Dietary Sodium Intake and Incidence of Diabetes Complications in Japanese Patients with Type 2 Diabetes – Analysis of the Japan Diabetes Complications Study (JDCS)

（日本人 2 型糖尿病患者における、塩分摂取量と糖尿病合併症との関係 ― JDCS による解析）

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Title

Dietary Sodium Intake and Incidence of Diabetes Complications in Japanese Patients with Type 2 Diabetes -- Analysis of the Japan Diabetes Complications Study (JDCS)

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Disclosure Summary

The authors declare that there is no duality of interest associated with this manuscript. All authors researched data, contributed to the discussion, and wrote and edited the manuscript. H.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Abstract

Context:

Many guidelines recommend that patients with type 2 diabetes should reduce their dietary sodium intake. However, the relationship between dietary sodium intake and incidence of diabetic complications in patients with type 2 diabetes has not been explored.

Objective:

To investigate the relationship between dietary sodium intake and incidence of diabetes complications.

Design, Setting, and Participants:

A nationwide cohort of patients with type 2 diabetes aged 40-70y with HbA1c ≥6.5%.

Main Outcome Measures:

After excluding non-responders to a dietary survey, 1588 patients were analyzed. Baseline dietary intake was assessed by the Food Frequency Questionnaire based on food groups. Primary outcomes were times to cardiovascular disease (CVD), overt nephropathy, diabetic retinopathy, and all-cause mortality.

Results:

Mean daily dietary sodium intake in quartiles ranged from 2.8 to 5.9g. After adjustment for confounders, hazard ratios (HRs) for CVD in patients in the 2nd, 3rd, and 4th quartiles of sodium intake compared with the 1st quartile were 1.70 (95% confidence interval, 0.98-2.94), 1.47 (0.82-2.62), and 2.07 (1.21-3.90), respectively (trend $p<0.01$). In addition, among patients who had HbA1c ≥9.0%, HR for CVD in patients in the top vs. bottom quartile of sodium intake was dramatically elevated compared with patients with HbA1c<9.0% (1.16 (0.56-2.39) and 9.91 (2.66-36.87), interaction $p<0.01$). Overt nephropathy, diabetic retinopathy, and all-cause mortality were not significantly associated with sodium intake.

Conclusions:

Findings suggested that high dietary sodium intake is associated with elevated incidence of CVD in patients with type 2 diabetes and that there is a synergistic effect between HbA1c values and dietary sodium intake for the development of CVD.

Introduction

Reduction of dietary salt intake is encouraged in guidelines for diabetes care in many countries (1-4), with various goals being set for daily intake of sodium (>2.3 g/day in the USA (1), >2.36 g/day in Europe (2), and >3.9 g/day in Japan (3).) However, current guidelines for salt reduction are based on epidemiological studies of participants without diabetes. In the position statement by the American Diabetes Association in 2013 (1), its recommendation for sodium reduction was based on the Dietary Approaches to Stop Hypertension diet designed for participants without diabetes in which sodium intake is limited to less than 1.5 g/day, consumption of fruits, vegetables, and low-fat dairy products is increased, and excessive alcohol consumption avoided, with the possible result of weight reduction (5).

Some relatively small short-term studies of patients with type 2 diabetes reported that dietary sodium restriction conferred a modest reduction in blood pressure (6) and that salt supplementation reduced the antihypertensive efficacy of blood pressure-lowering agents (7). In addition, there are few longitudinal studies of sodium intake in patients with diabetes and the results are limited to the association between 24-h urinary sodium excretion and the incidence of mortality and end-stage renal disease (8, 9). Therefore, epidemiological evidence of the relationship between dietary sodium intake and the incidence of diabetes complications in patients with type 2 diabetes remains uncertain.

Thus, in this study, we investigated the association between dietary sodium intake and the incidence of diabetes complications including cardiovascular disease (CVD), overt nephropathy, and diabetic retinopathy as well as all-cause mortality in patients with type 2 diabetes in the large nationwide multicenter cohort of the Japan Diabetes Complications Study (JDCS).

Materials and Methods

Study cohort

The present analysis was conducted as part of the JDCS, a multicenter prospective study on the incidence of and risk factors for macro- and microvascular complications among Japanese patients with type 2 diabetes from outpatient clinics in 59 university and general hospitals. The primary results (10) of the JDCS were described elsewhere. Eligibility criteria were previously diagnosed individuals with type 2 diabetes aged 40–70 years whose HbA1c levels were ≥6.5% and were diagnosed by fasting blood sugar or the 75g oral glucose tolerance test according to values established by the Japan Diabetes Society (JDS) and assays that were standardized by the Laboratory Test Committee of the JDS, which is almost identical in terms of cut-off values for glucose levels to those of the World Health Organization.

Figure 1 shows the flow diagram of the JDCS. From January 1995 to March 1996, 2205 patients were initially registered in the JDCS. Of the 2033 patients who met the eligibility criteria described above, 1588 patients responded to a baseline dietary survey. There was no notable difference in baseline characteristics between responders and non-responders (11).

The original primary endpoints of the JDCS were micro- and macrovascular complications. The following patient groups were followed as to whether or not they developed either CVD, nephropathy or retinopathy. The CVD group consisted of 1414 patients after excluding patients with impaired glucose tolerance, a history of angina pectoris, myocardial infarction, stroke, peripheral artery disease, familial hypercholesterolemia, type III hyperlipidemia (diagnosed by broad beta band on electrophoresis), or nephrotic syndrome (urine protein >3.5 g/day and serum total protein <6.0 mg/dL or serum creatinine levels >1.3 mg/dl (120 μmol/L) at baseline. The overt nephropathy group consisted of 1330 patients after excluding those with impaired glucose tolerance, a history of non-diabetic nephropathy, nephrotic syndrome, serum creatinine levels >120 μmol/l, or mean values of two spot urine examinations for an albumin excretion rate of <150 mg/g creatinine. The retinopathy-incident group consisted of 978 patients after excluding those with impaired glucose tolerance, a history of retinopathy, or a major ocular disease (e.g., glaucoma, dense cataract, or history of cataract surgery). We analyzed follow-up data collected until March 2003.

The protocol for the study, which is in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health Labor and Welfare, received ethical approval from the institutional review boards of all of the participating institutes. Written informed consent was obtained from all enrolled patients.

Outcome measures

Macroangiopathy endpoints included the incidence of definite coronary heart disease (angina pectoris or myocardial infarction) or stroke. The diagnosis of angina pectoris and myocardial infarction was according to criteria defined by the WHO/MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project, and the diagnosis of stroke was according to guidelines defined by the Ministry of Health, Labour and Welfare of Japan (12). Adjudication of endpoints was made by a central committee comprised of experts in each complication based on additional data such as a detailed history, sequential changes in ECG and serum cardiac biomarkers, and results of coronary angiography or brain imaging. The nephropathy endpoint was defined as the development of overt nephropathy (spot urinary albumin excretion >300 mg/g creatinine in two consecutive samples). Diabetic retinopathy was evaluated by qualified ophthalmologists at each institute using the following classification designed for this research: Stage 0, no retinopathy; Stage 1, hemorrhage and hard exudates; Stage 2, soft exudates; Stage 3, intraretinal microvascular abnormalities and venous changes including beading, loop, and duplication; and Stage 4, new vessels, vitreous hemorrhage, fibrous proliferation, and retinal detachment. The retinopathy endpoints were (i) development of retinopathy (from Stage 0 to any other stage confirmed in two continuous years) and (ii) progression from Stage 1 to Stage 3 or 4.

Dietary assessment

Nutritional and food intakes were assessed by the Food Frequency Questionnaire based on food groups (FFQg) at baseline and 5 years after registration. In brief, the FFQg elicited information on the average intake per week of 29 food groups and 10 kinds of cookery in commonly used units or portion sizes. After participants completed the questionnaire, a dietitian reviewed the completed

questionnaire with the participant. The FFQg was externally validated by comparison with dietary records for 7 continuous days of 66 subjects aged 19-60 years (13). The ratios of the estimates obtained by the FFQg against those by the dietary records ranged from 72% to 121% (average 104%). The correlation coefficient between the FFQg and dietary records for sodium intake was 0.43. We used standardized software for population-based surveys and nutrition counseling in Japan (EIYO-KUN v.4.5, manufactured at the site of the Shikoku University Nutrition Database) based on Standard Tables of Food Composition in Japan (14) edited by the Japanese Ministry of Education, Culture, Sports, Science, and Technology to calculate nutrient and food intakes.

Statistical analysis

Patient characteristics were described as mean ±SD, median, interquartile range, or percentage. Univariate and multivariate Cox regression analyses were used to estimate the adjusted hazard ratios (HR) and 95% CI for the incidence of CVD, overt nephropathy, and diabetic retinopathy and total mortality in relation to sodium intake. Multivariate adjusted analyses were conducted with adjustment for age, sex, body mass index (BMI), HbA1c, diabetes duration, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, treatment by insulin, treatment by lipid-lowering agents, current smoker, alcohol intake, energy intake, sodium intake, and physical activity. In addition to the multivariate adjustment, we made further adjustments for systolic blood pressure and the use of antihypertensive agents. All p-values are two-sided, and the significance level is 0.05. All statistical analyses and data management were conducted at a central data center using SAS ver. 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The baseline characteristics and daily dietary intake of the 1588 patients according to quartiles of total sodium intake are shown in **Table 1**. Mean daily dietary sodium intake across quartiles ranged from 2.8 to 5.9 g and mean energy intake across quartiles ranged from 1470 to 2010 kcal. Differences in the proportions of fat, protein, and carbohydrate as percentages of energy supply were small from the first to the fourth quartile of sodium intake although significant differences were observed ($p < 0.01$, < 0.01, and < 0.01, respectively). Patients in higher quartiles included significantly more men, and physical activity, alcohol intake, and energy intake were significantly greater in the higher quartiles. However, there were no significant trends in BMI, blood pressure, lipids, and medications. There were no differences in HbA1c values among quartiles and the HbA1c levels were well controlled.

During the 8-year follow-up with a follow-up rate of 76.0%, incidents according to the first to fourth quartiles of sodium intake were 23, 36, 32, and 41 for CVD, 26, 13, 26, and 18 for overt nephropathy, and 75, 66, 71, and 73 for diabetic retinopathy, respectively. Deaths according to the quartiles of sodium intake were 22, 23, 11, and 19, respectively. The crude incidence rates per 1000 patient-years of CVD, overt nephropathy, and diabetic retinopathy were 13.61, 8.70, and 42.49, respectively. The mortality rate per 1000 patient-years was 6.68. There was no notable difference in baseline characteristics between patients who completed the 8-year follow-up and the other patients (11).

Table 2 shows HRs for dietary sodium intake estimated by Cox regression models unadjusted (top model), adjusted for risk factors (middle model), and further adjusted for SBP and the use of antihypertensive agents (bottom model). In confounder-adjusted Cox regression, sodium intake was associated with an increment of incident CVD (trend $p = 0.03$). The adjusted HR for CVD in the fourth quartile compared with the first quartile was 2.07 (95% CI 1.16-3.71, $p = 0.01$). In another Cox regression model with the same adjustment factor but with a linear term for sodium intake, the adjusted HR for a 1 g per day increase in sodium intake was 1.20 (95% CI 1.03-1.41, $p = 0.02$). This association remained substantially unchanged even after further adjustment for SBP and the use of antihypertensive agents. There were no significant trends among overt nephropathy, diabetic

retinopathy, and mortality (**Table 2**).

Figure 2 shows results of subgroup analysis according to risk factors for CVD. Patients with HbA1c ≥9.0% who were in the top quartile of sodium intake had a significantly higher increase in risk of CVD due to sodium intake than patients with HbA1c <9.0% in the top quartile of sodium intake (1.58 (0.81-3.07) and 16.14 (2.86-91.19), interaction p <0.01). No notable differences were observed in overt nephropathy, diabetic retinopathy, and mortality. A significant effect modification was also observed if HbA1c was classified at 8.5% (1.21 (0.57-2.60) and 5.38 (1.86-15.55), interaction p= 0.02), but the interaction test was not significant if HbA1c was classified at 8.0% (2.00 (0.82-4.91) and 2.47 (1.12-5.43), interaction p= 0.58). **Table 3** shows the incidence of CVD for quartiles of sodium intake according to the HbA1c level. When limited to patients who had high HbA1c levels ≥9.0%, sodium intake was found to be associated with a dramatically increased incidence of CVD, and the adjusted HR for CVD of quartiles of sodium intake were 3.52 (0.95-13.09), 3.75 (0.95-14.83), and 9.91 (2.66-36.87), respectively, for Q2, Q3, and Q4 compared with Q1 (trend p <0.01, interaction p< 0.01). However, there was no significant difference between quartiles of sodium intake when analysis was restricted to patients who had HbA1c levels <9.0%.

Discussion

Many guidelines for diabetes care in many countries (1-4) recommend a reduction in dietary sodium intake; however, detailed evidence regarding the relationship between dietary sodium intake and the incidence of diabetes complications in patients with type 2 diabetes is sparse. This 8-year follow-up study of Japanese patients with type 2 diabetes revealed that those who consumed an average of 5.9 g of sodium per day had about a 2-fold higher risk of CVD than those who consumed an average of 2.8 g/day, although there were no significant associations of sodium intake with overt nephropathy, diabetic retinopathy, and all-cause mortality. These results of this longitudinal study show that high dietary sodium intake is associated with an elevated incidence of CVD in patients with type 2 diabetes, which supports current guidelines for patients with diabetes (1-4).

In addition, our study observed that among patients who had high HbA1c levels ≥9.0%, the HR for CVD in patients in the top vs. the bottom quartile of sodium intake was dramatically elevated compared with patients with HbA1c levels <9.0% (1.16 (0.56-2.39) and 9.91 (2.66-36.87), interaction p <0.01). This tendency was also clearly observed when the association between sodium intake and CVD risk was considered linearly (trend p < 0.01, interaction p <0.01). It is well known that poor glycemic control leads to an increase in diabetes complications, and a previous meta-analysis reported that the risk of CVD in patients with type 2 diabetes was associated with an 18% increase for each 1% point increase in HbA1C (15). Another previous meta-analysis that targeted the general population also reported that higher sodium intake was associated with a greater risk of CVD (1.14, 0.99-1.32, ~~P~~p =0.07) (16) though the differences between the highest sodium intake and lowest sodium intake ranged widely from 1.0 g/day to 3.45 g/day. In comparison with the results of our present study and this previous study, patients in the JDCS with poorly controlled HbA1c (HbA1c ≥9.0%) had a particularly high incidence of CVD compared with that of the general population. Therefore, it is speculated that there was a synergistic effect between the HbA1c level and dietary sodium intake for the development of CVD. This finding indicated that a long-term reduction of dietary sodium intake is particularly important in those with poorly controlled blood glucose.

The current goals for daily intake of dietary sodium in guidelines are below 1.5 g/day in the

USA (1), 2.36 g/day in Europe (2), and 3.9 g/day in Japan (3). Comparing these guidelines with the lowest quartile of sodium consumption in the JDCS patients (2.8 g/day), the JDCS patients still had a higher sodium intake compared with USA and European guidelines (+0.5 g/day and +0.44 g/day, respectively) even in the lowest quartile; however, intake was lower compared with Japanese guidelines (-1.1 g/day), a value that is similar to the 2nd quartile of sodium consumption in the JDCS patients. According to the distribution of mean dietary sodium intake, the mean sodium intake of the JDCS patients was 4.2 g/day and their intake was lower than that in the general Japanese population (4.6 g/day) (17) and higher than that in the US and UK general populations (3.6 and 3.4 g/day, respectively) (18), as well as a diabetic population in the US (2.5-3.4 g/day) (19). Further studies are needed to clarify whether medical nutritional treatment that restricts sodium intake to values according to USA and European guidelines would reduce incident CVD among persons with diabetes.

As shown above, JDCS patients in the bottom quartile of sodium intake had a low risk of CVD although their sodium intake was not as low as recommended in European guidelines (1, 2). Additionally, patients in the lower quartiles of sodium intake had significantly lower intakes of alcohol and energy than those in the higher quartiles of sodium intake. However, our current study showed that the relationship between sodium intake and the incidence of CVD was independent of alcohol and energy intakes because this relationship was still observed even after adjustment for alcohol and energy intake and when subgroup analysis was conducted according to alcohol and energy intake. It is well known that modifications of alcohol and energy intake are beneficial for diabetes management (1). It was reported that salted food acts to drive overeating and weight gain (20). Actually, some interventional studies have shown that a sodium-restricted diet decreased total energy intake (21, 22). Also, it was reported that sugar-sweetened beverage consumption was increased by 17 g/day with each additional 0.4 g/day of sodium intake, although this result was provided from underage participants (23). In addition, an interventional study showed that alcohol intake decreased under a sodium-restricted diet in men (22). We had previously reported that JDCS male patients consumed approximately 8-fold more alcoholic beverages than the female patients (115 and 14 g/day, respectively) (24). From our current results it might be said that reduction in dietary salt intake would also play a role in making medical nutritional therapy more effective by a reduction in alcohol and

energy intake. However, this study cannot show the effects of alcohol and energy intake on diabetes complications and all-cause mortality.

Our results showed that there was no significant difference between sodium intake and the incidence of overt nephropathy and diabetic retinopathy. In general, a reduction in dietary salt intake is recommended in order to prevent or slow the development of diabetic nephropathy. However, in a previous cohort study of patients with type 1 diabetes, urinary sodium excretion was inversely associated with end-stage renal disease (9); therefore, results are inconsistent regarding the relationship between sodium intake and renal disease. Given the unique phenomenon in patients with diabetes that involves an anomalous tendency for the glomerular filtration rate in the diabetic kidney to vary inversely with salt intake, as observed in rodents and humans with diabetes (25, 26), it might be important to take into account the differences in the micro- and macrovasculature because the influence of sodium intake on the micro- and macrovasculature has complex aspects from a biological viewpoint.

Confusing results of the association between all-cause mortality and sodium intake were obtained in previous studies. For example, Finnish patients with type 1 diabetes with the highest as well as the lowest daily urinary sodium excretion had reduced survival (9). Another study targeting patients with type 2 diabetes in Australia reported that lower daily urinary sodium excretion was paradoxically associated with increased all-cause and cardiovascular mortality (8). On the other hand, in JDCS patients there was not a significant difference between all-cause mortality and sodium intake. A possible reason for such inconsistent results might be that the large differences in the background of patients in each study such as ethnicity, age, duration of diabetes, body weight, control of blood pressure, and serum lipid values influenced the results. Further studies are needed to clarify the association between daily sodium intake and mortality risk based on a careful consideration of the characteristics of patients.

Another important finding of this study was that the mean BMI of the JDCS patients was within normal range and was much lower than in Western diabetic patients (19, 27-29). In terms of the biological aspects of ethnic differences, it is known that Asian people are more susceptible to

pancreatic β-cell secretory defects and pronounced dysfunction in early insulin secretion than Western people (30). In contrast, among Asian populations, the proportion of body fat and prevalence of prominent abdominal obesity are higher than in individuals of European origin with similar BMI values (30). In addition, the JDCS patients consumed a "high-carbohydrate low-fat" diet compared with Western patients with diabetes (24), and dietary sodium consumption in JDCS patients was generally higher than in Western general and diabetic populations as well as in the Japanese general population (17,18,19,24). The proportion of fat consumption by the JDCS patients met the definition of low fat intake reported in previous studies, which might improve serum triglyceride and cholesterol levels (31, 32). That might be the reason that the JDCS patients and Western patients with type 2 diabetes had similar blood cholesterol levels although the proportion of JDCS patients treated with lipid-lowering agents was half that of Western patients with type 2 diabetes compared with data obtained by a previous longitudinal study (8). Further studies are required to clarify the mechanism of the development of type 2 diabetes in consideration of an ethnic-specific constitution, and it should be investigated whether results of dietary assessments and actual food intake differ consistently between Asian and Western patients with diabetes.

To the best of our knowledge, this is the first study on dietary sodium intake and the incidence of diabetes complications in which patients with type 2 diabetes were prospectively registered based on their HbA1c levels and not retrospectively selected based on self-reported diabetes status. Other strengths include treatment and follow-up plans that were conducted in institutes specializing in diabetes care and adjudication of cardiovascular events by an independent central committee.

Limitations of this study must be considered. First, the potential for bias, such as measurement errors in dietary assessments, confounding factors, and informative censoring, cannot be ruled out entirely. We observed significant differences in age, sex, treatment by insulin, physical activity, and dietary intake across sodium intake (**Table 1**). In our analysis, these confounders were adjusted using Cox regression, but the estimated effects of sodium still can be biased because of residual confounding or unmeasured confounders. With regard to informative censoring, we found no

notable difference in baseline characteristics between patients who completed the 8-year follow-up and the other patients (11). Second, as an observational study rather than a randomized trial, we could not conclude cause-effect relationships as to whether medical nutritional treatment encouraging sodium reduction would reduce incident CVD in clinical practice. Third, our study did not observe any significant association between blood pressure and dietary sodium intake. The percentage of patients treated by antihypertensive agents was similar in each quartile of dietary sodium intake. Given these results, a possible explanation may be that chronic high blood pressure could have been compensated for by increasing doses of antihypertensive drugs. Another limitation is the accuracy of diabetic retinopathy staging based on clinical diagnosis compared with staging based on seven-field stereo fundus photography. Finally, our results may not be generally applicable to populations with different lifestyles or genetic factors. For example, our study did not include the very well controlled patients whose HbA1c value was less than 6.5%. Additionally, the JDCS patients and Western patients with type 2 diabetes had similar blood cholesterol and triglyceride levels although the proportion of JDCS patients treated with lipid-lowering agents was half as frequent as that of Western patients (8). Also, the JDCS patients consumed a "high-carbohydrate low-fat" diet compared with Western patients with diabetes (24), and dietary sodium consumption in Japanese was generally higher than in Western people (17,18,19,24). In addition, BMI and body weight are markedly different between patients in Japan and Western countries (33), and Asian patients have a much lower risk of CVD compared with Western patients and higher risk of end-stage renal disease (34). The contribution of such differences in patients' characteristics remains uncertain. Considering ethnic-specific characteristics and large inter-cultural differences is important in exploring effective medical nutritional therapy and further research is needed.

In conclusion, we found that high dietary sodium intake was associated with an elevated incidence of CVD in Japanese patients with type 2 diabetes and the association was synergistically strengthened when the patients with type 2 diabetes were limited to those whose blood glucose was poorly controlled. It was suggested that dietary salt restriction as medical nutritional treatment would be useful to prevent complications of diabetes in patients with type 2 diabetes.

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Table 1. Baseline characteristics and nutritional intakes of the 1588 patients with type 2 diabetes according to quartiles of sodium intake.

	Q1 (N=397)		Q2 (N=397)		Q3 (N=396)		Q4 (N=398)		
	mean	SD	mean	SD	mean	SD	mean	SD	Trend p
Sodium intake at registration (g)	2.8	±0.4	3.8	±0.2	4.5	±0.2	5.9	±0.8	<0.01
Sodium intake at 5 y after registration (g)	3.3	±1.2	3.8	±1.3	4.4	±1.5	4.6	±1.8	<0.01
Age **(y)**	58.1	±7.4	58.6	±6.9	59.0	±6.8	59.1	±6.4	0.03
Women (%)	49.6%		51.4%		47.2%		42.0%		0.02
HbA1c in NGSP value (%)	7.9	±1.3	7.9	±1.3	7.9	±1.3	7.9	±1.3	0.96
HbA1c (mmol/mol)	67.0	±14.1	67.4	±14.0	67.2	±15.0	67.0	±14.6	0.96
Years after diagnosis **(y)**	11.0	±7.2	11.2	±7.1	10.8	±7.0	10.9	±7.0	0.65
Body mass index (kg/m^2)	22.8	±2.9	23.1	±3.1	23.0	±2.9	23.0	±2.9	0.31
Systolic blood pressure (mmHg)	131.8	16.4	131.8	16.5	130.6	16.2	132.6	15.5	0.76
Diastolic blood pressure (mmHg)	77.1	10.3	76.1	10.1	75.9	9.5	77.5	9.6	0.66
Pulse pressure (mmHg)	54.7	13.3	55.7	13.7	54.7	13.7	55.1	13.4	0.96
Mean blood pressure (mmHg)	95.3	11.0	94.7	10.9	94.1	10.3	95.9	10.1	0.66
Serum LDL-cholesterol **(**mmol/L)	3.18	±0.81	3.22	±0.80	3.13	±0.86	3.12	±0.87	0.12
Serum HDL-cholesterol (mmol/L)	1.41	±0.48	1.42	±0.41	1.42	±0.42	1.39	±0.44	0.42
Serum triacylglycerol (mmol/L) a	1.16	±0.81	1.11	±0.81	1.07	±0.85	1.16	±0.75	0.42
Urine ACR (mg/gCre) a	16.2	±27.5	17.4	±29.5	16.6	±31.4	17.9	±33.9	0.89
eGFR (mL/min/1.73m^2)	86.0	±28.9	88.7	±30.0	86.9	±30.1	87.8	±30.5	0.59
Treated by insulin (%)	23.2%		23.2%		19.7%		16.3%		0.01
Treated by OHA without insulin (%)	64.7%		65.5%		64.4%		67.8%		0.44
Treated by antihypertensive agents (%)	30.3%		28.5%		22.8%		26.4%		0.08
Treated by lipid-lowering agents (%)	25.5%		26.3%		25.0%		21.6%		0.18
Current smoker (%)	32.8%		26.1%		25.9%		27.6%		0.12
Alcohol intake (g)	82.0	±145.4	76.3	±144.6	91.2	±183.6	107.7	±171.1	0.01
Alcohol drinker (%)	36.5%		38.0%		37.7%		43.4%		0.07
Physical activity (kJ/d) a, b	503.4	±1119.0	620.9	±974.0	590.1	±1022.8	613.8	±1319.5	<0.01
Energy intake (kcal)	1469.5	±327.0	1644.8	±314.2	1828.5	±341.6	2012.2	±438.8	<0.01
Protein (%energy)	16.0	±2.3	16.5	±2.2	17.0	±2.2	17.3	±2.4	<0.01
Fat (%energy)	25.0	±5.0	25.7	±4.9	25.8	±4.3	25.8	±4.7	<0.01
Carbohydrate (%energy)	55.6	±6.4	54.9	±6.1	54.3	±5.7	54.0	±6.4	<0.01

a Median±interquartile range

b Leisure-time physical activity was assessed at baseline by a self-administered questionnaire, which was almost identical to that used and validated in the Health Professionals' Follow-up Study (35). Patients were asked the average frequency (times/week) and duration (minutes/time) spent on normal walking, brisk walking, jogging, golfing, tennis, swimming, aerobics dancing, cycling, and other miscellaneous exercise (specified by each patient). The duration spent for each activity in min/time was multiplied by its typical energy expenditure expressed in metabolic equivalents (METs) based on the newest compendium of Ainsworth (36), then summed for all activities to yield a MET-hour score/week. One MET, the energy expended by sitting quietly, is equivalent to 3.5 ml of oxygen uptake/kg of body weight/min or 1 kcal/kg of body weight/h.

Abbreviations: ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; OHA, oral hypoglycemic agent.

Table 2. Cox regression analysis of diabetes complications and all-cause mortality according to quartiles of sodium intake.

	Q1		Q2			Q3			Q4			
	Mean	SD	mean	SD		mean	SD		mean	SD		
Sodium intake (g)	2.8	±0.4	3.8	±0.2		4.5	±0.2		5.9	±0.8		
Sodium at 5 y after registration (g)	3.3	±1.2	3.8	±1.3		4.4	±1.5		4.6	±1.8		
	HR		HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	Trend p
Cardiovascular disease (N=1414)												
Events/Patients	23/354		36/350			32/351			41/359			
Not adjusted	Ref		1.65	(0.98 to 2.78)	0.06	1.35	(0.79 to 2.30)	0.28	1.73	(1.04 to 2.89)	0.03	0.08
Adjusted a	Ref		1.70	(0.98 to 2.93)	0.06	1.47	(0.82 to 2.62)	0.20	2.07	(1.16 to 3.71)	0.01	0.03
Further adjusted b	Ref		1.73	(1.00 to 3.00)	0.05	1.58	(0.88 to 2.84)	0.12	2.17	(1.21 to 3.90)	0.01	0.02
Overt nephropathy (N=1330)												
Events/Patients	26/322		13/337			26/340			18/331			
Not adjusted	Ref		0.49	(0.25 to 0.95)	0.03	0.94	(0.54 to 1.61)	0.81	0.66	(0.36 to 1.21)	0.18	0.47
Adjusted a	Ref		0.50	(0.25 to 1.03)	0.06	1.04	(0.56 to 1.94)	0.89	0.79	(0.39 to 1.61)	0.52	0.95
Further adjusted b	Ref		0.50	(0.24 to 1.03)	0.06	1.17	(0.62 to 2.20)	0.63	0.83	(0.41 to 1.70)	0.61	0.88
Diabetic retinopathy (N=978)												
Events/Patients	75/241		66/244			71/258			73/235			
Not adjusted	Ref		0.86	(0.62 to 1.20)	0.36	0.84	(0.61 to 1.17)	0.31	1.00	(0.72 to 1.38)	0.99	0.93
Adjusted a	Ref		0.86	(0.61 to 1.23)	0.42	0.94	(0.66 to 1.35)	0.75	1.10	(0.75 to 1.61)	0.64	0.57
Further adjusted b	Ref		0.86	(0.60 to 1.23)	0.40	0.96	(0.67 to 1.37)	0.80	1.10	(0.75 to 1.61)	0.64	0.55
All-cause mortality (N=1588)												
Events/Patients	22/397		23/397			11/396			19/398			
Not adjusted	Ref		1.10	(0.62 to 1.98)	0.74	0.49	(0.24 to 1.01)	0.05	0.86	(0.46 to 1.58)	0.62	0.24
Adjusted a	Ref		1.03	(0.54 to 1.98)	0.92	0.56	(0.26 to 1.23)	0.15	0.82	(0.39 to 1.75)	0.61	0.37
Further adjusted b	Ref		1.02	(0.53 to 1.96)	0.95	0.58	(0.26 to 1.26)	0.17	0.81	(0.38 to 1.73)	0.59	0.36

a Adjusted for age, sex, BMI, HbA1c, diabetes duration, LDL-cholesterol, HDL-cholesterol, log-transformed triglycerides, treatment by insulin, treatment by lipid-lowering agents, current smoker, alcohol intake, energy intake, and physical activity.
b Further adjusted for systolic blood pressure and antihypertensive agents.

Table 3. Cox regression analysis of incident cardiovascular disease and quartile of sodium intake according to HbA1c level.

	Q1		Q2			Q3			Q4				
HbA1C <9.0% (N=1082)	Mean	SD	mean	SD		mean	SD		mean	SD			
Sodium intake at baseline (g)	2.8	±0.4	3.8	±0.2		4.5	±0.2		5.9	±0.8			
Sodium intake at 5 y after registration (g)	3.3	±1.2	3.8	±1.1		4.3	±1.4		4.6	±1.7			
	HR		HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	Trend p	Interaction p
Events/Patients	20/278		25/264			22/266			20/274				
Not adjusted	Ref		1.44	(0.80 to 2.62)	0.23	1.13	(0.61 to 2.09)	0.69	1.00	(0.53 to 1.87)	1.00	0.78	0.09
Adjusted a	Ref		1.36	(0.73 to 2.54)	0.33	1.17	(0.60 to 2.28)	0.65	1.14	(0.55 to 2.34)	0.73	0.85	<0.01
Further adjusted b	Ref		1.40	(0.75 to 2.62)	0.29	1.21	(0.62 to 2.37)	0.57	1.16	(0.56 to 2.39)	0.70	0.82	<0.01
HbA1C ≥9.0% (N=332)	mean	SD	mean	SD		mean	SD		mean	SD			
Sodium intake (g)	2.8	±0.5	3.8	±0.2		4.6	±0.2		6.0	±0.9			
Sodium intake at 5 y after registration (g)	3.2	±1.0	3.7	±1.6		4.5	±1.5		4.3	±1.5			
	HR		HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	Trend p	
Events/Patients	3/76		11/86			10/85			21/85				
Not adjusted	Ref		3.38	(0.94 to 12.10)	0.06	2.99	(0.82 to 10.86)	0.10	7.31	(2.18 to 24.53)	<0.01	<0.01	
Adjusted a	Ref		3.29	(0.90 to 12.04)	0.07	2.81	(0.73 to 10.72)	0.13	7.64	(2.12 to 27.56)	<0.01	<0.01	
Further adjusted b	Ref		3.52	(0.95 to 13.09)	0.06	3.75	(0.95 to 14.83)	0.06	9.91	(2.66 to 36.87)	<0.01	<0.01	

a Adjusted for age, sex, BMI, HbA1c, diabetes duration, LDL-cholesterol, HDL-cholesterol, triglycerides, treatment by insulin, treatment by lipid-lowering agents, current smoker, alcohol intake, energy intake, and physical activity.
b Further adjusted for systolic blood pressure and antihypertensive agents.

Figure Legends

Figure 1. Flow diagram of JDCS

Figure 2. Subgroup analysis of CVD according to background characteristics.

Figure 1.

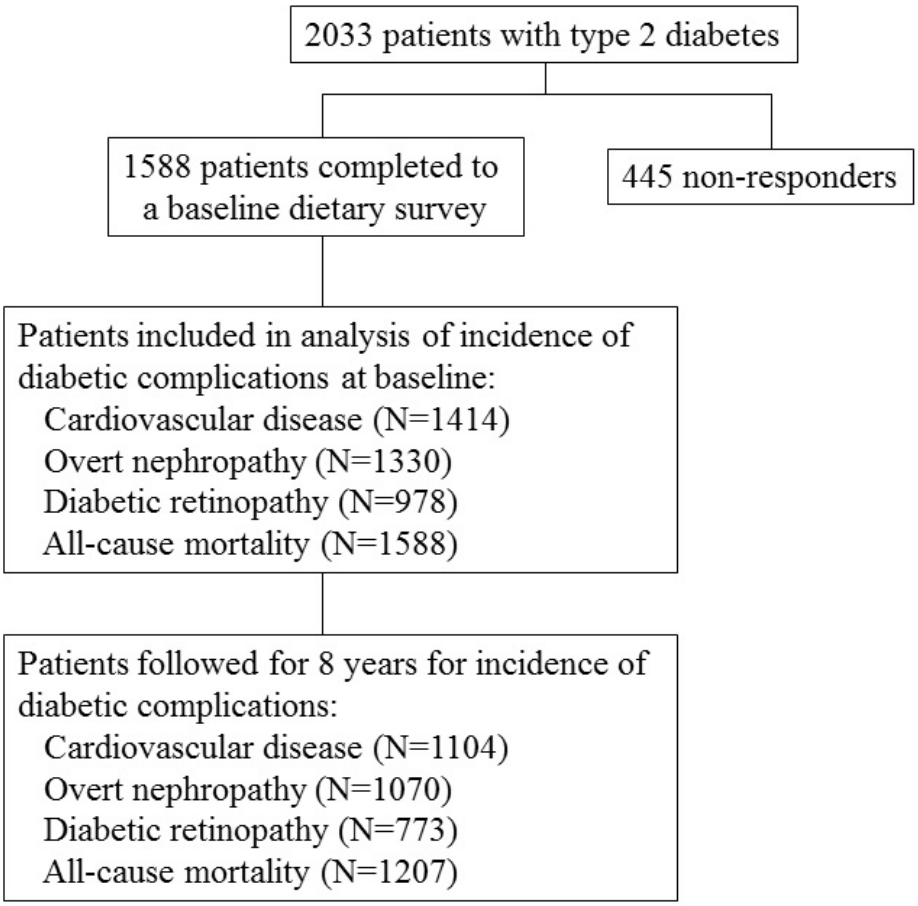
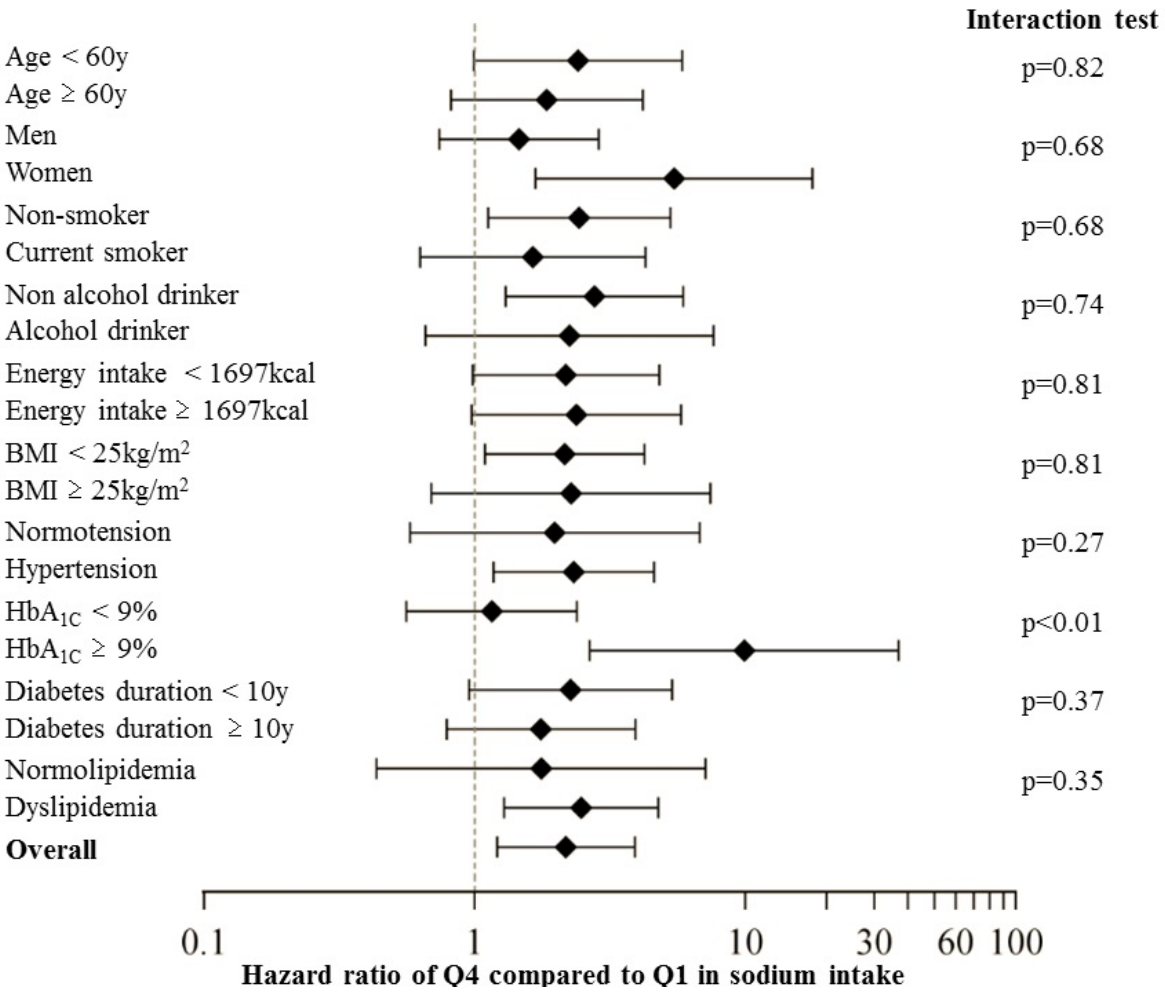

2033 patients with type 2 diabetes
1588 patients completed to a baseline dietary survey
445 non-responders
Patients included in analysis of incidence of diabetic complications at baseline:
Cardiovascular disease (N=1414)
Overt nephropathy (N=1330)
Diabetic retinopathy (N=978)
All-cause mortality (N=1588)
Patients followed for 8 years for incidence of diabetic complications:
Cardiovascular disease (N=1104)
Overt nephropathy (N=1070)
Diabetic retinopathy (N=773)
All-cause mortality (N=1207)

Figure 2.


Interaction test
Age < 60y
Age ≥ 60y
p=0.82
Men
Women
p=0.68
Non-smoker
Current smoker
p=0.68
Non alcohol drinker
Alcohol drinker
p=0.74
Energy intake < 1697kcal
Energy intake ≥ 1697kcal
p=0.81
BMI < 25kg/m2
BMI ≥ 25kg/m2
p=0.81
Normotension
Hypertension
p=0.27
HbA1C < 9%
HbA1C ≥ 9%
p<0.01
Diabetes duration < 10y
Diabetes duration ≥ 10y
p=0.37
Normolipidemia
Dyslipidemia
p=0.35
Overall
0.1
1
10
30
60
100
Hazard ratio of Q4 compared to Q1 in sodium intake