–6.90)
Elderly (≥65 years)	1.47 (95% CI, 0.47–4.59)	1.60 (95% CI, 0.49–5.19)	0.67 (95% CI, 0.16–2.84)

Model 1: Adjusted for age and gender

Model 2: Model 1 + total cholesterol, systolic blood pressure, smoking, and family history of diabetes mellitus

Model 3: Model 2 + fasting plasma glucose ≥ 110 mg/dL at baseline

ferent effects of AO on new onset of type 2 diabetes in elderly and non-elderly people may be important for the prevention of type 2 diabetes (Table 7.1).

To clarify the association between waist circumference and risk of all-cause or cardiovascular mortality in the Japanese population, we conducted pooled analysis of data from Japanese community-based studies including our cohort data [7]. A total of 3554 men and 4472 women who had no history of CVD were registered from 3 cohorts, and their waist circumferences were measured at baseline during the period from 1988 to 1996. Endpoints were all-cause death and CVD death, and the participants were followed up for 14.7 years. Hazard ratios (HRs) were calculated using the Cox proportional hazards model and a penalized spline method, after adjustment for the study cohort, age, smoking, alcohol drinking, hypertension, dyslipidemia, and diabetes. The highest quintile of waist circumference in men was associated with a linear reduction in all-cause mortality risk compared with the lowest quintile (HR, 0.73; 95% CI, 0.60–0.89; P for trend = 0.001). When stratifying participants according to age, CVD mortality risk was increased in men aged ≤ 65 years with a larger waist circumference. This relationship was U-shaped. On the other hand, in men aged >65 years, waist circumference was associated with all-cause mortality rather than CVD mortality (Fig. 7.1). In women, waist circumference was not associated with all-cause or CVD mortality risk.

A similar association was observed in a previous study. Hildrum et al. reported the relationship between metabolic syndrome and risk of mortality in middle-aged versus elderly individuals [8]. A total of 6748 men and women who participated in the Nord-Trøndelag Health Study, Norway, from 1995 to 1997 (HUNT 2) were followed up for 7.9 years. In individuals who were 40–59 years of age at baseline, the hazard ratios of metabolic syndrome defined by the International Diabetes Federation criteria for cardiovascular mortality and all-cause mortality were 3.97 (95% CI, 2.00–7.88) and 2.06 (95% CI, 1.35–3.13), respectively. After the age of 60 years, metabolic syndrome was not associated with increased mortality rates. These data suggest that the contribution of abdominal obesity to new onset of type 2 diabetes and CVD mortality may be small in the older population than in the younger population. Therefore, from the viewpoint of prevention of type 2 diabetes or CVD events, lifestyle intervention to lose body weight may be more effective for young- and middle-aged people than for elderly people. Moreover, from the

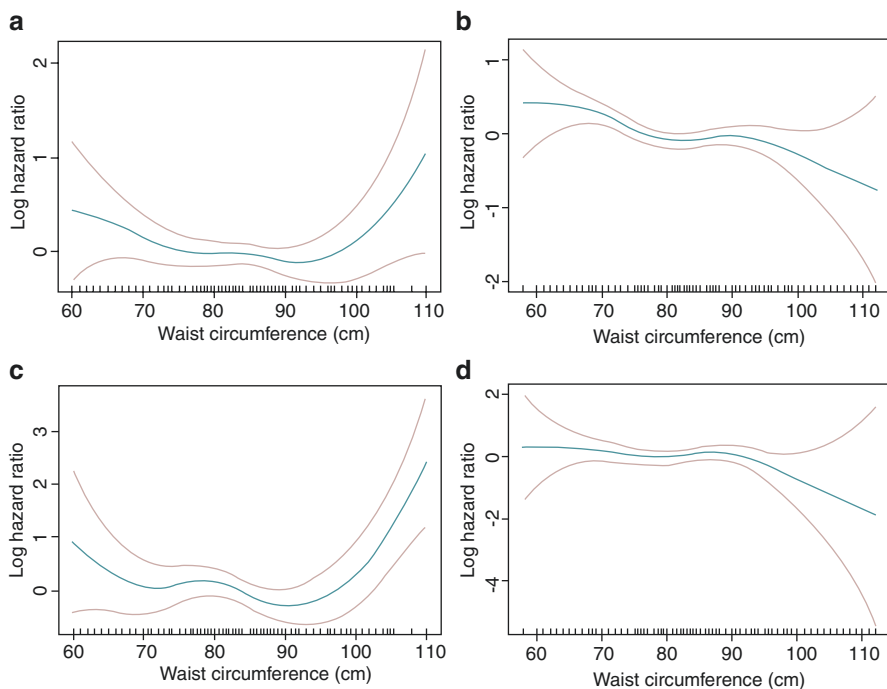


Fig. 7.1 P-spline fitting curves of hazard ratios and 95% confidence intervals for all-cause and cardiovascular disease deaths vs. waist circumference in men <65 years and ≥ 65 years of age. (a) All-cause death, age <65 years (nonlinear trend, $P = 0.089$); (b) all-cause death, age ≥ 65 years ($P = 0.11$); (c) CVD death, age <65 years ($P < 0.001$); (d) CVD death, age ≥ 65 years ($P = 0.31$). The hazard ratios were adjusted for age, study community, smoking habits, alcohol consumption, hypertension, hyperlipidemia, and diabetes mellitus. Actual waist circumference used in the present analysis is marked on the x-axis [7]

viewpoint of decrease in all-cause mortality in the elderly, we may have to intervene for individuals with low BMI using nutritional guidance by dietitians.

A state of having both sarcopenia and obesity is known as sarcopenic obesity [9]. Sarcopenic obesity cannot be assessed by only BMI because it consists of both an increase in body fat and decrease in muscle mass. Body composition that includes body fat and muscle mass is commonly measured using dual energy X-ray absorption (DXA) or bioelectrical impedance analysis (BIA), and obesity is commonly defined according to BMI, percentage of body fat, and waist circumference. Based on the existence of sarcopenia and obesity, the elderly population can be divided into four categories: non-sarcopenia and non-obesity (NS-NO), non-sarcopenia and obesity (NS-O), sarcopenia and non-obesity (S-NO), and sarcopenia and obesity (S-O, i.e., sarcopenic obesity). Several studies have shown differences in the prevalences and incidences of dyslipidemia, hypertension, and metabolic syndrome among these four categories in the elderly population. Baek et al. reported that sarcopenic obesity was associated with an increased risk for dyslipidemia in Korean elderly men according to the 2008–2010 Korea National Health and Nutrition Examination Survey

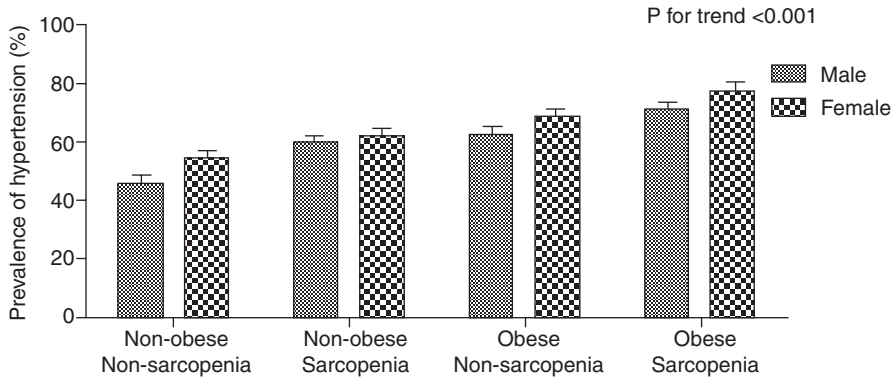


Fig. 7.2 Prevalence of hypertension according to the four body composition categories based on obesity and sarcopenia. In both the obese and non-obese groups, subjects with sarcopenia had a higher prevalence of hypertension than did subjects without sarcopenia [11]

(KNHANES) [10]. The odds ratio (OR) for dyslipidemia was higher in the S-O group (OR, 2.82; 95% CI, 1.76–4.51) than in the NS-O group (OR, 2.12; 95% CI, 1.11–4.07) and the S-NO group (OR, 1.46; 95% CI, 1.01–2.11). In another analysis based on data of the KNHANES 2008–2010 [11], sarcopenic obesity was more strongly associated with hypertension than was simply obesity or sarcopenia (Fig. 7.2). After adjustment for several confounding factors, the ORs for having hypertension were 1.5 (95% CI, 1.23–1.84) in the S-NO group, 2.08 (95% CI, 1.68–2.57) in the NS-O group, and 3.0 (95% CI, 2.48–3.63) in the S-O group, compared with the NS-NO group. Another study including a total of 600 community-dwelling individuals in Northern Taiwan showed the relationship between sarcopenic obesity and metabolic syndrome defined by the consensus of National Cholesterol Education Program Adult Treatment Panel III modified for Asians [12]. The ORs for having metabolic syndrome were 1.98 (95% CI, 1.25–3.16) in the S-NO group, 7.53 (95% CI, 4.01–14.14) in the NS-O group, and 11.59 (95% CI, 6.72–19.98) in the S-O group, compared with the NS-NO group. Although there is no evidence of a relationship of sarcopenic obesity with CVD events, sarcopenic obesity may be a risk for CVD via dyslipidemia, hypertension, and metabolic syndrome. These studies suggest that when assessing the impact of obesity on CVD, it may be important to assess the existence of sarcopenic obesity. However, the definition and gold standard for assessment of sarcopenic obesity have not yet been established, and further studies are therefore needed.

7.2 Diabetes Mellitus as a Risk Factor for Cardiovascular Disease in the Elderly

The epidemic of diabetes mellitus in the elderly is an important global problem as well as obesity. In Japan, the prevalence of diabetes mellitus increases with age, and prevalences of type 2 diabetes defined as HbA1c (NGSP) of 6.5% or more were

25% and 14% in men and women aged 60 years or over, respectively, based on the National Health and Nutrition Survey in 2015. A large-scale meta-regression analysis showed that a substantial increase in the prevalence of diabetes from 7.8% to 9.8% is expected in Japan during the next few decades, mainly as a result of aging of the adult population [13]. The proportion of individuals over 60 years of age who have diabetes mellitus is now more than two-thirds of the estimated total number of patients with diabetes mellitus in Japan. According to our cohort data, the prevalence of type 2 diabetes increased with age, and 48% of the individuals with type 2 diabetes who underwent health checkups were aged over 70 years. Decrease in both insulin secretion and action, decrease in muscle mass and relative increase in visceral fat, and decrease in insulin sensitivity with aging have been reported as mechanism of the deterioration in glucose tolerance in elderly people [14–17].

Elderly patients with type 2 diabetes are more likely than middle-aged patients to have diabetic microangiopathy and macroangiopathy. One of the reasons is that the duration of diabetes mellitus is likely to be longer in elderly patients than in the middle-aged patients. Another reason is that elderly patients frequently have several comorbidities such as hypertension and dyslipidemia, and accumulation of these risk factors accelerates the development of diabetic complications. Huang et al. reported the rates of complications in older patients with diabetes mellitus according to the results of the Diabetes and Aging Study [18]. The cohort study that included 72,310 older patients (≥ 60 years of age) with type 2 diabetes showed that the higher the age category was (60–69, 70–79, and ≥ 80 years of age), the higher were the incidences of atherosclerotic complications such as coronary artery disease, cerebrovascular disease, and congestive heart failure. In older adults with a shorter duration of type 2 diabetes (0–9 years), the incidences of coronary artery disease in the age group of 60–69, 70–79, and ≥ 80 years were 8.48, 11.47, and 15.09 (/1000 person-years), respectively; the incidences of cerebrovascular disease were 5.41, 9.83, and 17.79 (/1000 person-years), respectively; and the incidences of congestive heart failure were 6.82, 12.64, and 24.24 (/1000 person-years), respectively. In older adults with a longer duration of type 2 diabetes (≥ 10 years), similar relations of age categories with incidences of the above three cardiovascular events were observed, but all of the incidences were higher in the longer duration group than in the shorter duration group.

Kuusisto et al. reported that type 2 diabetes in the elderly was a strong risk factor for future occurrence of coronary heart disease (CHD) [19]. The results of their observational study that included 1298 elderly Finnish individuals (65–74 years of age) with a 3.5-year follow-up period showed that presence of hyperglycemia ($\text{HbA1c} \geq 7.0\%$) and duration of diabetes were significant risk factors for all CHD events or CHD death. The odds ratios of type 2 diabetes with $\text{HbA1c} \geq 7.0\%$ hyperglycemia for CHD events and CHD death were 2.2 and 4.3, respectively.

Cardiovascular Prevention from Observational Cohorts in the Japan Research Group (EPOCH-JAPAN), which is a large-scale pooled analysis of Japanese community-based cohort studies including our cohort data, showed an age-specific association of diabetes with cardiovascular risk, especially in the elderly [20]. A total of 38,854 individuals (including 1867 individuals with diabetes mellitus) who had no history of CVD were registered from 8 cohorts, and the mean follow-up

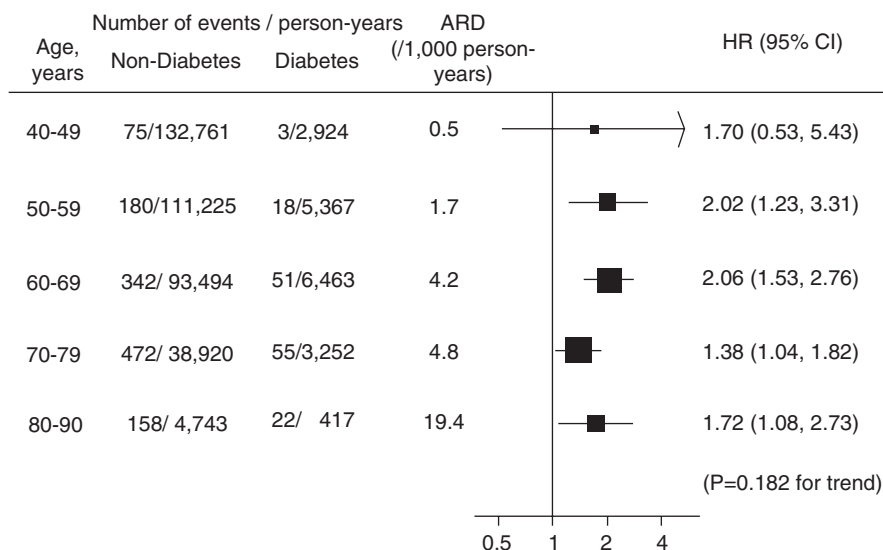


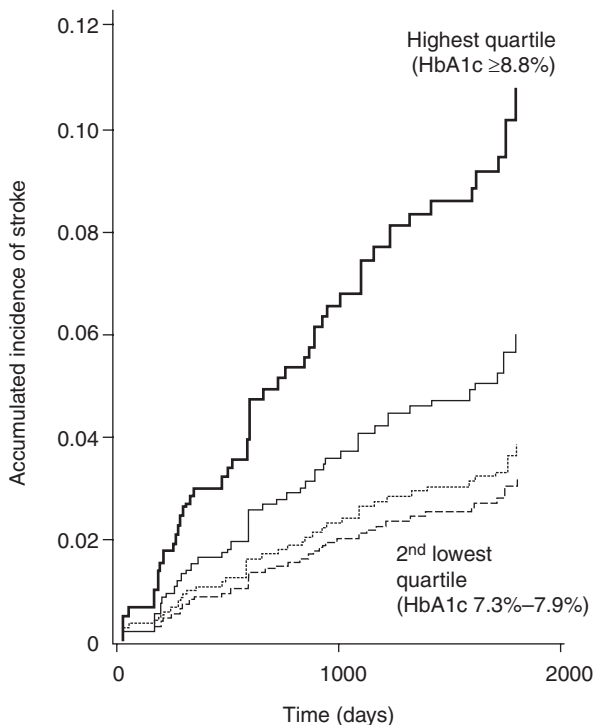
Fig. 7.3 Relative and absolute risks of death from cardiovascular disease associated with diabetes in each age group. The HRs and 95% CIs were calculated among age groups using the sex-adjusted stratified Cox model. The trend in the influence of diabetes on cardiovascular risk across age categories was tested by adding a multiplicative interaction term between diabetic status and ordinal age groups to the relevant Cox model.

HR hazard ratio, CI confidence interval, ARD absolute risk difference [20]

period was 10.3 years. The hazard ratios of diabetes mellitus for CVD death increased with age, and the hazard ratios in the age group of 40–49, 50–59, 60–69, 70–79, and 80–89 years were 1.70 (95% CI, 0.53–5.43), 2.02 (95% CI, 1.23–3.31), 2.06 (95% CI, 1.53–2.76), 1.38 (95% CI, 1.04–1.82), and 1.72 (95% CI, 1.08–2.73), respectively (Fig. 7.3).

Poorly controlled diabetes is one of the strong risk factors for CVD or all-cause death in the elderly population as well as in the middle-aged population [21]. However, several studies have shown that there is a J-curve phenomenon in the relationship between HbA1c and CVD events or all-cause mortality in elderly patients with type 2 diabetes. According to the results of the Japanese Elderly Diabetes Intervention Trial (J-EDIT) [22], which was a randomized control trial to evaluate the effects of multiple risk factor interventions on functional prognosis and development and on progression of diabetic complications and CVD in 1173 elderly type 2 diabetes patients (≥ 65 years of age) with a 6-year follow-up period, HbA1c and non-HDL cholesterol level were significant risk factors for stroke. The hazard ratios of HbA1c (1%) and non-HDL cholesterol (1 mg/dL) for stroke were 1.36 and 1.01, respectively. When participants were divided into quartile categories according to HbA1c level, the cumulative incidence of stroke was lowest in the second lowest quartile (HbA1c 7.3–7.9%), and the incidence was significantly higher in the highest quartile ($\geq 8.8\%$) than in the second quartile. The relationship was J-shaped (Fig. 7.4).

Fig. 7.4 Glycated hemoglobin A1c (HbA1c) and incidence of stroke. The highest HbA1c quartile (38.8%) had an increased incidence of stroke compared with the second lowest ($P = 0.003$), second highest ($P = 0.008$), and lowest ($P = 0.092$) quartiles. The incidence of stroke was lowest in the second lowest HbA1c quartile (7.3–7.9%). This suggests the existence of a J-curve incidence of stroke according to the HbA1c distribution [22]



A similar relation was observed in the Diabetes and Aging Study, which included 71,092 older patients with type 2 diabetes [23]. The mean age of the population was 71.0 years, and mean HbA1c was 7.0%. The mean follow-up period was 3.1 years, and mortality was 40.4 per 1000 person-years. The participants were divided into seven groups according to HbA1c level at baseline: HbA1c of <6.0%, 6.0–6.9%, 7.0–7.9%, 8.0–8.9%, 9.0–9.9%, 10.0–10.9%, and $\geq 11.0\%$. The hazard ratios of HbA1c categories for all-cause mortality compared with the reference group (HbA1c of <6.0%) were 0.84 (95% CI, 0.79–0.90), 0.83 (95% CI, 0.76–0.90), 0.90 (95% CI, 0.81–1.00), 1.02 (95% CI, 0.88–1.17), 1.21 (95% CI, 1.01–1.45), and 1.31 (95% CI, 1.09–1.57) in the 6.0–6.9%, 7.0–7.9%, 8.0–8.9%, 9.0–9.9%, 10.0–10.9%, and $\geq 11.0\%$ groups, respectively. The relationship was also J-curved in that analysis.

These J-curved relations suggest that intensive control of diabetes mellitus may be a risk of increase in stroke and mortality. Intensive control of diabetes mellitus causes severe hypoglycemia, and severe hypoglycemia may increase CVD events in elderly individuals with diabetes mellitus [24]. Severe hypoglycemia also leads to an increase in cognitive impairment in elderly patients [25]. It is necessary to achieve both maintenance of a good control level of blood glucose to avoid long-term complications and minimization of hypoglycemia- and hypoglycemia-associated morbidity and mortality.

References

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA*. 2012;307(5):491-7.
2. Han TS, Tajar A, Lean ME. Obesity and weight management in the elderly. *Br Med Bull*. 2011;97:169-96.
3. Ohnishi H, Saitoh S, Takagi S, Katoh N, Chiba Y, Akasaka H, et al. Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population: the Tanno and Sobetsu study. *Diabetes Care*. 2006;29(5):1128-9.
4. Ohnishi H, Saitoh S, Akasaka H, Mitsumata K, Chiba M, Furugen M, et al. Incidence of hypertension in individuals with abdominal obesity in a rural Japanese population: the Tanno and Sobetsu study. *Hypertens Res*. 2008;31(7):1385-90.
5. Fujii M, Ohnishi H, Saitoh S, Mori M, Shimamoto K. Comparison of the effect of abdominal obesity on new onset of type 2 diabetes in a general Japanese elderly population with that in a non-elderly population-the Tanno and Sobetsu study. *Nihon Ronen Igakkai Zasshi. Jpn J Geriatr*. 2011;48(1):71-7.
6. Mitsumata K, Saitoh S, Ohnishi H, Akasaka H, Miura T. Effects of parental hypertension on longitudinal trends in blood pressure and plasma metabolic profile: mixed-effects model analysis. *Hypertension*. 2012;60(5):1124-30.
7. Saito I, Kokubo Y, Kiyohara Y, Doi Y, Saitoh S, Ohnishi H, et al. Prospective study on waist circumference and risk of all-cause and cardiovascular mortality: pooled analysis of Japanese community-based studies. *Circ J*. 2012;76(12):2867-74.
8. Hildrum B, Mykletun A, Dahl AA, Midthjell K. Metabolic syndrome and risk of mortality in middle-aged versus elderly individuals: the Nord-Trøndelag Health Study (HUNT). *Diabetologia*. 2009;52(4):583-90.
9. Kohara K. Sarcopenic obesity in aging population: current status and future directions for research. *Endocrine*. 2014;45(1):15-25.
10. Baek SJ, Nam GE, Han KD, Choi SW, Jung SW, Bok AR, et al. Sarcopenia and sarcopenic obesity and their association with dyslipidemia in Korean elderly men: the 2008-2010 Korea National Health and Nutrition Examination Survey. *J Endocrinol Investig*. 2014;37(3):247-60.
11. Han K, Park YM, Kwon HS, Ko SH, Lee SH, Yim HW, et al. Sarcopenia as a determinant of blood pressure in older Koreans: findings from the Korea National Health and Nutrition Examination Surveys (KNHANES) 2008-2010. *PLoS One*. 2014;9(1):e86902.
12. Lu CW, Yang KC, Chang HH, Lee LT, Chen CY, Huang KC. Sarcopenic obesity is closely associated with metabolic syndrome. *Obes Res Clin Pract*. 2013;7(4):e301-7.
13. Charvat H, Goto A, Goto M, Inoue M, Heianza Y, Arase Y, et al. Impact of population aging on trends in diabetes prevalence: a meta-regression analysis of 160,000 Japanese adults. *J Diabetes Invest*. 2015;6(5):533-42.
14. Tamura Y, Izumiyama-Shimomura N, Kimbara Y, Nakamura K, Ishikawa N, Aida J, et al. Telomere attrition in beta and alpha cells with age. *Age*. 2016;38(3):61.
15. Basu R, Breda E, Oberg AL, Powell CC, Dalla Man C, Basu A, et al. Mechanisms of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. *Diabetes*. 2003;52(7):1738-48.
16. Sakurai T, Iimuro S, Araki A, Umegaki H, Ohashi Y, Yokono K, et al. Age-associated increase in abdominal obesity and insulin resistance, and usefulness of AHA/NHLBI definition of metabolic syndrome for predicting cardiovascular disease in Japanese elderly with type 2 diabetes mellitus. *Gerontology*. 2010;56(2):141-9.
17. Tamura Y, Izumiyama-Shimomura N, Kimbara Y, Nakamura K, Ishikawa N, Aida J, et al. beta-cell telomere attrition in diabetes: inverse correlation between HbA1c and telomere length. *J Clin Endocrinol Metab*. 2014;99(8):2771-7.

18. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Intern Med.* 2014;174(2):251–8.
19. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes.* 1994;43(8):960–7.
20. Hirakawa Y, Ninomiya T, Kiyohara Y, Murakami Y, Saitoh S, Nakagawa H, et al. Age-specific impact of diabetes mellitus on the risk of cardiovascular mortality: an overview from the evidence for Cardiovascular Prevention from Observational Cohorts in the Japan Research Group (EPOCH-JAPAN). *J Epidemiol.* 2017;27(3):123–9.
21. van Hateren KJ, Landman GW, Kleefstra N, Drion I, Groenier KH, Houweling ST, et al. Glycaemic control and the risk of mortality in elderly type 2 diabetic patients (ZODIAC-20). *Int J Clin Pract.* 2011;65(4):415–9.
22. Araki A, Iimuro S, Sakurai T, Umegaki H, Iijima K, Nakano H, et al. Non-high-density lipoprotein cholesterol: an important predictor of stroke and diabetes-related mortality in Japanese elderly diabetic patients. *Geriatr Gerontol Int.* 2012;12(Suppl 1):18–28.
23. Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. *Diabetes Care.* 2011;34(6):1329–36.
24. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care.* 2010;33(6):1389–94.
25. Mattishent K, Loke YK. Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. *Diabetes Obes Metab.* 2016;18(2):135–41.