# Cardiorespiratory Fitness and the Incidence of Type 2 Diabetes

## Prospective study of Japanese men

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**OBJECTIVE** — To investigate the association between cardiorespiratory fitness and the incidence of type 2 diabetes among Japanese men.

**RESEARCH DESIGN AND METHODS** — This prospective cohort study was conducted in 4,747 nondiabetic Japanese men, aged 20–40 years at baseline, enrolled in 1985 with follow-up to June 1999. Cardiorespiratory fitness was measured using a cycle ergometer test, and $\dot{V}o_{2max}$ was estimated. During a 14-year follow-up, 280 men developed type 2 diabetes.

**RESULTS** — The age-adjusted relative risks of developing type 2 diabetes across quartiles of cardiorespiratory fitness (lowest to highest) were 1.0 (referent), 0.56 (95% CI 0.42–0.75), 0.35 (0.25–0.50), and 0.25 (0.17–0.37) (for trend, $P < 0.001$). After further adjustment for BMI, systolic blood pressure, family history of diabetes, smoking status, and alcohol intake, the association between type 2 diabetes risk and cardiorespiratory fitness was attenuated but remained significant (1.0, 0.78, 0.63, and 0.56, respectively; for trend, $P = 0.001$).

**CONCLUSIONS** — These results indicate that a low cardiorespiratory fitness level is an important risk factor for incidence of type 2 diabetes among Japanese men.

*Diabetes Care* 26:2918–2922, 2003

A 1997 survey conducted by the Japanese government's Ministry of Health, Labor and Welfare reported the estimated number of patients with type 2 diabetes to be 6.9 million in Japan, and it is currently projected that the number of diabetic patients is dramatically increasing (1). In view of the fact that insulin secretion capacity is reported to be genetically lower among the Japanese than among Caucasians (2,3), Japanese appear to be more prone to the development of type 2 diabetes (4,5). With the overall Japanese lifestyle becoming more like the western lifestyle, a high-fat diet and low physical activity (which are known to be risk factors for the development of type 2 diabetes) are becoming more prevalent in Japan. Therefore, preventing type 2 diabetes is an important issue to be resolved. Because people who have low cardiorespiratory fitness are more likely to be insulin resistant (6), it is reasonable to surmise that a lower cardiorespiratory fitness level is a risk factor for the development of type 2 diabetes.

To our knowledge, only two prospective cohort studies have examined the association between cardiorespiratory fitness and the risk of type 2 diabetes. Both studies show an inverse relationship between cardiorespiratory fitness and the development of type 2 diabetes among the western populations (7,8). However, no such studies have been conducted in the Japanese population. Thus, this study was designed to prospectively determine whether low cardiorespiratory fitness in Japanese men is a risk factor for the development of type 2 diabetes.

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Received for publication 8 May 2003 and accepted in revised form 10 July 2003.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.



## RESEARCH DESIGN AND METHODS

### Subjects

The subjects for this study were 5,984 male employees between 20 and 40 years of age who had participated in an annual health examination conducted at the Tokyo Gas Company in 1985. Among these men, 335 were excluded because they were found at the health examination to have at least one of the following: diabetes ($n = 102$), cardiovascular disease including hypertension ($n = 228$), tuberculosis ($n = 3$), and gastrointestinal disease ($n = 9$). Also excluded were 904 other men who did not perform and/or complete a submaximal exercise test. These exclusions left 4,745 men who were followed until June 1999 to determine whether they subsequently developed type 2 diabetes.

### Clinical examination

The Industrial Safety and Health Law in Japan requires the employer to conduct annual health examinations of all employees, and employees are required by law to participate. Height and weight were measured on a standard physician's scale and stadiometer, and BMI was calculated. Blood pressure was measured by the auscultatory method with a mercury sphygmomanometer; diastolic pressure was recorded as the disappearance of sound. Fasting blood glucose tests have been adopted since 1988 in subjects 35 years of age and those ≥40 years of age. A questionnaire was administered before the

Table 1—*Baseline characteristics of men according to cardiorespiratory fitness levels (quartiles)*

| Characteristic | All men | $Q_1$ (lowest) | $Q_2$ | $Q_3$ | $Q_4$ (highest) | *P* |
|---|---|---|---|---|---|---|
| *n* | 4,745 | 1,184 | 1,178 | 1,187 | 1,196 | |
| $Vo_{2max}$ (ml · kg$^{-1}$ · min$^{-1}$) | 41.0 ± 7.9 | 32.4 ± 3.1 | 38.0 ± 2.5 | 42.4 ± 3.0 | 51.1 ± 6.2 | <0.001* |
| Age (years) | 31.4 ± 5.0 | 31.6 ± 4.9 | 31.2 ± 4.9 | 31.5 ± 5.0 | 31.2 ± 5.0 | 0.158* |
| BMI (kg/m$^2$) | 22.9 ± 2.5 | 24.3 ± 2.7 | 22.9 ± 2.3 | 22.3 ± 2.4 | 22.0 ± 2.1 | <0.001* |
| Systolic blood pressure (mmHg) | 125.4 ± 11.6 | 129.0 ± 11.1 | 126.4 ± 11.5 | 124.4 ± 11.5 | 121.8 ± 11.2 | <0.001* |
| Diastolic blood pressure (mmHg) | 72.7 ± 9.0 | 75.7 ± 8.8 | 73.1 ± 8.8 | 72.0 ± 9.0 | 70.1 ± 8.4 | <0.001* |
| Current smokers (%) | 67.2 | 69.6 | 71.3 | 66.0 | 62.1 | <0.001† |
| Current drinkers (%) | 69.1 | 69.1 | 71.2 | 69.8 | 66.7 | 0.118† |

Data are means ± SD, unless otherwise specified. *ANOVA; †Kruskal-Wallis test.

start of the submaximal exercise test to assess smoking and alcohol intake.

### Cardiorespiratory fitness test

Subjects underwent a submaximal exercise test on a cycle ergometer to assess cardiorespiratory fitness. The exercise test consisted of three 4-min progressively increasing exercise stages. The initial exercise loads for subjects in the 20- to 29-, 30- to 39-, and 40- to 45-year age-groups were 600, 525, and 450 kpm, respectively. Heart rate was calculated from the R-R interval on an electrocardiogram, and 85% of their age-predicted maximal heart rate (220 − age [years]) was set as the target heart rate. The exercise load was increased by 225 kpm for each stage among all age-groups until heart rates during the course of the exercise reached the target heart rate or until completion of the third stage. Based on the exercise rate during the last 1 min of the final stage completed and the heart rate obtained from the last 10 s of exercise, $Vo_{2max}$ was estimated using Åstrand-Ryhming Nomogram (9) and Åstrand's Nomogram correction factors (10).

### Diagnosis of type 2 diabetes

The development of type 2 diabetes was based on any one of the following three diagnostic parameters. First, the serum glucose levels exceeded 11.1 mmol/l (200 mg/dl) 2 h after an oral glucose tolerance test, conducted in men with urinary glucose detected at a follow-up annual health examination. Second, the participants themselves reported current therapy with hypoglycemic medication (insulin or oral hypoglycemic agent) when they were interviewed at the subsequent health examination. Third, fasting blood glucose tests have been adopted since 1988. The criteria for fasting blood glucose levels for the diagnosis of type 2 diabetes were based on the American Diabetes Association's diagnostic guidelines published in 1997 (11).

Subjects contributed person-years of follow-up until the first of the following events: development of diabetes ($n$ = 280), death ($n$ = 42), or completion of the study (including 143 men lost to follow-up because of retirement).

### Statistical analysis

We categorized men into quartiles depending on age-specific (20–24, 25–29, 30–34, 35–39, and 40–45 years) distributions of estimated $Vo_{2max}$. We used Cox proportional hazards models (12) to study the relationship between cardiorespiratory fitness and incidence of type 2 diabetes, adjusted for age, BMI, systolic blood pressure, family history of diabetes, smoking status (nonsmokers, 1–20 cigarettes per day, or ≥21 cigarettes per day), and alcohol intake (none, 1–45 g per day, or ≥46 g per day). Relative risks (RRs) for incidence of type 2 diabetes and 95% CI were obtained by using the group with the lowest estimated $Vo_{2max}$ as the reference category. We tested proportionality assumptions and found no evidence of violation. All statistical analyses were conducted using SPSS 11.0J for Windows (Chicago, IL).

**RESULTS** — During a 14-year follow-up period that included 64,434 person-years of observation, 280 men developed type 2 diabetes. The average

Table 2—*Adjusted RRs for incidence of type 2 diabetes by potential risk factors*

| Variable | Participants | RR* | 95% CI | *P* |
|---|---|---|---|---|
| BMI | | | | |
| 1st tertile | 1,578 | 1.00 (Referent) | — | — |
| 2nd tertile | 1,585 | 1.90 | 1.20–3.02 | 0.006 |
| 3rd tertile | 1,582 | 4.60 | 3.01–7.02 | <0.001 |
| Age (single year) | 4,745 | 1.07 | 1.04–1.10 | <0.001 |
| High blood pressure | | | | |
| <140/90 mmHg | 4,194 | 1.00 (Referent) | — | — |
| ≥140/90 mmHg | 551 | 1.73 | 1.31–2.28 | <0.001 |
| Family history | | | | |
| No | 3,709 | 1.00 (Referent) | — | — |
| Yes | 1,036 | 3.57 | 2.82–4.51 | <0.001 |
| Smoking status | | | | |
| None | 1,555 | 1.00 (Referent) | — | — |
| 1–20/day | 1,829 | 1.22 | 0.91–1.63 | 0.185 |
| ≥21/day | 1,361 | 1.27 | 0.94–1.71 | 0.119 |
| Alcohol intake | | | | |
| None | 1,462 | 1.00 (Referent) | — | — |
| 1–45 g/day | 3,020 | 1.59 | 1.16–2.17 | 0.004 |
| ≥46 g/day | 263 | 1.68 | 1.03–2.76 | 0.039 |

*Adjusted for cardiorespiratory fitness level and all items in the table.

**Table 3—*RRs of incidence of type 2 diabetes according to cardiorespiratory fitness levels***

| | Cardiorespiratory fitness levels, quartiles | | | | |
|---|---|---|---|---|---|
| | $Q_1$ (lowest) | $Q_2$ | $Q_3$ | $Q_4$ (highest) | *P* for trend |
| *n* | 1,184 | 1,178 | 1,187 | 1,196 | |
| Person-years of follow-up | 15,730 | 16,038 | 16,252 | 16,415 | — |
| Number of cases | 128 | 72 | 47 | 33 | — |
| Age-adjusted RR (95% CI) | 1.00 (Referent) | 0.56 (0.42–0.75) | 0.35 (0.25–0.50) | 0.25 (0.17–0.37) | <0.001 |
| Multivariate RR* (95% CI) | 1.00 (Referent) | 0.78 (0.58–1.05) | 0.63 (0.45–0.89) | 0.56 (0.37–0.84) | 0.001 |

*Adjusted for age, BMI, systolic blood pressure, family history of diabetes, smoking status, and alcohol intake.

age of subjects was 31.4 ± 5.0 years at baseline. Table 1 shows the physical characteristics at the baseline of this study according to cardiorespiratory fitness levels. Men in the highest cardiorespiratory fitness group had the lowest levels of BMI, systolic blood pressure, and diastolic blood pressure. The highest cardiorespiratory fitness group also had the lowest prevalence of current smoking.

Table 2 shows the relationship between potential risk factors estimated by Cox proportional hazards model. Men in the higher BMI groups had greater RRs for type 2 diabetes than men in the lowest BMI group. In addition, older age, high blood pressure, a family history of diabetes, and alcohol intake significantly increased the risk of type 2 diabetes.

There were progressively lower age-adjusted RRs of type 2 diabetes across cardiorespiratory fitness levels (Table 3). After further adjustment for BMI, systolic blood pressure, family history of diabetes, smoking status, and alcohol intake, there remained an inverse association between type 2 diabetes risk and cardiorespiratory fitness (for trend, $P = 0.001$). Overall, men in the highest fitness group had a 44% lower risk of type 2 diabetes when compared with men in the lowest fit quartile.

Cardiorespiratory fitness level was estimated from heart rate obtained during the submaximal exercise test. The heart rate obtained during the submaximal exercise test may be influenced by premeasurement cigarette smoking (13), and cigarette smoking is known to be an independent risk factor for the development of type 2 diabetes (14). Therefore, we investigated the RRs for developing type 2 diabetes by categorizing the subjects as "smokers" or "nonsmokers." Inverse associations between cardiorespiratory fitness and type 2 diabetes were observed in the two smoking status groups (Table 4).

**CONCLUSIONS** — In this study, we prospectively investigated the relationship between cardiorespiratory fitness level and the development of type 2 diabetes among Japanese, in whom obesity is less common and insulin secretion capacity smaller than that among Caucasians. Our results show that low cardiorespiratory fitness was associated with higher risk for the development of type 2 diabetes in Japanese men, as has been shown in Caucasian groups. To our knowledge, only two prospective studies have been conducted on the relationship between cardiorespiratory fitness level and the incidence of type 2 diabetes (7,8). Lynch et al. (7) reported that Finnish men with a higher cardiorespiratory fitness level, measured using a bicycle ergometer, had a significantly lower risk of developing type 2 diabetes over the 4-year follow-up period. In a study of U.S. men with the study group consisting primarily of Caucasian men, Wei et al. (8) found a significant inverse relationship between cardiorespiratory fitness (measured by treadmill time) and the incidence of type 2 diabetes.

Although cardiorespiratory fitness is a highly objective parameter, it is not readily measured. Therefore, few studies have investigated the relationship between cardiorespiratory fitness and the incidence of type 2 diabetes. However, several studies have examined the relationship between physical activity as determined through questionnaire surveys and the incidence of type 2 diabetes (15–25). All of the studies of physical activity, conducted primarily among Caucasians, have reported an inverse relationship between physical activity level and the incidence of type 2 diabetes. Only one study on physical activity and type 2 diabetes in a Japanese population has been reported, and the investigators showed that leisure-time physical activity contributes to the prevention of type 2 diabetes even when it is performed only one time per week (25). There are plausible mechanisms that link low cardiorespiratory fitness to risk of type 2 diabetes; for example, individuals with low cardiorespiratory fitness have



**Table 4—*RRs of incidence of type 2 diabetes among smokers and nonsmokers according to cardiorespiratory fitness levels***

| | Cardiorespiratory fitness levels, quartiles | | | | |
|---|---|---|---|---|---|
| | $Q_1$ (lowest) | $Q_2$ | $Q_3$ | $Q_4$ (highest) | *P* for trend |
| Smokers (*n*) | 824 | 840 | 783 | 743 | |
| Multivariate RR* (95% CI) | 1.00 | 0.70 (0.49–1.00) | 0.67 (0.44–1.00) | 0.58 (0.35–0.95) | 0.012 |
| Nonsmoker (*n*) | 360 | 338 | 404 | 453 | |
| Multivariate RR† (95% CI) | 1.00 | 1.02 (0.59–1.74) | 0.56 (0.28–1.10) | 0.53 (0.26–1.10) | 0.036 |

*Adjusted for age, BMI systolic blood pressure, family history of diabetes, smoking status, and alcohol intake; †adjusted for age, BMI, systolic blood pressure, family history of diabetes, and alcohol status.

high insulin resistance. This was demonstrated by Sato et al. (6), who showed that there is a positive relationship between the rate of glucose metabolism and $Vo_{2max}$. Additionally, Ivy and Kuo (26) reported that individuals with lower cardiorespiratory fitness levels have fewer glucose transporters compared with those more fit.

The laboratory measurement of cardiorespiratory fitness is a strength of our study, even with the submaximal exercise protocol we used. Previous studies assessing the estimated precision of the nomogram used in this study have shown that the measured values of $Vo_{2max}$ are closely correlated with the estimated values with our protocol (27). In addition, we used values obtained in oral glucose tolerance tests and fasting blood glucose levels as objective measures of the study outcome, type 2 diabetes. Another strength is that this was a prospective cohort study in a Japanese population; previous studies investigating the relationship between cardiorespiratory fitness and the development of type 2 diabetes were limited to Caucasian populations. The incidence of type 2 diabetes differs among ethnic populations, and the association may also be different in various ethnic groups.

Several limitations of this study need to be discussed. The subjects are not representative of the entire Japanese population but were men employed in a large metropolitan company. In addition, we excluded men without a submaximal exercise test at baseline. However, this limits the generalizability of the study but not its validity. Another limitation is that cardiorespiratory fitness was based on data obtained at the baseline examination, and possible changes in cardiorespiratory fitness level were not taken into account during the follow-up period. However, not accounting for changes would only dilute the true association between physical fitness and the risk of developing diabetes. Further research will be necessary to investigate the relationship between changes in cardiorespiratory fitness and the development of type 2 diabetes.

In conclusion, our results showed a strong inverse relationship between cardiorespiratory fitness and the development of type 2 diabetes. This relationship was independent of age, BMI, family history of type 2 diabetes, alcohol intake, and smoking status. We conclude that maintaining a high cardiorespiratory fitness level may contribute to the prevention of type 2 diabetes.

**Acknowledgments**— This study was supported in part by U.S. National Institute on Aging Grant AG06945 (to S.N.B.).

We thank the Tokyo Gas Health Promotion Center physicians and staff for assistance with data collection and Ayumi S. for secretarial support.

## References

1. Health and Welfare Statistics Association: Current status of national health and welfare (In Japanese). *J Health Welfare Stat* 48:93–94, 2001
2. Kadowaki T, Miyake Y, Hagura R, Akanuma Y, Kajinuma H, Kuzuya N, Takaku F, Kosaka K: Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 26: 44–49, 1984
3. Wasada T, Arii H, Kuroki H, Saeki A, Katsumori K, Saito S, Omori Y: The relationship between insulin resistance and insulin secretiosn in japanese subjects with borderline glucose intolerance. *Diabetes Res Clin Pract* 30:53–57, 1995
4. Fujimoto WY, Leonetti DL, Bergstrom RW, Kinyoun JL, Stolov WC, Wahl PW: Glucose intolerance and diabetic complications among Japanese-American Women. *Diabetes Res Clin Pract* 13:119–130, 1991
5. Zimmer P, Alberti KGMM, Shaw J: Global and societal implications of the diabetes epidemic. *Nature* 414:782–787, 2001
6. Sato Y, Iguchi A, Sakamoto N: Biochemical determination of training effects using insulin clamp technique. *Horm Metab Res* 16:483–486, 1984
7. Lynch J, Helmrich SP, Lakka TA, George AK, Cohen RD, Salonen R, Salonen JT: Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch Intern Med* 156:1307–1314, 1996
8. Wei M, Gibbons LW, Mitchell TL, Kampert JB, Lee CD, Blair SN: The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Intern Med* 130:89–96, 1999
9. Åstrand PO, Ryhming I: A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. *J Appl Physiol* 7:218–221, 1954
10. Åstrand I: Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand* 49:45–60, 1960
11. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (Position Statement). *Diabetes Care* 20: 1183–1197, 1997
12. Cox DR: Regression models and life-tables. *J R Stat Soc (B)* 34:187–220, 1972
13. Vogel JA, Gleser MA: Effect of carbon monoxide on oxygen transport during exercise. *J Appl Physiol* 32:234–239, 1972
14. Nakanishi N, Nakamura K, Matsuo Y, Suzuki K, Tatara K: Cigarette smoking and risk for impaired fasting glucose and type 2 diabetes in middle-aged Japanese men. *Ann Intern Med* 133:183–191, 2000
15. Helmrich SP, Ragland DR, Leung RW, Paffenbarger Jr RS: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147–152, 1991
16. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774–778, 1991
17. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer RE: A prospective study of exercise and incidence of diabetes among U.S. male physicians. *JAMA* 268:63–67, 1992
18. Lipton RB, Liao Y, Cao G, Cooper RS, McGee D: Determinants of incident non-insulin-dependent diabetes mellitus among blacks and whites in a national sample. *Am J Epidemiol* 138:826–839, 1993
19. Helmrich SP, Ragland DR, Paffenbarger RS Jr: Prevention of non-insulin-dependent diabetes mellitus with physical activity. *Med Sci Sports Exerc* 26:824–830, 1994
20. Gurwitz JH, Field TS, Glynn RJ, Manson JE, Avorn J, Taylor JO, Hennekens CH: Risk factors for non-insulin-dependent diabetes mellitus requiring treatment in the elderly. *J Am Geriatr Soc* 42:1235–1240, 1994
21. Burchfiel CM, Sharp DS, Curb JD, Rodriguez BL, Hwang LJ, Marcus EB, Yano K: Physical activity and incidence of diabetes: the Honolulu Heart Program. *Am J Epidemiol* 141:360–368, 1995
22. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin-dependent diabetes in middle aged British men. *BMJ* 310: 560–564, 1995
23. Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE, Manson JE: Walking compared with vigorous physical activity and risk of type 2 diabetes in women. *JAMA* 282:1433–1439, 1999
24. Wannamethee SG, Shaper AG, Alberti KGMM: Physical activity, metabolic factors, and the incidence of coronary heart disease and type 2 diabetes. *Arch Intern Med* 160:2108–2116, 2000

25. Okada K, Hayashi T, Tsumura K, Suematsu C, Endo G, Jujii S: Leisure-time physical activity at weekends and the risk of type 2 diabetes mellitus in Japanese men: the Osaka Health Survey. *Diabet Med* 17:53–58, 2000
26. Ivy JL, Kuo CH: Regulation of GLUT4 protein and glycogen synthase during muscle glycogen synthesis after exercise. *Acta Physiol Scand* 162:295–304, 1998
27. Siconolfi SF, Cullinane EM, Carleton RA, Thompson PD: Assessing VO2max in epidemiologic studies: modification of the Åstrand-Ryhming test. *Med Sci Sports Exerc* 14:335–338, 1982