focused on lifestyle education. The primary results of the clinical trial have been described elsewhere.[19] Incidence rates of diabetic retinopathy were similar for the conventional treatment group and the intervention group (36/1,000 and 39/1,000 patient-years, respectively); therefore, we combined data from both randomized groups for this study. Eligibility criteria were previously diagnosed patients with type 2 diabetes 40–70 years of age whose hemoglobin (Hb)A_{1C} levels were ≥6.5%. From outpatient clinics in 59 university and general hospitals nationwide that specialize in diabetes care, 2205 patients were initially registered from January 1995 to March 1996. Of 2033 patients who met the eligibility criteria and were randomized, 1588 patients responded to the baseline dietary survey. There was no notable difference in baseline characteristics between responders and nonresponders. After excluding 610 patients who had diabetic retinopathy or a major ocular disease (eg, glaucoma, dense cataract, or history of cataract surgery) at baseline, 978 patients were included in the current analysis. We analyzed follow-up data until March 2003. The protocol was approved by the institutional review boards of all the participating institutes. We obtained written informed consent from all patients.

Laboratory Measurements

Patients were assessed yearly after the baseline evaluation. Mean values of at least two measurements each year were obtained for HbA_{1C}, fasting plasma glucose, and fasting serum lipids. HbA_{1C} assays were performed according to procedures outlined by the Laboratory Test Committee of the JDS. These values can be converted by the formula: HbA_{1C} (JDS) (%) = 0.98 × HbA_{1C} (National Glycohemoglobin Standardization Program) (%) + 0.25%. All other laboratory measurements were performed at the participating institutes. Serum low-density lipoprotein (LDL)-cholesterol was calculated using Friedewald's equation except where triglycerides exceeded 400 mg/dl, in which case LDL-cholesterol data were treated as missing.

Assessment of Diabetic Retinopathy

Presence and severity of diabetic retinopathy were determined annually by qualified ophthalmologists at each institute using the international diabetic retinopathy and diabetic macular edema disease scales with minor modification.[20] Severity of diabetic retinopathy was categorized as "none," "mild nonproliferative," "moderate nonproliferative," "severe nonproliferative," and "proliferative." We collected both paper-based clinical assessment forms and retinal images, but only 70% of the images were suitable for assessment. We therefore adopted clinical assessments to determine incident diabetic retinopathy, which would improve statistical power. We also evaluated the agreement in staging between local ophthalmologists and retinal specialists; the kappa statistic for agreement of severity was 0.59 (95% confidence interval [CI] = 0.54–0.65). History of ocular surgery was also surveyed.

Dietary Assessment

A food frequency questionnaire (FFQ) based on food groups[21] was administered at baseline, and information for the 24-hour dietary record was also collected at baseline. In brief, the FFQ elicited information on the average intake per week of 29 food groups and 10 kinds of cookery, in commonly used units or portion sizes. After the patients completed the questionnaire or dietary records, a dietician reviewed the answers and in the case of questionable responses interviewed the patient. We used standardized software for population-based surveys and nutrition counseling in Japan (Excel EIYO-KUN version 4.5, developed by the Shikoku University Nutrition Database; KENPAKUSHA, Tokyo, Japan) based on the Standard Tables of Food Composition in Japan[22] edited by the Japanese Ministry of Education, Culture, Sports, Science and Technology to calculate nutrient and food intakes from both the FFQ and 24-hour dietary records.

To confirm the robustness against measurement errors, we estimated fruit and nutritional intakes by the averages of the FFQ and 24-hour dietary records, which may reduce attenuation bias due to measurement error. Mean intakes correlations were as follows: 130.6 g/day from the FFQ and 125.4 g/day from the average (r = 0.80) for fruit; 1749.0 and 1733 kcal/day (r = 0.84) for energy; 133 and 123 mg/day (r = 0.79) for vitamin C; 9.1 and 8.7 mg/day (r = 0.76) for vitamin E; 6475 and 5480 μg/day (r = 0.79) for carotene; 1304 and 1150 μg/day (r = 0.77) for retinol equivalent; 14.8 and 14.7 g/day (r = 0.83) for dietary fiber; and 2775 and 2825 mg/day (r = 0.82) for potassium. The FFQ was also externally validated by comparison with dietary records for seven continuous days of 66 subjects 19–60 years of age.[21] The ratios of the estimates obtained by the FFQ against those by the dietary records ranged from 72 to 121%; the average was 104%.

Statistical Analysis

The primary outcome was time from registration to incidence of diabetic retinopathy. Incidence was defined as having no signs of diabetic retinopathy in either eye at baseline but subsequently having any of the following conditions in either eye at two consecutive follow-up years: mild to severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, or laser photocoagulation treatment for diabetic retinopathy. Date of incident retinopathy was determined by the date of the ophthalmoscopic examination or laser photocoagulation treatment. Intraocular or cataract surgery was censored at the date of surgery.

Probability of incident diabetic retinopathy during 8 years was estimated by the Kaplan-Meier method. We estimated hazard ratios (HRs) of incident diabetic retinopathy in relation to quartiles of dietary intake by Cox regression with the standard multivariate method for energy adjustment,[23] adjusted for the following variables: age, sex, body mass index (BMI), HbA_{1C}, duration of diabetes, treatment by insulin, treatment by oral hypoglycemic agents without insulin, systolic blood

pressure (SBP), LDL-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides (log-transformed), current smoker, alcohol intake, physical activity, total energy intake, proportions of dietary protein, fat, carbohydrate, saturated fatty acids, n-6 polyunsaturated fatty acids and n-3 polyunsaturated fatty acids, cholesterol, and sodium. A trend across quartiles was examined by a trend test using multivariate Cox regression with scores from 1 to 4 for quartiles. By means of subgroup analysis and interaction tests using energy-adjusted Cox regression, we explored potential effect modification by age ≥60 years, sex, HbA_{1C} ≥9%, diabetes duration ≥10 years, overweight (BMI ≥25 kg/m^2), smoking status, and hypertension (SBP ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or treatment by antihypertensive agents). Gradients per year for HbA_{1C}, BMI, triglycerides, and SBP were estimated using linear mixed models. All statistical analyses and data management were conducted at a central data center using SAS version 9·2 (SAS Institute Inc., Cary, NC).

RESULTS

Table 1 describes the baseline characteristics and dietary intake of the 978 patients according to quartiles of fruit intake. Mean fruit intake in the quartiles ranged from 23 to 253 g/day. Mean energy intake in the quartiles ranged from 1640 to 1860 kcal/day, and fat intake was approximately 25%. The increasing trend in energy intake is attributable to

TABLE 1. Baseline Characteristics and Nutritional Intake[a] of the 978 Patients with Type 2 Diabetes According to Quartiles of Fruit Intake

	Q1 (<53.6 g/day) (n = 239)	Q2 (53.7–114.1 g/day) (n = 250)	Q3 (114.2–173.2 g/day) (n = 243)	Q4 (>173.3 g/day) (n = 246)	Test for Trend
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Fruits (g/day)	22.6 (15.8)	82.9 (17.6)	140.9 (17.3)	253.0 (82.0)	$P < 0.01$
		Baseline characteristics			
Age (years)	56.8 (7.3)	58.3 (7.0)	59.4 (6.3)	58.9 (6.5)	$P < 0.01$
Women (%)	33	52	51	53	$P < 0.01$
HbA_{1C} (%)	7.7 (1.2)	7.9 (1.3)	7.9 (1.4)	7.8 (1.5)	$P = 0.42$
Years after diagnosis (years)	9.3 (6.3)	10.4 (7.4)	10.3 (6.9)	9.7 (6.8)	$P = 0.53$
Treated by insulin (%)	13	13	18	15	$P = 0.22$
Treated by oral hypoglycemic agents without insulin (%)	64	66	59	65	$P = 0.79$
BMI (kg/m^2)	23.2 (3.0)	23.0 (3.0)	22.9 (3.2)	22.9 (2.9)	$P = 0.17$
Systolic BP (mmHg)	132.4 (16.1)	130.3 (16.5)	131.7 (15.9)	128.8 (14.6)	$P = 0.04$
LDL-cholesterol (mg/dl)	123.7 (33.3)	124.6 (36.0)	123.3 (31.4)	121.9 (28.3)	$P = 0.46$
HDL-cholesterol (mg/dl)	53.8 (18.2)	53.6 (15.6)	55.2 (17.3)	54.0 (15.9)	$P = 0.63$
Triglycerides (mg/dl)[b]	102.5 (72.0–145.5)	105.0 (71.0–147.0)	98.0 (75.0–135.5)	102.5 (74.0–156.0)	$P = 0.66$
Current smoker (%)	46	27	25	22	$P < 0.01$
Alcohol intake (g/day)[b]	21.5 (0.0–200.0)	4.0 (0.0–85.7)	3.0 (0.0–48.2)	1.3 (0.0–32.2)	$P < 0.01$
Physical activity (kJ/day)[b]	575.7 (128.2–1 073.9)	605.7 (173.0–1,158.3)	692.7 (243.0–1,388.9)	734.9 (223.7–1,628.0)	$P = 0.02$
		Nutritional intake			
Energy intake (kcal/day)	1,644 (370)	1,693 (346)	1,732 (316)	1,864 (373)	$P < 0.01$
Protein (% energy)	16.5 (2.4)	16.5 (2.3)	16.9 (2.2)	16.8 (2.2)	$P = 0.03$
Fat (% energy)	25.9 (4.9)	25.4 (4.4)	25.6 (4.6)	25.2 (4.5)	$P = 0.22$
Carbohydrate (% energy)	52.5 (6.4)	55.0 (5.7)	55.2 (5.7)	56.2 (6.0)	$P < 0.01$
Vitamin C (mg/day)	86.2 (44.9)	111.6 (37.8)	129.1 (40.1)	165.5 (48.3)	$P < 0.01$
Vitamin E (mg/day)	7.8 (2.7)	8.4 (2.3)	8.7 (2.3)	9.8 (2.5)	$P < 0.01$
Carotene (μg/day)	4,127 (2,243)	5,379 (2,621)	5,763 (2,321)	6,616 (2,719)	$P < 0.01$
Retinol equivalent (μg/day)	911 (473)	1,119 (524)	1,202 (499)	1,362 (549)	$P < 0.01$
Dietary fiber (g/day)	11.8 (4.0)	14.0 (4.2)	15.4 (4.1)	17.5 (4.5)	$P < 0.01$
Potassium (mg/day)	2,371 (750)	2,692 (672)	2,973 (706)	3,253 (742)	$P < 0.01$
Sodium (g/day)	3.9 (1.1)	4.2 (1.2)	4.3 (1.2)	4.6 (1.2)	$P < 0.01$
Grains (g/day)	201.9 (56.9)	206.8 (58.7)	204.3 (52.2)	208.7 (56.6)	$P = 0.27$
Vegetables (g/day)	266.3 (129.9)	315.2 (143.7)	338.3 (139.8)	362.8 (143.1)	$P < 0.01$
Seafood (g/day)	93.9 (54.0)	94.4 (43.7)	98.5 (52.8)	112.5 (57.8)	$P < 0.01$

[a]Mean (SD) unless otherwise indicated.
[b]Median (25th percentile–75th percentile).

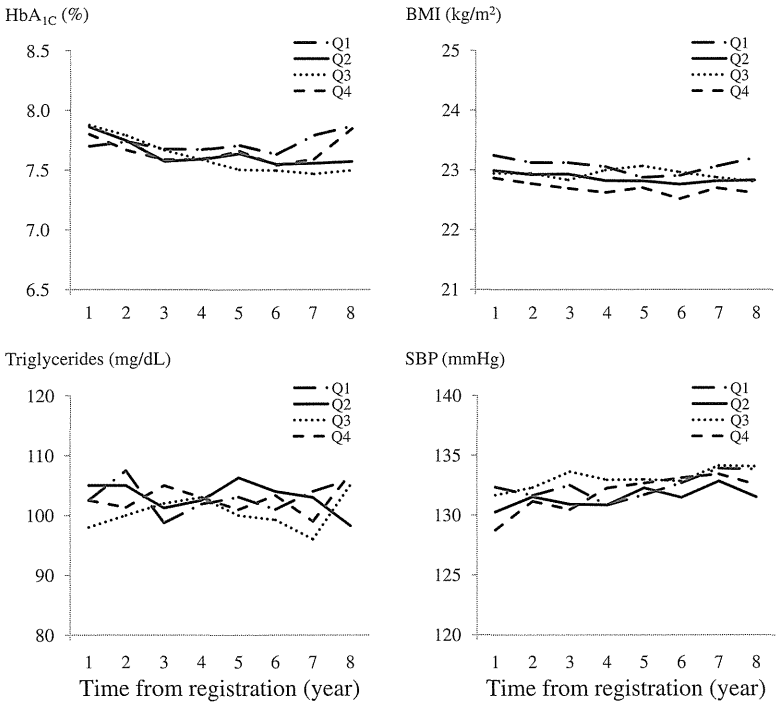
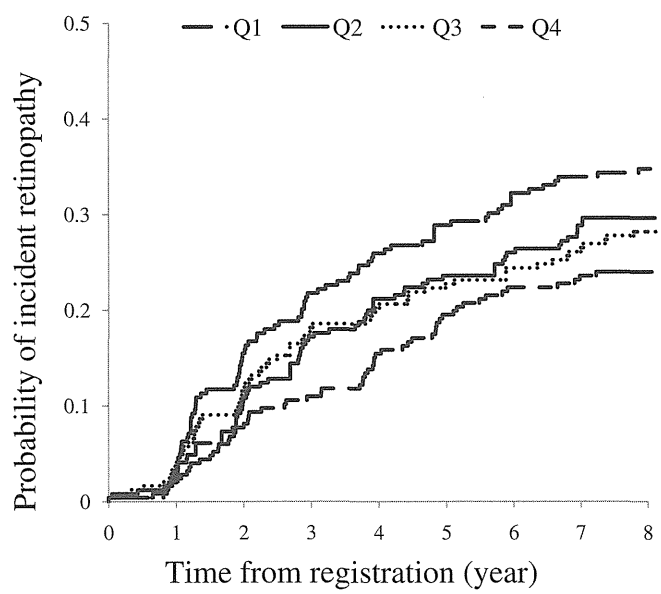


FIGURE 1. Longitudinal trends in mean HbA_{1C} (upper left), mean body mass index (upper right), median triglycerides (lower left), and mean systolic blood pressure (lower right) over 8 years according to quartiles of fruit intake.

calories from fruits, vegetables, and seafood (given that fruit intake was positively correlated with intakes of carbohydrate, vegetables, and seafood), but not grains. Patients in higher quartiles were older, with lower SBP and preferable lifestyles such as a lower smoking rate and increased physical activity. As expected, increase in fruit intake was positively associated with higher intake of total energy, vitamin C, vitamin E, carotene, retinol equivalent, dietary fiber, potassium, and sodium.

Figure 1 shows longitudinal trends for mean HbA_{1C}, mean BMI, median triglycerides, and mean SBP over 8 years. Overall, these parameters were well controlled. Gradients per year according to the quartiles of fruit intake (Q1 to Q4, respectively) were 0.018, −0.032, −0.049, and 0.001 for HbA_{1C} (test for a trend across quartiles, $P = 0.25$); −0.006, −0.035, −0.006, and −0.038 for BMI ($P = 0.13$); 0.667, −2.200, −0.479, and −0.509 for triglycerides ($P = 0.58$); and 0.256, 0.248, 0.290, and 0.550 for SBP ($P = 0.09$).

During the follow-up of a median of 8 years, 6707 person-years were studied and 285 incidents of diabetic retinopathy were observed. The follow-up rate at 8 years was 79%. Incidence of diabetic retinopathy according to the quartiles of fruit intake was 83 (Q1), 74, 69, and 59 (Q4). The overall annual incidence rate of diabetic retinopathy was 0.0425 (95% CI = 0.0378–0.0477). Figure 2 shows Kaplan-Meier curves for incident diabetic retinopathy according to quartiles. In confounder- and nutrient-adjusted Cox regression, fruit intake was inversely associated with incident diabetic retinopathy (Table 2). The nutrient-adjusted HR between the fourth and first quartiles was 0.48 (95% CI = 0.32–0.71; test for trend, $P < 0.01$). Other important variables in this model were HbA_{1C} (HR per 1% increment = 1.30 [95% CI = 1.20–1.41], $P < 0.01$), diabetes duration (HR per 1 year = 1.04 [1.02–1.06], $P < 0.01$), BMI (HR per 1 kg/m^2 = 1.05 [1.00–1.09], $P = 0.05$), insulin (1.68 [1.13–2.49], $P < 0.01$), and oral hypoglycemic agents (1.52 [1.10–2.11], $P = 0.01$). These trends remained if we alternatively used fruit intake estimated by the FFQ (Table 2).



Q1	239	235	203	188	178	170	162	157	79
Q2	250	246	224	208	198	192	185	176	77
Q3	243	235	215	198	193	186	181	178	96
Q4	246	239	228	220	209	199	190	187	97

FIGURE 2. Kaplan-Meier curves of incident diabetic retinopathy according to quartiles of fruit intake.

TABLE 2. Cox Regression Analysis of Incident Diabetic Retinopathy and Quartiles of Fruit Intake and of Fruit and Vegetable Intake

	Q1[a]	Q2	Q3	Q4	Test for Trend
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	
			Fruit intake		
Median intake (min–max) (g/day):	21.5 (0–53.2)	82.2 (53.6–114.0)	138.5 (114.3–172.9)	225.4 (173.2–657.5)	
No. events/no. person-years:	83/1,552.5	74/1,711.1	69/1,674.5	59/1,768.7	
FFQ					
Adjusted for risk factors[b]	1.00	1.06 (0.77–1.48)	0.84 (0.60–1.18)	0.61 (0.42–0.89)	$P < 0.01$
Further adjusted for nutrients[c]	1.00	1.05 (0.74–1.48)	0.83 (0.57–1.22)	0.63 (0.41–0.97)	$P = 0.02$
FFQ and 24-hour dietary recall					
Adjusted for risk factors[b,d]	1.00	0.68 (0.49–0.94)	0.64 (0.46–0.90)	0.50 (0.35–0.72)	$P < 0.01$
Further adjusted for nutrients[c,d]	1.00	0.66 (0.46–0.92)	0.59 (0.41–0.85)	0.48 (0.32–0.71)	$P < 0.01$
			Fruit and vegetable intake		
Median intake (min–max) (g/day):	232.6 (38.5–310.7)	378.0 (310.7–428.2)	485.5 (428.6–561.5)	670.7 (561.8–1,269.0)	
No. events/no. person-years:	75/1,642.0	80/1,618.1	67/1,703.0	63/1,743.7	
FFQ					
Adjusted for risk factors[b]	1.00	1.11 (0.80–1.55)	0.97 (0.69–1.37)	0.72 (0.49–1.04)	$P = 0.06$
Further adjusted for nutrients[c]	1.00	1.02 (0.72–1.45)	0.92 (0.61–1.37)	0.66 (0.40–1.10)	$P = 0.12$
FFQ and 24-hour dietary recall					
Adjusted for risk factors[b,d]	1.00	0.98 (0.70–1.36)	0.76 (0.53–1.07)	0.68 (0.47–0.98)	$P = 0.02$
Further adjusted for nutrients[c,d]	1.00	0.89 (0.63–1.25)	0.67 (0.46–0.98)	0.59 (0.37–0.92)	$P = 0.01$

[a]Reference category.
[b]Adjusted for age, sex, body mass index, HbA_{1C}, diabetes duration, treatment by insulin or oral hypoglycemic agents, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglycerides, current smoker, alcohol intake, and physical activity.
[c]Further adjusted for total energy intake, proportions of carbohydrate, saturated fatty acids, n-6 polyunsaturated fatty acids and n-3 polyunsaturated fatty acids, cholesterol, and sodium.
[d]Dietary intakes were estimated by the average of FFQ and 24-hour diabetic retinopathy.

If we alternatively used fruit and vegetable intake, the associations were weakened and remained significant only in the analysis of averages of the FFQ and 24-hour dietary records (Table 2). If we treated incident diabetic retinopathy in the first 2 years as censored, nutrient-adjusted HRs of quartiles of fruit intake were 0.69 (0.44–1.07), 0.58 (0.36–0.92), and 0.46 (0.28–0.76), respectively, for Q2, Q3, and Q4 compared with Q1 (test trend for $P < 0.01$). Figure 3 shows results of subgroup analysis according to risk factors for diabetic retinopathy.

Table 3 shows incidence of diabetic retinopathy in relation to quartiles of antioxidants, dietary fiber, and potassium. Decreasing trends were observed for vitamin C and carotene. Nutrient-adjusted HRs between the fourth and first quartiles were 0.61 (95% CI = 0.39–0.96) for vitamin C, 0.84 (0.51–1.40) for vitamin E, 0.52 (0.33–0.81) for carotene, 0.68 (0.44–1.05) for retinol equivalent, 0.63 (0.38–1.03) for dietary fiber, and 0.82 (0.49–1.38) for potassium.

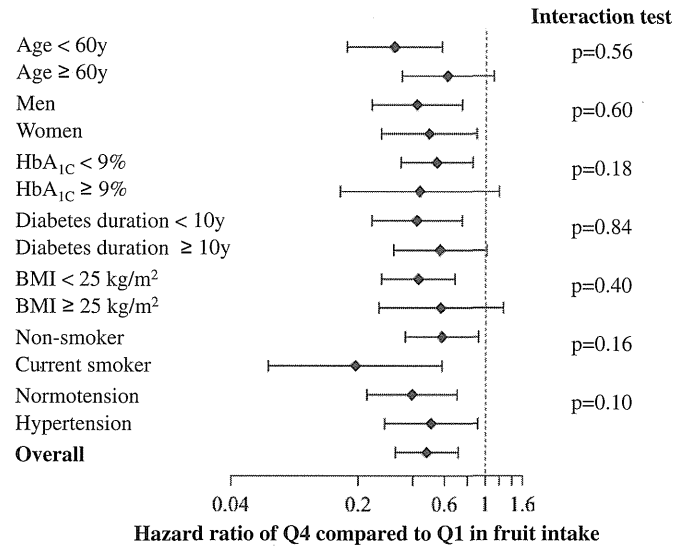


FIGURE 3. Subgroup analysis of the effect of fruit intake on incident diabetic retinopathy according to risk factors for diabetic retinopathy. The preventive effect of fruit intake was not modified by age (test for interaction, $P = 0.56$), sex ($P = 0.60$), HbA_{1C} ($P = 0.18$), diabetes duration ($P = 0.84$), overweight ($P = 0.40$), smoking status ($P = 0.16$), or hypertension ($P = 0.10$).

DISCUSSION

Medical nutritional treatment is essential in secondary prevention of diabetes complications, but the preventive effect of nutrition on diabetic retinopathy is generally not well

TABLE 3. Cox Regression Analysis of Incident Diabetic Retinopathy and Quartiles of Antioxidants, Dietary Fiber, and Potassium

	Q1[a]	Q2		Q3		Q4		Test for Trend
	HR	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	
Vitamin C								
Median intake (min–max) (mg/day):	67.0 (12.6–86.4)	103.3 (86.5–118.8)		133.4 (119.1–152.4)		182.8 (153.1–460.4)		
FFQ								
Adjusted for risk factors[b]	1.00	1.19 (0.86–1.64)	0.31	0.73 (0.51–1.05)	0.09	0.74 (0.52–1.08)	0.12	$P = 0.02$
Further adjusted for nutrients[c]	1.00	1.07 (0.76–1.52)	0.70	0.65 (0.42–1.00)	0.05	0.62 (0.37–1.05)	0.08	$P = 0.02$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.98 (0.70–1.38)	0.92	0.90 (0.63–1.27)	0.53	0.69 (0.48–1.00)	0.05	$P = 0.04$
Further adjusted for nutrients[c,d]	1.00	0.91 (0.63–1.31)	0.62	0.84 (0.57–1.23)	0.37	0.61 (0.39–0.96)	0.03	$P = 0.03$
Vitamin E								
Median intake (min–max) (mg/day):	6.0 (2.6–6.9)	7.7 (6.9–8.4)		9.2 (8.4–10.2)		11.4 (10.2–25.4)		
FFQ								
Adjusted for risk factors[b]	1.00	1.09 (0.79–1.52)	0.59	0.97 (0.69–1.37)	0.87	0.79 (0.55–1.13)	0.20	$P = 0.14$
Further adjusted for nutrients[c]	1.00	1.05 (0.70–1.57)	0.80	0.88 (0.52–1.48)	0.62	0.70 (0.33–1.52)	0.37	$P = 0.34$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.90 (0.64–1.26)	0.52	0.81 (0.57–1.14)	0.22	0.82 (0.58–1.17)	0.28	$P = 0.23$
Further adjusted for nutrients[c,d]	1.0	0.94 (0.64–1.36)	0.72	0.82 (0.54–1.24)	0.35	0.84 (0.51–1.40)	0.51	$P = 0.41$
Carotene								
Median intake (min–max) (μg/day):	2,643.2 (285.2–3,485.2)	4,308.7 (3,494.3–5,216.2)		6,034.9 (5,221.5–6,912.0)		8,442.7 (6,915.7–1,9203.1)		
FFQ								
Adjusted for risk factors[b]	1.00	1.01 (0.73–1.42)	0.94	0.99 (0.71–1.38)	0.95	0.74 (0.51–1.06)	0.10	$P = 0.11$
Further adjusted for nutrients[c]	1.00	0.92 (0.64–1.33)	0.66	0.85 (0.57–1.29)	0.45	0.62 (0.35–1.10)	0.10	$P = 0.14$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	1.00 (0.73–1.38)	0.99	0.64 (0.45–0.91)	0.01	0.69 (0.49–0.98)	0.04	$P = 0.01$
Further adjusted for nutrients[c,d]	1.00	0.85 (0.61–1.20)	0.36	0.51 (0.34–0.77)	<0.01	0.52 (0.33–0.81)	<0.01	$P < 0.01$
Retinol equivalent								
Median intake (min–max) (μg/day):	621.7 (88.9–779.4)	924.9 (782.4–1,080.0)		1,229.6 (1,080.6–1,377.7)		1,683.3 (1,377.8–4,559.6)		
FFQ								
Adjusted for risk factors[b]	1.00	0.99 (0.70–1.39)	0.94	1.08 (0.78–1.50)	0.64	0.74 (0.52–1.06)	0.10	$P = 0.19$
Further adjusted for nutrients[c]	1.00	0.85 (0.58–1.24)	0.40	0.89 (0.59–1.35)	0.58	0.57 (0.31–1.04)	0.06	$P = 0.16$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.85 (0.61–1.19)	0.35	0.75 (0.53–1.06)	0.10	0.79 (0.56–1.11)	0.18	$P = 0.14$
Further adjusted for nutrients[c,d]	1.00	0.77 (0.54–1.10)	0.15	0.66 (0.44–0.97)	0.04	0.68 (0.44–1.05)	0.08	$P = 0.07$
Dietary fiber								
Median intake (min–max) (g/day):	9.6 (4.2–11.4)	13.0 (11.4–14.3)		15.7 (14.3–17.3)		19.7 (17.3–38.1)		
FFQ								
Adjusted for risk factors[b]	1.00	0.99 (0.71–1.39)	0.95	0.85 (0.60–1.20)	0.34	0.82 (0.57–1.18)	0.29	$P = 0.19$
Further adjusted for nutrients[c]	1.00	1.07 (0.74–1.56)	0.71	0.89 (0.57–1.40)	0.62	0.99 (0.53–1.84)	0.97	$P = 0.71$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.89 (0.64–1.25)	0.51	0.85 (0.61–1.20)	0.37	0.74 (0.52–1.06)	0.10	$P = 0.11$
Further adjusted for nutrients[c,d]	1.00	0.86 (0.60–1.23)	0.41	0.76 (0.50–1.16)	0.20	0.63 (0.38–1.03)	0.07	$P = 0.07$
Potassium								
Median intake (min–max) (mg/day):	1977.1 (1,051.9–2,293.3)	2,521.5 (2298.1–2,754.8)		2,997.1 (2,756.5–3,257.6)		3,710.8 (3,258.5–7,249.5)		
FFQ								
Adjusted for risk factors[b]	1.00	1.48 (1.06–2.05)	0.02	0.94 (0.66–1.34)	0.73	0.84 (0.58–1.22)	0.36	$P = 0.09$
Further adjusted for nutrients[c]	1.00	1.36 (0.94–1.97)	0.10	0.83 (0.53–1.31)	0.43	0.72 (0.38–1.38)	0.33	$P = 0.16$

(*Continued*)

TABLE 3. (Continued)

	Q1[a]	Q2		Q3		Q4		Test for Trend
	HR	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.98 (0.70–1.38)	0.90	0.88 (0.62–1.24)	0.47	0.86 (0.60–1.22)	0.39	$P = 0.31$
Further adjusted for nutrients[c,d]	1.00	0.98 (0.67–1.41)	0.90	0.87 (0.57–1.33)	0.51	0.82 (0.49–1.38)	0.45	$P = 0.39$

[a]Reference category.
[b]Adjusted for age, sex, body mass index, HbA_{1C}, diabetes duration, treatment by insulin or oral hypoglycemic agents, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglycerides, current smoker, alcohol intake, and physical activity.
[c]Further adjusted for total energy intake, proportions of carbohydrate, saturated fatty acids, n-6 polyunsaturated fatty acids, and n-3 polyunsaturated fatty acids, cholesterol, and sodium.
[d]Dietary intakes were estimated by the average of FFQ and 24-hour DR.

understood. In this 8-year follow-up study of patients with type 2 diabetes in Japan, those who consumed an average of 253 g of fruit per day had a 50% lower risk of incident retinopathy compared with those consuming an average of 23 g/day. HbA_{1C}, BMI, triglycerides, and SBP were well controlled over 8 years even in the fourth quartile. This is the first report of a follow-up study on the temporal associations between antioxidants, dietary fiber, and potassium and incident diabetic retinopathy, which previously has been examined only cross-sectionally.[12–15] Decreasing trends in HRs were noted for vitamin C and carotene.

The mechanisms whereby fruits exert preventive effects on diabetic retinopathy are not entirely clear, but our data suggest the potential involvement of vitamin C, carotene, retinol equivalent, and dietary fiber. A high-fruit-vegetable intervention is known to increase carotene and vitamin C levels in plasma.[24] However, a previous systematic review found no clear association between vitamin C and E and prevalent diabetic retinopathy.[12] Our findings are not consistent with these results. This may reflect the cross-sectional design of those previous studies, which limits the ability to establish a temporal relationship and may suggest that it takes several years for antioxidants to have an effect on diabetic retinopathy. Another possibility is that the preventive effects of fruits are mediated through glycemic control. Fruits are low-glycemic-index foods rich in dietary fiber, which can slow glucose response after ingestion.[18] Our findings also suggest that dietary fiber might reduce damage to the retina caused by glucose.

Guidelines for diabetic patients in the United States,[3–5] Europe,[6] and Canada[7] (but not in Japan)[11] recommend a diet rich in fruits. Fruits and vegetables have a variety of beneficial effects; the Dietary Approaches to Stop Hypertension diet lowers blood pressure,[8] and increased fruit-vegetable intake reduces the incidence of stroke,[9] coronary heart disease,[10] and cancer.[25] Our findings support guidelines in Western countries encouraging diabetics to consume a diet rich in fruits,[3–7] in addition to those benefits already shown. However, this is a single observational study; randomized trials would be needed to establish the clinical benefit of high-fruit diet for reducing incident diabetic retinopathy.

Determining a tentative goal of fruit intake to achieve clinical benefit in preventing diabetic retinopathy is a difficult task, but it is notable that the association between fruit intake and incident diabetic retinopathy was in the range of amounts commonly consumed. The average intake in the fourth quartile was 253 g/day, which is approximately one fruit serving (eg, one apple or two bananas). This is twice the average intake for Japanese adults in the National Health and Nutrition Survey[26] and achieving such intake would be a realistic goal. It is also important that most patients in the larger study had a "low-fat energy-restricted diet." The proportion of protein, fat, and carbohydrate consumption met the Western guidelines,[5–7] which recommended carbohydrate intake from 45 to 65%, fat intake less than 35%, and protein intake from 10 to 20%. Unexpectedly, there was no increasing trend in BMI and triglycerides even in the fourth quartile (Figure 2), although patients consumed more energy than in the lower quartiles by 100 to 200 kcal (Table 1). The European Prospective Investigation into Cancer and Nutrition study recently reported that increasing baseline fruit-vegetable intake while keeping total energy intake constant did not substantially influence midterm weight change.[27] These data suggest that the benefits of consuming fruits up to 250 g/day outweigh the potential impact on weight control under a low-fat energy-restricted diet. The possible benefits of antioxidant supplements would be difficult to assess, based on our data, given the fact that micronutrients are highly correlated with each other and difficult to isolate in preventive effects of fruits.

These findings must be interpreted in the context of study limitations. First, the potential for bias, such as measurement errors in dietary assessments, confounding factors, and informative censoring, cannot be ruled out entirely. For example, use of vitamin supplements was assessed only by 24-hour dietary records, and intake of vitamins C and E and carotene could be underestimated. We believe, however, that measurement error and the possibility of unmeasured confounders were minimized by the use of two instruments for dietary assessment and by the comprehensive lifestyle survey of diet, physical activity, and smoking status. Second, as an observational study rather than a randomized trial, it is impossible to conclude whether

medical nutritional treatment encouraging fruits would reduce incident retinopathy in clinical practice. Another limitation is the accuracy of diabetic retinopathy staging based on clinical diagnosis compared with staging based on seven-field stereo fundus photography. Finally, our results may not be generally applicable to populations with different genetic or lifestyle factors. Fruits commonly consumed in Japan include pome fruits (apples, Japanese pears, and Japanese persimmons), citrus fruits (oranges, grapefruits, and lemons), drupes (peaches, cherries, and Japanese apricots), berries (strawberries, blueberries, and grapes), bananas, watermelon, and other melons; people in other locations may consume different types of fruits. Moreover, as we previously reported, BMI and body weight are markedly different between patients in Japan and Western countries, although energy intakes were similar.[28] Verifying our findings in studies of different ethnic populations would be useful.

These limitations notwithstanding, we conclude that increased fruit intake within the range commonly consumed is associated with reduced incident diabetic retinopathy. Further randomized trials are needed to clarify whether medical nutritional treatment that encourages consumption of fruits reduces incident retinopathy in the management of diabetes.

ACKNOWLEDGMENTS

We thank all the patients and diabetologists at the 59 participating institutes for longstanding collaboration in the Japanese Diabetes Complications Study. Thanks are extended to S. Kodama of University of Tsukuba for valuable advice in the systematic review and S. Fukuya and Y. Maruyama of University of Tsukuba for excellent secretarial assistance.

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

A meta-analysis

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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

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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

Table 1—*Stratified analyses of pooled RR of ACM for high versus low PA*

	Number of datasets*	RR (95% CI)	Q statistics	I^2 (%)	*P* value of heterogeneity	Meta-regression**
Total	13	0.60 (0.52–0.70)	45.0	73.3	<0.001	—
Country						
U.S.	8	0.59 (0.49–0.70)	16.9	58.6	0.02	Referent
Others	5	0.63 (0.47–0.84)	26.7	85.0	<0.001	0.51
Mean age (years)						
<60	8	0.67 (0.57–0.79)	21.3	75.8	<0.001	Referent
≥60	5	0.51 (0.42–0.61)	23.2	36.9	0.18	0.03
% men						
≥50	8	0.64 (0.54–0.76)	30.7	77.2	<0.001	Referent
<50	5	0.50 (0.35–0.71)	12.5	68.0	0.01	0.27
Overweight***						
No	6	0.50 (0.36–0.70)	15.9	68.5	0.007	Referent
Yes	7	0.64 (0.52–0.78)	27.9	78.5	<0.001	0.25
Methods for ascertainment of diabetes						
Self-reported	8	0.60 (0.50–0.72)	33.2	78.9	<0.001	Referent
Registry	3	0.38 (0.13–1.17)	6.7	70.1	0.04	0.83
Doctor diagnosis	2	0.57 (0.44–0.75)	0.1	0.0	0.78	0.87
Type of diabetes						
Type 1	2	0.20 (0.07–0.57)	0.1	0.0	0.70	0.04
Type 2	6	0.64 (0.55–0.75)	21.6	76.8	0.001	Referent
Nonspecified	5	0.55 (0.36–0.80)	17.3	76.8	0.002	0.57
Validation of PA questionnaire						
No	4	0.62 (0.45–0.87)	10.9	72.5	0.01	Referent
Yes	9	0.59 (0.50–0.71)	34.0	76.5	<0.001	0.66
Number of PA categories						
≥3	11	0.58 (0.48–0.69)	39.1	74.4	<0.001	Referent
2 (i.e., category was dichotomized)	2	0.75 (0.66–0.86)	2.6	61.2	0.11	0.32
PA type						
Total PA	7	0.63 (0.50–0.79)	35.1	82.9	<0.001	Referent
LTPA	5	0.62 (0.54–0.70)	6.7	40.1	0.15	0.62
Walking	1	0.54 (0.33–0.88)	—	—	—	0.69
Quantification of PA						
No	7	0.61 (0.50–0.75)	26.2	77.1	<0.001	Referent
Yes	6	0.58 (0.45–0.75)	16.7	66.0	0.01	0.63
Methods for ascertainment of mortality						
Questionnaire or self-report	4	0.71 (0.66–0.76)	13.5	77.8	0.004	0.43
Registry	8	0.60 (0.51–0.70)	23.4	70.1	0.001	Referent
Combination of registry and medical record	1	1.00 (0.66–1.52)	—	—	—	0.12
Mean follow-up duration (years)						
≥10	5	0.58 (0.45–0.74)	20.3	80.3	0.00	Referent
<10	8	0.62 (0.51–0.76)	20.2	65.3	0.005	0.70
Presence of lost to follow-up						
No	2	0.51 (0.44–0.58)	1.1	5.4	0.30	Referent
Yes	11	0.65 (0.57–0.75)	24.8	59.7	0.006	<0.001
Adjustment for classic risk factors****						
No	7	0.58 (0.43–0.78)	23.8	74.7	0.001	Referent
Yes	6	0.59 (0.49–0.70)	19.1	73.8	0.002	0.77

*Total number of studies was 12. One study (Moy et al. [15]) had two separate datasets by sex. **Represents test for significance of the study modification across strata. ***Cut-off value was 27.8 kg/m^2 for men, 27.3 kg/m^2 for women, and 27.5 kg/m^2 for men and women combined (10). ****Age, sex, blood pressure (or hypertension), and total cholesterol level (or dyslipidemia) were specified as classic risk factors.

(14). To standardize the PA dose, we used a common unit (MET-h), where 1 MET-h corresponds to energy expenditure (EE) while sitting at rest for 1 h. For example, a person who regularly walks 3 h/week at 3 METs of intensity has an EE calculated as 3 × 3 = 9 MET-h/week. In the study (15) that estimated the PA dose in terms of kcal, PA was converted to MET-h by dividing the product of the coefficient β = 1.05 and mean body weight estimated from mean BMI, where we

assumed that 1 MET-h = 1.05 kcal/kg and the mean height of men was 1.75 m and that of women was 1.60 m. If PA was expressed as daily total EE (16), we assumed that daily total PA is equal to total EE minus resting EE although, strictly speaking, the estimated PA would be lower than the actual PA due to ignoring the resting metabolic rate during exercise.

When a study expressed PA as a specific activity (e.g., walking, gardening, etc.) and its duration, we defined the intensity of the activity according to the globally used compendium of PAs by Ainsworth et al. (17): gardening, 5.5 METs; cycling, 7.5 METs; lifting, 6 METs; swimming, 6 METs; aerobics, 5.5 METs; jogging, 7.3 METs; golf, 4.8 METs; basketball, 6.5 METs; tennis, 5.5 METs; and brisk walking, 4.3 METs. This compendium (17) defines the intensity of light, moderate, and vigorous PA as <3, 3–6, and >6 METs, respectively. We converted the point estimates of intensity of these PAs into 1.5, 4.5, and 7.5 METs.

Firstly, we assumed a log-linear relationship between PA and ACM and CVD risk and adopted weighted, least-squared regression models. Secondly, we added the restricted cubic spline regression model for further investigation of the shape of the relationship. In these models, the log RR for each nonreferent group was regressed on the higher PA dose compared with the lowest PA category. Data were analyzed using STATA software version 12 (StataCorp, College Station, TX). Two-sided $P < 0.05$ was considered as statistically significant except for the test of publication bias, in which the level of significance was $P < 0.10$ (18).

RESULTS

Literature search

Supplementary Fig. 1 shows details of the literature search. Of 4,815 articles retrieved from the combination of MEDLINE and EMBASE electronic literature searches, 17 studies (15,16,19–33) met the prespecified inclusion criteria. Only one study (20) was a retrospective cohort study and in only one study (15) did all patients have type 1 diabetes. Nevertheless, these studies were included in this meta-analysis.

Supplementary Table 2 shows the details of the characteristics of the 17 included studies of which 13 and 12 assessed ACM and CVD risk, respectively. Ten studies (15,16,21,24–26,29,31–33) validated the instrument for measuring PA, and quantification of PA was allowed in seven studies (15,16,24,25,29,31,33) of which six (15,16,25,29,31,33) and five (24,25,29,31,33) studies assessed ACM and CVD risk, respectively. Only two studies (27,31) exclusively used medical records for ascertainment of CVD. None of the 13 studies evaluating the risk of ACM used medical records. Only four studies (20,22,25,26) excluded patients who were lost to follow-up. Although the consideration of confounders varied among studies, less than half of the included studies (eight studies) (19,21,24–26,29,31,33) adjusted the effect measure for all of the five following classic CVD risk factors: age, sex, smoking, dyslipidemia, and hypertension. The details of the confounding factors in each study are shown in Supplementary Table 3.

Qualitative assessment of the association of high PA with ACM and CVD risk

Of the 17 included studies, 13 and 12 assessed ACM and CVD risk, respectively. In two studies that assessed the risk of ACM and CVD, the same patients were investigated (25,26). We chose one of these studies (26) for the qualitative analysis because it assessed total PA while the other study (25) examined the risk of ACM and CVD according to several types of PA. However, we used the latter study (25) for the subsequent quantitative analysis because it allowed quantification of PA while the former (26) did not. One study (15) that investigated ACM risk had two datasets since men and women were analyzed separately. Finally, the number of available datasets for ACM and CVD risk in relation to high PA was 13 and 11, respectively.

Figure 1 is a forest plot for ACM and CVD risk in relation to high PA in patients with diabetes. The definition of the highest and lowest PA varied among studies. The pooled RR (95% CI) of ACM and CVD was 0.60 (0.52–0.70) and 0.71 (0.60–0.84), respectively. Between-study heterogeneity in the log RR was highly significant ($P < 0.001$ for ACM risk; $P < 0.001$ for CVD risk. However, the risk measure was below 1 except for two studies [28,29]).

Table 1 (ACM risk) and Table 2 (CVD risk), respectively, show the results of the stratified analyses for the key study characteristics and of the meta-regression analyses testing the significance for the effect of the characteristics on the magnitude of the risk measure for the highest versus lowest PA group in patients with diabetes. The lower risk associated with high PA was remarkable in studies that excluded diabetic patients who were lost to follow-up for both ACM and CVD risk ($P < 0.001$ and $P = 0.006$, respectively). Additionally, ACM risk was lower in studies with a relatively older population (mean age ≥60 years) ($P = 0.03$), and CVD risk was lower in studies with adjustment for classic CVD risk factors ($P = 0.003$). However, lower risks of ACM and CVD were consistently observed throughout all strata with each study characteristic.

Statistically significant publication bias was suspected for ACM risk ($P = 0.04$ for the Begg and Egger tests) while it was not for CVD risk (Begg test, $P = 0.39$; Egger test, $P = 0.24$). The visual funnel plot as shown in Supplementary Fig. 2 also suggested publication bias that tended to overestimate the lower risk of ACM associated with the high PA due to missing studies showing a nonsignificant association that should have been published. Therefore, we tried to detect the predicted missing studies and adjusted for the publication bias using the trim and fill method as described in RESEARCH DESIGN AND METHODS. However, ACM risk was not changed after the adjustment because of insufficient statistical power to detect these hypothetical missing studies.

Dose-response relationship between PA and ACM or CVD risk

Figure 2 illustrates the linear and spline regression curves describing the logarithm of ACM and CVD risk against the higher weekly PA in terms of MET-h in patients with diabetes. The linear regression model had 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% (95% CI, 5.0–13.8%) and 7.9 (4.3–11.4) reductions in ACM and CVD risk, respectively. Spline regression curves also indicated high goodness of fit for the risk of ACM (adjusted $R^2 = 0.60$, $P = 0.003$) and CVD (adjusted $R^2 = 0.57$, $P = 0.01$). The spline curve showed the tendency of an accelerated risk reduction for ACM and attenuated risk reduction for CVD with a high PA dose. However, the goodness of fit was not significantly different between linear and spline models ($P = 0.14$ for ACM risk; $P = 0.60$ for CVD risk). For consideration of the

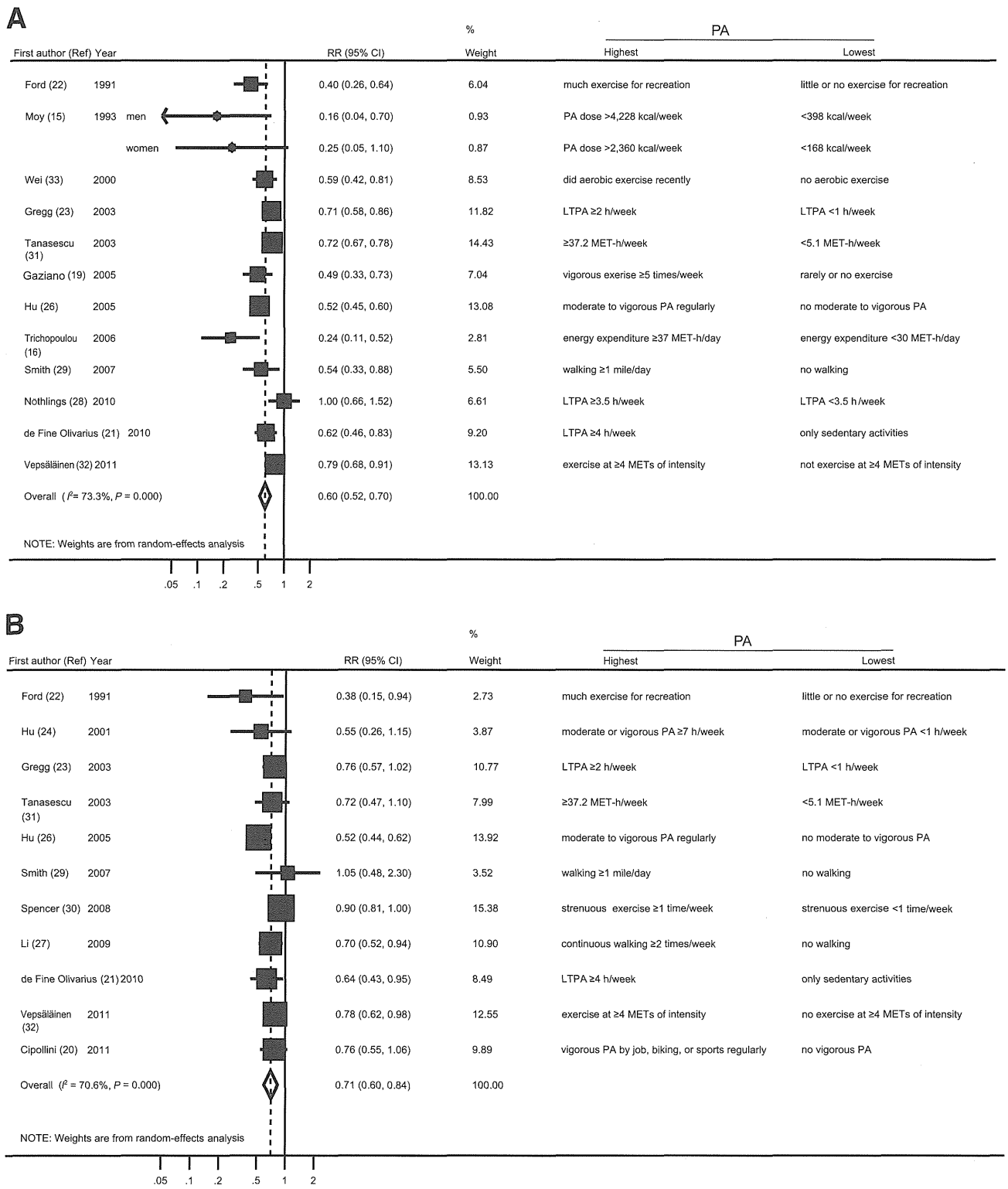

Figure 1—*Pooled risk with 95% CI of ACM (A) and CVD risk (B) for the highest vs. the lowest PA in patients with diabetes. Point estimates in each study and the overall risk measure are indicated in circles and diamonds, respectively. Horizontal lines indicate the range of 95% CI. Areas of the square are proportional to the study weight (i.e., inverse of variance).*

influence of the PA type, we additionally conducted multivariate linear and spline regression where both the higher PA dose and the PA type (i.e., total PA, LTPA, or walking) were entered as independent variables. However, results after adjustment for the PA type were unchanged (data not shown).

CONCLUSIONS—According to the report of the International Association for the Study of Obesity (34), the PA level that was defined as the ratio of average

Table 2—*Stratified analyses of pooled RR of CVD*

	Number of studies	RR (95% CI)	Q statistics	I^2 (%)	*P* value of heterogeneity	Meta-regression*
Total	11	0.71 (0.60–0.83)	34.1	70.6	<0.001	—
Outcome of interest						
CVD	7	0.65 (0.58–0.72)	11.4	47.2	0.08	Referent
CHD only	4	0.87 (0.79–0.95)	6.0	49.9	0.11	0.17
Nonfatal end point included						
No	6	0.66 (0.53–0.83)	12.7	60.5	0.03	Referent
Yes	5	0.85 (0.78–0.93)	5.3	24.0	0.26	0.18
Country						
U.S.	6	0.71 (0.60–0.85)	3.5	0.0	0.63	Referent
Others	5	0.71 (0.55–0.92)	29.9	86.6	<0.001	0.56
Mean age (years)						
<60	6	0.77 (0.72–0.84)	2.0	83.3	<0.001	Referent
≥60	5	0.70 (0.59–0.84)	9.5	0.0	0.52	0.86
% men						
≥50	7	0.68 (0.51–0.91)	10.3	70.7	0.02	Referent
<50	4	0.83 (0.77–0.91)	10.1	40.4	0.12	0.77
Overweight**						
No	4	0.71 (0.50–0.997)	2.8	28.4	0.25	Referent
Yes	6	0.70 (0.57–0.86)	31.1	80.7	<0.001	0.76
Not available	1	0.76 (0.55–1.06)	—	—	—	0.54
Methods for ascertainment of diabetes						
Questionnaire or self-reported	8	0.67 (0.54–0.84)	33.3	79.0	<0.001	Referent
Registry	2	0.77 (0.64–0.93)	0.0	0.0	0.90	0.12
Doctor diagnosis	1	1.05 (0.48–2.30)	—	—	—	0.21
Type of diabetes						
Type 2	6	0.64 (0.56–0.71)	10.8	53.6	0.06	Referent
Nonspecified	5	0.86 (0.78–0.94)	6.5	38.2	0.17	0.75
Validation of PA questionnaire						
No	5	0.85 (0.78–0.93)	6.9	42.1	0.14	0.15
Yes	6	0.62 (0.55–0.70)	10.4	51.8	0.07	Referent
Number of PA categories						
≥3	7	0.61 (0.54–0.69)	9.9	39.3	0.13	0.24
2 (i.e., category was dichotomized)	4	0.86 (0.78–0.93)	4.2	28.3	0.04	Referent
PA type						
Total PA	4	0.63 (0.56–0.71)	9.9	69.7	0.02	Referent
LTPA	5	0.85 (0.78–0.94)	8.1	50.8	0.09	0.88
Walking	2	0.74 (0.56–0.97)	0.9	0.0	0.34	0.55
Quantification of PA						
No	7	0.69 (0.56–0.86)	32.6	81.6	<0.001	Referent
Yes	4	0.75 (0.60–0.93)	1.4	0.0	0.70	0.72
Methods for ascertainment of CVD/CHD						
Registry	8	0.71 (0.58–0.88)	32.9	78.7	<0.001	Referent
Medical record	2	0.71 (0.56–0.90)	0.0	0.0	0.91	0.78
Combination of registry and medical record	1	0.55 (0.26–1.15)	—	—	—	0.63
Mean follow-up duration (years)						
≥10	6	0.65 (0.51–0.84)	12.4	59.8	0.03	Referent
<10	5	0.84 (0.77–0.92)	6.1	34.1	0.19	0.54
Presence of lost to follow-up						
No	3	0.56 (0.48–0.85)	4.7	57.2	0.10	Referent
Yes	8	0.83 (0.77–0.90)	8.0	12.7	0.33	0.006
Direction of follow-up						
Prospectively	10	0.70 (0.58–0.84)	34.1	73.6	<0.001	Referent
Retrospectively	1	0.76 (0.55–1.06)	—	—	—	0.55

Continued on p. 477

Table 2—*Continued*

	Number of studies	RR (95% CI)	Q statistics	I^2 (%)	*P* value of heterogeneity	Meta-regression*
Adjustment for classical risk factors***						
No	6	0.84 (0.77–0.91)	7.4	32.2	0.19	Referent
Yes	5	0.57 (0.49–0.66)	4.9	18.7	0.30	0.003

*Represents test for significance of the study modification across strata. **Cut-off value of mean BMI in each study was 27.8 kg/m^2 for men, 27.3 kg/m^2 for women, and 27.5 kg/m^2 for men and women combined (10). ***Age, sex, blood pressure (or hypertension), and total cholesterol level (or dyslipidemia) were specified as classic risk factors.

daily metabolic rate to resting metabolic rate ranged from 1.5–1.6 for men and 1.4–1.5 for women in sedentary groups. Additionally, in general, the minimum PA volume for avoiding a sedentary lifestyle was indicated to be 30 min of daily activity at 3 METs of intensity (34). In the studies in the current meta-analysis, the mean PA dose in the lowest group was at most 30 MET-h/day in terms of EE (i.e., 1.25 [= 30/24] in the PA level unit) or 30 min/day of LTPA. Therefore, these PA levels can be considered to represent inactivity. The results of the current meta-analysis can be interpreted to indicate that a high PA in patients with diabetes was associated with a 40 and 29% lower risk of ACM and CVD, respectively, in comparison with inactivity, although definitions of high PA varied among studies. In comparison with other lifestyle factors, these values corresponded to the CVD risk reduction for daily light-to-moderate alcohol consumption compared with rarely or never drinking in diabetic patients (35). In other words, an inactive lifestyle is interpreted to have a 1.64-fold (= 1.0/0.61) and 1.40-fold (= 1.0/0.71) risk of ACM and CVD, respectively, compared with an active lifestyle. These risk values are comparable to those for smoking in comparison with no-smoking in diabetic patients (ACM risk, 1.6 [22]; CHD risk, 1.8 [36]).

Although observational studies are generally subject to high risk of bias that correlates with low strength of evidence, the strength of evidence for PA benefit in prevention of ACM and CVD can be increased to moderate according to the Evidence-based Practice Center approach (37) for the following two reasons: *1*) presence of a dose-response pattern between PA dose and lower risk of ACM or CVD risk and 2) absence of plausible confounders, in particular, the main classic CVD risk factors, which can decrease the observed effect as indicated in the several stratified analyses (Tables 1 and 2). The major concern in judging the strength of evidence is a statistically suspected publication bias for the lower ACM risk associated with high PA, which may change the strength of the association.

As previously described, the results of this meta-analysis suggested that the lower risk of ACM or CVD associated with daily PA was not only qualitative but was dependent on the PA dose, which was, in most part, explained by log-linearity. The Physical Activity Guidelines for Americans from the U.S. Department of Health and Human Services recommended 150 min/week of moderate intensity PA to achieve a total of 8.3 MET-h/week of EE as the minimum PA level required for substantial health enhancement (medium PA) and 150 min/week of vigorous PA or 300 min/week of moderate PA to achieve a total of 16.7 MET-h/week of EE as the minimum PA level required for additional health benefit (high PA) (38). The medium/high PA level was estimated to lower the risk of ACM by 11.2%/21.2% and CVD by 9.3%/17.9%. The strength of the association between the increase in PA and the lowered risk in patients with diabetes was comparable to that in the general population in both ACM (14%/26%) (39) and CVD (14%/20%) (14).

It may be difficult for most working people to find much time to engage in PA. Moreover, diabetic patients often have

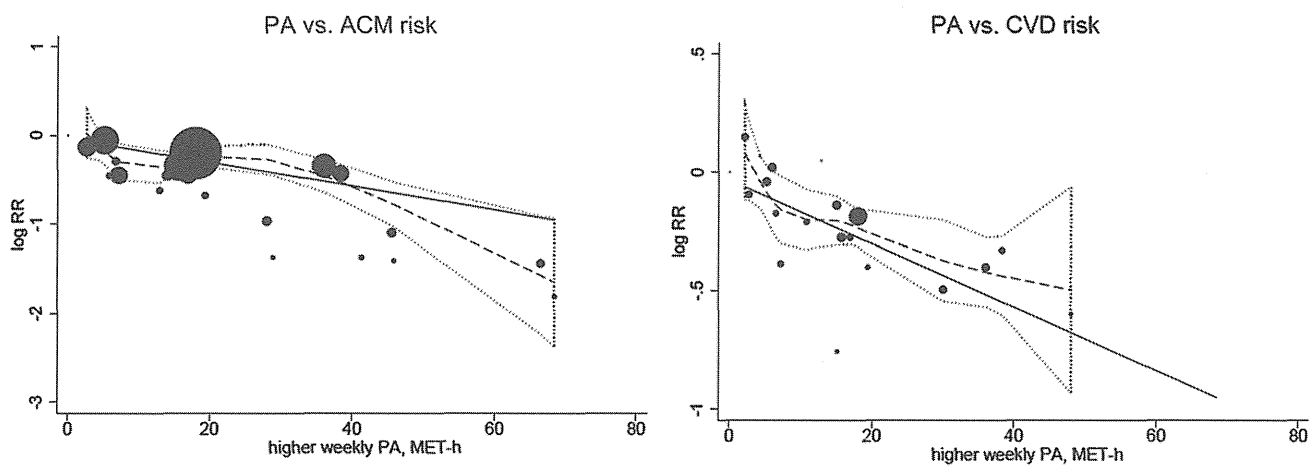

Figure 2—*Relationship between higher weekly PA and the logarithm (log RR) of ACM and CVD risk in patients with diabetes. Solid line indicates a log-linear relationship. Dashed line and the area surrounded by the dotted line indicate the cubic spline regression curve and its accompanying 95% confidence region, respectively. Size of each data point is proportional to its statistical weight.*

various barriers to exercise, which inevitably restrict the total amount of habitual PA (40). Therefore, most people will want to know the minimum level below which PA has no benefit or above which PA has no additional benefit. However, the spline curve indicating the relationship between PA dose and lower risk of ACM and CVD risk neither detected these levels nor had significant improvement in goodness of fit compared with linearity. Current results suggested that any amount of habitual PA was better than none, although PA cannot be too great from the viewpoint of cardiovascular benefit and longevity in people with diabetes.

Several limitations should be addressed. First, we combined LTPA and total PA in the dose-response relationship between PA and ACM or CVD risk because too few studies analyzed them separately. However, after adjustment for the PA type, the result of regression analysis was unchanged. Nevertheless, the estimated PA might not reflect true PA because different studies used different questionnaires, and different studies quantified different spectra of PA even within each PA type. Second, the current meta-analysis based on observational studies could not principally prove causation nor avoid the possibility of residual confounding for the observed association. Third, the current stratified and meta-regression analyses based on stratification generally had insufficient statistical power to detect a significant interaction because of the limited number of included studies. Fourth, publication bias toward the overestimation of the risk reduction was suspected in ACM. We had difficulty in controlling the bias, considering that the belief in PA-related benefits is so strong that researchers possibly hesitated to report negative data. Lastly, it should be noted that there were no eligible data on ACM or CVD risk in relation to PA for Asian diabetic populations, an issue that should be investigated in the future. Therefore, we could not stratify the analysis into Asian/non-Asian populations, although alternatively data were stratified according to country (U.S./non-U.S.).

Despite these limitations, our study has strength in that it is the first to estimate quantitatively the magnitude of risk reduction in ACM and CVD that could be expected by habitual PA in patients with diabetes and, in particular, to clarify the dose-response association. In conclusion, results of the current meta-analysis suggested that 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.

Acknowledgments—H.So. and S.K. are recipients of a Grant-in-Aid for Scientific Research (No. 20300227) and Postdoctoral Research Fellowship (No. 202965), respectively, both from the Japan Society for the Promotion of Science, Japan Cardiovascular Research Foundation, and Ministry of Health Labor and Welfare, Japan. The sponsors had no influence over the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

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

All study members contributed substantially to the following roles: *1*) conception and design of the study or acquisition of data, or analysis and interpretation of data; 2) drafting the manuscript or reviewing it; and 3) providing final approval of the version to be published. In addition, all the authors certify that they have participated sufficiently in the work to believe in its overall validity and to take public responsibility for appropriate portions of its context. S.K. played a leading role in conception and designing of the study, all processes of the study methods, and drafting all sections of the manuscript. S.T. and Y.O. designed the study's analytic strategy and provided technical support in carrying out the statistical analyses. Y.H., K.F., and C.H. selected studies that met the inclusion criteria and acquired the full paper of studies that should be left for further review. H.Sh., K.S., and N.Y. gave various opinions in their interpretions of the study results and helped draft the manuscript. H.So. made the study supervision and revised the draft critically for important intellectual content.

Parts of this study were presented at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012.

The authors thank Satomi Fukuya (University of Tsukuba) for her excellent secretarial work.

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American Journal of Epidemiology

Vol. 176, No. 11
DOI: 10.1093/aje/kws172
Advance Access publication: November 9, 2012

Systematic Reviews and Meta- and Pooled Analyses

Comparisons of the Strength of Associations With Future Type 2 Diabetes Risk Among Anthropometric Obesity Indicators, Including Waist-to-Height Ratio: A Meta-Analysis

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Initially submitted September 26, 2011; accepted for publication March 13, 2012.

The aim of this meta-analysis was to compare the association of waist-to-height ratio (WHtR) with risk of incident diabetes with the associations of 3 other conventional obesity indicators (body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR)) with risk of incident diabetes. Literature searches in MEDLINE (January 1950 to April 27, 2011) and EMBASE (January 1974 to April 27, 2011) were conducted for prospective studies that made it possible to estimate the relative risk of diabetes per 1-standard deviation increase in WHtR, in addition to the RR of BMI, WC, or WHR. Strength of the estimated pooled relative risk for a 1-standard deviation increase of each indicator (expressed as RR_{WHtR}, RR_{BMI}, RR_{WC}, and RR_{WHR}) was compared with a bivariate random-effects model. Pooled relative risks of the 15 eligible studies with 6,472 diabetes cases were 1.62 (95% CI: 1.48, 1.78) for RR_{WHtR}, 1.55 (95% CI: 1.43, 1.69) for RR_{BMI}, 1.63 (95% CI: 1.49, 1.79) for RR_{WC}, and 1.52 (95% CI: 1.40, 1.66) for RR_{WHR}. WHtR had an association stronger than that of BMI ($P<0.001$) or WHR ($P<0.001$). The present meta-analysis showed that WHtR has a modestly but statistically greater importance than BMI and WHR in prediction of diabetes. Nevertheless, measuring height in addition to WC appeared to have no additional benefit.

anthropometry; meta-analysis; obesity; type 2 diabetes mellitus

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

It is commonly recognized that obesity is an established risk factor for type 2 diabetes mellitus. Body mass index (BMI, calculated as weight (kg)/height $(m)^2$), waist circumference (WC), and waist-to-hip ratio (WHR) traditionally have been proposed as major anthropometric obesity indicators that have a substantial association with future diabetes risk. However, these obesity indicators represent different aspects of body composition: Whereas BMI reflects total body mass, WC and WHR reflect abdominal obesity, for which visceral fat is largely responsible. In particular, WC values are simpler to obtain than are those for BMI or WHR because only 1 measurement must be made. Moreover, compared with BMI, WC is more true to the biologically well-established mechanism that visceral fat has a greater association with insulin resistance than does subcutaneous fat (1).

Recently, the waist-to-height ratio (WHtR) was introduced as the hypothetically best abdominal obesity indicator of risk of type 2 diabetes mellitus because it is reasonable to think that short subjects generally will have more abdominal fat and associated cardiovascular risk factors than will tall subjects under the condition of a similar WC (2). Actually, it has been suggested that WHtR might be an effective screening tool for various diseases, including diabetes (3).

However, evidence for the superiority of WHtR in prediction of type 2 diabetes compared with other anthropometric indicators remains uncertain. The present meta-analysis aimed to summarize the risk of development of type 2 diabetes related to each anthropometric obesity indicator, including WHtR, and to compare the strength of the association among the obesity indicators.

MATERIALS AND METHODS

Data sources and study selection

We conducted an electronic search in MEDLINE (January 1950 to April 27, 2011) and EMBASE (January 1974 to April 27, 2011), with an additional manual search. Search terms used are shown in the Web Table 1 (available at http://aje.oxfordjournals.org/). Studies were included if 1) a prospective design was used; 2) type 2 diabetes was analyzed as a study endpoint; and 3) in addition to WHtR, at least 1 of the 3 obesity indicators (i.e., BMI, WC, or WHR) was analyzed as a continuous (i.e., relative risk per 1-unit increase) or categorical variable so that comparison of the strength of the association among the anthropometric indicators was possible. Even if a study did not indicate whether diabetes was type 1 or type 2, we considered the diabetes to be type 2 if it was adult onset. When multiple articles were available for a single observational study, the first priority for selection was the article describing the longest follow-up, and the second priority was the article with full cohort analysis covering the largest number of participants.

Data abstraction

From the included studies, 2 authors (S. K. and H. Sone) extracted data on study characteristics and risk measures. Discrepancies were solved by discussion. In addition to risk measures for diabetes, the following study characteristics were extracted: characteristics of the study population (sex, geographic region, ethnicity or race); methods for assessment of diabetes (definition of diabetes and instruments for ascertaining the endpoint); and model assumption (methods for representing associations of the obesity indicators with diabetes risk (i.e., categorical or continuous) and study-specific covariates). Study quality was assessed according to follow-up periods, percentage of subjects lost to follow-up, and extent of adjustment for covariates. When both unadjusted and adjusted risk estimates were reported in the same study, the most adjusted risk estimate was used.

Risk measures in an individual study were standardized into relative risks per 1-standard deviation increase in the obesity indicators. To make comparisons among the obesity indicators possible, we made 2 assumptions: 1) Frequency distributions of the obesity indicators were normal, and 2) a linear relation was observed between obesity measures and diabetes risk. If studies expressed relative risks based on categorical variables, they were regressed on the Z values for the mean or median value in each category. The standardized risk measure was estimated with the method of Berlin et al. (4) in a program developed by Orsini et al. (5). In summary, this program can calculate a weighted linear regression of a natural logarithm (log) of the relative risk across categories of obesity indicators, taking into account the covariance among risk measures if data on the adjusted RR and the number of participants and cases for each category are provided.

Data synthesis

Each log relative risk was pooled with the use of a univariate random-effects model (6). The pooled relative risk s ultimately were expressed as per 1-standard deviation increase in WHtR (RR_{WHtR}), BMI (RR_{BMI}), WC (RR_{WC}), and WHR (RR_{WHR}). For each pooled relative risk, between-study heterogeneity was assessed by I-squared (7). The possibility of publication bias was assessed by 2 formal tests (the Begg-adjusted rank correlation test (8) and Egger's regression asymmetry test (9)), as well as by visual inspection of a funnel plot.

Significance for differences was calculated between each pair of pooled relative risks by using a bivariate random-effects model that considered both within- and between-study correlations to estimate the standard error of the difference (10). In summary, when 2 parameters ($j = 1$ or 2) for $i = 1$ to n studies are examined, and the associated standard errors for each study's results are calculated as s_{ij} in a meta-analysis, the standard error for the difference between the pooled estimate of the 2 parameters (S_{diff}) can be calculated from the following formula:

$$\frac{1}{S^2_{\text{diff}}} = \sum\nolimits_{i=1}^{n} \frac{1}{(s^2_{i1}+s^2_{i2}-2\rho_{wi}s_{i1}s_{i2}) + (\tau^2_1+\tau^2_2-2\rho_B\tau_1\tau_2)},$$

where τ^2_j is the between-study variance and ρ_{wi} and ρ_B are the within- and between-study correlations, respectively. We used the "mvmeta" function provided by Stata software (StataCorp LP, College Station, Texas), which could calculate the between-study matrix and make it possible to estimate τ^2_i and ρ_B, if ρ_{wi} were known. Because the within-study correlation was generally unknown, we imputed the correlation coefficient on the basis of the between-study covariance matrix as the within-study correlation coefficient. According to the formula, when the results from the 2 parameters within each study are similar (i.e., ρ_{wi} and ρ_B are high), the statistical power for detecting the difference between the 2 results from each parameter is increased because S_{diff} is lowered.

Analyses were repeated for subgroups with similar study characteristics where we a priori stratified the included studies. Meta-regression analyses also were conducted to examine the impact of potential confounding factors on the strength of the association with diabetes risk within each obesity indicator. Data were analyzed in Stata software, version 11. Two-sided P values ≤ 0.05 were considered statistically significant, except for the test of publication bias, for which the level of significance was $P < 0.10$ (11).

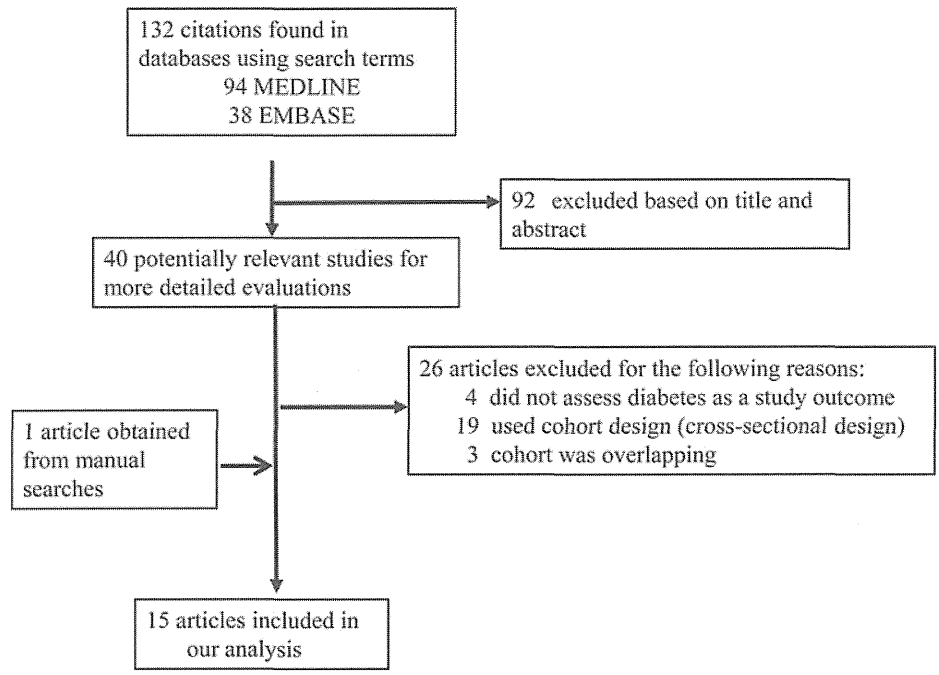

Figure 1. Study flow chart of the literature search in this meta-analysis.

RESULTS

Literature search

Figure 1 shows details of the literature search. Of the 132 citations that were retrieved by the electronic literature search, 14 studies (12–25) met the inclusion criteria. We added 1 article (26) obtained by a manual search of the reference lists in each of the 14 studies. Finally, 15 studies that included 120,102 participants (average length of follow-up, 6.0 years) were included in this meta-analysis. With the exception of the 1 study (12) that presented no data on the number of diabetes cases, the analyzed studies reported a total of 6,472 cases. Of the 15 studies, 4 (14–16, 20) had a single cohort. One study (18) consisted of 3 cohorts according to ethnicity, and 1 study (21) consisted of 2 United Kingdom cohorts. Six studies (17, 22–26) had 2 data sets according to sex. Additionally, 1 study (12) had 6 data sets (2 according to sex × 3 with intervention groups), and 2 studies (13, 19) had 4 data sets (2 according to sex × 2 cohorts). Consequently, a total of 35 data sets were generated on the basis of the published data in the 15 articles.

Study characteristics

Table 1 summarizes the characteristics of the 15 eligible studies. Averages of mean age, WHtR, BMI, WC, and WHR in each study population were 50 years, 0.55, 27.2, 89.3 cm, and 0.88, respectively. Participants in a major portion of the included studies were from the general population, although in 3 studies (12, 16, 18), participants were selected on the basis of being at high risk of diabetes. From the viewpoint of study quality, 4 studies (12, 19, 23, 24) had observational periods of 10 years or more. Participants who were lost to follow-up from their analysis were excluded in all but 3 studies (12, 17, 26) (lost to follow-up range, 0.2%–10%). Although all studies controlled risk measures for at least age, sex, and race or ethnicity, only 8 studies (13–15, 19, 21, 23–25) did so for 3 or more of the following main lifestyle and metabolic confounders: smoking, alcohol, physical activity, baseline fasting plasma glucose values or fasting glycemic status, systolic blood pressure or presence of hypertension, and triglyceride level. Other prespecified confounders were family history of diabetes (in 7 studies) (14–16, 18, 19, 23, 25), education (in 2 studies) (25, 26), and socioeconomic status (in 2 studies) (19, 21). Five studies (13, 17, 20, 21, 25) did not state whether diabetes was type 2 or not, although they did note that it was adult onset. Reports of the remaining 10 studies stated that study outcome was type 2 diabetes.

Overall absolute and relative contributions of each anthropometric indicator to the development of diabetes

Web Figure 1 shows a forest plot with relative risks for a 1-standard deviation increase in the 4 obesity indicators and their corresponding 95% confidence intervals in each study and overall. Overall, the incremental diabetes risk was 1.62 (95% confidence interval (CI): 1.48, 1.78) for RR_{WHtR}, 1.55 (95% CI: 1.43, 1.69) for RR_{BMI}, 1.63 (95%

Table 1. Summary of Characteristics of 15 Included Studies Included in the Meta-Analysis

Category	No. of Studies[a]	Range	Reference No.	No. of Data Sets	No. of Participants
Participants (total $n = 120,012$)		704–61,703			
Cases[b] (total $n = 6,472$)		51–2,991			
Geographic region					
Western	8		12, 17, 18, 22, 24	20	42,871
Non-Western	7		13–16, 19, 23, 25	15	77,231
Race					
>50% white	6		12, 17, 18, 21, 24, 26	16	40,168
>50% black	3		18–20	4	2,164
Other	8		13–16, 19, 22, 23, 25	15	77,770
Sex					
Men only	11		12, 13, 15, 17, 19, 21–26	15	69,754
Women only	11		12–14, 17, 19, 21–26	15	47,843
Bboth men and women	3		16, 18, 20	5	2,505
Percentage of men		21–78			
Mean age, years		40–73			
≥50	5		12, 13, 21, 24, 25	13	16,673
<50	8		12, 14–17, 19, 20, 23	15	75,629
Not described	3		18, 22, 26	7	27,800
Mean BMI[c,d]		23.0–34.0			
≥28	4		12, 16, 18, 22	11	6,162
<28	12		13–15, 17–21, 23–26	24	113,940
Mean WHtR[e]		0.49–0.65			
Mean WC[f,g]		79.3–107.5			
Mean WHR[f,g]		0.81–0.93			
Duration of follow-up, years		2.0–12.4			
≥10	4		13, 19, 23, 24	11	13,139
<10	12		12, 14–18, 20–22, 25, 26	24	106,963
Criteria for diabetes					
FPG ≥7.0 mmol/L or 2hPG ≥11.1 mmol/L	7		12, 14, 15, 17, 19, 20, 22	17	15,871
Other[h]	8		16, 18, 21, 23–26	18	104,231
Methods for ascertainment of diabetes					
Blood test only	8		12–18, 24, 25	22	21,780
Self-report or medical record	7		19–23, 26	13	98,322
Representation of risk estimates for obesity indicators					
Continuous	9		12, 13, 17–22, 24	26	24,898
Categorical	6		14–16, 23, 25, 26	9	95,204
Variables as study confounders: factors other than age, sex, and ethnicity					
Considered	10		13–15, 18, 19, 21, 23–26	23	112,125
Not considered	5		12, 16, 17, 20, 22	12	7,977

Table continues

CI: 1.49, 1.79) for RR_{WC}, and 1.52 (95% CI: 1.40, 1.66) for RR_{WHR}. For all 4 obesity indicators, study heterogeneity in the strength of association between each obesity indicator and diabetes was highly significant ($P<0.001$).

Because all 15 included studies assessed the risk of diabetes in relation to all 4 anthropometric indicators (i.e., WHtR, BMI, WC, and WHR), we compared the strength of the association with diabetes risk not only between WHtR and 1 of the