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

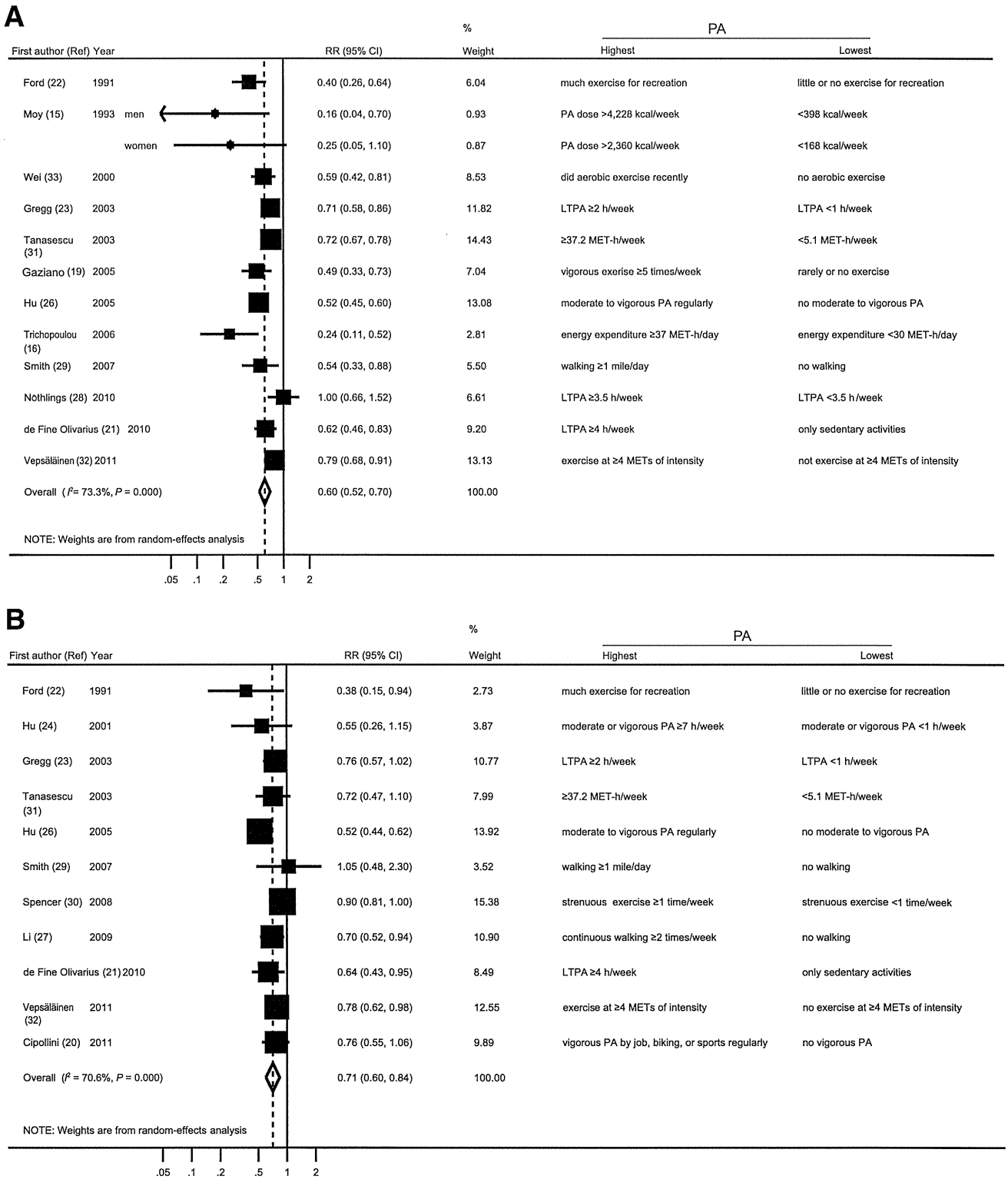

Figure 1—*Pooled risk with 95% CI of ACM (A) and CVD risk (B) for the highest vs. the lowest PA in patients with diabetes. Point estimates in each study and the overall risk measure are indicated in circles and diamonds, respectively. Horizontal lines indicate the range of 95% CI. Areas of the square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

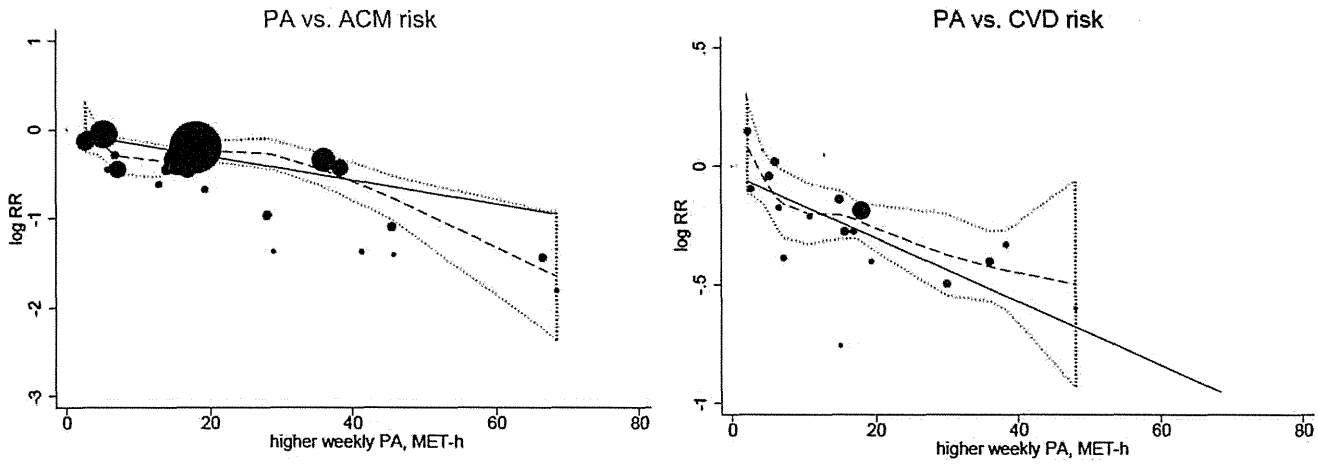

Figure 2—*Relationship between higher weekly PA and the logarithm (log RR) of ACM and CVD risk in patients with diabetes. Solid line indicates a log-linear relationship. Dashed line and the area surrounded by the dotted line indicate the cubic spline regression curve and its accompanying 95% confidence 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.

References

1. Gregg EW, Cheng YJ, Saydah S, et al. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. Diabetes Care 2012;35:1252–1257
2. American Diabetes Association. Standards of medical care in diabetes—2011. Diabetes Care 2011;34(Suppl. 1):S11–S61
3. Shinji S, Shigeru M, Ryusei U, Mitsuru M, Shigehiro K. Adherence to a home-based exercise program and incidence of cardiovascular disease in type 2 diabetes patients. Int J Sports Med 2007;28:877–879
4. 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
5. Praet SF, van Rooij ES, Wijtvliet A, et al. Brisk walking compared with an individualised medical fitness programme for patients with type 2 diabetes: a randomised controlled trial. Diabetologia 2008;51:736–746
6. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690–1691
7. Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. Annu Rev Public Health 1987;8:253–287
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558
9. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188
10. Van Itallie TB. Health implications of overweight and obesity in the United States. Ann Intern Med 1985;103:983–988
11. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1101
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634
13. 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
14. Sattelmair J, Pertman J, Ding EL, Kohl HW 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation 2011;124:789–795
15. Moy CS, Songer TJ, LaPorte RE, et al. Insulin-dependent diabetes mellitus, physical activity, and death. Am J Epidemiol 1993;137:74–81
16. Trichopoulou A, Psaltopoulou T, Orfanos P, Trichopoulos D. Diet and physical activity in relation to overall mortality amongst adult diabetics in a general population cohort. J Intern Med 2006;259:583–591
17. 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
18. 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
19. Gaziano TA, Bubes V, Gaziano JM. Exercise and mortality among diabetics in the Physicians' Health Study enrolment cohort. Cardiovasc J S Afr 2005;16 (Suppl.):12
20. Cipollini F, Gussoni G, Pacifici R, et al. The influence of physical activity performed at 20-40 years of age on cardiovascular outcomes in medical patients aged 65-75. Ital J Med 2011;5:114–119
21. de Fine Olivarius N, Siersma V, Nielsen AB, Hansen LJ, Rosenvinge L, Mogensen CE. Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study. BMC Endocr Disord 2010;10:14
22. Ford ES, DeStefano F. Risk factors for mortality from all causes and from coronary heart disease among persons with diabetes. Findings from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Am J Epidemiol 1991;133:1220–1230
23. Gregg EW, Gerzoff RB, Caspersen CJ, Williamson DF, Narayan KM. Relationship of walking to mortality among US adults with diabetes. Arch Intern Med 2003;163:1440–1447
24. Hu FB, Stampfer MJ, Solomon C, et al. Physical activity and risk for cardiovascular events in diabetic women. Ann Intern Med 2001;134:96–105
25. Hu G, Eriksson J, Barengo NC, et al. Occupational, commuting, and leisure-time physical activity in relation to total and cardiovascular mortality among Finnish subjects with type 2 diabetes. Circulation 2004;110:666–673
26. 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
27. Li R, O'Sullivan MJ, Robinson J, Safford MM, Curb D, Johnson KC. Family history of myocardial infarction predicts incident coronary heart disease in postmenopausal women with diabetes: the Women's Health Initiative Observational Study. Diabetes Metab Res Rev 2009;25:725–732
28. Nöthlings U, Ford ES, Kröger J, Boeing H. Lifestyle factors and mortality among adults with diabetes: findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam study*. J Diabetes 2010;2:112–117
29. Smith TC, Wingard DL, Smith B, Kritz-Silverstein D, Barrett-Connor E. Walking decreased risk of cardiovascular disease mortality in older adults with diabetes. J Clin Epidemiol 2007;60:309–317
30. Spencer EA, Pirie KL, Stevens RJ, et al.; Million Women Study Collaborators. Diabetes and modifiable risk factors for cardiovascular disease: the prospective Million Women Study. Eur J Epidemiol 2008;23:793–799
31. 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
32. Vepsäläinen T, Soinio M, Marniemi J, et al. Physical activity, high-sensitivity C-reactive protein, and total and cardiovascular disease mortality in type 2 diabetes. Diabetes Care 2011;34:1492–1496
33. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 2000;132:605–611
34. Saris WH, Blair SN, van Baak MA, et al. How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st Stock Conference and consensus statement. Obes Rev 2003;4:101–114
35. Ajani UA, Gaziano JM, Lotufo PA, et al. Alcohol consumption and risk of coronary heart disease by diabetes status. Circulation 2000;102:500–505
36. DeStefano F, Ford ES, Newman J, et al. Risk factors for coronary heart disease mortality among persons with diabetes. Ann Epidemiol 1993;3:27–34
37. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol 2010;63:513–523
38. U.S. Department of Health and Human Services. *2008 Physical Activity Guidelines for Americans*. Washington, DC, 2008 (Office of Disease Prevention and Health Promotion Publication No. U0036)
39. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. Int J Epidemiol 2011;40:1382–1400
40. Korkiakangas EE, Alahuhta MA, Laitinen JH. Barriers to regular exercise among adults at high risk or diagnosed with type 2 diabetes: a systematic review. Health Promot Int 2009;24:416–427

Diabetes and Risk of Hearing Impairment in Adults: A Meta-Analysis

Chika Horikawa, Satoru Kodama, Shiro Tanaka, Kazuya Fujihara, Reiko Hirasawa, Yoko Yachi, Hitoshi Shimano, Nobuhiro Yamada, Kazumi Saito, and Hirohito Sone

Department of Hematology, Endocrinology, and Metabolism (C.H., S.K., K.F., R.H., Y.Y., H.So.), Niigata University Faculty of Medicine, 951-8510 Japan; Department of Internal Medicine (C.H., K.F., H.Sh., N.Y.), University of Tsukuba Institute of Clinical Medicine, 305-8575 Japan; Translational Research Center (S.T.), Kyoto University Hospital, Kyoto, 606-8507 Japan; and Ibaraki Prefectural University of Health Sciences Center for Medical Sciences (K.S.), Amimachi, Inashikigun, Ibaraki, 300-0394, Japan

Context: Recently, several studies have investigated the relationship between diabetes and hearing impairment, but results were inconsistent.

Objective: Our objective was to compare the prevalence of hearing impairment between diabetic and nondiabetic adults.

Data Sources : We performed a systematic literature search using MEDLINE (1950 to May 30, 2011) and EMBASE (1974 to May 30, 2011).

Study Selection: Cross-sectional studies were included if data on numbers of hearing-impaired and non-hearing-impaired cases with diabetes were presented. Hearing impairment was limited to that assessed by pure-tone audiometry that included at least 2 kHz of frequency range and was defined as progressive, chronic, sensorineural, or without specified cause.

Data Extraction: Two authors independently extracted relevant data. Odd ratios (ORs) of hearing impairment related to diabetes calculated in each study were pooled with the random-effects model.

Data Synthesis: Data were obtained from 13 eligible studies (20,194 participants and 7,377 cases). Overall pooled OR (95% confidence interval) of hearing impairment for diabetic participants compared with nondiabetic participants was 2.15 (1.72–2.68). OR was higher in younger participants (mean age, ≤60 yr) than in those over 60 yr among which the OR remained significant (2.61 and 1.58, $P = 0.008$). The strength of the association between diabetes and prevalence of hearing impairment was not significantly influenced by whether participants were matched for age and gender ($P = 0.68$) or whether participants chronically exposed to noisy environments were excluded ($P = 0.19$).

Conclusions: Current meta-analysis suggests that the higher prevalence of hearing impairment in diabetic patients compared with nondiabetic patients was consistent regardless of age. ***(J Clin Endocrinol Metab* 98: 0000–0000, 2013)**

Prevalence of hearing impairment is dramatically increasing with the development of an aging society. The number of those with impaired hearing more than doubled in the period from 1995–2004 (from 120 million to 275 million) (1, 2). The World Health Organization (WHO) (3) defines hearing impairment as pure-tone thresholds of more than 25 dB hearing loss in the better ear, above which the hearing impairment makes it difficult

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2012–2119 Received May 2, 2012. Accepted October 11, 2012.

Abbreviations: CI, Confidence interval; OR, odds ratio.

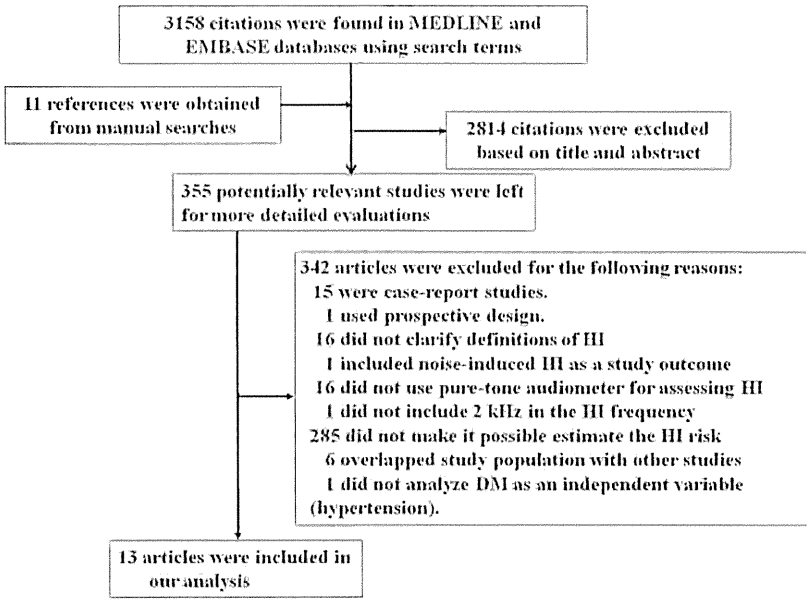

FIG. 1. Flowchart of meta-analysis. DM, Diabetes mellitus; HI, hearing impairment.

to hear lower than normal voices and may cause individuals to miss parts or all of words in ordinary communication. Epidemiologically, several health problems in relation to hearing impairment have been reported such as depression (4) and dementia (5). Lin *et al.* (5) reported that the risks of all-cause dementia and Alzheimer's disease for a 10-dB hearing impairment increase by 27 and 20%, respectively.

Hearing impairment has many causes. The most common is presbycusis, followed by noise exposure, ototoxic drugs, and viral infections (4). In addition to these factors, the association of hearing impairment with diabetes is controversial (http://www.nature.com/news/2004/040227/full/news040223-12.html) (7). It is believed that, over time, high blood glucose levels can damage the vessels in the stria vascularis and nerves, diminishing the ability to hear (8). However, there is insufficient evidence of a significant relationship between diabetes and hearing impairment from the epidemiological viewpoint. Therefore, we aimed to compare the prevalence of hearing impairment between diabetic and nondiabetic adults.

Materials and Methods

Search strategy

The meta-analysis was conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology (9).

TABLE 1. Characteristics of studies included in the meta-analysis

Author	Year	Country	Designation	Hospital or population based	Type of diabetes	Mean duration of diabetes (yr)	Age range (yr) (mean)	Men (%)
Bamanie *et al.* (30)	2011	Saudi Arabia		Hospital	T2DM	10.5	29–69 (46.7)	50.0
Mozaffari *et al.* (31)	2010	Iran		Population	9 T1DM 71 T2DM1	9.3	20–60 (45.0)	36.3
Uchida *et al.* (32)	2010	Japan	NILS-LSA	Population	FPG >126 mg/dl, HbA1c >6.5%	NA	40–86	50.1
Cheng *et al.* (25)	2009	United States	NHANESI, NHANES	Population	NA	4.8 6.1	25–69 (44.9) 25–69 (44.3)	47.3 49.1
de Sousa *et al.* (33)	2009	Brazil		Hospital	NA	NA	40– (50.5)	85.4
Aladag *et al.* (34)	2009	Turkey		Population	T2DM	NA	(46.9)	57
Mitchell *et al.* (27)	2009	Australia	BMHS	Population	T2DM	<10 (159) ≥10 (51)	55– (69.8)	42.9
Sakuta *et al.* (39)	2006	Japan	SDFs	Population	T2DM	NA	51–59 (52.8)	100
Helzner *et al.* (35)	2005	United States	Health ABC study	Population	NA	NA	73–84 (77.5)	47.3
Huang (36)	2004	China		Hospital	T2DM	NA	23– (56.1)	54.2
Dalton *et al.* (37)	1998	United States	EHLS, BDES	Population	T2DM	NA	43–84 (65.6)	43.3
Marumo *et al.* (29)	1984	Japan		Hospital	Primary DM	NA	18–75 (45.5)	55.6
Minami *et al.* (38)	1977	Japan		Hospital	NA	NA	15–79	61.1

BDES, Beaver Dam Eye Study; BMHS, Blue Mountains Hearing Study; EHLS, Epidemiology of Hearing Loss Study; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin level; HI, hearing impairment; NHANES, National Health and Nutrition Examination Survey; NILS-LSA, National Institute for Longevity Sciences-Longitudinal Study of Aging; SDFs, Self-Defense Forces; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[a] Data were based on findings for the most modestly affected ear if both ears were assessed.

[b] Each diabetic subject was matched with a nondiabetic subject for age and gender.

[c] Subjects exposed to noisy environments were excluded.

We used an electronic literature search engine, EMBASE.com, which makes it possible to search the MEDLINE (1950 to May 30, 2011) and EMBASE (1974 to May 30, 2011) databases simultaneously, to identify articles examining the relationship between diabetes and the prevalence of hearing impairment. We added a manual search using the reference lists of the relevant articles. No language restriction was imposed.

Two search themes were combined using the Boolean operator, and the first keywords were related to hearing impairment using hearing disorder, hearing impairment, hearing loss, hypoacusis, monaural hearing, perception deadness, unilateral hearing loss, hearing, deaf, and deafness as EMTREE terms, and hearing disorder, hearing impairment, hearing loss, deaf, deafness, hearing damage, hearing defect, hearing difficulty, and impaired hearing as text words. The second keywords were related to diabetes. Diabetes and diabetic were used as EMTREE terms corresponding to MeSH terms in MEDLINE, and diabetes mellitus, diabetes, and diabetic as text words.

Inclusion and exclusion criteria

The study inclusion criteria were as follows: 1) observational study using a cross-sectional design, 2) adult subjects targeted, 3) data given on the number of hearing-impaired and non-hearing-impaired cases in the presence of diabetes, and 4) hearing impairment objectively assessed using pure-tone audiometry that included a frequency range of at least 2 kHz.

We focused on studies using a cross-sectional design because there has been only one prospective study on this topic (10). We considered hearing impairment in this meta-analysis as chronic, progressive, or sensorineural and without specific cause [*e.g.* noise or heredity (11–13) or Wolfram syndrome (14)]. The most updated article was selected if multiple articles were published for the same population. We included studies that examined the prevalence of hearing impairment based on both the best and worst ear. However, if a study presented both unilateral and bilateral data on hearing impairment, priority was given to data on hearing impairment in the better ear (*i.e.* bilateral ear) to maintain consistency with the criteria of hearing impairment by the WHO as much as possible.

Data abstraction

We extracted the following data from each publication: first author's name, year of publication, number of total and hearing-impaired participants, mean or range of age, proportion of males, geographic region, whether hearing loss was unilateral or bilateral, surveyed frequency range, and definition of hearing loss for each study.

We assessed study quality by the presence of the following items: 1) identification of the type of diabetes, 2) description of the mean duration of diabetes, 3) data given on the presence of diabetic macrovascular and microvascular complications, 4) diabetic and nondiabetic subjects matched for age and gender, 5) exclusion of subjects exposed to noisy environments. Two of our investigators (C.H. and S.K.) independently abstracted these data. Discrepancies were resolved by a third investigator (H.So.).

Data synthesis and analysis

The pooled odds ratio (OR) of hearing impairment in persons with diabetes compared with those without diabetes was calcu-

TABLE 1. Continued

Number of subjects[a]			Hearing loss (%)			Criteria for hearing loss			Matched for age and sex[b]	Excluded for noisy environments[c]
Total	HI	Non-HI	Total	Diabetes	Nondiabetes	Symmetry of hearing loss	Frequency range (kHz)	Threshold for hearing loss (dB)		
196	79	117	40.3	52.3	25.3	Bilateral and unilateral	0.25–8	>25, average	No	No
160	34	126	21.3	30.0	12.5	Unilateral	0.5–4	>25, average	Yes	Yes
2306	576	1730	25.0	39.1	24.0	Bilateral and unilateral	0.125–8	>25, average	No	No
3183	1039	2144	32.6	46.0	7.7	Unilateral	1–4	>25, average	No	No
4486	1038	3448	23.1	46.8	19.6	Unilateral	1–4	>25, average	No	No
625	226	399	36.2	59.3	5.0	Bilateral	2–8	>25, partial and symmetrical	No	Yes
100	46	54	46.0	44.4	66.0	Bilateral	0.25–8	>30, average	Yes	Yes
1858	735	1123	39.6	50.0	14.3	Bilateral	0.5–4	>25, average	No	No
697	336	361	48.2	60.2	13.0	Unilateral	0.5–6	>25, average	No	No
2052	1230	822	59.9	66.8	11.1	Unilateral	0.5–2	>25, average	No	No
							2–8	>40, average	No	No
155	81	74	52.3	74.7	43.2	Bilateral	0.5–2	>25, average	Yes	Yes
3373	1536	1837	45.5	59.0	9.6	Unilateral	0.5–4	>25, overall	No	No
151	110	41	72.8	78.2	50.0	Bilateral	0.125–0.25	≥25, partial	No	Yes
							0.5–2	≥20	No	
							4–8	≥25	No	
852	311	541	36.5	61.8	11.7	Unilateral	0.25–4	>15, partial	No	Yes
							0.125, 8	>20		

lated with a random-effects model using the DerSimonian and Laird method (15) and using between-study heterogeneity derived from the Mantel-Haenszel model (16). The extent of between-study heterogeneity was assessed by I-squared statistics (17). To explore the origin of between-study heterogeneity, analyses were stratified by the following prespecified confounders that potentially influenced the study results: mean age (≥60 or <60 yr), percentage of men (≥50% or <50%), country (Asian or Western), origin of the study population (general or hospital-based population), and criteria for detection of hearing impairment such as threshold (≥25 dB or <25dB), frequency range (all or partial), and ear (bilateral or unilateral). Publication bias was statistically assessed by two formal methods: by Begg's rank correlation and Egger's regression test (18, 19). Two-sided P value <0.05 was considered as statistically significant except for the test for publication bias where $P < 0.10$ was used (20). All analyses were conducted with Stata statistical software version 11 (Stata Corp., College Station, TX).

Results

Literature research and study characteristics

Figure 1 shows details of the literature search. First, 3158 citations were identified. Of these, 2814 articles were excluded according to information given in the title and abstract, and 355 articles, including 11 articles obtained from the manual search, were included for a more detailed review. The review identified four articles (21–24) that were based on overlapping data from the National Health and Nutrition Examination Survey (25), one article (26) that was based on overlapping data from the Blue Mountains Hearing Study (27), and one article (28) that was based on overlapping data from the study of Marumo *et al.* (29). We avoided duplicate inclusion of data by selecting only the more complete article from each study. Finally, 13 articles describing studies with a cross-sectional design met our initial inclusion criteria. A complete reference list of studies included in our meta-analysis is reported in the Supplemental Data.

Characteristics of the 13 selected studies comprising 20,194 participants (range, 100-7669) and 7377 cases (range, 46–2077) of hearing impairment are shown in Table 1. Twelve studies included both males and females (25, 27, 29, 30–38), and one study involved males only (39). No study involved females only. In a large number of included studies (nine studies) (25, 29–31, 33, 34, 36, 38, 39), the mean age of participants was 60 yr or less. Eight studies (27, 30–32, 34, 36, 38, 39) were of the Asian region and five studies (25, 33, 35, 37, 38) of non-Asian regions. In five studies (29, 30, 33, 36, 38), participants were hospital based, and in eight studies (25, 27, 31, 32, 34, 35, 37, 39), participants were from the general population. All studies described the method for assessment of hearing impairment. Most studies (10 studies) (25, 27, 29, 30–32, 35–37, 39) used 25 dB for the hearing impairment threshold with the exception of three studies (33, 34, 38) that used 26, 30, and 20 dB, respectively, as the threshold. Therefore, in all of those included studies, the threshold levels were almost consistent with that of hearing impairment according to the WHO (3). Six studies surveyed unilateral hearing impairment only (25, 31, 35, 37–39), and five surveyed bilateral hearing impairment only (27, 29, 33, 34, 36). The remaining two studies included both unilateral and bilateral hearing impairment (30, 32). In 10 studies, hearing impairment was declared if the disability was present at all frequency ranges, (25, 27, 30–32, 34–37, 39), and in three studies, impairment was declared if the disability was observed in one or more frequencies (29, 33, 38).

Nine of 13 studies (27, 29–32, 34, 36, 37, 39) identified the type of diabetes. Six studies (27, 29, 34, 36, 37, 39) included only participants with type 2 diabetes, and three studies (29, 31, 32) included both type 1 diabetic and type 2 diabetic participants. Mean duration of diabetes was given in only four studies (25, 27, 30, 31). No study described diabetic complications experienced by the subjects. In three studies (31, 34, 36), each diabetic subject was matched with a nondiabetic subject for age and gender. In six studies (29, 31, 33, 34, 36, 38), subjects exposed to noisy environments were excluded; however, no study matched diabetic subjects with nondiabetic subjects according to locations in which specific sources of noise exposure existed, such as industrial, farming, and urban areas.

Overall estimate of prevalence of hearing impairment associated with diabetes

Three studies consisted of two datasets; two (30, 31) analyzed bilateral and unilateral hearing impairment separately, and one (25) included two independent research studies. One study (32) was composed of four datasets based on both age bracket and symmetry of hearing impairment.

A total of 19 datasets were included in this meta-analysis. We used the data surveyed for unilateral hearing impairment (30–32) when the results of the same study overlapped. Figure 2 shows the pooled estimates for hearing impairment in persons with diabetes. The overall pooled OR of hearing impairment for diabetic patients compared with the nondiabetic participants was 2.15 [95% confidence interval (CI) = 1.72–2.68]. Between-study heterogeneity was highly significant in the strength of the association ($I^2 = 76.2\%$; $P < 0.001$). Only one study, that reported by Aladag *et al.* (34), indicated the negative association between diabetes and hearing impairment risk. However, between-study heterogeneity after excluding

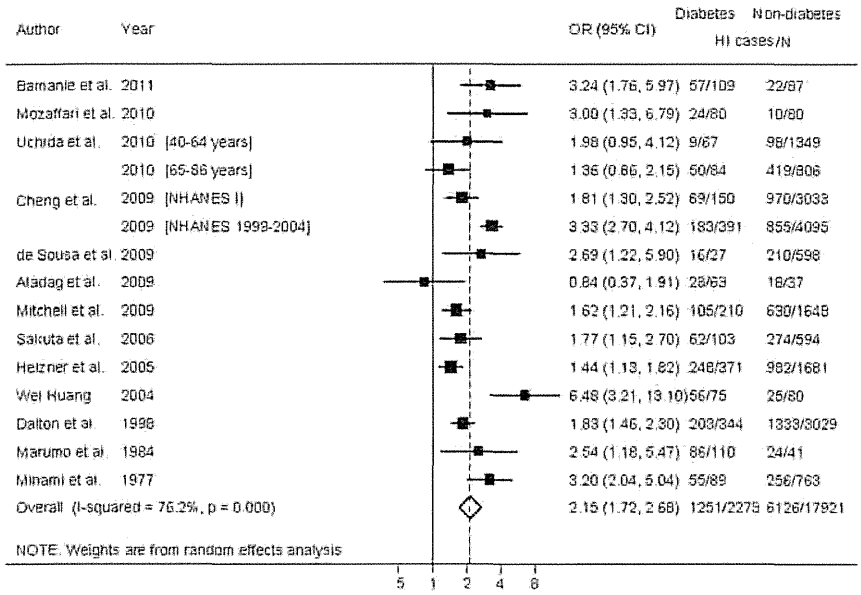

FIG. 2. Forest plot of ORs of hearing impairment (HI) for diabetic participants compared with nondiabetic participants. The size of *squares* reflects the statistical weight of each study. Pooled OR is indicated by *unshaded diamond*.

this study remained highly significant (I^2 = 76.0%; $P < 0.001$). Publication bias was not statistically detected by Egger's test ($P = 0.79$) and Begg's test ($P = 0.54$).

Stratified analysis

Table 2 shows the results of the stratified and meta-regression analyses across a number of key study characteristics to explore the origin of the heterogeneity and the influence of the characteristics on study results. A positive association between diabetes and prevalence of impaired hearing was consistently observed throughout all strata of the specified study characteristics. No significant difference in the strength of the association of diabetes with hearing impairment was observed according to whether hearing impairment was unilateral or bilateral [2.21 (95% CI = 1.55–3.15) and 2.10 (95% CI = 1.54–2.87), $P = 0.85$].

A statistically stronger association between hearing impairment and diabetes incidence was observed in the younger participants (mean age of participants, ≤60 yr) in comparison with those over 60 yr, and the difference was statistically significant [2.61 (95% CI = 2.00–3.45) and 1.58 (95% CI = 1.38–1.81), $P = 0.008$]. Studies comprised of hospital-based populations reported a significantly stronger association than those studies of the general population [3.56 (95% CI = 2.51–5.05) and 1.90 (95% CI = 1.51–2.41), $P = 0.05$]. When the study that defined the threshold of hearing impairment as more than 25 dB was excluded, the pooled risk of hearing impairment was 2.08 (95% CI = 1.65–2.62), but the influence of the exclusion was not significant ($P = 0.35$). The strength of the association between diabetes and hearing impairment was not influenced by differences in the region that the study took place ($P = 0.21$), threshold for hearing impairment ($P = 0.35$), impaired frequency range ($P = 0.34$), whether diabetes was specified as type 2 ($P = 0.49$), whether diabetic participants and nondiabetic participants were matched for age and sex ($P = 0.68$), and whether subjects exposed to noisy environments were excluded ($P = 0.19$).

Discussion

The current meta-analysis indicated that hearing impairment in subjects with diabetes was 2.1-fold more prevalent than in those without diabetes. The significant association between hearing impairment and diabetes was maintained throughout several subgroup-stratified analyses.

Especially, it is well known that aging is associated with both prevalence of hearing impairment and diabetes. Therefore, it is possible that the observed significant relationship between hearing impairment and diabetes is merely a phenomenon of aging. However, according to the stratified analyses, a stronger association was observed in studies of younger participants (mean age of participants, ≤60 yr) compared with studies of older participants. Nevertheless, the OR remained significant when studies were limited to those with participants having a mean age over 60 yr. In addition, a nonsignificant but larger OR was observed in age-matched studies compared with those not age matched, although there were only three studies in which participants were age matched. Our results suggest an independent association of hearing impairment and diabetes, although the possibility of residual confounding by age cannot be eliminated.

A meta-analysis of observational studies in principle can never prove causality. However, there is a plausible explanation of why diabetes could lead to progression of hearing impairment. Fukushima *et al.* (8) reported that thickened walls of vessels in the stria vascularis and their atrophy were observed in patients treated with insulin or hyperglycemic agents compared with those in healthy subjects. It will be important to clarify the dose-response association between the severity of diabetes and risk of hearing impairment (*i.e.* the relationship between hyperglycemia, duration of diabetes, and the prevalence of hearing impairment) for elucidating the causality between hearing impairment and diabetes

TABLE 2. Stratified analyses of pooled OR of hearing loss for diabetes mellitus patients compared with control participants

	No. of data units	OR (95% CI)	Q statistics	I^2 (%)	*P* value of heterogeneity	Meta-regression[a]
Bilateral *vs.* unilateral						
Bilateral	6	2.10 (1.54–2.87)	34.4	85.5	<0.001	Referent
Unilateral	9	2.21 (1.55–3.15)	24.1	66.8	0.002	0.85
Mean age (yr)						
≤60	11[b]	2.61 (2.00–3.45)	32.2	68.0	<0.001	Referent
>60	5[b]	1.58 (1.38–1.81)	8.8	54.6	0.066	0.008
% Men						
≤50%	7	2.10 (1.57–2.80)	36.0	83.3	<0.001	Referent
>50%	9	2.39 (1.62–3.54)	26.2	69.4	<0.001	0.66
Region						
Asia	9	2.37 (1.75–3.22)	23.4	65.9	0.003	Referent
Non-Asia	6	1.89 (1.33–2.70)	35.5	85.9	<0.001	0.29
Study population						
Hospital based	4	3.56 (2.51–5.05)	4.1	27.2	0.25	Referent
Population based	11	1.90 (1.51–2.41)	45.4	78.0	<0.001	0.05
Impaired frequency range						
Full range	13	2.06 (1.62–2.61)	54.9	78.1%	<0.001	Referent
Partial range	2	3.02 (2.05–4.46)	0.26	0.0	0.61	0.34
Study quality						
Type of diabetes						
Type 2 diabetes mellitus only	6	2.07 (1.46–2.95)	19.9	74.8	0.001	Referent
Type 1 and type 2 diabetes mellitus	4	1.83 (1.33–2.51)	3.8	20.7	0.29	0.67
Not available	5	2.33 (1.53–3.53)	31.3	87.2	<0.001	0.56
Age and sex matched						
Not applied	12	2.06 (1.66–2.56)	43.3	74.6	<0.001	Referent
Applied	3	2.58 (0.79–8.38)	13.8	85.5	0.001	0.68
Whether subjects exposed to noisy environments were excluded						
Not excluded	9	1.92 (1.51–2.45)	38.3	79.1	<0.001	Referent
Excluded	6	2.74 (1.69–4.45)	14.2	64.8	0.014	0.19

Except for the top characteristic, assessed ear, data based on the better ear were used if both the better and worst ear were assessed.

[a] Represents the test for the significance of the study modification across strata.

[b] One study by Minami *et al.* (38) presented data by age (≤60 and >60 yr). Therefore, the total number of data is 16.

mellitus. Furthermore, the significance of strict glycemic control in the prevention of hearing loss should be studied.

Limitations of this meta-analysis must be considered. First, our meta-analysis is based on findings of observational studies; therefore, it is impossible to control residual confounders linking diabetes and hearing impairment (*e.g.* drug use) (6). Second no data were provided on the prevalence of diabetic complications in any of the included studies. Given that microangiopathy in the inner ear was suggested in patients with diabetes (8), it is possible that the severity of diabetes might influence the strength of the association between diabetes and hearing impairment and produce between-study heterogeneity in the association. That possibility might have been reflected by the result of the stratified analysis that showed a stronger association in hospital-based populations that included patients with severe diabetes compared with studies of general populations.

Third, we limited our analysis to adult-onset hearing impairment. However, persons with hearing impairment before adulthood might have been included among subjects in this meta-analysis. For example, it is possible that patients with diabetic cheiropathy developed asymptomatic hearing impairment before adulthood, although there has been no report showing clear evidence for the coexistence of hearing impairment among such patients.

Fourth, there were no studies that matched diabetic individuals and nondiabetic individuals in locations where sources of noise exposure were similar. Therefore, the extent of noise exposure might have been different between diabetic and nondiabetic subjects. However, noise exposure is unlikely to be a confounder because the current stratified analysis indicated that the strength of association between diabetes and prevalence of hearing impairment was not significantly influenced by whether or not subjects who were chronically exposed to a noisy environment were excluded.

Finally, publication bias is inevitable because researchers are not as likely to report negative findings. Its possibility could not be ruled out even if it were not statistically derived.

In conclusion, our meta-analysis indicated a significantly higher prevalence of hearing impairment in patients with diabetes compared with that in nondiabetic people. Moreover, the finding is likely to be independent of the effect of aging or a noisy environment. Additional studies are needed to clarify the relationship between diabetes severity and prevalence of hearing impairment and the effect of glycemic control on hearing loss.

Acknowledgments

We thank Hiromitsu Akizuki, M.D., Ph.D., The Head of Department of Otolaryngology, Mito Kyodo General Hospital, for helpful advice from an otological standpoint. Thanks are extended to Ms. Satomi Fukuya and Ms. Yasuko Maruyama, University of Tsukuba, for their excellent secretarial assistance.

Address all correspondence and requests for reprints to: Hirohito Sone, M.D., Ph.D., F.A.C.P., Professor of Internal Medicine, Department of Hematology, Endocrinology, and Metabolism, Niigata Univeristy Faculty of Medicine, 1-757 Asahimachi-dori, Chuoh-ku, Niigata, Japan 951-8510. E-mail: sone@med.niigata-u.ac.jp.

This work was supported by the Ministry of Health, Labor and Welfare, Japan. The sponsor had no role in the design and conduct of the study. H.Sh. 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 research organizations providing funding support did not have any role in the design and conduct of the study; in the correction, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

All authors researched data, contributed to the discussion, and wrote and edited the manuscript. H.So. had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. C.H., S.K., K.F., H.Sh., N.Y., and H.So. were responsible for study concept and design. C.H., S.K., R.H., Y.Y., K.S. were responsible for acquisition of data. C.H., S.K., S.T., K.F., R.H., K.S., and H.So. were responsible for analysis and interpretation of data. C.H., S.K., S.T., and H.So. were responsible for drafting of the manuscript. C.H., S.K., H.Sh., N.Y., and H.So. were responsible for critical revision of the manuscript for important intellectual content. C.H., S.K., S.T., Y.Y., K.S., H.So. were responsible for statistical analysis. H.So. obtained funding. H.Sh., N.Y., R.H., Y.Y., and H.So. provided administrative, technical, or material support. S.K. and H.So. were responsible for study supervision.

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

References

1. **World Health Organization** 2012 Deafness and hearing impairment.FactsheetN°300.http://www.who.int/mediacentre/factsheets/fs300/en/index.html (accessed July 16, 2012)
2. **Nelson DI, Nelson RY, Concha-Barrientos M, Fingerhut M** 2005 The global burden of occupational noise-induced hearing loss. Am J Ind Med 48:446–458
3. **World Health Organization** 2012 Prevention of blindness and deafness: grades of hearing impairment. http://www.who.int/pbd/deafness/hearing[lowem]impairment_grades/en/index.html (accessed July 16, 2012)
4. **Yueh B, Shapiro N, MacLean CH, Shekelle PG** 2003 Screening and management of adult hearing loss in primary care: scientific review. JAMA 289:1976–1985
5. **Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L** 2011 Hearing loss and incident dementia. Arch Neurol 68: 214–220
6. **Rybak LP** 1986 Drug ototoxicity. Annu Rev Pharmacol Toxicol 26:79–99
7. **Hirose K** 2008 Hearing loss and diabetes: you might not know what you're missing. Ann Intern Med 149:54–55
8. **Fukushima H, Cureoglu S, Schachern PA, Paparella MM, Harada T, Oktay MF** 2006 Effects of type 2 diabetes mellitus on cochlear structure in humans. Arch Otolaryngol Head Neck Surg 132:934–938
9. **Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB** 2000 Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 283:2008–2012
10. **Vaughan N, James K, McDermott D, Griest S, Fausti S** 2006 A 5-year prospective study of diabetes and hearing loss in a veteran population. Otol Neurotol 27:37–43
11. **Ishii EK, Talbott EO, Findlay RC, D'Antonio JA, Kuller LH** 1992 Is NIDDM a risk factor for noise-induced hearing loss in an occupationally noise exposed cohort? Sci Total Environ 127:155–165
12. **Rath PP, Jenkins S, Michaelides M, Smith A, Sweeney MG, Davis MB, Fitzke FW, Bird AC** 2008 Characterisation of the macular dystrophy in patients with the A3243G mitochondrial DNA point mutation with fundus autofluorescence. Br J Ophthalmol 92:623–629
13. **Deschauer M, Müller T, Wieser T, Schulte-Mattler W, Kornhuber M, Zierz S** 2001 Hearing impairment is common in various phenotypes of the mitochondrial DNA A3243G mutation. Arch Neurol 58:1885–1888
14. **Barrett TG, Bundey SE, Macleod AF** 1995 Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. Lancet 346:1458–1463
15. **DerSimonian R, Laird N** 1986 Meta-analysis in clinical trials. Control Clin Trials 7:177–188
16. **Mantel N, Haenszel W** 1959 Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748
17. **Higgins JP, Thompson SG** 2002 Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558
18. **Begg CB, Mazumdar M** 1994 Operating characteristics of a rank correlation test for publication bias. Biometrics 50:1088–1101
19. **Egger M, Davey Smith G, Schneider M, Minder C** 1997 Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
20. **Sterne JA, Gavaghan D, Egger M** 2000 Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 53:1119–1129
21. **Bainbridge KE, Cheng YJ, Cowie CC** 2010 Potential mediators of diabetes-related hearing impairment in the U.S. population: National Health and Nutrition Examination Survey 1999–2004. Diabetes Care 33:811–816
22. **Bainbridge KE** 2009 Correlates of hearing impairment in the U.S. population with diabetes, national health and nutrition examination survey, 1999–2004. Diabetes 58(Suppl 1):957-P
23. **Agrawal Y, Platz EA, Niparko JK** 2009 Risk factors for hearing loss in US adults: data from the National Health and Nutrition Examination Survey, 1999 to 2002. Otol Neurotol 30:139–145
24. **Bainbridge KE, Hoffman HJ, Cowie CC** 2008 Diabetes and hearing impairment in the United States: audiometric evidence from the Na-

tional Health and Nutrition Examination Survey, 1999 to 2004. Ann Intern Med 149:1–10
25. **Cheng YJ, Gregg EW, Saaddine JB, Imperatore G, Zhang X, Albright AL** 2009 Three decade change in the prevalence of hearing impairment and its association with diabetes in the United States. Prev Med 49:360–364
26. **Manwaring N, Jones MM, Wang JJ, Rochtchina E, Howard C, Newall P, Mitchell P, Sue CM** 2007 Mitochondrial DNA haplogroups and agerelated hearing loss. Arch Otolaryng Head Neck Surg 133:929–933
27. **Mitchell P, Gopinath B, McMahon CM, Rochtchina E, Wang JJ, Boyages SC, Leeder SR** 2009 Relationship of type 2 diabetes to the prevalence, incidence and progression of age-related hearing loss. Diabet Med 26:483–488
28. **Marumo K** 1982 Studies on hearing impairment in patients with diabetes mellitus. J Osaka City Med Center 31:305–321
29. **Marumo K, Fujii S, Tsurusaki M, Soh K, Seki J, Wada M** 1984 Clinical studies on hearing impairment in diabetic patients. J Jpn Diabetes Soc 27:1105–1114
30. **Bamanie AH, Al-Noury KI** 2011 Prevalence of hearing loss among Saudi type 2 diabetic patients. Saudi Med J 32:271–274
31. **Mozaffari M, Tajik A, Ariaei N, Ali-Ehyaii F, Behnam H** 2010 Diabetes mellitus and sensorineural hearing loss among non-elderly people. East Mediterr Health J 16:947–952
32. **Uchida Y, Sugiura S, Ando F, Nakashima T, Shimokata H** 2010 Diabetes reduces auditory sensitivity in middle-aged listeners more than in elderly listeners: a population- based study of age-related hearing loss. Med Sci Monit 16:PH63–PH68
33. **Sousa CS, Castro Junior N, Larsson EJ, Ching TH** 2009 Risk factors for presbycusis in a socio-economic middle-class sample. Braz J Otorhinolaryngol 75:530–536
34. **Aladag I, Eyibilen A, Guven M, Atis O, Erkokmaz U** 2009 Role of oxidative stress in hearing impairment in patients with type two diabetes mellitus. J Laryngol Otol 123:957–963
35. **Helzner EP, Cauley JA, Pratt SR, Wisniewski SR, Zmuda JM, Talbott EO, de Rekeneire N, Harris TB, Rubin SM, Simonsick EM, Tylavsky FA, Newman AB** 2005 Race and sex differences in age-related hearing loss: the Health, Aging and Body Composition Study. J Am Geriatr Soc 53:2119–2127
36. **Huang W** 2004 Characteristics of hearing loss in type 2 diabetic patients. Chin J Clin Rehab 8:1612–1613
37. **Dalton DS, Cruickshanks KJ, Klein R, Klein BE, Wiley TL** 1998 Association of NIDDM and hearing loss. Diabetes Care 21:1540–1544
38. **Minami Y, Hori A** 1977 [Hearing impairment in diabetics (author's transl)]. Nihon Jibiinkoka Gakkai kaiho 80:354–365
39. **Sakuta H, Suzuki T, Yasuda H, Ito T** 2007 Type 2 diabetes and hearing loss in personnel of the Self-Defense Forces. Diabetes Res Clin Pract 75:229–234

HbA_{1c} 5·7–6·4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study

Yoriko Heianza, Shigeko Hara, Yasuji Arase, Kazumi Saito, Kazuya Fujiwara, Hiroshi Tsuji, Satoru Kodama, Shiun Dong Hsieh, Yasumichi Mori, Hitoshi Shimano, Nobuhiro Yamada, Kinori Kosaka, Hirohito Sone

Summary

Background The clinical relevance of the diagnostic criteria for prediabetes to prediction of progression to diabetes has been little studied. We aimed to compare the prevalence of prediabetes when assessed by the new glycated haemoglobin A_{1c} (HbA_{1c}) 5·7–6·4% criterion or by impaired fasting glucose, and assessed differences in progression rate to diabetes between these two criteria for prediabetes in a Japanese population.

Methods Our longitudinal cohort study included 4670 men and 1571 women aged 24–82 years without diabetes at baseline (diabetes was defined as fasting plasma glucose ≥7·0 mmol/L, self-reported clinician-diagnosed diabetes, or HbA_{1c} ≥6·5%) who attended Toranomon Hospital (Tokyo, Japan) for a routine health check between 1997 and 2003. Participants with a baseline diagnosis of prediabetes according to impaired fasting glucose (fasting plasma glucose 5·6–6·9 mmol/L) or HbA_{1c} 5·7–6·4%, or both, were divided into four groups on the basis of baseline diagnosis of prediabetes. Rate of progression to diabetes was assessed annually.

Findings Mean follow-up was 4·7 (SD 0·7) years. 412 (7%) of 6241 participants were diagnosed with prediabetes on the basis of the HbA_{1c} 5·7–6·4% criterion. Screening by HbA_{1c} alone missed 1270 (61%) of the 2092 prediabetic individuals diagnosed by a combination of impaired fasting glucose and HbA_{1c} 5·7–6·4%. Overall cumulative probability of progression to diabetes did not differ significantly between participants with prediabetes discordantly diagnosed by either HbA_{1c} or impaired fasting glucose alone (incidence was 7% for HbA_{1c} alone [n=412 individuals and 30 incident cases] and 9% for impaired fasting glucose alone [n=1270, 108 cases]; log-rank test, p=0·3317). Multivariate-adjusted hazard ratios for incident diabetes were 6·16 (95% CI 4·33–8·77) for those diagnosed with prediabetes by impaired fasting glucose alone and 6·00 (3·76–9·56) for diagnosis by HbA_{1c} alone, and were substantially increased to 31·9 (22·6–45·0) for diagnosis by both impaired fasting glucose and HbA_{1c} compared with normoglycaemic individuals.

Interpretation Diagnosis of prediabetes by both the new HbA_{1c} criterion and impaired fasting glucose identified individuals with an increased risk of progression to diabetes. Although the new HbA_{1c} criterion identified fewer individuals at high risk than did impaired fasting glucose, the predictive value for progression to diabetes assessed by HbA_{1c} 5·7–6·4% was similar to that assessed by impaired fasting glucose alone. The two tests used together could efficiently target people who are most likely to develop diabetes and allow for early intervention.

Funding Japan Society for the Promotion of Science; Ministry of Health Labor and Welfare, Japan.

Lancet 2011; 378: 147–55
Published Online June 25, 2011
DOI:10.1016/S0140-6736(11)60472-8

See Comment page 104

Department of Internal Medicine, University of Tsukuba Institute of Clinical Medicine, Ibaraki, Japan (Y Heianza RD, K Saito MD, K Fujiwara MD, S Kodama MD, Prof H Shimano MD, Prof N Yamada MD, Prof H Sone MD); **Health Management Center, Toranomon Hospital, Tokyo, Japan** (Y Heianza, S Hara MD, Y Arase MD, K Saito, H Tsuji MD, S Kodama, S D Hsieh MD, Prof K Kosaka MD, Prof H Sone); **and Okinaka Memorial Institute for Medical Research, Toranomon Hospital, Tokyo, Japan** (S Hara, Y Arase, H Tsuji, S D Hsieh, Y Mori MD, Prof K Kosaka)

Correspondence to:
Prof Hirohito Sone, Health Management Center, Toranomon Hospital, Tokyo 105-8470, Japan
hsone@md.tsukuba.ac.jp

Introduction

In prediabetes, blood glucose concentrations are higher than normal, but are not high enough for diagnosis of diabetes. The disorder is thought to place individuals at high risk of future diabetes, according to the American Diabetes Association (ADA).[1] ADA guidelines suggest targeting of individuals identified as having prediabetes for early intervention.[1] A new criterion has been proposed for the diagnosis of prediabetes: glycated haemoglobin A_{1c} (HbA_{1c}) 5·7–6·4%. However, the performance of HbA_{1c} as a screening test for identification of prediabetic individuals has been controversial.[2–6] Many individuals who were diagnosed as having prediabetes on the basis of impaired fasting glucose are reclassified as not having the disorder when the new HbA_{1c} 5·7–6·4% criterion is used; thus, screening by HbA_{1c} alone might miss a large number of prediabetic individuals.[2–5] The new criterion's performance in detection of prediabetic individuals differs according to ethnic origin,[4,5] and more evidence of its usefulness in non-western populations is needed.[4,6]

Few studies[7,8] have longitudinally compared the difference in progression rate to diabetes after diagnosis of prediabetes with the HbA_{1c} 5·7–6·4% criterion or by impaired fasting glucose, or established which criterion for prediabetes is clinically relevant for prediction of progression. Whether introduction of the new HbA_{1c} criterion in addition to assessment of fasting glucose could efficiently target prediabetic individuals who are most likely to progress to diabetes is unclear. We aimed to evaluate the effect of introduction of the HbA_{1c} 5·7–6·4% criterion into diagnosis of prediabetes by

impaired fasting glucose, and to longitudinally assess differences in the progression rate to diabetes between individuals diagnosed with prediabetes on the basis of these two criteria in a large Japanese cohort. We tested whether the two tests used together could target people most likely to progress to diabetes, which would allow early intervention.

	Study participants (n=6241)
Age (years)	49·9 (8·7)
Men	4670 (75%)
Smoking habit	
Never	3342 (54%)
Former	1503 (24%)
Current	1396 (22%)
BMI ≥25·0 kg/m²	1215 (19%)
Hypertension	1320 (21%)
Dyslipidaemia	1962 (31%)
History of coronary heart disease	84 (1%)
History of stroke	16 (<1%)

Data are n (%) or mean (SD). Hypertension is defined as systolic blood pressure 140 mm Hg or higher, diastolic blood pressure 90 mm Hg or higher, or on treatment. Dyslipidaemia is defined as triglyceride concentration 1·7 mmol/L or higher, HDL cholesterol lower than 1·03 mmol/L, or on treatment. BMI=body-mass index.

Table 1: **Overall baseline characteristics**

Methods

Study population

The Toranomon Hospital Health Management Center Study (TOPICS) included a cohort consisting mainly of apparently healthy Japanese government employees who underwent annual examinations for health screening. The details of the study have been described previously.[9] The cohort consisted of 32 057 individuals who had a routine health check for the first time between 1997 and 2003 at the Health Management Center, Toranomon Hospital (Tokyo, Japan). Of these 32 057 individuals, our investigation included 6636 individuals who had annual examinations regularly for 4 years (n=1716) or 5 years (n=4920) after the initial examination. Registered nurses interviewed all participants at the time of each annual examination using standard questionnaires that gathered information about demographic characteristics, medical history, and health-related habits. We excluded 310 individuals who had diabetes at the baseline examination (192 individuals were previously diagnosed and 118 were undiagnosed) or who had missing data for baseline characteristics (n=89). Subsequently, 6241 individuals aged 24–82 years were eligible for our analysis.

The study protocol was consistent with the Japanese Government's ethics guidelines regarding epidemiological studies in accordance with the Declaration of Helsinki and was reviewed by the institutional review

		Prediabetes			p value		
	Normoglycaemia (group 1, n=4149)	IFG alone (group 2, n=1270)	HbA_{1c} 5·7–6·4% alone (group 3, n=412)	Both HbA_{1c} 5·7–6·4% and IFG (group 4, n=410)	1 *vs* 2	1 *vs* 3	1 *vs* 4
Age (years)	49·2 (48·9–49·4)	49·9 (49·5–50·4)	54·3 (53·5–55·1)	53·7 (52·8–54·5)	0·0048	<0·0001	<0·0001
Women	1252 (30%)	118 (9%)	130 (32%)	71 (17%)	<0·0001	0·56	<0·0001
Family history of diabetes	532 (13%)	194 (15%)	69 (17%)	90 (22%)	0·0247	0·0247	<0·0001
Current smoking	880 (21%)	312 (25%)	101 (25%)	103 (25%)	0·0115	0·12	0·0661
BMI (kg/m²)*	22·5 (22·4–22·6)	23·5 (23·3–23·6)	22·9 (22·7–23·2)	23·8 (23·6–24·1)	<0·0001	0·0034	<0·0001
Obesity (BMI ≥25·0 kg/m²)*	648 (16%)	370 (29%)	73 (18%)	124 (30%)	<0·0001	0·27	<0·0001
Systolic blood pressure (mm Hg)*	123 (123–124)	130 (129–131)	123 (121–124)	127 (126–129)	<0·0001	0·52	<0·0001
Diastolic blood pressure (mm Hg)*	75 (75–76)	80 (80–81)	75 (74–76)	78 (77–79)	<0·0001	0·37	<0·0001
Triglycerides (mmol/L)*	1·23 (1·21–1·26)	1·43 (1·38–1·47)	1·33 (1·25–1·41)	1·59 (1·51–1·67)	<0·0001	0·0179	<0·0001
Total cholesterol (mmol/L)*	5·22 (5·19–5·24)	5·37 (5·33–5·42)	5·35 (5·27–5·43)	5·46 (5·38–5·54)	<0·0001	0·0015	<0·0001
HDL cholesterol (mmol/L)*	1·41 (1·40–1·42)	1·42 (1·40–1·44)	1·33 (1·29–1·36)	1·31 (1·28–1·34)	0·49	<0·0001	<0·0001
γ-glutamyltransferase (units per L)*	46·1 (44·5–47·8)	63·8 (60·8–66·8)	50·3 (45·0–55·5)	65·0 (59·7–70·3)	<0·0001	0·14	<0·0001
Uric acid (μmol/L)*	333·7 (331·6–335·8)	349·1 (345·3–352·9)	334·5 (327·8–341·2)	354·9 (348·2–361·6)	<0·0001	0·83	<0·0001
eGFR (ml/min per 1·73m²)*	75·5 (75·1–75·8)	76·2 (75·6–76·9)	74·5 (73·3–75·6)	75·9 (74·7–77·1)	0·0559	0·11	0·50
White cell count (×10⁹/L)*	5·2 (5·2–5·3)	5·3 (5·2–5·4)	5·5 (5·4–5·7)	5·6 (5·5–5·8)	0·0654	0·0001	<0·0001
Haemoglobin (g/L)*	145 (144–145)	146 (146–147)	141 (140–142)	145 (144–146)	<0·0001	<0·0001	0·18
Fasting plasma glucose (mmol/L)*	5·1 (5·0–5·1)	5·8 (5·8–5·8)	5·1 (5·1–5·2)	6·0 (6·0–6·0)	<0·0001	<0·0001	<0·0001
HbA_{1c} (%)*	5·2% (5·2–5·2)	5·3% (5·3–5·3)	5·8% (5·8–5·8)	5·9% (5·8–5·9)	<0·0001	<0·0001	<0·0001

Data are n (%) or mean (95% CI). Categorical data were analysed with the χ^2 test. HbA_{1c} was estimated as the National Glycohemoglobin Standardization Program equivalent value (%). Normoglycaemia was defined as HbA_{1c} less than 5·7% and FPG lower than 5·6 mmol/L. Diagnosis of prediabetes was by IFG alone when HbA_{1c} less than 5·7% and FPG 5·6–6·9 mmol/L, by HbA_{1c} alone when HbA_{1c} 5·7–6·4% and FPG lower than 5·6 mmol/L, and by both HbA_{1c} and IFG when HbA_{1c} 5·7–6·4% and FPG 5·6–6·9 mmol/L. HbA_{1c}=glycated haemoglobin A_{1c}. IFG=impaired fasting glucose. FPG=fasting plasma glucose. BMI=body-mass index. eGFR=estimated glomerular filtration rate. *Adjusted for age and sex.

Table 2: **Baseline characteristics according to diagnosis of prediabetes by HbA_{1c} and IFG criteria**

board at Toranomon Hospital. Written informed consent was obtained from all participants.

Procedures

Blood samples were obtained after an overnight fast (12 h) and tested with an automatic clinical chemistry analyser (Hitachi, LABOSPECT 008, Tokyo, Japan). Blood glucose, serum triglyceride, total cholesterol, HDL cholesterol, and uric acid concentrations were measured by enzymatic methods. HbA_{1c} was assessed by high-performance liquid chromatography. The intra-assay coefficient of variation was 0·7% with a mean of 4·29%, and the interassay coefficient of variation was 0·7% with a mean of 4·29%. The value for HbA_{1c} was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the formula:[10]

$$HbA_{1c}(\%) = HbA_{1c}(\text{Japan Diabetes Society})(\%) + 0{\cdot}4\%$$

Diabetes was defined in accordance with ADA guidelines[1] as a fasting plasma glucose (FPG) concentration of 7·0 mmol/L or higher, self-reported clinician-diagnosed diabetes, or HbA_{1c} 6·5% or higher. Baseline diagnosis of prediabetes was based on the new ADA criterion[1] of impaired fasting glucose (FPG 5·6–6·9 mmol/L) or HbA_{1c} 5·7–6·4%, or both. Participants were divided into four groups on the basis of baseline diagnosis of prediabetes: (1) normoglycaemia (HbA_{1c} <5·7% and FPG <5·6 mmol/L); (2) impaired fasting glucose alone (HbA_{1c} <5·7% and FPG 5·6–6·9 mmol/L); (3) HbA_{1c} 5·7–6·4% alone (HbA_{1c} 5·7–6·4% and FPG <5·6 mmol/L); and (4) both HbA_{1c} 5·7–6·4% and impaired fasting glucose (HbA_{1c} 5·7–6·4% and FPG 5·6–6·9 mmol/L). Additionally, to investigate whether similar associations between a baseline diagnosis of prediabetes and future risk of diabetes would be identified irrespective of the diagnostic criteria for incident diabetes, we did an analysis of incident cases of diabetes that were diagnosed with three other criteria: diabetes indicated by self-reported clinician-diagnosis; diabetes indicated by self-reported clinician-diagnosis or FPG 7·0 mmol/L or higher; or diabetes indicated by self-reported clinician-diagnosis or HbA_{1c} 6·5% or higher.

Statistical analysis

We used SPSS (version 16.0) for all analyses and regarded p values lower than 0·05 as significant. We compared baseline characteristics between the four prediabetic groups using a general linear model with adjustments for age and sex. The level of agreement of the diagnostic categories between FPG and HbA_{1c} criteria was examined with κ statistics.[11] The diagnostic property of HbA_{1c} for FPG 5·6–6·9 mmol/L was cross-sectionally evaluated by a receiver operating characteristic (ROC) curve. We also did an analysis when FPG concentrations of

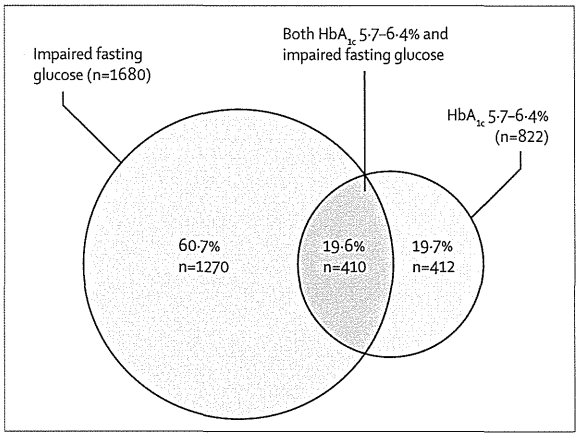

Figure 1: **Prevalence of individuals with prediabetes according to diagnosis by glycated haemoglobin A_{1c} (HbA_{1c}) 5·7–6·4% and impaired fasting glucose (fasting plasma glucose 5·6–6·9 mmol/L) criteria at a baseline examination (n=2092)**

	Proportion of total population (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
6·4%	<1%	1%	100%	100%	73%
6·3%	<1%	1%	100%	89%	73%
6·2%	1%	3%	100%	79%	74%
6·1%	2%	5%	99%	72%	74%
6·0%	3%	8%	99%	67%	74%
5·9%	5%	12%	97%	59%	75%
5·8%	8%	17%	95%	54%	76%
5·7%	13%	24%	91%	50%	77%
5·6%	21%	35%	85%	46%	78%
5·5%	30%	46%	76%	42%	79%
5·4%	41%	57%	65%	37%	80%
5·3%	53%	69%	52%	35%	82%
5·2%	66%	79%	40%	33%	84%

Impaired fasting glucose was defined as fasting plasma glucose 5·6–6·9 mmol/L. HbA_{1c}=glycated haemoglobin A_{1c}.

Table 3: **Sensitivity, specificity, and positive and negative predictive values for identification of individuals with impaired fasting glucose at different HbA_{1c} thresholds**

	Participants without diabetes (n=5903)	Participants with diabetes (n=338)
Normoglycaemia	4103 (70%)	46 (14%)
Baseline diagnosis of prediabetes		
IFG alone	1162 (20%)	108 (32%)
HbA_{1c} 5·7–6·4% alone	382 (6%)	30 (9%)
Both HbA_{1c} 5·7–6·4% and IFG	256 (4%)	154 (46%)

Data are n (%). Normoglycaemia was defined as HbA_{1c} lower than 5·7% and FPG lower than 5·6 mmol/L. Diagnosis of prediabetes was by IFG alone when HbA_{1c} lower than 5·7% and FPG 5·6–6·9 mmol/L, by HbA_{1c} alone when HbA_{1c} 5·7–6·4% and FPG lower than 5·6 mmol/L, and by both HbA_{1c} and IFG when HbA_{1c} 5·7–6·4% and FPG 5·6–6·9 mmol/L. IFG=impaired fasting glucose. HbA_{1c}=glycated haemoglobin A_{1c}. FPG=fasting plasma glucose.

Table 4: **Comparison of baseline diagnosis of prediabetes between individuals who did and did not develop type 2 diabetes**

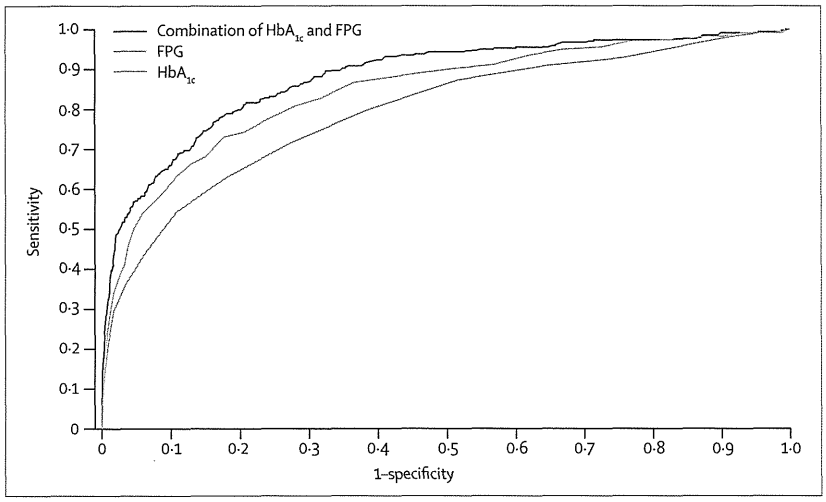

Figure 2: **ROC curve for prediction of future diabetes by HbA_{1c}, by FPG, and by the combination of HbA_{1c} and FPG**
ROC curve for HbA_{1c}, AUC 0·795 (95% CI 0·767–0·822); ROC curve for FPG, AUC 0·846 (0·821–0·870); ROC curve for the combination of HbA_{1c} and FPG, AUC 0·880 (0·859–0·901). ROC=receiver operating characteristic. HbA_{1c}=glycated haemoglobin A_{1c}. FPG=fasting plasma glucose. AUC=area under the curve.

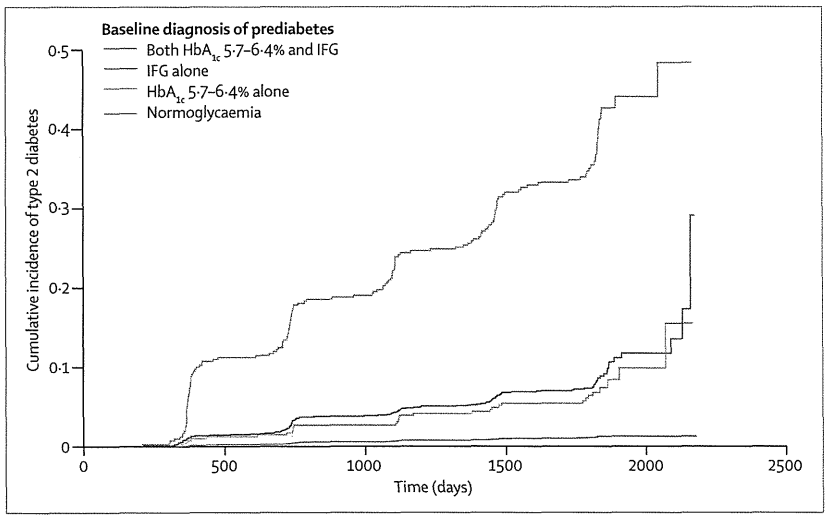

Figure 3: **Cumulative incidence of diabetes during follow-up according to baseline diagnosis of prediabetes**
Log-rank test, p=0·3317 between IFG alone and HbA_{1c} 5·7–6·4% alone. Normoglycaemia defined as HbA_{1c} lower than 5·7% and FPG lower than 5·6 mmol/L. Diagnosis of prediabetes by IFG alone defined as HbA_{1c} less than 5·7% and FPG 5·6–6·9 mmol/L, by HbA_{1c} alone defined as HbA_{1c} 5·7–6·4% and FPG lower than 5·6 mmol/L, and by both HbA_{1c} and IFG defined as HbA_{1c} 5·7–6·4% and FPG 5·6–6·9 mmol/L. HbA_{1c}=glycated haemoglobin A_{1c}. IFG=impaired fasting glucose. FPG=fasting plasma glucose.

6·1–6·9 mmol/L rather than 5·6–6·9 mmol/L were applied as the reference criterion.

In prospective analyses, we undertook an ROC analysis for prediction of risk of future diabetes on the basis of HbA_{1c}, FPG, and the combination of the two values (HbA_{1c} and FPG). Risk established for the combination of the two tests was calculated as: log hazard ratio = (β1×FPG) + (β2×HbA_{1c}). Unadjusted overall time to the development of diabetes was described by Kaplan-Meier analysis with log-rank testing. Cox regression was used to estimate the hazard ratios (HRs) and their 95% CIs for each baseline diagnosis of prediabetes with a normoglycaemic group as the reference. Follow-up for each participant was calculated from the date of the first examination to the date of confirmed diabetes or the date of the last follow-up examination.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Prevalence of diabetes in the entire study population was 5% (1684 of 32 057 people). Table 1 shows characteristics of study participants (n=6241). On the basis of the HbA_{1c} 5·7–6·4% criterion, 412 (7%) individuals in the study population had newly diagnosed prediabetes (table 2). Prediabetic individuals diagnosed by impaired fasting glucose but not by HbA_{1c} had significantly different characteristics at the baseline examination compared with those diagnosed by HbA_{1c} but not by fasting glucose. Those diagnosed on the basis of HbA_{1c} alone were more likely to be women, older, and less hypertensive, to have a lower body-mass index (BMI), lower triglyceride, uric acid, HDL cholesterol, and γ-glutamyltransferase concentrations, and higher leucocyte counts than those diagnosed by impaired fasting glucose alone (adjusted for age and sex).

Of 2092 prediabetic individuals at the baseline examination, only 20% (n=412) were classified as having prediabetes by the HbA_{1c} criterion without impaired fasting glucose (figure 1). Screening by HbA_{1c} alone missed 61% of the total number of prediabetic individuals diagnosed by a combination of impaired fasting glucose and HbA_{1c} 5·7–6·4%, and 1270 prediabetic individuals previously diagnosed by impaired fasting glucose (n=1680) were not classified as having prediabetes. The magnitude of overlap between the two criteria was low: 50% of prediabetic individuals diagnosed by HbA_{1c} also had impaired fasting glucose (n=410/822), and 24% of those diagnosed by impaired fasting glucose also had HbA_{1c} 5·7–6·4% (n=410/1680). We noted poor agreement between impaired fasting glucose and HbA_{1c} criteria (κ 0·18, 95% CI 0·16–0·21). HbA_{1c} ranging between 5·6% and 6·4% provided the highest agreement with impaired fasting glucose (κ 0·22, 0·19–0·24), although the improvement was small.

The area under the curve for the ROC analysis with HbA_{1c} for diagnosis of prediabetes by impaired fasting glucose was 0·656 (95% CI 0·641–0·672). For identification of individuals with impaired fasting glucose, a threshold of HbA_{1c} 5·7% showed high specificity of 91% and low sensitivity of 24%, wher eas HbA_{1c} 5·5% gave the highest combination of specificity (76%) and sensitivity (46%; table 3). When the more restrictive definition for impaired fasting glucose of FPG 6·1–6·9 mmol/L was

applied instead of 5·6–6·9 mmol/L, the prevalence of prediabetes by impaired fasting glucose decreased from 27% (n=1680) to 6% (n=380) among the total population, and 17% (n=1043) had prediabetes by either FPG 6·1–6·9 mmol/L or HbA_{1c} 5·7–6·4%. The area under the curve for the ROC analysis with HbA_{1c} for detection of FPG 6·1–6·9 mmol/L was 0·740 (95% CI 0·714–0·766), and the threshold of HbA_{1c} 5·7% showed a sensitivity of 42% and specificity of 89%.

After the baseline diagnosis of prediabetes, we documented 338 incident cases of diabetes during a mean 4·7 years' (SD 0·7) annual follow-up. A prediabetic state assessed by impaired fasting glucose alone, by HbA_{1c} 5·7–6·4% alone, or by both fasting glucose and HbA_{1c} preceded diabetes in 32% (n=108), 9% (n=30), and 46% (n=154) of incident cases of diabetes, respectively (table 4). Of the incident cases, 86% (n=292) were predicted by either impaired fasting glucose or HbA_{1c} 5·7–6·4%, whereas 14% (n=46) with normoglycaemia at baseline progressed straight to diabetes. Among normoglycaemic individuals (HbA_{1c} <5·7% and FPG <5·6 mmol/L), higher baseline levels of both HbA_{1c} and FPG, even though within a normal range, were associated with development of diabetes. As to age-adjusted and sex-adjusted HRs, for each 0·5% increase in HbA_{1c} there was a 2·57 (95% CI 1·32–5·00) increase in the HR and for each 0·55 mmol/L (10 mg/dl) increase in FPG values there was an increase of 2·33 (95% CI 1·19–4·57) in the HR.

The ROC curve plot for prediction of future diabetes by HbA_{1c}, by FPG, or by the combination of the two tests showed that the combination of FPG and HbA_{1c} slightly but significantly (p<0·0001) improved the area under the curve for prediction of future diabetes compared with use of only one test for screening (figure 2).

Figure 3 shows a Kaplan-Meier survival curve for prediction of diabetes after a baseline diagnosis of prediabetes. Incidence was 7% for HbA_{1c} alone (n=412 individuals and 30 incident cases) and 9% for impaired fasting glucose alone (n=1270, 108 incident cases). Overall cumulative probability did not differ significantly between the two (log-rank test, p=0·3317). Of prediabetic individuals who fulfilled both HbA_{1c} and fasting glucose criteria at baseline, 38% (n=154) progressed to diabetes within 5 years. If a definition for impaired fasting glucose of FPG 6·1–6·9 mmol/L was applied rather than FPG 5·6–6·9 mmol/L, incidence was 2% for HbA_{1c} lower than 5·7% and FPG lower than 6·1 mmol/L (n=5198 individuals and 100 incident cases). With HbA_{1c} alone, FPG alone, and both FPG and

	Total (n=6241)	Normoglycaemia (n=4149)	Prediabetes		
			IFG alone (n=1270)	HbA_{1c} 5·7–6·4% alone (n=412)	Both HbA_{1c} 5·7–6·4% and IFG (n=410)
Incidence of diabetes by self-reported clinician diagnosis					
Incident cases/person-years	157/29 856	34/19 982	43/6029	14/1985	66/1860
Incident rate (per 1000 person-years)	5·3	1·7	7·1	7·1	35·5
Age-adjusted and sex-adjusted hazard ratio (95% CI)	..	1·00	3·53 (2·24–5·55)	3·68 (1·96–6·91)	17·4 (11·4–26·6)
Multivariate hazard ratio (95% CI)	..	1·00	3·40 (2·14–5·39)	3·48 (1·85–6·54)	15·8 (10·2–24·6)
Incidence of diabetes by self-reported clinician diagnosis or HbA_{1c} ≥6·5%					
Incident cases/person-years	250/29 684	39/19 973	62/6006	26/1968	123/1737
Incident rate (per 1000 person-years)	8·4	2·0	10·3	13·2	70·8
Age-adjusted and sex-adjusted hazard ratio (95% CI)	..	1·00	4·54 (3·03–6·79)	6·63 (4·02–11·0)	33·8 (23·4–48·8)
Multivariate hazard ratio (95% CI)	..	1·00	4·34 (2·88–6·54)	6·24 (3·77–10·3)	30·5 (20·9–44·6)
Incidence of diabetes by self-reported clinician diagnosis or FPG ≥7·0 mmol/L					
Incident cases/person-years	298/29 558	43/19 965	101/5927	21/1978	133/1688
Incident rate (per 1000 person-years)	10·1	2·2	17·0	10·6	78·8
Age-adjusted and sex-adjusted hazard ratio (95% CI)	..	1·00	6·77 (4·73–9·7)	4·83 (2·85–8·17)	33·8 (23·8–47·9)
Multivariate hazard ratio (95% CI)	..	1·00	6·00 (4·16–8·6)	4·34 (2·56–7·35)	26·8 (18·7–38·4)
Incidence of diabetes by self-reported clinician diagnosis, HbA_{1c} ≥6·5% or FPG ≥7·0 mmol/L					
Incident cases/person-years	338/29 487	46/19 961	108/5920	30/1965	154/1641
Incident rate (per 1000 person-years)	11·5	2·3	18·2	15·3	93·8
Age-adjusted and sex-adjusted hazard ratio (95% CI)	..	1·00	6·86 (4·84–9·71)	6·53 (4·10–10·4)	38·6 (27·6–54·0)
Multivariate hazard ratio (95% CI)	..	1·00	6·16 (4·33–8·77)	6·00 (3·76–9·56)	31·9 (22·6–45·0)

Normoglycaemia was defined as HbA_{1c} lower than 5·7% and FPG less than 5·6 mmol/L. Diagnosis of prediabetes was by IFG alone when HbA_{1c} less than 5·7% and FPG 5·6–6·9 mmol/L, by HbA_{1c} alone when HbA_{1c} 5·7–6·4% and FPG less than 5·6 mmol/L, and by both HbA_{1c} and IFG when HbA_{1c} 5·7–6·4% and FPG 5·6–6·9 mmol/L. Multivariate model was adjusted for age, sex, smoking habit (never/former/current), parental history of diabetes, body-mass index, hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or treatment), HDL cholesterol, log-transformed triglycerides, and γ-glutamyltransferase. IFG=impaired fasting glucose. HbA_{1c}=glycated haemoglobin A_{1c}. FPG=fasting plasma glucose.

Table 5: **Hazard ratios for development of type 2 diabetes according to baseline diagnosis of prediabetes**