Table 3. Cox Regression Analysis of Incident Cardiovascular Disease and Quartile of Sodium Intake According to HbA1c Level

	Q1		Q2				Q3				Q4					
	Mean ± SD	HR	Mean ± SD	HR	95% CI	*P*	Mean ± SD	HR	95% CI	*P*	Mean ± SD	HR	95% CI	*P*	Trend *P*	Interaction *P*
HbA1C <9.0% (n = 1082)																
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					
Events/patients		20/278		25/264				22/266				20/274				
Not adjusted		Ref.		1.44	0.80–2.62	.23		1.13	0.61–2.09	.69		1.00	0.53–1.87	1.00	.78	.09
Adjusted[a]		Ref.		1.36	0.73–2.54	.33		1.17	0.60–2.28	.65		1.14	0.55–2.34	.73	.85	<.01
Further adjusted[b]		Ref.		1.40	0.75–2.62	.29		1.21	0.62–2.37	.57		1.16	0.56–2.39	.70	.82	<.01
HbA1C ≥9.0% (n = 332)																
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					
Events/patients		3/76		11/86				10/85				21/85				
Not adjusted		Ref.		3.38	0.94–12.10	.06		2.99	0.82–10.86	.10		7.31	2.18–24.53	<.01	<.01	
Adjusted[a]		Ref.		3.29	0.90–12.04	.07		2.81	0.73–10.72	.13		7.64	2.12–27.56	<.01	<.01	
Further adjusted[b]		Ref.		3.52	0.95–13.09	.06		3.75	0.95–14.83	.06		9.91	2.66–36.87	<.01	<.01	

Abbreviations: Q1, quartile 1; Ref., reference.

[a] Adjusted for age, sex, BMI, HbA1c, diabetes duration, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, log-transformed triglycerides, treatment by insulin, treatment by lipid-lowering agents, current smoking, alcohol intake, energy intake, and physical activity.

[b] Further adjusted for systolic BP and antihypertensive agents.

between the highest sodium intake and lowest sodium intake ranged widely from 1.0 to 3.45 g/d. In comparison with the results of our present study and this previous study, patients in the JDCS with poorly controlled 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/d in the United States (1), 2.36 g/d in Europe (2), and 3.9 g/d in Japan (3). Comparing these guidelines with the lowest quartile of sodium consumption in the JDCS patients (2.8 g/d), the JDCS patients still had a higher sodium intake compared with U.S. and European guidelines (+0.5 g/d and +0.44 g/d, respectively) even in the lowest quartile; however, intake was lower compared with Japanese guidelines (−1.1 g/d), a value that is similar to the second 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/d, and their intake was lower than that in the general Japanese population (4.6 g/d) (17) and higher than that in the United States and United Kingdom general populations (3.6 and 3.4 g/d, respectively) (18) as well as a diabetic population in the United States (2.5–3.4 g/d) (19). Further studies are needed to clarify whether medical nutritional treatment that restricts sodium intake to values according to U.S. 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/d with each additional 0.4 g/d 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/d, 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 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 ESRD (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 BP, 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 BP

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 BP 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 7-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 <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 ESRD (34). The contribution of such differences in patients' characteristics remains uncertain. Considering ethnic-specific characteristics and large intercultural 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.

Acknowledgments

We thank all the patients, staff, and the diabetologists throughout Japan for their longstanding collaboration in this study. Thanks are extended to Ms Mami Haga and Ms Natsuko Tada, Niigata University, for their excellent secretarial assistance.

Address all correspondence and requests for reprints to: Hirohito Sone, MD, PhD, FACP, Professor of Internal Medicine, Department of Hematology, Endocrinology, and Metabolism, Niigata University Faculty of Medicine, 1-757 Asahimachi-dori, Chuoh-ku, Niigata 951-8510, Japan. E-mail sone@med.niigata-u.ac.jp.

C.H. is a recipient of a Grant-in-Aid from Honjo International Scholarship Foundation, Japan, and University of Tsukuba Research Infrastructure Support Program, Japan. H.S. is a recipient of a Grant-in-Aid for Scientific Research (20300227) from the Japan Society for the Promotion of Science. This work is also financially supported by the Ministry of Health, Labor, and Welfare, Japan. The sponsor had no role in the design and conduct of the study.

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.

Disclosure Summary: The authors declare that there is no duality of interest associated with this manuscript.

References

1. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2013;36:3821–3842.
2. Mann JI, De Leeuw I, Hermansen K, et al; Diabetes and Nutrition Study Group (DNSG) of the European Association. Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. *Nutr Metab Cardiovasc Dis*. 2004;14:373–394.
3. Guideline Committee of the Japan Diabetes Society. *Japan Diabetes Society Evidence-Based Practice Guidelines for the Treatment of Diabetes in Japan, Nankodo*. Tokyo, Japan: Japan Diabetes Society; 2010.
4. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Nutrition therapy. *Can J Diabetes*. 2013;37:S45–S55.
5. Sacks FM, Svetkey LP, Vollmer WM, et al; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344:3–10.
6. Houlihan CA, Allen TJ, Baxter AL, et al. A low-sodium diet potentiates the effects of losartan in type 2 diabetes. *Diabetes Care*. 2002; 25:663–671.
7. Ekinci EI, Thomas G, MacIsaac RJ, et al. Salt supplementation blunts the blood pressure response to telmisartan with or without hydrochlorothiazide in hypertensive patients with type 2 diabetes. *Diabetologia*. 2010;53:1295–1303.
8. Ekinci EI, Clarke S, Thomas MC, et al. Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care*. 2011;34: 703–709.
9. Thomas MC, Moran J, Forsblom C, et al; FinnDiane Study Group. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care*. 2011;34: 861–866.
10. Sone H, Tanaka S, Iimuro S, et al; Japan Diabetes Complications Study Group. Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study). *Diabetologia*. 2010;53:419–428.
11. Tanaka S, Tanaka S, Iimuro S, et al; the Japan Diabetes Complications Study Group. Cohort Profile: The Japan Diabetes Complications Study: a long-term follow-up of a randomised lifestyle intervention study of type 2 diabetes. *Int J Epidemiol*. 2014;43:1054–1062.
12. Sone H, Katagiri A, Ishibashi S, et al; the Japan Diabetes Complications Study Group. Effects of lifestyle modifications on patients with type 2 diabetes: the Japan Diabetes Complications Study (JDCS) study design, baseline analysis and three-year interim report. *Horm Metab Res*. 2002;34:509–515.
13. Takahashi K, Yoshimura Y, Kaimoto T, Kunii D, Komatsu T,

Yamamoto S. Validation of a food frequency questionnaire based on food groups for estimating individual nutrient intake. *Jpn J Nutr.* 2001;59:221–232.
14. Standard Tables of Food Composition in Japan 2005 [in Japanese]. Ministry of Education, Culture, Sports, Science and Technology-Japan website. http://www.mext.go.jp/b_menu/shingi/gijyutu/gijyutu3/toushin/05031802.htm. Accessed November 30, 2013.
15. **Selvin E, Marinopoulos S, Berkenblit G, et al.** Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med.* 2004;141:421–431.
16. **Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP.** Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ.* 2009;339:b4567.
17. Outline of the National Health and Nutrition Survey Japan, 2007. Ministry of Health, Labour and Welfare-Japan website. http://www0.nih.go.jp/eiken/english/research/pdf/nhns2007.pdf. Accessed November 30, 2013.
18. **Anderson CA, Appel LJ, Okuda N, et al.** Dietary sources of sodium in China, Japan, the United Kingdom, and the United States, women and men aged 40 to 59 years: The INTERMAP Study. *J Am Diet Assoc.* 2010;110:736–745.
19. **Eilat-Adar S, Xu J, Zephier E, O'Leary V, Howard BV, Resnick HE.** Adherence to dietary recommendations for saturated fat, fiber, and sodium is low in American Indians and other U.S. adults with diabetes. *J Nutr.* 2008;138:1699–1704.
20. **Cocores JA, Gold MS.** The salted food addiction hypothesis may explain overeating and the obesity epidemic. *Med Hypotheses.* 2009;73:892–899.
21. **Korhonen MH, Järvinen RM, Sarkkinen ES, Uusitupa MI.** Effects of a salt-restricted diet on the intake of other nutrients. *Am J Clin Nutr.* 2000;72:414–420.
22. **Morris CD.** Effect of dietary sodium restriction on overall nutrient intake. *Am J Clin Nutr.* 1997;65:687S–691S.
23. **Grimes CA, Riddell LJ, Campbell KJ, Nowson CA.** Dietary salt intake, sugar-sweetened beverage consumption, and obesity risk. *Pediatrics.* 2013;131:14–21.
24. **Horikawa C, Yoshimura Y, Kamada C, et al; the Japan Diabetes Complications Study Group.** Dietary intake in Japanese patients with type 2 diabetes: analysis from Japan Diabetes Complications Study. *J Diabetes Invest.* 2014;5:176–187.
25. **Thomson SC, Vallon V, Blantz RC.** Kidney function in early diabetes: the tubular hypothesis of glomerular filtration. *Am J Physiol Renal Physiol.* 2004;286:F8–F15.
26. **Vallon V.** The proximal tubule in the pathophysiology of the diabetic kidney. *Am J Physiol Regul Integr Comp Physiol.* 2011;300:R1009–R1022.
27. **Diabetes and Nutrition Study Group of the Spanish Diabetes Association (GSEDNu).** Diabetes nutrition and complications trial (DNCT): food intake and targets of diabetes treatment in a sample of Spanish people with diabetes. *Diabetes Care.* 1997;20:1078–1080.
28. **Ma Y, Olendzki BC, Hafner AR, et al.** Low-carbohydrate and high-fat intake among adult patients with poorly controlled type 2 diabetes mellitus. *Nutrition.* 2006;22:1129–1136.
29. **Toeller M, Klischan A, Heitkamp G, et al.** Nutritional intake of 2868 IDDM patients from 30 centres in Europe. EURODIAB IDDM Complications Study Group. *Diabetologia.* 1996;39:929–939.
30. **Yoon KH, Lee JH, Kim JW, et al.** Epidemic obesity and type 2 diabetes in Asia. *Lancet.* 2006;368:1681–1688.
31. **Wheeler ML, Dunbar SA, Jaacks LM, et al.** Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. *Diabetes Care.* 2012;35:434–445.
32. **Jacobs B, De Angelis-Schierbaum G, Egert S, Assmann G, Kratz M.** Individual serum triglyceride responses to high-fat and low-fat diets differ in men with modest and severe hypertriglyceridemia. J *Nutr.* 2004;134:1400–1405.
33. **Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Complication Study Group.** Obesity and type 2 diabetes in Japanese patients. *Lancet.* 2003;361:85.
34. **Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV.** Ethnic disparities in diabetic complications in an insured population. *JAMA.* 2002;287:2519–2527.
35. **Tanasescu M, Leitzmann MF, Rimm EB, Hu FB.** Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation.* 2003;107:2435–2439.
36. **Ainsworth BE, Haskell WL, Herrmann SD, et al.** 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc.* 2011;43:1575–1581.

Predicting Macro- and Microvascular Complications in Type 2 Diabetes

The Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine

SHIRO TANAKA, PHD[1]
SACHIKO TANAKA, PHD[2]
SATOSHI IIMURO, MD, PHD[3]
HIDETOSHI YAMASHITA, MD, PHD[4]
SHIGEHIRO KATAYAMA, MD, PHD[5]
YASUO AKANUMA, MD, PHD[6]
NOBUHIRO YAMADA, MD, PHD[7]
ATSUSHI ARAKI, MD, PHD[8]
HIDEKI ITO, MD, PHD[8]
HIROHITO SONE, MD, PHD[7]
YASUO OHASHI, PHD[3]
FOR THE JAPAN DIABETES COMPLICATIONS STUDY GROUP AND THE JAPANESE ELDERLY DIABETES INTERVENTION TRIAL GROUP*

OBJECTIVE—To develop and validate a risk engine that calculates the risks of macro- and microvascular complications in type 2 diabetes.

RESEARCH DESIGN AND METHODS—We analyzed pooled data from two clinical trials on 1,748 Japanese type 2 diabetic patients without diabetes complications other than mild diabetic retinopathy with a median follow-up of 7.2 years. End points were coronary heart disease (CHD), stroke, noncardiovascular mortality, overt nephropathy defined by persistent proteinuria, and progression of retinopathy. We fit a multistate Cox regression model to derive an algorithm for prediction. The predictive accuracy of the calculated 5-year risks was cross-validated.

RESULTS—Sex, age, HbA_{1c}, years after diagnosis, BMI, systolic blood pressure, non-HDL cholesterol, albumin-to-creatinine ratio, atrial fibrillation, current smoker, and leisure-time physical activity were risk factors for macro- and microvascular complications and were incorporated into the risk engine. The observed-to-predicted (O/P) ratios for each event were between 0.93 and 1.08, and Hosmer-Lemeshow tests showed no significant deviations between observed and predicted events. In contrast, the UK Prospective Diabetes Study (UKPDS) risk engine overestimated CHD risk (O/P ratios: 0.30 for CHD and 0.72 for stroke). C statistics in our Japanese patients were high for CHD, noncardiovascular mortality, and overt nephropathy (0.725, 0.696, and 0.767) but moderate for stroke and progression of retinopathy (0.636 and 0.614). By combining macro- and microvascular risks, the classification of low- and high-risk patients was improved by a net reclassification improvement of 5.7% ($P = 0.02$).

CONCLUSIONS—The risk engine accurately predicts macro- and microvascular complications and would provide helpful information in risk classification and health economic simulations.

Diabetes Care 36:1193–1199, 2013

From the [1]Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital, Kyoto, Japan; the [2]EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan; the [3]Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan; the [4]Department of Ophthalmology, Yamagata University Faculty of Medicine, Yamagata, Japan; the [5]Department of Endocrinology and Diabetes, School of Medicine, Saitama Medical University, Saitama, Japan; [6]The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan; the [7]Department of Internal Medicine, University of Tsukuba Institute of Clinical Medicine, Ibaraki, Japan; and the [8]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan.
Corresponding author: Yasuo Ohashi, ohashi@epistat.m.u-tokyo.ac.jp.
Received 17 May 2012 and accepted 7 October 2012.
DOI: 10.2337/dc12-0958. Clinical trial reg. no. UMIN CTR C000000222 for the Japan Diabetes Complications Study and UMIN 000000890 for the Japanese Elderly Diabetes Intervention Trial, www.umin.ac.jp/ctr/.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0958/-/DC1.
*A complete list of the primary investigators and committee members can be found in the Supplementary Data online.

Risk classification for vascular complications is of particular importance in diabetes care, and there is a need for validated diabetes-specific risk engines (1,2). Asian populations account for >60% of the world's diabetes patients (3,4), but data used for most of the engines specific to diabetes include only a limited number of Asians (5–9). Asian patients with diabetes have several important features. We previously reported that Japanese patients have a markedly low prevalence of obesity and low incidence rates of overt nephropathy and diabetic retinopathy (10–13). Furthermore, the risk factor profiles of diabetes complications are quite different between Japanese and Western subjects with diabetes (14). In cohort studies of multiple ethnic groups, lower incidence rates of cardiovascular disease (CVD) were observed in Asian patients than in whites (15,16). Given the overestimation of risks of coronary heart disease (CHD) and stroke in Chinese patients by the UK Prospective Diabetes Study (UKPDS) risk engine (17,18), risk engines for non-Asian populations may not be transportable to Asian patients. To our knowledge, only the Hong Kong Diabetes Registry (HKDR) has developed risk engines for Asian patients with diabetes (17–20).

Most risk engines have focused on classical cardiovascular risk factors such as control of HbA_{1c}, blood pressure, and lipids (5–9,17–20), but, increasingly, studies have suggested the importance of lifestyle factors. In fact, exercise has been shown to reduce all-cause mortality (21,22) and is encouraged by guidelines for type 2 diabetes (23,24). A recent survey of general practitioners in Germany indicated that those physicians thought that to be useful, risk engines should link estimated risks with appropriate recommendations for lifestyle changes (25). Another concern is the lack of capacity to assess multiple diseases simultaneously (25). However, just combining the results of risk engines specific to each vascular complication may yield biased estimates

of absolute risks since it is likely that each engine was developed independently, and a correlation between incidences of vascular complications is not accounted for in the development process.

Data from the 1,748 patients with type 2 diabetes in the Japan Diabetes Complications Study (JDCS) (26) and the Japanese Elderly Diabetes Intervention Trial (J-EDIT) (27) provide an opportunity to develop a comprehensive risk engine for Asian patients with type 2 diabetes. The aim of the current study was therefore to develop and validate an algorithm that separately calculates each risk of the first occurrence for five events: fatal and nonfatal CHD, fatal and nonfatal stroke, noncardiovascular mortality, overt nephropathy, and progression of retinopathy. This was done by fitting a multistate Cox regression model (28), an extension of the Cox model to multiple time-to-event end points, to the pooled data from these trials.

RESEARCH DESIGN AND METHODS

Patients and measurements

Design of the JDCS and the J-EDIT has been described in detail elsewhere (26,27). In the JDCS, 2,033 Japanese type 2 diabetes patients 40–70 years of age whose HbA_{1c} levels were ≥7.0% were randomized to a conventional treatment group and a lifestyle intervention group; throughout the paper, we present the National Glycohemoglobin Standardization Program value of HbA_{1c} calculated as follows: 0.25 + 1.02 × JDC value (29). The latter group received education on lifestyle modification by telephone counseling and at each outpatient clinic visit in addition to usual care. The J-EDIT is a randomized, controlled trial of intensive and conventional treatments for diabetes that registered a total of 1,173 Japanese type 2 diabetes patients 65–85 years of age whose HbA_{1c} levels were ≥8.1%, or ≥7.5% with at least one of the following criteria: BMI ≥25 kg/m^2; blood pressure ≥130/85 mmHg; serum total cholesterol ≥200 mg/dL (5.17 mmol/L) or LDL cholesterol ≥120 mg/dL (3.10 mmol/L) in participants without CHD; serum total cholesterol ≥180 mg/dL (4.65 mmol/L) or LDL cholesterol ≥100 mg/dL (2.59 mmol/L) in participants with CHD; triglycerides ≥150 mg/dL (1.68 mmol/L); and HDL cholesterol <40 mg/dL (1.03 mmol/L). The protocols of the JDCS and J-EDIT received approval from the ethical committees of all of the participating institutes, and written informed consent was obtained from all patients before enrollment. The present analysis excluded patients who had any history of angina pectoris, myocardial infarction, stroke, peripheral artery disease, familial hypercholesterolemia (diagnosed clinically by markedly elevated LDL cholesterol levels with enlarged Achilles tendons and/or family history of premature coronary artery disease), type III hyperlipidemia (diagnosed by broad β-band on electrophoresis), nephrotic syndrome, serum creatinine levels >1.3 mg/dL (120 μmol/L), mean values of two spot urine examinations for an albumin excretion rate of 150 mg/g creatinine (17.0 mg/mmol) or more, microscopic hematuria, or other clinical findings indicating other renal diseases, preproliferative and proliferative retinopathy, and major ocular disease (e.g., glaucoma, dense cataract, or history of cataract surgery). Baseline data were collected for demographics, results of clinical examinations, laboratory measurements performed at local laboratories, and lifestyle factors such as dietary content and smoking status determined by self-reported questionnaires. Leisure-time physical activity (LTPA) was also assessed at baseline by a self-administered questionnaire, which was almost identical to that used and validated in the Health Professionals' Follow-up Study (30). The patients were asked to report their average frequency (times/week) and duration (min/time) of normal walking, brisk walking, jogging, golfing, tennis, swimming, aerobics dancing, cycling, and other miscellaneous exercise as specified by each patient. The duration engaged in each activity in min/time was multiplied by that activity's typical energy expenditure, expressed in metabolic equivalents (METs), and overall activities were summed to yield a MET/h score per week (31). Data management was conducted by a central data center. Follow-up data were collected through a standardized annual report from each investigator. Non-HDL cholesterol (NHDL-C) levels were calculated by total cholesterol subtracted by HDL cholesterol. LDL cholesterol levels were calculated using the Friedewald formula, that is, NHDL-C subtracted by triglycerides divided by 5 if triglyceride levels are <400 mg/dL (4.48 mmol/L); otherwise, LDL cholesterol levels were treated as missing data.

End points

End points were five time-to-event variables: fatal or nonfatal CHD, fatal or nonfatal stroke, noncardiovascular mortality, overt nephropathy defined by persistent proteinuria, and progression of retinopathy since randomization. The definitions of the events have been described in detail elsewhere (12,13,27,32). In brief, diabetic retinopathy was determined annually by qualified ophthalmologists at each institute using the international diabetic retinopathy and diabetic macular edema disease scales (33) with minor modification: 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. A retinopathy event was progression to stage 3 or 4. A nephropathy event was defined as the development of overt nephropathy (spot urinary albumin excretion >33.9 mg/mmol creatinine in two consecutive samples) (12). Macrovascular events included the occurrence of fatal and nonfatal definite CHD (angina pectoris or myocardial infarction) and fatal and nonfatal stroke. The diagnosis of angina pectoris and myocardial infarction was according to criteria defined by the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease project, and diagnosis of stroke was according to guidelines defined by the Ministry of Health, Labour, and Welfare of Japan (32). Adjudication of end points was performed by central committees comprised of experts in each complication based on additional data such as those obtained by computed tomography or magnetic resonance imaging of the brain or sequential changes in electrocardiograms.

Statistical analysis

The JDCS/J-EDIT (JJ) risk engine calculates each risk of the first occurrence within a user-specified time point for the five events described above. The occurrences of these events are viewed as transitions between disease states and were modeled by a multistate model that follows the Markov renewal process (28). The disease states and transitions assumed in the multistate model are detailed in Supplementary Data. We fit a multistate model using a standard procedure for the stratified Cox regression model. That is, we assumed that baseline intensities for any of the transitions were possibly different but that transition intensities to a disease state share common

hazard ratios (HRs) for risk factors. The following risk factors were screened through a backward variable selection with the critical value of $P = 0.1$: age, sex, HbA_{1c}, years after diagnosis, BMI, systolic blood pressure (SBP), NHDL-C, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, log-transformed urine albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate, atrial fibrillation, smoking status, alcohol intake, and LTPA. BMI was categorized by cutoff points of 18.5 and 25 kg/m^2. LTPA was categorized by the cutoff point of 3.8 METs-h/week, which corresponds to the intensity of home activity or conditioning exercise (31). HRs in this model were estimated by maximizing the partial likelihood, and then baseline intensity functions were calculated by the Breslow estimator. Missing data were substituted using the multiple imputation method.

We assessed the predictive accuracy of the 5-year risks based on the JJ risk engine using 10-fold cross-validation, i.e., we performed 10 rounds of cross-validation using different partitions. One round of cross-validation involved randomly partitioning a sample of data on 1,748 patients into complementary subsets, fitting the stratified Cox regression model to one subset of 90% of patients, and validating the model on the remaining subset with the criteria described below. We compared hazards for end points between tertiles of the calculated 5-year risks from the 10-fold cross-validation by the Cox regression. Calibration, namely, how closely the prediction reflected observed events, was assessed for each event by the Hosmer-Lemeshow test and the mean of observed-to-predicted (O/P) ratios, which was calculated as the mean of ratios of the observed-to-expected events across the strata used in the Hosmer-Lemeshow test. Discrimination, the ability to distinguish between those who experienced the event and those who did not, was evaluated using Harrell C statistics, the proportion of all patient pairs in which the predictions of the model and observed events were concordant. Further, we constructed a reclassification table of macro- and microvascular complications (34).

All analyses were conducted by the central data center with the use of SAS software version 9.2 (SAS Institute, Cary, NC). The authors had full access to the data and take responsibility for their integrity. All reported P values for statistical tests are two tailed, and $P < 0.05$ was taken to indicate statistical significance.

RESULTS—The mean ± SD (range) age and HbA_{1c} level at baseline of the 1,748 Japanese type 2 diabetic patients was 62.1 ± 8.6 (40–84) years and 7.9 ± 1.2 (6.0–15.8)%, respectively, and 49.9% of the subjects were women. Their mean baseline values indicated that the subjects had good control of weight (BMI = 23.2 ± 3.1 kg/m^2; waist circumference = 80.3 ± 9.6 cm), blood pressure (SBP = 132.9 ± 16.0 mmHg), and serum cholesterol levels (NHDL-C = 3.78 ± 0.90 mmol/L; LDL cholesterol = 3.16 ± 0.82 mmol/L; HDL cholesterol = 1.43 ± 0.44 mmol/L; triglycerides = 1.39 ± 0.88 mmol/L). Their baseline ACR levels were quite low, with a median ± IQR of 1.8 ± 3.0 mg/mmol, as we excluded those with ACR of 17.0 g/mmol or more. Current smokers and past smokers accounted for 24.4 and 24.0%, respectively, of patients. The median (IQR) LTPA at baseline was 10.5 (1.6–22.5) METs-h/week, and 34.0% of patients had no exercise habit (<3.8 METs-h/week). During the median follow-up of 7.2 years, among the 1,748 subjects, we observed 96 (5.5%) events of fatal or nonfatal CHD, 89 (5.1%) fatal or nonfatal strokes, 71 (4.1%) overt nephropathies defined by persistent proteinuria, and 64 (3.7%) noncardiovascular deaths. Of the 1,297 patients without retinopathy at baseline, 415 (32.0%) developed retinopathy. Of the 866 patients who had retinopathy or developed retinopathy after baseline, 113 (13.0%) had progression to retinopathy of stage 3 or 4.

The backward variable selection procedure identified 11 baseline risk factors

Table 1—*HRs of risk factors incorporated in the best-fitting multistate Cox regression model*

	CHD				Stroke				Noncardiovascular mortality			
	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
Sex (woman/man)	0.41	0.24	0.70	<0.01	0.46	0.29	0.73	<0.01	0.55	0.29	1.04	0.07
Age (+10 years)	1.38	1.02	1.85	0.04	1.55	1.17	2.06	<0.01	2.44	1.70	3.50	<0.01
HbA_{1c} (+1%)	1.22	1.02	1.45	0.03	1.23	1.04	1.44	0.02				
BMI (<18.5/18.5–25 kg/m^2)									3.22	1.40	7.37	0.01
BMI (≥ 25/18.5–25 kg/m^2)									1.16	0.60	2.21	0.66
SBP (+10 mmHg)	1.13	0.98	1.31	0.10	1.16	1.00	1.33	0.045				
NHDL-C (+1 mmol/L)	1.56	1.26	1.93	<0.01	1.38	1.10	1.74	0.01				
Atrial fibrillation (yes/no)					12.48	3.77	41.29	<0.01				
Current smoker (yes/no)	1.67	1.00	2.81	0.052					2.11	1.04	4.26	0.04
LTPA (≥3.8/<3.8 METs-h/week)					0.63	0.39	1.01	0.053	0.57	0.33	1.01	0.054
	Overt nephropathy				Retinopathy							
Age (+10 years)					1.16	1.04	1.30	0.01				
HbA_{1c} (+1%)	1.28	1.08	1.53	0.01	1.32	1.25	1.40	<0.01				
Years after diagnosis (+1 years)					1.04	1.03	1.06	<0.01				
BMI (<18.5/18.5–25 kg/m^2)					0.67	0.43	1.03	0.07				
BMI (≥25/18.5–25 kg/m^2)					1.22	0.99	1.49	0.06				
SBP (+10 mmHg)	1.14	0.97	1.33	0.11								
Log ACR (+1 unit)	3.02	2.16	4.23	<0.01	1.11	1.01	1.22	0.03				
Atrial fibrillation (yes/no)	5.54	0.74	41.49	0.10								
Current smoker (yes/no)	2.18	1.28	3.71	<0.01								

for macro- and microvascular complications and noncardiovascular mortality. Table 1 shows the HRs, 95% CIs, and *P* values for these risk factors. Significant modifiable risk factors were HbA_{1c} and NHDL-C for CHD, HbA_{1c}, SBP, and NHDL-C for stroke, BMI <18.5 kg/m^2 and being a current smoker for noncardiovascular mortality, HbA_{1c} and being a current smoker for overt nephropathy, and HbA_{1c} for retinopathy. Having an exercise habit was associated with reduced risks of stroke and mortality, although with only borderline statistical significance. All of the risk factors that were retained through the variable selection procedure were incorporated into the JJ risk engine. The algorithm of the JJ risk engine is described in Supplementary Data.

The performance of the JJ risk engine was evaluated by several validation criteria. Tertile Cox regression showed that the 5-year risks calculated by the JJ risk engine effectively classified populations at low and high risk for each complication. The HRs (95% CI) of the second and third tertiles compared with the first tertile were 2.09 (1.07–4.09) and 5.22 (2.84–9.58) for CHD; 1.78 (0.96–3.30) and 3.32 (1.86–5.92) for stroke; 2.14 (1.09–4.18) and 3.17 (1.65–6.09) for noncardiovascular mortality; 1.54 (0.55–4.34) and 10.59 (4.56–24.59) for overt nephropathy; and 1.18 (0.58–2.40) and 2.56 (1.37–4.81) for progression of retinopathy.

Table 2 shows the predictive accuracy of the JJ risk engine regarding calibration and discrimination. The O/P ratios for each complication, including noncardiovascular mortality, ranged between 0.93 and 1.08, and Hosmer-Lemeshow tests did not show any significant deviations between the observed and predicted events. In contrast, the UKPDS risk engine (5,6) overestimated CHD risk in Japanese patients (O/P ratios [Hosmer-Lemeshow *P*]: 0.30 [$P < 0.01$] for CHD and 0.72 [$P = 0.54$] for stroke) (Table 2). Discrimination according to C statistics was high for CHD, noncardiovascular mortality, and overt nephropathy (0.696–0.767) but was moderate for stroke and progression of retinopathy (0.636 and 0.614).

Table 3 compares risk classification by the 5-year risk of macrovascular disease based on the JJ risk engine with that based on the UKPDS risk engine. By the UKPDS risk engine, more than half of patients had a macrovascular risk of 10% or more (249 of the 376 cases and 697 of the 1,372 noncases), as expected by the tendency of overestimation The sensitivity and specificity of the UKPDS risk engine with a cutoff value of 10% risk were 66.2 and 49.2%, respectively. In contrast, only 101 of the 376 cases (26.9%) who developed any of the events had a macrovascular risk of 10% or more based on the JJ risk engine, yielding sensitivity of 26.9% and specificity of 89.1%.

Table 4 shows how the combination of 5-year risks of macro- and microvascular complications based on the JJ risk engine classified low-risk and high-risk patients. If we combined macro- and microvascular risks, 73 of 376 cases (19.4%) and 187 of 1,372 noncases (13.6%) were newly classified as a high-risk population, and sensitivity increased up to 46.3% while specificity was maintained at 75.4%. The net reclassification improvement (total of sensitivity and specificity in this case) was improved by 5.7% ($P = 0.02$).

To illustrate the use of the JJ risk engine, consider two Japanese men 60 years of age with simple diabetic retinopathy and without atrial fibrillation who do not have smoking and exercise habits. The clinical characteristics of both patients are HbA_{1c} = 9%, duration of diabetes = 20 years, BMI = 23 kg/m^2, NHDL-C = 3.88 mmol/L, and ACR = 6.79 mg/mmol creatinine. The SBP of one patient is 120 mmHg. His leading risk is estimated to be the progression of retinopathy (5-year risk, 15.5%), and his macrovascular risks are moderate (9.2% for CHD and 9.6% for stroke). His 5-year risks of noncardiovascular death and overt nephropathy are low (4.8 and 3.7%, respectively). The other patient has

Table 2—*Predictive accuracy of the JJ risk engine in 1,748 patients*

	Calibration				Discrimination	
	Mean predicted 5-year risk	Observed 5-year risk	O/P ratio	*P*†	C statistic	95% CI
CHD	2.70%	2.92%	1.08	0.14	0.725	0.656–0.793
By the UKPDS risk engine	(9.66%)	—	(0.30)	(<0.01)	(0.695)	(0.626–0.764)
Stroke	3.36%	3.26%	0.97	0.12	0.636	0.564–0.708
By the UKPDS risk engine	(4.52%)	—	(0.72)	(0.54)	(0.638)	(0.566–0.711)
Noncardiovascular mortality	2.08%	2.12%	1.02	0.12	0.696	0.613–0.778
Overt nephropathy	2.28%	2.40%	1.04	0.11	0.767	0.690–0.845
Progression of retinopathy*	10.96%	10.20%	0.93	0.13	0.614	0.524–0.705

*Patients without diabetes retinopathy at baseline were excluded. †The Hosmer-Lemeshow test with eight degrees of freedom. $P < 0.05$ indicates significant deviation between predicted and observed events.

Table 3—*Risk classification of the 1,748 patients according to 5-year risks of macrovascular disease based on the JJ risk engine and the UKPDS risk engine*

	5-Year risk by the JJ risk engine*						
5-Year risk by the UKPDS risk engine*	<5%		5–10%		10% or more		Total
Patients who developed events							
<5%	37	9.8%	2	0.5%	0	0.0%	39
5–10%	66	17.6%	19	5.1%	3	0.8%	88
10% or more	37	9.8%	114	30.3%	98	26.1%	249
Total	140		135		101		376
Patients who did not develop any events							
<5%	245	17.9%	7	0.5%	0	0.0%	252
5–10%	341	24.9%	78	5.7%	4	0.3%	423
10% or more	202	14.7%	349	25.4%	146	10.6%	697
Total	788		434		150		1,372

*Data are *n* and percent. Probability of any occurrence of CHD or stroke within 5 years.

Table 4—*Risk classification of the 1,748 patients according to 5-year risks of macro- and microvascular diseases based on the JJ risk engine*

5-Year risk of microvascular disease†	5-Year risk of macrovascular disease* <5%		5–10%		10% or more		Total
Patients who developed events							
<5%	79	21.0%	48	12.8%	19	5.1%	146
5–10%	40	10.6%	35	9.3%	20	5.3%	95
10% or more	21	5.6%	52	13.8%	62	16.5%	135
Total	140		135		101		376
Patients who did not develop any events							
<5%	601	43.8%	215	15.7%	40	2.9%	865
5–10%	115	8.4%	104	7.6%	34	2.5%	240
10% or more	72	5.2%	115	8.4%	76	5.5%	267
Total	759		434		150		1,372

*Data are *n* and percent. Probability of any occurrence of CHD or stroke within 5 years. †Probability of any occurrence of overt nephropathy defined by persistent proteinuria or progression of retinopathy within 5 years.

an SBP of 180 mmHg. His leading risks are macrovascular diseases (16.1% for CHD and 17.6% for stroke), and his microvascular risks are moderate (7.8% for nephropathy and 13.6% for retinopathy). The risk of noncardiovascular mortality is estimated to be 4.0%.

CONCLUSIONS—In this study, we developed a novel risk engine that integrates modifiable lifestyle and clinical risk factors, including HbA_{1c}, BMI, SBP, NHDL-C, current smoking, and LTPA into the risks of a first occurrence of macro- and microvascular complications. We confirmed that the risk engine performed reasonably well and that combining macro- and microvascular risks improved the classification of low-risk and high-risk patients by a net reclassification improvement of 5.7%. In contrast, the UKPDS risk engine overestimated CHD risk, and this tendency is consistent with a previous report in Asian patients (18). A web application for the JJ risk engine, which works in both Windows and Macintosh environments, is available at http://www.biostatistics.jp/prediction/jjre.

With the advent of modern therapeutics, especially hypoglycemic and antihypertensive agents, the early identification of high-risk patients is an appealing strategy (35). A novelty of the JJ risk engine is that it allows risk classification based on the risk not only of CVD but also of renal and eye diseases. Although the prevalence of micro- or macroalbuminuria in Asian hypertensive diabetes is alarmingly high (36), most of the progression to overt nephropathy occurs in a small fraction of patients with elevated HbA_{1c} and SBP values and a smoking habit (12). In this study, patients in the fourth quartile of the calculated risk developed overt nephropathy at a rate 10 times greater than those in the first quartile. Most risk engines are specific to CVD; however, greater emphasis on the risk of microvascular diseases should be placed when assessing risk among diabetic patients given that diabetic nephropathy and retinopathy are major causes of ESRD and blindness, respectively. Combining macro- and microvascular risks resulted in the net reclassification improvement of 5.7% ($P = 0.02$) and a sensitivity and specificity of 46.3 and 75.4%, respectively; only 16.5% of cases were classified as the high-risk population for macro- and microvascular diseases and only 43.8% of noncases were in the low-risk population (Table 4). Thus, the discriminatory power of the JJ risk engine was only moderate, despite the statistically significant improvement in prediction, and exploring novel risk factors would be of particular importance for more accurate risk classification.

The JJ risk engine shares features similar to those with previously developed risk engines. The predictors of CHD are the same as in the UKPDS risk engine (5) except for the inclusion of NHDL-C instead of the total cholesterol–to-HDL cholesterol ratio. Donnan et al. (7) added diabetes duration, treated hypertension, height, and two interaction terms into their model, and the risk equation of the HKDR includes diabetes duration, estimated glomerular filtration rate, and ACR additionally but does not use HbA_{1c} (18). A recent cohort study in Japan also suggested that the progression of the albuminuria stage is a risk factor of CVD (37). In contrast, log ACR was not associated with CHD or stroke in our study. This discordant observation would be attributable to the exclusion of low microalbuminuria in our study. The elevation of ACR within a range of normoalbuminuria may not lead to an increase in the risk of CVD. We also found that the UKPDS risk engine overestimated CHD risk (Table 2) and the C statistic of the JJ risk engine (0.725) was slightly higher than that of the risk equation of the HKDR (0.704) (18), indicating that the JJ risk engine may outperform the previously developed risk engines for the prediction of CHD. For the prediction of stroke, we did not identify smoking status and years after diagnosis as predictors, which are included in the UKPDS risk engine (6). The risk equation from the Swedish National Diabetes Register incorporates the use of antihypertensive drugs and lipid-lowering drugs as predictors (9). However, medical therapies are not considered in the current analysis, since the effects of medications on vascular complications were likely to be confounded by other clinical factors. In contrast to CHD, the C statistic of the JJ risk engine (0.636) was similar to the UKPDS risk engine (0.638) and lower than the risk equation of the HKDR (0.749) (17). With regard to lifestyle factors, we identified LTPA as a risk factor for stroke and noncardiovascular mortality, although the statistical significance was borderline. On the other hand, BMI, which has been recognized as one of the most important risk factors in the deterioration of type 2 diabetes, was not associated with CVD. We previously reported that the BMI of Japanese patients is much lower than that of white patients, although in those reports, other patient characteristics were similar in terms of age, HbA_{1c}, and daily energy intake (10,11). Our findings run contrary to the results of studies of white patients, but data on diet in diabetic patients are sparse, particularly in Asia. In this study, the contribution of lifestyle factors to the risk assessment appears to be limited, and the associations between lifestyle and diabetes complications are worthy of further research.

One important feature of this study is that we analyzed pooled data from two nationwide clinical trials in Japan. The end points were defined similarly in both trials and follow-up was performed by diabetes specialists, ensuring data of relatively high quality. Patients generally

had fair or good glycemic, weight, blood pressure, and lipid control. The major difference between the two trials was eligible age, i.e., age between 40 and 70 years in the JDCS and age between 65 and 85 years in the J-EDIT. Prior to pooling the datasets, we compared important clinical factors between patients in the two trials and found no notable differences except for age; therefore, pooling of the datasets was considered to be valid. Consequently, the study population in the present analysis included subjects spanning several decades, i.e., those from 40 to 84 years. This can be expected to enhance the generalizability of the algorithm.

Statistical modeling can be much more complex if we handle multiple events simultaneously. To the best of our knowledge, this is the first study that applies a multistate model to the construction of a risk engine. It is notable that these events are not inherently independent and the JJ risk engine calculates each probability of the first occurrence for five events. Thus, if the risk of an event (e.g., overt nephropathy) was increased by a risk factor (e.g., log ACR), the probability of the first occurrence of other events (e.g., stroke) can decrease theoretically even if there are no direct associations with the risk factor.

Several limitations warrant mention. First, transportability of prognostic information is critical, but in this study we evaluated only the internal validity. Thus, external validation is required in other populations. Second, updating the algorithm by long-term follow-up data or pooled analysis with other studies in Asia is desirable given that the size of our cohort is relatively small and the observed events of CVD and overt nephropathy in this population were relatively few. Third, we included angina pectoris and transient ischemic attack as components of the cardiovascular events, although they are soft end points. Consequently, the JJ risk engine would provide macrovascular risks higher than those by other risk engines based on only hard cardiovascular events. Fourth, data on peripheral arterial disease and hemoglobin levels were not available. These factors were included as inputs into the HKDR all-cause mortality risk score (19), and peripheral arterial disease is a clinically relevant cardiovascular outcome. Fifth, the use of aspirin, which might increase the risk of hemorrhagic stroke, was not investigated. Finally, we defined overt nephropathy as the presence of persistent proteinuria, since an elevated urinary albumin excretion due to nondiabetic renal lesions or conditions is not rare.

In conclusion, the risk engine allowed accurate and comprehensive risk assessment of macro- and microvascular complications, although external validation is required in other populations. The calculated absolute risks of vascular complications can be used in risk classification for individual patients, health economic simulations, and estimation of the burden of the disease.

Acknowledgments—This work was funded by the Ministry of Health, Labour, and Welfare of Japan. The sponsor had no role in the design or conduct of the study.

No potential conflicts of interest relevant to this article were reported.

Sh.T., Sa.T., and Y.O. performed statistical analysis and wrote the manuscript. S.I. managed data. H.Y., S.K., Y.A., N.Y., A.A., H.I., and H.S. planned and conducted the JDCS and the J-EDIT. H.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank the many diabetologists and patients at the 59 participating institutes of the JDCS and 42 participating institutes of the J-EDIT throughout Japan. The authors thank Satomi Fukuya and Yasuko Maruyama (University of Tsukuba Institute of Clinical Medicine) for their excellent secretarial assistance.

References

1. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes Care 2007;30:1292–1293
2. Chamnan P, Simmons RK, Sharp SJ, Griffin SJ, Wareham NJP. Cardiovascular risk assessment scores for people with diabetes: a systematic review. Diabetologia 2009;52:2001–2014
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
4. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 2009;301:2129–2140
5. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671–679
6. Kothari V, Stevens RJ, Adler AI, et al. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke 2002;33:1776–1781
7. Donnan PT, Donnelly L, New JP, Morris AD. Derivation and validation of a prediction score for major coronary heart disease events in a U.K. type 2 diabetic population. Diabetes Care 2006;29:1231–1236
8. Balkau B, Hu G, Qiao Q, Tuomilehto J, Borch-Johnsen K, Pyörälä K; DECODE Study Group; European Diabetes Epidemiology Group. Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor. Diabetologia 2004;47:2118–2128
9. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Nilsson PM, Gudbjörnsdottir S; Swedish National Diabetes Register. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes Care 2008;31:2038–2043
10. Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Complication Study Group. Obesity and type 2 diabetes in Japanese patients. Lancet 2003;361:85
11. Sone H, Yoshimura Y, Ito H, Ohashi Y, Yamada N; Japan Diabetes Complications Study Group. Energy intake and obesity in Japanese patients with type 2 diabetes. Lancet 2004;363:248–249
12. Katayama S, Moriya T, Tanaka S, et al.; Japan Diabetes Complications Study Group. Low transition rate from normo- and low microalbuminuria to proteinuria in Japanese type 2 diabetic individuals: the Japan Diabetes Complications Study (JDCS). Diabetologia 2011;54:1025–1031
13. Kawasaki R, Tanaka S, Tanaka S, et al.; Japan Diabetes Complications Study Group. Incidence and progression of diabetic retinopathy in Japanese adults with type 2 diabetes: 8 year follow-up study of the Japan Diabetes Complications Study (JDCS). Diabetologia 2011;54:2288–2294
14. Sone H, Mizuno S, Yamada N. Vascular risk factors and diabetic neuropathy. N Engl J Med 2005;352:1925–1927; author reply 1925–1927
15. Lee ET, Keen H, Bennett PH, Fuller JH, Lu M. Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: general description and morbidity. Diabetologia 2001;44(Suppl. 2):S3–S13
16. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. JAMA 2002;287:2519–2527
17. Yang X, So WY, Kong AP, et al. Development and validation of stroke risk equation for Hong Kong Chinese patients with type 2 diabetes: the Hong Kong Diabetes Registry. Diabetes Care 2007;30:65–70

18. Yang X, So WY, Kong AP, et al. Development and validation of a total coronary heart disease risk score in type 2 diabetes mellitus. Am J Cardiol 2008;101: 596–601
19. Yang X, So WY, Tong PC, et al.; Hong Kong Diabetes Registry. Development and validation of an all-cause mortality risk score in type 2 diabetes. Arch Intern Med 2008;168:451–457
20. Yang X, Ma RC, So WY, et al. Development and validation of a risk score for hospitalization for heart failure in patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2008;7:9
21. Hu G, Jousilahti P, Barengo NC, Qiao Q, Lakka TA, Tuomilehto J. Physical activity, cardiovascular risk factors, and mortality among Finnish adults with diabetes. Diabetes Care 2005;28:799–805
22. Kokkinos P, Myers J, Nylen E, et al. Exercise capacity and all-cause mortality in African American and Caucasian men with type 2 diabetes. Diabetes Care 2009; 32:623–628
23. Marwick TH, Hordern MD, Miller T, et al.; Council on Clinical Cardiology, American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; Council on Nutrition, Physical Activity, and Metabolism; Interdisciplinary Council on Quality of Care and Outcomes Research. Exercise training for type 2 diabetes mellitus: impact on cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:3244–3262
24. Colberg SR, Sigal RJ, Fernhall B, et al.; American College of Sports Medicine; American Diabetes Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care 2010;33:e147–e167
25. Müller-Riemenschneider F, Holmberg C, Rieckmann N, et al. Barriers to routine risk-score use for healthy primary care patients: survey and qualitative study. Arch Intern Med 2010;170:719–724
26. Sone H, Tanaka S, Iimuro S, et al.; Japan Diabetes Complications Study Group. Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study). Diabetologia 2010;53:419–428
27. Araki A, Iimuro S, Sakurai T, et al.; Japanese Elderly Diabetes Intervention Trial Study Group. Long-term multiple risk factor interventions in Japanese elderly diabetic patients: the Japanese Elderly Diabetes Intervention Trial—study design, baseline characteristics and effects of intervention. Geriatr Gerontol Int 2012; 12(Suppl. 1):7–17
28. Andersen PK, Keiding N. Multi-state models for event history analysis. Stat Methods Med Res 2002;11:91–115
29. The Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of hemoglobin A1c in Japan: from JDS to NGSP values [Internet]. Available from http://www.jds.or.jp/jds_or_jp0/uploads/photos/813.pdf. Accessed 31 January 2012
30. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. Circulation 2003;107:2435–2439
31. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011; 43:1575–1581
32. Sone H, Tanaka S, Tanaka S, et al.; Japan Diabetes Complications Study Group. Serum level of triglycerides is a potent risk factor comparable to LDL cholesterol for coronary heart disease in Japanese patients with type 2 diabetes: subanalysis of the Japan Diabetes Complications Study (JDCS). J Clin Endocrinol Metab 2011;96: 3448–3456
33. Wilkinson CP, Ferris FL 3rd, Klein RE, et al.; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677–1682
34. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27: 157–172; discussion 207–212
35. National Institute for Clinical Excellence. Inherited Clinical Guideline H. Management of type 2 diabetes: management of blood pressure and blood lipids. London: National Institute for Clinical Excellence [article online], 2002. Available from http://www.nice.org.uk/nicemedia/pdf/NICE_INHERITEd_Hv8.pdf. Accessed at 25 April 2011
36. Wu AY, Kong NC, de Leon FA, et al. An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetic patients: the MicroAlbuminuria Prevalence (MAP) Study. Diabetologia 2005;48:17–26
37. Yokoyama H, Araki S, Haneda M, et al.; Japan Diabetes Clinical Data Management Study Group. Chronic kidney disease categories and renal-cardiovascular outcomes in type 2 diabetes without prevalent cardiovascular disease: a prospective cohort study (JDDM25). Diabetologia 2012;55: 1911–1918

Influence of Fat and Carbohydrate Proportions on the Metabolic Profile in Patients With Type 2 Diabetes: A Meta-Analysis

SATORU KODAMA, MD, PHD[1]
KAZUMI SAITO, MD, PHD[1]
SHIRO TANAKA, PHD[2]
MIHO MAKI, MS[1]
YOKO YACHI, RD[1]
MUTSUMI SATO, RD[1]
AYUMI SUGAWARA, RD[1]
KUMIKO TOTSUKA, RD[1]
HITOSHI SHIMANO, MD, PHD[3]
YASUO OHASHI, PHD[2]
NOBUHIRO YAMADA, MD, PHD[3]
HIROHITO SONE, MD, PHD, FACP[1]

OBJECTIVE — The effects of dietary macronutrient composition on metabolic profiles in patients with type 2 diabetes have been inconsistent. This meta-analysis aimed to elucidate the effect of replacing dietary fat with carbohydrate on glucose and lipid parameters in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We searched for randomized trials that investigated the effects of two kinds of prescribed diets (a low-fat, high-carbohydrate [LFHC] diet and a high-fat, low-carbohydrate [HFLC] diet); in these studies, energy and protein intake did not differ significantly between the two dietary groups. Nineteen studies that included 306 patients met our inclusion criteria. Median diet composition of carbohydrate/fat in the LFHC and HFLC diets was 58%/24% and 40%/40%, respectively.

RESULTS — Changes in values for A1C, fasting plasma glucose (FPG), and total and LDL cholesterol did not differ significantly between the LFHC and HFLC groups. However, the LFHC diet significantly increased fasting insulin and triglycerides by 8% ($P = 0.02$) and 13% ($P < 0.001$), respectively, and lowered HDL cholesterol by 6% ($P < 0.001$) compared with the HFLC diet. There were positive associations among the magnitude of changes in FPG, fasting insulin, and triglycerides for the diets analyzed. However, stratified analysis indicated that the increase in triglycerides was insignificant when accompanied by energy intake restriction.

CONCLUSIONS — Our findings suggested that replacing fat with carbohydrate could deteriorate insulin resistance while the adverse effect on triglycerides from the LFHC diet could be avoided by restricting energy intake to a degree sufficient for the attainment of weight reduction.

Diabetes Care 32:959–965, 2009

Medical nutrition therapy (MNT) is the most important aspect of diabetes treatment (1). Optimizing energy intake and macronutrient composition are especially major topics in MNT. Whereas it is well-known that caloric restriction is essential for the achievement of good glycemic and lipid profiles, mainly through weight loss, the optimal dietary macronutrient composition for patients with type 2 diabetes remains controversial.

Since a high-protein diet is not recommended for diabetic patients because of the risk of nephropathy (1), macronutrient composition is mainly regulated by the carbohydrate-to-fat (C/F) ratio. Conventionally, restricting fat intake has been promoted to decrease energy intake and reduce weight (2). However, a low-fat diet, inevitably accompanied by high carbohydrate intake, may increase postprandial plasma glucose, insulin, and triglyceride levels (1). Therefore, the benefit of raising the dietary C/F ratio on metabolic control in type 2 diabetes has not been established. The effects of a low-fat, high-carbohydrate (LFHC) diet or a high-fat, low-carbohydrate (HFLC) diet in which total energy and protein intake are consistent in patients with type 2 diabetes have often been compared. The aim of this meta-analysis is to systematically compare the effects of LFHC and HFLC diets on glucose and lipid control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— We searched MEDLINE (between 1966 and 2007) and the Cochrane Library Central Registry of Controlled Trials (between 1984 and 2007) for relevant publications using the following medical subject heading terms: diabetes and (food or diet). We examined reference lists of those publications to identify additional studies suitable for our purpose. We restricted the search to randomized controlled trials published in English. We searched for studies of the effects of two kinds of prescribed diets differing according to proportions of carbohydrate and fat under conditions that the prescribed total energy and protein intake did not differ significantly between groups of patients with type 2 diabetes. Trials in patients with type 1 diabetes were excluded. We designated one diet as the LFHC diet, which was defined as having a relatively high C/F ratio, and the other as the HFLC diet, which had a relatively low C/F ratio. As shown in detail in Table 1, in examining these studies, we found that the C/F ratio ranged from 0.60 to 1.56 for the HFLC diets and from 1.67 to 7.30 for the LFHC diets.

Among the studies identified, we included only randomized controlled trials with measurements of fasting plasma glucose (FPG) and fasting insulin and intervention periods of ≥1 week. Both parallel-group and crossover designs

From the [1]Department of Lifestyle Medicine and Applied Nutrition, Ochanomizu University, Tokyo, Japan; the [2]Department of Biostatistic, Epidemiology and Preventive Health Sciences, University of Tokyo, Tokyo, Japan; and [3]Endocrinology and Metabolism, University of Tsukuba, Tsukuba, Japan.
Corresponding author: Hirohito Sone, sone.hirohito@ocha.ac.jp.
Received 22 September 2008 and accepted 4 February 2009.
DOI: 10.2337/dc08-1716

Table 1—*Descriptive statistics of studies included in the meta-analysis*

	Intervention period (weeks)	Dropout (%)	LFHC		HFLC		Age (years)	Men (%)	BMI	Using antihyperglycemia agents (%)	Diabetes duration (years)
			n	C/F/P (%)	*n*	C/F/P (%)					
Campbell et al. (1994; ref. 13)	2	N/A	10	55/22/23	10	40/37/23	55	100	26.5	10	5
Chen et al. (1995; ref. 14)	6	N/A	9	55/30/15	9	40/45/15	49	67	27.5	N/A	N/A
Coulston et al. (1989; ref. 15)	6	0	8	60/20/20	8	40/40/20	66	63	25.5	75	N/A
Fuh et al. (1990; ref. 16)	2	N/A	11	60/20/20	11	40/40/20	58	100	25.8	100	N/A
Garg et al. (1992; ref. 17)	3	N/A	8	60/25/15	8	35/50/15	63	100	30	0	N/A
Garg et al. (1994; ref. 18)	6	0	42	55/30/15	42	40/45/15	58	79	28.1	100	N/A
Heilbronn et al. (1999a; ref. 19)	12	17	12	73/10/17	10	50/32/18	58	27	32.9	58	5
Heilbronn et al. (1999b; ref. 19)	12	15	12	73/10/17	13	50/32/18	58	20	33.1	52	6
Lovejoy et al. (2002a; ref. 20)	4	12	30	58/27/15	30	46/39/15	54	43	33	47	N/A
Lovejoy et al. (2002b; ref. 20)	4	12	30	58/27/15	30	46/39/15	54	43	33	47	N/A
Luscombe et al. (1999; ref. 21)	4	25	21	53/21/26	21	42/35/23	57	67	30.4	76	6
Miyashita et al. (2004; ref. 22)	4	N/A	11	63/10/27	11	40/35/25	52	73	27	0	N/A
Parillo et al. (1992; ref. 23)	2	0	10	60/20/20	10	40/40/20	53	70	26.7	50	8
Parillo et al. (1996a; ref. 24)	2	0	9	60/20/20	9	40/40/20	48	N/A	24.7	0	6
Parillo et al. (1996b; ref. 24)	2	0	9	60/20/20	9	40/40/20	50	N/A	24.6	100	8
Rodriguez-Villar et al. (2000; ref. 25)	6	25	12	55/30/15	12	45/40/15	N/A	N/A	27.9	N/A	6
Rodriguez-Villar et al. (2004; ref. 26)	6	15	22	55/30/15	22	45/40/15	61	54	28.3	N/A	N/A
Rusmussen et al. (1994; refs. 27, 28)	3	N/A	15	50/30/20	15	30/50/20	57	67	27	47	6
Sestoft et al. (1985; ref. 29)	1.4	N/A	8	50/30/20	8	42/36/22	48	50	22.7	0	5
Simpson et al. (1982; ref. 30)	4	N/A	10	60/22/18	10	35/47/18	58	N/A	26.2	80	6
Storm et al. (1997a; ref. 31)	3	0	15	50/30/20	15	40/45/15	53	53	29.7	73	6
Storm et al. (1997b; ref. 31)	3	0	15	50/30/20	15	40/45/15	53	53	29.7	73	6
Median	4	6	12	58/24/20	12	40/40/20	55	65	27.7	52	6
Minimum	1.4	0	8		8		48	20	22.7	0	5
Maximum	12	25	42		42		66	100	33.1	100	8

C/F/P, proportion of carbohydrate/fat/protein to total energy of the prescribed diet; N/A, not assessed.

were included. Studies that included an intervention with a change in the content or quality of carbohydrate such as an increase in fiber and whole grains were excluded because such diets are high in fiber, which in itself ameliorates glycemia and lipemia regardless of changes in the C/F ratio (3,4). Studies of very-low-calorie or enteral (not oral) diets and those in which the dosage of hypoglycemic agents was changed during the intervention period were also excluded. One of three reviewers extracted all studies that met the eligibility criteria, and a second reviewed all extracted data. When necessary, disagreement was resolved by discussion with a third author.

Extracted data included features of the study design (i.e., crossover or parallel design and presence of a washout period), intervention periods, characteristics of patients (mean age, BMI, percent men, and percent those using hypoglycemia agents). Other extracted data regarded the characteristics of each diet, such as macronutrient composition; a weight-loss diet, which was defined as caloric restriction resulting in weight reduction; a weight-maintenance diet, which was defined by a weight change of ≤1 kg during the intervention period, and a monounsaturated fat (MUFA) diet within the HFLC-diet group, which was defined as the addition of MUFA to the HFLC diet. We also extracted baseline and final means and statistical dispersions of each group for the following metabolic profiles: A1C, FPG, fasting insulin, total cholesterol, fasting triglycerides, LDL cholesterol, HDL cholesterol, and 2-h postprandial levels of glucose and insulin. If VLDL cholesterol but not triglyceride data were provided, the triglyceride value was calculated by multiplying VLDL cholesterol × 5 according to the Friedewald formula (5). Also, if HbA_1 but not A1C data were provided, A1C was estimated by the relation between HbA_1 and A1C concentrations according to the methodology of Kilpatrick et al. (6). If necessary, measures of means and dispersion were approximated from figures in the articles using an image scanner (CanoScan LiDE 500F [resolution 600 dpi]; Canon, Tokyo, Japan). Study quality was assessed according to the scale described by Jadad et al. (7), with each included trial evaluated according to randomization, double blinding, withdrawals, and dropouts.

The effect on each metabolic profile, which is expressed as the mean difference between LFHC- and HFLC-diet groups in individual studies, was calculated by subtracting the change from baseline to final values in the HFLC-diet group from that in the LFHC-diet group. The SE of the

change from baseline values was directly extracted from the reported data or estimated from the SEs of the baseline and final values in the LFHC- and HFLC-diet groups, assuming a correlation of 0.5 between the baseline and final measures within each group, according to the formula of Follmann et al. (8), as follows:

$$\sqrt{(SE_{baseline})^2 + (SE_{final})^2 - 2 \times 0.5 \times (SE_{baseline}) \times (SE_{final})}$$

We chose the percent change from baseline values because the mean baseline and final values in patients in each study were highly skewed. To estimate percent change, we divided each change from baseline values and its SE by the baseline value. When no baseline value was reported, as in some crossover studies, we summarized the intervention effect by the ratio of the difference in final values between LFHC- and HFLC-diet groups to the final value in the HFLC-diet group and assumed that the baseline SE was equal to the final SE. This method of estimating percent change has limitations, especially in studies without washout periods. Therefore, we performed a sensitivity analysis to examine the effect of these studies on the results.

All percent changes were firstly pooled with a fixed-effects model (9). For each outcome measure, influence analysis was conducted to detect an outlier (i.e., a single estimate with an extreme result), which influenced overall outcome. Study heterogeneity was statistically assessed by Q statistics (9). If heterogeneity was significant, the percent changes were secondarily re-pooled with a random-effects model (9). Publication bias was assessed using two formal methods: Begg's test (10) and Egger's test (11). The trim-and-fill technique (12) was used to investigate the impact of any suggested bias.

We also calculated the weighted mean difference (WMD) in individual trials by multiplying each percent change by the inverse of its SE squared. We ecologically examined the mutual association among each metabolic effect of the LFHC diet compared with the HFLC diet by Spearman's correlation analyses among WMDs.

To investigate the effect of study characteristics, stratified analyses were performed for the following possible confounders: study design (i.e., whether each trial used a crossover design and, if so, whether the trial had a washout period or data on baseline values), intervention period (<4 vs. ≥4 weeks), percent the study of female sex (<50 or ≥50%), mean age (<55 vs. ≥55 years), BMI (<28 vs. ≥28 kg/m^2), percentage using hypoglycemia agents (zero vs. above zero), C/F ratio in the LFHC (>3 vs. ≤3) and HFLC (>1 vs. ≤1) groups, prescription of the MUFA diet (yes vs. no), and prescription of a weight-loss or weight-maintenance diet. We additionally conducted linear multivariable regression analyses to determine whether the characteristics of the patients were independent predictors that influenced the effect of the LFHC diet versus that of the HFLC diet. In this analysis, age, BMI, and the carbohydrate proportion in the LFHC and HFLC diets were entered as continuous variables. A P value of ≤0.05 was considered statistically significant. All analyses were performed with STATA software version 10 (STATA Corporation, College Station, TX).

RESULTS

Descriptive statistics on studies included in the meta-analysis (Table 1)

Of 2,203 potentially relevant publications based on search terms and 22 references obtained from manual searches, 19 (13–31) met the inclusion criteria. Four articles (19,20,24,31) included two trials in one study, and two articles (27,28) used the same cohort. Finally, 22 trials (306 patients) were included in our analyses. Studies included in the current analysis had intervention periods ranging from 10 days to 6 weeks and patient numbers ranging from 8 to 42. Means ± between-study SDs for the mean study characteristics from 22 trials were as follows: age 55 ± 5 years, percent men 63 ± 23, BMI 28 ± 3 kg/m^2, percent using hypoglycemia agents 52 ± 31, and diabetes duration 6 ± 1 years.

Ten studies (15,18–21,23–26,31) described the number of dropouts, and nine (13,14,16,17,22,27–30) did not. The dropout rate ranged from 0 to 25%. None of the 19 articles described methods of randomization, which led to a low quality score for the trial. A crossover design was used in 17 studies (13–18,20,21,23–31) (with 19 trials), whereas a parallel design was used in two studies (19,22) with three trials. Median carbohydrate/fat proportion of total energy (C/F ratio) in the LFHC and HFLC diets was 58%/24% (2.4) and 40%/40% (1.0), respectively. Three studies (19,22,26) with 4 trials prescribed a weight-loss diet, and 11 studies (13,14,17–19,21,23–25,27,28) with 11 trials provided a MUFA diet to the HFLC-diet group.

Overall effects of the LFHC diet compared with those of the HFLC diet on metabolic outcomes and study heterogeneity

Table 2 provides a summary of pooled estimates of various outcome measures. There were no significant differences in the reduction in A1C, total cholesterol, and LDL cholesterol between the LFHC and HFLC diets. However, the LFHC diet produced significant increases in fasting insulin and triglycerides levels of 8.4% (P = 0.02) and 13.4% (P < 0.001), respectively, and a significant reduction in HDL cholesterol compared with that associated with the HFLC diet. Two-h glucose and insulin values were higher in the LFHC-diet group than in the HFLC-diet group by 10.3% (P < 0.001) and 12.8% (P < 0.001), respectively.

Influence analyses indicated that there were a few outliers for percent change in total (22), HDL (22), and LDL (29) cholesterol (see online appendix Tables A1 and A2, available at http://care.diabetesjournals.org/cgi/content/full/dc08-1716/DC1). When these trials were omitted from the analyses, percent change in total cholesterol, HDL cholesterol, and LDL cholesterol significantly changed from −0.0% (95% CI −2.1 to 2.0) to −1.6% (−4.5 to 1.3; P = 0.03), from −10.4% (−12.2 to −8.6) to −5.6% (−2.9 to −8.4; P < 0.001), and from −3.0% (−6.3 to 0.4) to −0.1% (−4.1 to 3.8; P = 0.001), respectively. These outlying trials comprised a large part of study heterogeneity in percent change in total, HDL, and LDL cholesterol (22.2, 59.1, and 53.0%, respectively.) Therefore, they were excluded from the following analyses for the outcome that they affected. After omission of these outliers, there was no evidence of significant study heterogeneity (P > 0.4 for all outcomes).

Relationships among the magnitude of effects on metabolic profiles

Ecological analyses showed trends indicating that the WMD in FPG was positively associated with that in fasting insulin (r = 0.45; P = 0.04) and triglycerides (r = 0.59; P = 0.004) and that the WMD in fasting insulin and triglycerides was mutually associated (r = 0.43; P = 0.04). These associations remained signif-

Table 2—*Overall percent changes resulting from LFHC versus HFLC diet on metabolic profiles and data on publication bias and their likely effect on the estimates*

	A1C	FPG	2-h glucose	Fasting insulin	2-h fasting insulin	Total cholesterol	Triglycerides	HDL cholesterol	LDL cholesterol
Trials (*n*)	10	22	10	22	9	20	22	20	16
Overall percent change	−1.5	0.3	10.3	8.4	12.8	1.6	13.4	−5.6	0.1
95% CI	−5.3 to 2.3	−2.8 to 3.4	6.7–13.9	1.3–15.6	5.2–20.4	−1.3 to 4.5	7.1–19.8	−8.4 to −2.9	−3.8 to 4.1
P	0.70	0.87	<0.001	0.02	<0.001	0.27	<0.001	<0.001	0.94
Publication bias									
Begg's	0.80	0.82	0.25	0.30	0.40	0.85	0.48	0.75	0.86
Egger's	0.47	0.30	0.12	0.13	0.16	0.26	0.75	0.08	0.92
Trim and fill									
Fill*								7	
Adjusted†								−7.6	
95% CI								−10.2 to −5.0	

*Studies (*n*) added by the trim-and-fill method. †Percent change after adjustment for publication bias by the trim-and-fill method. Begg's, Begg's adjusted rank correlation test; Egger's, Egger's regression asymmetry test.

icant after adjustment for whether a weight-loss diet was prescribed (FPG vs. fasting insulin, $r = 0.58$ and $P = 0.004$; FPG vs. triglycerides, $r = 0.44$ and $P = 0.04$; and fasting insulin vs. triglycerides, $r = 0.44$ and $P = 0.04$).

Test of publication bias

Table 2 also shows data on publication bias and its likely effect on estimates of outcome according to the trim-and-fill method (12). There was a relatively strong suspicion of publication bias for HDL cholesterol (Egger's test, $P = 0.08$ for HDL cholesterol; recommended level of significance, $P \leq 0.10$ [32]). According to results of the compensatory trim-and-fill method, the effect of publication bias would slightly underestimate the adverse effect of the LFHC diet.

Sensitivity analysis

Results of our stratified analysis to detect characteristics of studies and patients included in our analyses that might have modulated study outcomes are shown in Table 3. Of the 17 studies with a crossover design, 9 with 10 trials (14–16,21,23–26,29) did not include a washout period, which could lead to an underestimation due to a carryover effect (33). Moreover, none of these studies had baseline data. However, the effect of these nine studies on results was not significant for any of the measures.

The elevation in fasting insulin was remarkable (17.1%; $P = 0.001$) in LFHC diets with a C/F ratio ≥3 (in this case, an LFHC diet with ≥60% carbohydrate and ≤20% fat of total energy) while the C/F ratio in the LFHC diet did not influence triglycerides. There was a greater elevation in triglycerides (21.0%; $P<0.001$) with the LFHC diet when the LFHC diet and MUFA diet were compared; i.e., MUFA was replaced with carbohydrate. However, the magnitude of the elevation in fasting insulin did not differ between the MUFA diet and non-MUFA diet (i.e., regardless of dietary fat quality). Whereas a larger elevation in triglycerides was observed in trials limited to weight-maintenance diets, the LFHC diet did not significantly elevate triglycerides compared with the HFLC diet when only trials with weight-loss diets were examined (i.e., diets for weight loss) ($P = 0.48$).

The elevation in fasting insulin was greater in younger and leaner patients in response to the LFHC diet compared with that in response to the HFLC diet. Moreover, mean age and BMI were independent predictors of percent change in fasting insulin. Multiple regression analysis indicated that every −1 kg/m^2 of BMI and −1 year of age were independently associated with a greater elevation in fasting insulin by 2.6% ($P = 0.002$) and 1.7% ($P = 0.005$), respectively. For patients not taking antihyperglycemic drugs, the LFHC diet could be more harmful for fasting insulin than the HFLC diet. However, because only a few studies included patients not receiving antihyperglycemic drugs, the results should perhaps be interpreted with caution.

CONCLUSIONS — Although central to MNT, the influences of various dietary C/F ratios on glycemic control and lipid profiles in patients with type 2 diabetes have not been systematically reviewed. Our meta-analysis is the first to quantify the effect of the LFHC diet compared with that of the HFLC diet on each metabolic outcome.

Our results fundamentally support current dietary guidelines (1) stating that replacing fat with carbohydrate significantly elevates postprandial glucose and insulin levels when total energy intake is consistent. We additionally found that the LFHC diet significantly elevated fasting insulin compared with the HFLC diet, with marked elevations noted when the C/F ratio was ≥3. Moreover, there were significantly positive relationships among the change in FPG and the magnitude of the elevation in fasting insulin and triglycerides, independent of energy restriction for weight control.

Postprandial hyperglycemia with postprandial hyperinsulinemia and failure to maintain glucose homeostasis are often clustered in insulin-resistant individuals, who are representative of those with type 2 diabetes (34). This suggests that an LFHC diet is unfavorable compared with an HFLC diet for insulin-resistant patients, at least when energy intake is consistent. However, our findings do not support the benefit of an extremely high-fat diet because the carbohydrate proportion in the HFLC diets included in our analyses was ≤50%. Moreover, we cannot comment on the possible benefit of a high-carbohydrate diet with a high-fiber component because we excluded studies investigating the effect of such a diet. Moreover, there is concern that increased fat intake ad libitum may promote weight gain (35). It is worth repeating that total caloric intake and nu-

Table 3—*Stratified analysis to examine the effects of characteristics of studies and patients on each metabolic profile*

	FPG		Fasting insulin		Triglycerides		Total cholesterol		HDL cholesterol		LDL cholesterol	
	N	Percent change (95% CI)	*N*	Percent change (95% CI)	*N*	Percent change (95% CI)	*N*	Percent change (95% CI)	*N*	Percent change (95% CI)	*N*	Percent change (95% CI)
Study with washout period or baseline data												
Neither*	10	0.9 (−4.6 to 6.3)	10	9.0 (−1.7 to 19.7)	10	18.2 (7.3–29.1)	9	0.7 (−4.2 to 5.5)	9	−6.8 (−10.3 to −3.2)	5	−0.7 (−8 to 6.6)
Others†	12	0.0 (−3.8 to 3.7)	12	8.0 (−1.6 to 17.6)		11.0 (3.2–18.8)	11	2.2 (−1.5 to 5.8)	11	−4.0 (−8.2 to 0.3)	11	0.5 (−4.2 to 5.1)
Period <4 weeks	10	1.3 (−2.9 to 5.5)	10	15.2 (3.1–27.3)	10	15.8 (4.9–26.6)	10	1.7 (−3 to 6.4)	10	−7.3 (−10.9 to −3.6)	6	0.8 (−7.5 to 9.1)
Period ≥4 weeks	12	−1 (−5.5 to 3.6)	12	4.9 (−3.9 to 13.7)	12	12.2 (4.4–20)	10	1.6 (−2.1 to 5.3)	10	−3.6 (−7.7 to 0.6)	10	0.0 (−4.5 to 4.4)
<50% of subjects female	13	0.4 (−3.3 to 4.1)	13	6.2 (−3.4 to 15.9)	13	13.7 (5.8–21.6)	11	2 (−1.8 to 5.9)	11	−3.4 (−8.1 to 1.2)	10	0.6 (−4.6 to 5.8)
≥50% of subjects female	5	1.6 (−4.6 to 7.8)	5	11.5 (−0.1 to 23.2)	5	15.1 (2.8–27.3)	5	1.8 (−3.8 to 7.4)	5	−7.4 (−11 to −3.7)	4	−0.5 (−7 to 6.1)
Mean age <55 years	10	−0.2 (−4.1 to 3.7)	10	17.2 (6.7–27.8)‡	10	12.7 (4.6–20.8)	8	1.2 (−3.9 to 6.2)	8	−5.8 (−9.2 to −2.4)	4	−0.6 (−7.5 to 6.3)
Mean age ≥55 years	11	1.2 (−3.9 to 6.4)	11	1.7 (−8.2 to 11.7)‡	11	15.1 (4.5–25.7)	11	1.9 (−1.7 to 5.5)	11	−5.6 (−10.3 to −0.8)	11	0.7 (−4.2 to 5.5)
BMI <28.0 kg/m^2	12	1.9 (−2.8 to 6.6)	12	18.2 (7.6–28.8)‡	12	12.5 (4.6–20.4)	10	1.2 (−3.5 to 5.8)	10	−7.8 (−11.6 to −4.1)	6	−0.9 (−8.6 to 6.9)
BMI ≥28.0 kg/m^2	10	−1 (−5.1 to 3.1)	10	0.3 (−9.4 to 9.9)‡	10	15.1 (4.6–25.7)	10	1.9 (−1.8 to 5.6)	10	−3.1 (−7.1 to 0.9)	10	0.5 (−4.1 to 5)
Taking hypoglycemic agents	18	−0.6 (−4.1 to 2.9)	18	4.4 (−3.8 to 12.7)§	18	15.4 (6.9–23.8)	17	1.5 (−1.5 to 4.6)	17	−3.1 (−6.6 to 0.4)	15	0.1 (−3.8 to 4.1)
Not taking hypoglycemic agents	4	2.9 (−3.3 to 9.1)	4	20.7 (6.3–35.1)§	4	10.9 (1.4–20.5)	3	2.6 (−6.7 to 11.8)	3	−9.4 (−13.7 to −5.1)	1	0 (−31.8 to 31.8)
C/F ratio in LFHC ≥3	8	0.5 (−5.5 to 6.5)	8	17.1 (5.7–28.6)§	8	9.3 (−0.9 to 19.4)	7	−0.1 (−5.4 to 5.1)	7	−4.6 (−10.9 to 1.6)	4	−3.1 (−11.4 to 5.2)
C/F ratio in LFHC <3	14	0.2 (−3.4 to 3.8)	14	2.9 (−6.2 to 12.1)§	14	16 (8–24.1)	13	2.4 (−1.1 to 5.9)	13	−5.9 (−8.9 to −2.8)	12	1.1 (−3.4 to 5.5)
C/F ratio in HFLC ≤1	12	0.2 (−3.8 to 4.2)	12	8.1 (−4 to 20.2)	12	18.7 (8.3–29.1)	11	1.2 (−2.7 to 5)	11	−4.2 (−9.1 to 0.6)	8	−0.6 (−6.4 to 5.2)
C/F ratio in HFLC >1	10	0.4 (−4.5 to 5.2)	10	8.6 (−0.2 to 17.5)	10	10.4 (2.4–18.3)	9	2.2 (−2.2 to 6.6)	9	−6.3 (−9.6 to −3)	8	0.8 (−4.5 to 6.1)
MUFA diet in HFLC diet	11	1.9 (−3.9 to 7.7)	11	5.2 (−4.9 to 15.2)	11	21.0 (10.2–31.7)§	10	3.1 (−1.1 to 7.2)	10	−4.3 (−9.4 to 0.8)	7	2.8 (−3.4 to 8.9)
No MUFA diet in HFLC diet	11	−0.4 (−4.0 to 3.3)	11	11.8 (1.7–22)	11	9.4 (1.6–17.2)§	10	0.2 (−3.8 to 4.3)	10	−6.2 (−9.4 to −3)	9	−1.6 (−6.7 to 3.4)
WL diet in LFHC and HFLC diets	4	−2.1 (−9.6 to 5.5)	4	12.5 (−1 to 25.9)	4	4.0 (−7.1 to 15.2)‡	3	1.3 (−6 to 8.5)	3	−3.9 (−12.4 to 4.6)	3	1.9 (−7.4 to 11.2)
No WL diet in LFHC and HFLC diets	18	0.7 (−2.7 to 4.1)	18	6.9 (−1.5 to 15.3)	18	17.9 (10.2–25.5)‡	17	1.7 (−1.5 to 4.9)	17	−5.8 (−8.7 to −3)	13	−0.2 (−4.6 to 4.1)

*Studies having neither a washout period nor baseline data. †Parallel study design or cross-sectional design studies that have a washout period and/or baseline data. ‡$P < 0.01$; §$P < 0.05$. WL diet, energy intake restricted for weight loss.

tritional content must be appropriate for metabolic control regardless of macronutrient proportions (1).

Changes in FPG and A1C did not differ between the two diets despite significant elevations in 2-h and fasting insulin with the LFHC diet. One possible explanation is that the elevation in postprandial glucose level was overcompensated for by increased insulin secretion. However, only three studies concurrently assessed A1C, fasting insulin, and FPG values, with an intervention period of, at most, 6 weeks. Therefore, we could not conclude whether the elevation in postprandial glucose and insulin level achieved by raising the dietary C/F ratio leads to the deterioration of glycemic control represented by elevations in FPG and A1C.

A previous meta-analysis suggested that replacing carbohydrate with MUFA reduced fasting triglycerides in patients with type 2 diabetes on weight-maintenance diets (36); this was supported by our results. However, it is uncertain whether the effect on triglycerides was caused by the C/F ratio or the ratio of energy from MUFA to total energy. Moreover, whether the effect of this replacement was independent of that of a weight-loss diet has not been investigated. According to our stratified analyses, no dose-response relationship between the C/F ratio in the LFHC diet and the elevation in triglycerides was indicated, although replacement of the MUFA diet with the LFHC diet induced a greater elevation in triglycerides. Moreover, the LFHC diet did not significantly elevate triglycerides compared with the HFLC diet when a weight-loss diet was prescribed. Therefore, controlling total caloric intake and the quality of dietary fat appear to be more important than carbohydrate and fat composition in improving triglycerides levels. In other words, these findings suggest that a high-carbohydrate diet has little harmful effect on triglycerides levels if such a diet provides sufficient energy restriction for weight control.

Our study has some limitations. First, although we omitted studies investigating the effect of high-carbohydrate diets that were also high in dietary fiber, it is possible that the additional phytochemicals (including fiber itself), which are inevitably accompanied by a substantial amount of carbohydrate, influence the metabolic effects regardless of the change in C/F ratio. Second, we assumed that energy intake from the two diet groups would be similar if a weight-maintenance diet was equal to an isocaloric diet based on evidence of the meta-analysis by Bravata et al. (37) that indicated that weight change was associated with restriction of caloric intake but not reduced carbohydrate content. However, some recent studies showed that low-carbohydrate diets resulted in greater weight loss than low-fat diets despite their similar energy content (38), as is often the case with high-fiber diets (e.g., whole grains) (39). More investigation is needed to determine whether the relationship between change in energy intake and body weight is independent of the proportions of dietary carbohydrate and fat. Third, few studies investigated long-term effects (e.g., >2 months) of changing the proportions of carbohydrate and fat on metabolic profiles in patients with type 2 diabetes. Actually, a larger elevation in fasting insulin in association with the LFHC diet was observed for an intervention period of <4 weeks compared with ≥4 weeks but without statistical significance ($P = 0.10$). Possibly, a prolonged intervention involving changes in macronutrient composition causes some adaptation of insulin metabolism. Fourth, most studies provided insufficient data about baseline glucose and lipid levels, and few focused on black or Asian patients. Therefore, the current meta-analysis provides limited suggestions on identifying patients for whom a low-fat or low-carbohydrate diet is especially effective in terms of their circumstances or metabolic profiles (1).

Future studies focused on the following are suggested: *1*) providing a possible explanation for the greater adverse effect on the fasting insulin by the LFHC diet than by the HFLC diet, especially in younger and leaner individuals; 2) identifying the long-term effect of a low-carbohydrate diet on factors other than metabolic effects (e.g., adaptation in glucose and lipid metabolism, ad libitum energy intake in patients with type 2 diabetes or obesity [40]) and the safety of such a diet (e.g., with regard to the digestive system); and *3*) addressing whether a subject's medication status and the characteristics of diabetes drugs could influence the effect of changing the dietary C/F ratio in patients with type 2 diabetes.

In conclusion, replacement of dietary fat with carbohydrate is not recommended for improvement of insulin resistance in patients with type 2 diabetes under conditions whereby total energy and protein intake and the content of carbohydrate are similar and the proportion of carbohydrate to total energy is ≥30%. We found that younger and leaner patients had higher fasting insulin responses with the LFHC diet, although the biological mechanism was not fully investigated. The LFHC diet also adversely affects triglycerides and HDL cholesterol compared with the HFLC diet. However, energy restriction and dietary fat quality seemed more important for lowering the triglyceride concentration than the proportion of carbohydrate and fat.

Acknowledgments— This work was financially supported by the Japan Society for the Promotion of Science and Japan Cardiovascular Research Foundation.

No potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in abstract form at the American Diabetes Association 68th Scientific Sessions, San Francisco, California, 6–10 June 2008.

References

1. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care 2008;31 (Suppl. 1):S61–S78
2. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, Kahn SE, Knowler WC, Yanovski SZ. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials 2003;24:610–628
3. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ, Wheeler M. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care 2002;25:148–198
4. Brand-Miller J, Hayne S, Petocz P, Colagiuri S. Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. Diabetes Care 2003;26:2261–2267
5. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502
6. Kilpatrick ES, Rumley AG, Dominiczak MH, Small M. Glycated haemoglobin values: problems in assessing blood glucose control in diabetes mellitus. BMJ 1994; 309:983–986
7. Jadad AR, Moore RA, Carroll D, Jenkinson

C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12
8. Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. J Clin Epidemiol 1992;45:769–773
9. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7: 177–188
10. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50: 1088–1101
11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–634
12. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–463
13. Campbell LV, Marmot PE, Dyer JA, Borkman M, Storlien LH. The high-monounsaturated fat diet as a practical alternative for NIDDM. Diabetes Care 1994;17:177–182
14. Chen YD, Coulston AM, Zhou MY, Hollenbeck CB, Reaven GM. Why do low-fat high-carbohydrate diets accentuate postprandial lipemia in patients with NIDDM? Diabetes Care 1995;18:10–16
15. Coulston AM, Hollenbeck CB, Swislocki AL, Reaven GM. Persistence of hypertriglyceridemic effect of low-fat high-carbohydrate diets in NIDDM patients. Diabetes Care 1989;12:94–101
16. Fuh MM, Lee MM, Jeng CY, Ma F, Chen YD, Reaven GM. Effect of low fat-high carbohydrate diets in hypertensive patients with non-insulin-dependent diabetes mellitus. Am J Hypertens 1990;3:527–532
17. Garg A, Grundy SM, Unger RH. Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM. Diabetes 1992;41:1278–1285
18. Garg A, Bantle JP, Henry RR, Coulston AM, Griver KA, Raatz SK, Brinkley L, Chen YD, Grundy SM, Huet BA, Reaven GM. Effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus. JAMA 1994; 271:1421–1428
19. Heilbronn LK, Noakes M, Clifton PM. Effect of energy restriction, weight loss, and diet composition on plasma lipids and glucose in patients with type 2 diabetes. Diabetes Care 1999;22:889–895
20. Lovejoy JC, Most MM, Lefevre M, Greenway FL, Rood JC. Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. Am J Clin Nutr 2002;76:1000–1006
21. Luscombe ND, Noakes M, Clifton PM. Diets high and low in glycemic index versus high monounsaturated fat diets: effects on glucose and lipid metabolism in NIDDM. Eur J Clin Nutr 1999;53:473–478
22. Miyashita Y, Koide N, Ohtsuka M, Ozaki H, Itoh Y, Oyama T, Uetake T, Ariga K, Shirai K. Beneficial effect of low carbohydrate in low calorie diets on visceral fat reduction in type 2 diabetic patients with obesity. Diabetes Res Clin Pract 2004;65: 235–241
23. Parillo M, Rivellese AA, Ciardullo AV, Capaldo B, Giacco A, Genovese S, Riccardi G. A high-monounsaturated-fat/low-carbohydrate diet improves peripheral insulin sensitivity in non-insulin-dependent diabetic patients. Metabolism 1992;41: 1373–1378
24. Parillo M, Giacco R, Ciardullo AV, Rivellese AA, Riccardi G. Does a high-carbohydrate diet have different effects in NIDDM patients treated with diet alone or hypoglycemic drugs? Diabetes Care 1996; 19:498–500
25. Rodriguez-Villar C, Manzanares JM, Casals E, Perez-Heras A, Zambon D, Gomis R, Ros E. High-monounsaturated fat, olive oil-rich diet has effects similar to a high-carbohydrate diet on fasting and postprandial state and metabolic profiles of patients with type 2 diabetes. Metabolism 2000;49:1511–1517
26. Rodriguez-Villar C, Perez-Heras A, Mercade I, Casals E, Ros E. Comparison of a high-carbohydrate and a high-monounsaturated fat, olive oil-rich diet on the susceptibility of LDL cholesterol to oxidative modification in subjects with type 2 diabetes mellitus. Diabet Med 2004;21:142–149
27. Rasmussen OW, Thomsen C, Hansen KW, Vesterlund M, Winther E, Hermansen K. Effects on blood pressure, glucose, and lipid levels of a high-monounsaturated fat diet compared with a high-carbohydrate diet in NIDDM subjects. Diabetes Care 1993;16:1565–1571
28. Rasmussen O, Thomsen C, Ingerslev J, Hermansen K. Decrease in von Willebrand factor levels after a high-monounsaturated-fat diet in non-insulin-dependent diabetic subjects. Metabolism 1994;43:1406–1409
29. Sestoft L, Krarup T, Palmvig B, Meinertz H, Faergeman O. High-carbohydrate, low-fat diet: effect on lipid and carbohydrate metabolism, GIP and insulin secretion in diabetics. Dan Med Bull 1985;32: 64–69
30. Simpson HC, Carter RD, Lousley S, Mann JI. Digestible carbohydrate–an independent effect on diabetic control in type 2 (non-insulin-dependent) diabetic patients? Diabetologia 1982;23:235–239
31. Storm H, Thomsen C, Pedersen E, Rasmussen O, Christiansen C, Hermansen K. Comparison of a carbohydrate-rich diet and diets rich in stearic or palmitic acid in NIDDM patients: effects on lipids, glycemic control, and diurnal blood pressure. Diabetes Care 1997;20:1807–1813
32. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53: 1119–1129
33. Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials. III. The issue of carry-over. Stat Med 2002;21:2161–2173
34. Reaven GM. Banting lecture 1988: role of insulin resistance in human disease. Diabetes 1988;37:1595–1607
35. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ, Wheeler M. Nutrition principles and recommendations in diabetes (Position Statement). Diabetes Care 2004;27 (Suppl. 1):S36–S46
36. Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. Am J Clin Nutr 1998;67: 577S–582S
37. Bravata DM, Sanders L, Huang J, Krumholz HM, Olkin I, Gardner CD, Bravata DM. Efficacy and safety of low-carbohydrate diets: a systematic review. JAMA 2003;289:1837–1850
38. Brehm BJ, D'Alessio DA. Weight loss and metabolic benefits with diets of varying fat and carbohydrate content: separating the wheat from the chaff. Nat Clin Pract Endocrinol Metab 2008;4:140–146
39. Ello-Martin JA, Roe LS, Ledikwe JH, Beach AM, Rolls BJ. Dietary energy density in the treatment of obesity: a year-long trial comparing 2 weight-loss diets. Am J Clin Nutr 2007;85:1465–1477
40. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thiery J, Fiedler GM, Bluher M, Stumvoll M, Stampfer MJ. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359: 229–241

Association Between Physical Activity and Risk of All-Cause Mortality and Cardiovascular Disease in Patients With Diabetes

A meta-analysis

SATORU KODAMA, MD, PHD[1,2]
SHIRO TANAKA, PHD[3]
YORIKO HEIANZA, RD, MS[2]
KAZUYA FUJIHARA, MD[4]
CHIKA HORIKAWA, RD, MS[2]
HITOSHI SHIMANO, MD, PHD[4]
KAZUMI SAITO, MD, PHD[4]
NOBUHIRO YAMADA, MD, PHD[4]
YASUO OHASHI, PHD[5]
HIROHITO SONE, MD, PHD, FACP[2]

OBJECTIVE—The association between habitual physical activity (PA) and lowered risk of all-cause mortality (ACM) and cardiovascular disease (CVD) has been suggested in patients with diabetes. This meta-analysis summarizes the risk reduction in relation to PA, focusing on clarifying dose-response associations.

RESEARCH DESIGN AND METHODS—Electronic literature searches were conducted for cohort studies that examined relative risk (RR) of ACM or CVD in relation to PA in patients with diabetes. For the qualitative assessment, RR for the highest versus the lowest PA category in each study was pooled with a random-effects model. We added linear and spline regression analyses to assess the quantitative relationship between increases in PA and ACM and CVD risk.

RESULTS—There were 17 eligible studies. Qualitatively, the highest PA category had a lower RR [95% CI] for ACM (0.61 [0.52–0.70]) and CVD (0.71 [0.60–0.84]) than the lowest PA category. The linear regression model indicated a high goodness of fit for the risk of ACM (adjusted R^2 = 0.44, P = 0.001) and CVD (adjusted R^2 = 0.51, P = 0.001), with the result that a 1 MET-h/day incrementally higher PA was associated with 9.5% (5.0–13.8%) and 7.9% (4.3–11.4%) reductions in ACM and CVD risk, respectively. The spline regression model was not significantly different from the linear model in goodness of fit (P = 0.14 for ACM risk; P = 0.60 for CVD risk).

CONCLUSIONS—More PA was associated with a larger reduction in future ACM and CVD risk in patients with diabetes. Nevertheless, any amount of habitual PA was better than inactivity.

Diabetes Care 36:471–479, 2013

Persons with diabetes have a 50–60% higher risk of all-cause mortality (ACM) and cardiovascular death than those without diabetes, and cardiovascular disease (CVD) remains the primary cause of death in the U.S. among diabetic patients (1). Lifestyle modification, which mainly focuses on controlling energy intake and increasing daily physical activity (PA), is a major component of programs to reduce cardiovascular risk factors that coexist with diabetes in addition to pharmacologic approaches (2).

Results of lifestyle alterations in controlled settings, in particular exercise interventions, have not yet been replicated in primary care settings or in actual daily life, as only a few studies have indicated that such interventions have contributed to reductions in incident CVD (3,4). In addition, implementing supervised exercise therapy often may be difficult due to the perceived high cost per patient and the amount of time necessary per patient for each session (5). Therefore, exercise therapy is inevitably limited to merely general recommendations rather than interventions supervised by practitioners. Quantitative evidence for PA-related benefits is essential for practitioners to prescribe self-management goals of a specific PA volume for patients with diabetes and to motivate patients to maintain adherence to this prescription. The aim of this meta-analysis is to clarify the relationship between habitual PA and future ACM or incident CVD in patients with diabetes, focusing on the dose-response association.

RESEARCH DESIGN AND METHODS

Search strategy

We conducted electronic literature searches (MEDLINE, 1950–2011 September; EMBASE, 1974–2011 September) for cohort studies that investigated the relationship between PA and ACM/CVD risk, where study keywords were thesaurus terms registered in MEDLINE (MeSH) or EMBASE (EMTREE) and text words related to diabetes, PA, ACM/CVD, and text words related to cohort studies. These key concepts were combined using the Boolean operator "and." Details of the keywords are shown in Supplementary Table 1. Reference lists from the identified articles were manually examined for

From the [1]Department of Health Management Center, Mito Kyodo General Hospital, Mito City, Japan; the [2]Department of Internal Medicine, Niigata University Faculty of Medicine, Niigata, Japan; the [3]Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital, Kyoto, Japan; the [4]Department of Internal Medicine, University of Tsukuba Institute of Clinical Medicine, Tsukuba, Japan; and the [5]Department of Biostatistics, Epidemiology and Preventive Health Sciences, University of Tokyo, Tokyo, Japan.
Corresponding author: Hirohito Sone, hsone@md.tsukuba.ac.jp.
Received 24 April 2012 and accepted 13 August 2012.
DOI: 10.2337/dc12-0783
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0783/-/DC1.

relevant articles. No language restriction was imposed.

Inclusion criteria

The initial inclusion criteria were as follows *1*) prospective or retrospective cohort study without exercise intervention; *2*) all subjects had diabetes; *3*) ACM or CVD was an independent study end point; and *4*) the effect measure (i.e., relative risk [RR] or odds ratio [OR]) and its corresponding SE for high PA categories compared with the lowest PA category in each study were provided or could be calculated.

Studies that included coronary heart disease (CHD) but that did not include stroke as an end point were also included because CHD represents the greatest portion of CVDs. If a study separately assessed CHD and stroke risk in relation to PA, we gave priority to data on CHD risk. We also included studies if they considered fatal CVD but did not include nonfatal CVD as an end point. However, if the risk of CVD death and a CVD event were separately investigated, priority was given to the CVD event because a CVD event, which includes both fatal and nonfatal outcomes, is a broader concept. Similarly, priority was given to CVD risk if a study separately investigated both CVD and CHD risk.

Any type of PA was considered. However, we selected the data on the wider spectrum of PA if a study separately investigated two or more types of PA (e.g., total PA and leisure-time PA [LTPA], LTPA and walking, etc.).

Data extraction

Two authors (S.K. and H.So.) independently extracted key study characteristics. Disagreement was solved by discussion. The effect measure in each study was extracted or, if not directly provided, calculated based on data on the number of cases and noncases in referent (i.e., lowest PA category) and nonreferent (i.e., other PA categories) groups. We considered the OR as an indicator of RR based on the assumption that the OR is an approximation of the RR, although this assumption has some limitations (6). If a study provided several effect measures, such as unadjusted and adjusted effect measures, the most completely adjusted effect measure was used.

For assessment of study quality, we selected the five relevant items, which were formed as questions, from the 16 components in the study quality assessment guidelines proposed by Powell et al. (7) and modified them as follows *1*) Is the instrument for measuring PA validated? *2*) Does PA allow quantification? *3*) Were the outcomes determined by the specified criteria when the patient's medical record was considered to have information on the specific outcome for that patient while other sources of information such as registries for study outcomes, death certificates, or the patient's self-report did not? *4*) Was the adjustment for the confounders sufficient when "sufficient adjustment" was defined as considering the following five classic cardiovascular risk factors: age, sex, smoking, dyslipidemia (or LDL/total cholesterol level), and hypertension? and *5*) Were subjects that were lost to follow-up excluded from the analysis?

Data synthesis

We conducted separate meta-analyses for ACM and CVD risk, but types of PA were not separately analyzed. Generally, the SE is provided for a logarithm of each risk measure (log RR) rather than the risk measure itself. Therefore, log RR was used as an expression of the effect size (i.e., strength of the association). The SE was calculated from the CI or, if not provided, was calculated by the following formula:

$$SE^2 = [\frac{1}{C_1} + \frac{1}{N_1}] + [\frac{1}{C_0} + \frac{1}{N_0}]$$

where C_0 and N_0 indicate the number of cases and noncases in the referent group, respectively, and C_1 and N_1 indicate the number of cases and noncases in the nonreferent group, respectively.

For qualitative assessment of PA benefit for ACM and CVD risk, the log RR for the highest versus the lowest PA category in each study was pooled with an inverse variance method. The pooled RR was calculated by an exponentiation of the pooled log RR. Study heterogeneity was assessed by Q statistics or I^2 overall and within each strata after the stratification (8). The pooled estimate was based on a random-effects model if the between-study heterogeneity was statistically significant; otherwise it was based on a fixed-effects model (9).

Stratified analyses were conducted on the following study characteristics that we identified on the basis of previously extracted data from the included studies: study outcome (CVD/CHD only, fatal only/both fatal and nonfatal), country (U.S./non-U.S.), mean age (<60 years/≥60 years) (the cut-off value was a priori determined because it approximated the median of the mean age in each included study in this meta-analysis), proportion of men (≥50%/<50%), mean BMI (<27.8 kg/m^2 [in men], <27.3 kg/m^2 [in women], <27.5 [in men and women combined]/≥27.8 kg/m^2 [in men], ≥27.3 kg/m^2 [in women], ≥27.5 [in men and women combined]/not available) (10), validation of PA questionnaire (no/yes), number of PA categories (≥3/<3 [i.e., dichotomized]), PA type (total PA/LTPA/walking), PA quantification (no/yes), methods for ascertainment of outcome (self-report or questionnaire/registry/medical record/combined), mean follow-up duration (≥10 years/<10 years), presence of lost to follow-up (no/yes), and sufficient adjustment for classic risk factors (no/yes). Meta-regression analysis was used to test the differences in RR among strata in the stratified analysis.

Publication bias was primarily based on visual assessment using a funnel plot, where the SE of log RR for the highest versus the lowest PA category in each study was plotted against the log RR, where it was assumed that if there was no publication bias the plot would be symmetrical. Secondarily, goodness of symmetry was confirmed by statistical assessment using two formal methods, Begg rank correlation test and Egger regression asymmetry test (11,12). For statistically suspected publication bias, the trim and fill method was adopted to adjust the pooled risk (13). This method includes assumption of some unpublished studies that cause the funnel plot to be asymmetrical, plotting the data points so that the funnel plot is symmetrical, and recalculating the pooled risk estimates based on the hypothesis that studies corresponding to these data points actually had existed.

We added the quantitative assessment of the relationship between PA and ACM or CVD risk for studies that allowed qualification of PA, where we assigned point estimates of PA for each category by extracting the mean level of daily PA. If mean data were not provided, we alternatively used the midpoint of the upper and lower boundaries in each category. If the upper boundary of the highest PA category or the lowest PA category was not described, we assumed that the breadth of PA in these categories was equal to that of their closest PA category