Long-term trends in cardiorespiratory fitness and the incidence of type 2 diabetes

Running title: Long-term trends in fitness and diabetes

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Objective: While single assessments of cardiorespiratory fitness have been shown to predict lower incidence of type 2 diabetes mellitus, there are no data on long-term trends in fitness and risk. We investigated the relationship between long-term trends in fitness and the incidence of type 2 diabetes.

Research Design and Methods: A cohort of 4187 Japanese men free of diabetes completed annual health check-ups and fitness tests for estimated maximal oxygen uptake at least four times over seven years (1979-1985). We modeled the trend in fitness over seven years for each man using simple linear regression. Men were then divided into quartiles based on the regression coefficient (slope) from the model. During the follow-up period 1985-1999, 274 men developed diabetes. Hazard ratios and 95% CI for the incidence of diabetes were obtained using Cox proportional hazards model.

Results: Men in the lowest quartile of the distribution decreased in fitness over the seven years (median slope, -1.25 ml/kg/min), while men in the highest quartile increased in fitness (median slope, 1.33 ml/kg/min). Adjusting for age, initial fitness level, body mass index (BMI), systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes, and using the lowest quartile, the hazard ratios and 95% CI for the 2nd through 4th quartiles were 0.64 (0.46-0.89), 0.40 (0.27-0.58), and 0.33 (0.21-0.50), respectively (P < 0.001 for trend).

Conclusions: These results indicate that the long-term trend in fitness is a strong predictor of the incidence of type 2 diabetes in Japanese men.
Type 2 diabetes is a global problem with devastating human, social and economic impact. Today more than 240 million people worldwide are living with diabetes. Each year another seven million people develop diabetes. Thus, the prevention of type 2 diabetes is an important public health priority (1).

It is well known that physical inactivity is one of the primary causes of type 2 diabetes (2,3). Previous cohort studies also have shown a strong inverse relationship between cardiorespiratory fitness and the incidence of type 2 diabetes (4-7). However, these studies considered only once or twice measure of fitness level at baseline as the exposure. There are no data on long-term trends in activity or fitness as they relate to the risk of developing type 2 diabetes. Several randomized controlled trials of lifestyle, including physical activity, healthful diet, and weight reduction, in relation to type 2 diabetes over a period of years, have shown that such lifestyle changes decrease the incidence of developing type 2 diabetes among individuals with impaired glucose tolerance (8-10). No data are available from individuals at usual risk. This study was thus designed to investigate the relationship between long-term trends in fitness and the incidence of type 2 diabetes using a cohort study design among nondiabetic Japanese men.

RESEARCH DESIGN AND METHODS

Participants: Participants were employees of the Tokyo Gas Company that supplies natural gas to the Tokyo area. All employees received annual health check-ups and completed a health questionnaire in accordance with the Industrial Safety and Health Law. Employees are required by law to participate.

The participants for this study were 5,984 male employees who had participated in an annual health check-up and annual submaximal exercise tests in 1985. Among these men, 335 were excluded because they were found at the health check-up to have at least one of the following: diabetes (n = 102), cardiovascular disease including hypertension (n = 228), tuberculosis (n = 3), or gastrointestinal disease (n = 9). For the present study, we also required participants to have at least four submaximal exercise tests in the previous seven years (1979-1985). This excluded 1,462 men, leaving 4,187 men, who were followed until June 1999 for the development of type 2 diabetes.

Cardiorespiratory Fitness test: Participants underwent a submaximal exercise test on a cycle ergometer to assess fitness. This test consisted of two to three progressively increasing 4-minute exercise stages. The initial exercise loads were 600, 525, and 450 kilopond meter per minute (kpm/min) for participants aged 20-29, 30-39, and 40-49 years 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/min for each stage amongst all age groups, until heart rates during the course of the exercise reached the target heart rate, or until the completion of the third stage. Maximal oxygen uptake ($V_o^{2\max}$) was estimated using the Åstrand-Ryhming Nomogram (11) and the Åstrand age correction factors (12).

First, we used a simple linear regression of $V_o^{2\max}$ against time to assess the individual regression coefficient (slope) of fitness over seven years. Next,
all participants were divided into quartiles based on the slope from their individual model. Initial fitness levels in 1979 were estimated using the regression line.

**Diagnosis of type 2 diabetes:** The annual health check-up included a measurement of height, body weight, blood pressure, and a urinary glucose test. Fasting plasma glucose tests have been used since 1988.

During 1985-1999, participants were followed for the development of type 2 diabetes, which was based on any one of the following three diagnostic parameters: 1) plasma glucose levels exceeded 11.1 mmol/l (200 mg/dl) two hours after an oral glucose tolerance test, conducted in men with urinary glucose detected at a follow-up annual health check-up, 2) participants themselves reported current therapy with hypoglycemic medication (insulin or oral hypoglycemic agent) when they were interviewed at their health check-up, or 3) fasting plasma glucose levels exceeded more than 7.0 mmol/l (126 mg/dl).

**Statistical analysis:** We first compared baseline characteristics of participants according to quartiles of the fitness trend using one-way analysis of variance for continuous variables and chi-square test for categorical variables as appropriate.

We used Cox proportional hazards models to estimate the hazard ratios of the incidence of type 2 diabetes. We adjusted for age, initial fitness level (continuous \( \text{VO}_{2\text{max}} \)), body mass index (BMI, continuous variable), systolic blood pressure (continuous variable), cigarette smoking (non-smokers, 1-20 cigarettes per day, 21 or more cigarettes per day), alcohol intake (none, 1-45g per day, 46g or more per day), and a family history of diabetes (present or not) in a multivariate model. A family history of diabetes was defined as the known presence of family members with diabetes in any of three generations, as determined by self-report on the health questionnaire. The proportionality assumption of the model was tested using a log-minus-log plot; no evidence of violation was found. All analyses were performed using SPSS 15.0J for windows (SPSS Inc., Chicago, Illinois).

**RESULTS**

The mean age of the participants was 32.0 years (range: 22-40 yr) at baseline. The mean number of fitness tests during 7 years was 6.0 (SD: 0.96). The mean time between the first and last fitness test in each single individual was 6.5 years (SD: 0.73). The median follow-up time was 14 years, with a total of 56,749 man-years of observation. During follow-up, 274 participants developed type 2 diabetes. There were 42 deaths, and 143 were lost to follow-up due to retirement.

Table 1 shows the baseline characteristics of men in each fitness trend quartile. Men in the lowest fitness trend quartile (quartile 1) decreased their average \( \text{VO}_{2\text{max}} \) from 45.3 ml/kg/min to 36.6 ml/kg/min (median slope, -1.25 ml/kg/min) between 1979 and 1985, while men in the highest fitness trend quartile (quartile 4) increased their average \( \text{VO}_{2\text{max}} \) from 36.3 ml/kg/min to 45.6 ml/kg/min (median slope, 1.33 ml/kg/min) over the same time. There was an inverse relationship across categories with regard to initial fitness levels. The men in the lowest fitness trend quartile had the highest level of fitness in 1979, while those in the highest fitness trend quartile had the lowest level of fitness. The men in the highest quartile were more likely to
have a lower systolic and diastolic blood pressure, and a lower rate of smoking compared with the lowest quartile.

Table 2 shows the relationship between potential risk factors and type 2 diabetes. Men with higher initial fitness had lower hazard ratios for type 2 diabetes than men in the lower initial fitness group. In addition, older age, high BMI, high systolic blood pressure, alcohol intake, and a family history of diabetes all significantly increased the risk of type 2 diabetes.

Table 3 shows the hazard ratios for type 2 diabetes by fitness trend quartiles, with the lowest quartile used as the referent. There were progressively lower age-adjusted hazard ratios of type 2 diabetes across fitness trend quartiles. After further adjustment for initial fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes, there remained a strong inverse association between type 2 diabetes risk and fitness trend quartiles ($P < 0.001$ for trend). Men in the highest quartile of fitness trend had about a 70% lower risk of developing type 2 diabetes compared with men in the lowest quartile.

We next investigated the hazard ratios of type 2 diabetes associated with quartiles of fitness trend, among men classified according to their initial fitness levels in 1979. (Figure 1). The inverse gradient for diabetes across long-term trends in fitness categories was generally observed for all levels of fitness in 1979, except for men in the highest category of initial fitness ($\geq 45.0$ ml/kg/min). We also investigated the hazard ratios of type 2 diabetes among men with different levels of BMI at baseline (1985). Again, there generally was an inverse gradient for diabetes risk across long-term trends in fitness categories for all BMI categories, except the lowest.

**CONCLUSIONS**

In this study, we prospectively investigated the relationship between long-term trends in fitness and the incidence of type 2 diabetes in nondiabetic Japanese men. There was a strong inverse relationship between long-term trends in fitness and the incidence of type 2 diabetes, with men increasing their fitness over a seven-year period having lower risks than men with decreasing fitness over the same span.

The observed association is biologically plausible, since physical activity or fitness is a strong independent predictor of lower type 2 diabetes incidence rates (2,3). Physical activity or fitness may prevent and delay type 2 diabetes by improving glucose levels, reducing adiposity, increasing muscle mass and the glucose-transporter 4 in muscle tissues, and reducing insulin resistance (13,14).

The major strength of this study is the objective measurement of fitness, repeated over time. Fitness, an objective marker of daily physical activity, is a stronger predictor of morbidity or mortality, compared with self-reported physical activity (15). Teräslinna et al. investigated the relationship, among 31 subjects, between measured $V_{O2}$max and estimated $V_{O2}$max using the Åstrand-Ryhming Nomogram and correction factors utilized in the present study, obtaining a correlation coefficient of 0.92 (16). Furthermore, we used values obtained in oral glucose tolerance tests or fasting blood glucose levels as objective measures of the study outcome, type 2 diabetes.

Individuals at high risk of type 2
diabetes, such as impaired glucose tolerance or obesity, have been studied in randomized controlled trials of lifestyle, including physical activity, and type 2 diabetes (8-10). However, there are no data in low risk populations. Also, most of the data have been in Caucasian subjects. Type 2 diabetes is a global problem; thus, data are needed not only in high risk populations, but also low risk populations, as well as other race/ethnic groups.

One limitation of the present study is that subjects may not be representative of the entire Japanese population, and women were not included. Nonetheless, this study provides important and valid information on Japanese male workers. Another limitation is that possible changes in fitness levels were taken into account between 1979 and 1985, but not during the follow-up period, 1985-1999. However, not accounting for changes during the latter period would likely dilute the true association between fitness and the risk of developing diabetes.

In conclusion, this cohort study showed a strong inverse relationship between long-term trends in fitness and the development of type 2 diabetes in Japanese men. This relationship was independent of age, initial fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes. Thus, regular physical activity, which is associated with an increase or preservation of fitness, should be promoted by health professionals, since it decreases the risk of type 2 diabetes, in addition to decreasing the risks of many chronic diseases (17).

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Table 1  Baseline Characteristics by Cardiorespiratory Fitness Trend

| Characteristic                                      | All men | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | \( P \)  |
|----------------------------------------------------|---------|------------|------------|------------|------------|---------|
| \( n \)                                            | 4,187   | 1,047      | 1,048      | 1,046      | 1,046      |         |
| Median regression coefficient or slope (ml/kg/min) * | -0.04 (-6.41, 6.19) | -1.25 (-6.41, -0.77) | -0.40 (-0.77, -0.04) | 0.32 (0.04, 0.73) | 1.33 (0.73, 6.19) | \(<0.001\) |
| Age (years)                                        | 32.0 ± 4.3 | 31.4 ± 4.0 | 32.2 ± 4.0 | 32.6 ± 4.2 | 32.0 ± 4.9 | \(<0.001\) |
| Initial cardiorespiratory fitness (1979), predicted \( \text{Vo}_2\text{max} \) (ml/kg/min) | 40.0 ± 6.9 | 45.3 ± 6.7 | 40.5 ± 5.5 | 38.1 ± 5.6 | 36.3 ± 6.3 | \(<0.001\) |
| BMI (kg/m\(^2\))                                   | 23.0 ± 2.5 | 22.9 ± 2.5 | 23.1 ± 2.5 | 23.0 ± 2.6 | 22.9 ± 2.5 | 0.237   |
| Systolic blood pressure (mmHg)                     | 125.5 ± 11.7 | 125.8 ± 11.3 | 125.9 ± 11.8 | 125.6 ± 11.9 | 124.5 ± 11.7 | 0.020   |
| Diastolic blood pressure (mmHg)                    | 72.9 ± 8.9  | 72.9 ± 8.9  | 72.9 ± 9.3  | 73.6 ± 8.8  | 72.2 ± 8.8  | 0.004   |
| Current smokers (%)                                | 68.1     | 70.1       | 71.3       | 67.5       | 63.5       | 0.003   |
| Current drinkers (%)                               | 71.1     | 71.2       | 71.4       | 73.0       | 69.0       | 0.178   |
| Family history of diabetes (%)                     | 23.5     | 21.9       | 25.2       | 25.1       | 21.7       | 0.083   |

* Slope data represent median (range), while the other data represent mean ± SD or percent.
## Table 2: Adjusted Hazard Ratios for Incidence of Type 2 Diabetes by Potential Risk Factors at Baseline (1985)

| Variable                                           | Participants (%) | Hazard ratio* (95% CI) | P      | P for Trend |
|----------------------------------------------------|------------------|-------------------------|--------|-------------|
| **Age (years)**                                    |                  |                         |        |             |
| 22 - 30                                            | 1,614 (38.5)     | 1.00 (Referent)         | -      |             |
| 31 - 35                                            | 1,497 (35.8)     | 1.20 (0.89-1.62)        | 0.241  | 0.018       |
| 36 - 40                                            | 1,076 (25.7)     | 1.45 (1.06-1.99)        | 0.019  |             |
| **Initial (1979) cardiorespiratory fitness**       |                  |                         |        |             |
| (ml/kg/min)                                        |                  |                         |        |             |
| < 35.0                                             | 961 (23.0)       | 1.00 (Referent)         | -      |             |
| 35.0 - 39.9                                        | 1,213 (29.0)     | 0.88 (0.66-1.18)        | 0.386  | 0.003       |
| 40.0 - 44.9                                        | 1,083 (25.9)     | 0.72 (0.50-1.02)        | 0.065  |             |
| ≥ 45.0                                             | 930 (22.2)       | 0.50 (0.31-0.81)        | 0.005  |             |
| **BMI (kg/m²)**                                    |                  |                         |        |             |
| < 21.0                                             | 949 (22.7)       | 1.00 (Referent)         | -      |             |
| 21.0 - 22.9                                        | 1,299 (31.0)     | 1.45 (0.84-2.48)        | 0.180  | <0.001      |
| 23.0 - 24.9                                        | 1,125 (26.9)     | 2.52 (1.51-4.20)        | <0.001 |             |
| ≥ 25.0                                             | 814 (19.4)       | 5.34 (3.23-8.82)        | <0.001 |             |
| **Systolic blood pressure (mmHg)**                 |                  |                         |        |             |
| < 120                                              | 1,209 (25.4)     | 1.00 (Referent)         | -      |             |
| 120 - 129                                          | 1,317 (26.2)     | 1.32 (0.92-1.90)        | 0.135  | 0.001       |
| 130 - 139                                          | 1,248 (22.7)     | 1.30 (0.91-1.86)        | 0.149  |             |
| ≥ 140                                              | 413 (25.7)       | 2.17 (1.46-3.23)        | <0.001 |             |
| **Cigarette smoking**                              |                  |                         |        |             |
| None                                               | 1,336 (31.9)     | 1.00 (Referent)         | -      |             |
| 1-20/day                                           | 1,609 (38.4)     | 1.20 (0.89-1.61)        | 0.224  | 0.151       |
| ≥ 21/day                                           | 1,242 (29.7)     | 1.25 (0.92-1.69)        | 0.150  |             |
| **Alcohol intake**                                 |                  |                         |        |             |
| None                                               | 1,209 (28.9)     | 1.00 (Referent)         | -      |             |
| 1-45 g/day                                         | 2,731 (65.2)     | 1.64 (1.20-2.24)        | 0.002  | 0.008       |
| ≥ 46g/day                                          | 247 (5.9)        | 1.59 (0.96-2.62)        | 0.071  |             |
| **Family history of diabetes**                     |                  |                         |        |             |
| No                                                 | 3,204 (76.5)     | 1.00 (Referent)         | -      |             |
| Yes                                                | 983 (23.5)       | 3.26 (2.57-4.14)        | <0.001 |             |

* Adjusted for all items in the table.
Table 3  *Hazard Ratios of Incidence of Type 2 Diabetes, According to Quartiles of Cardiorespiratory Fitness Trend*

| Variable | Slope (range) ml/kg/min | Participants | Man-years of follow-up | No. of cases | Age-adjusted Hazard ratio (95% CI) | Multivariate Hazard ratio* (95% CI) |
|----------|--------------------------|--------------|------------------------|--------------|-----------------------------------|-----------------------------------|
| Quartile 1 | -1.25 (-6.41, -0.77) | 1,047 | 14,114 | 75 | 1.00 (Referent) | 1.00 (Referent) |
| Quartile 2 | -0.40 (-0.77, -0.04) | 1,048 | 14,152 | 82 | 1.03 (0.75-1.41) | 0.64 (0.46-0.89) |
| Quartile 3 | 0.32 ( 0.04, 0.73) | 1,046 | 14,212 | 64 | 0.77 (0.55-1.07) | 0.40 (0.27-0.58) |
| Quartile 4 | 1.33 ( 0.73, 6.19) | 1,046 | 14,271 | 53 | 0.65 (0.46-0.93) | 0.33 (0.21-0.50) |

* Adjusted for age, initial cardiorespiratory fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes.

**Figure Legend**

Figure 1 Hazard ratios* for incidence of type 2 diabetes associated with quartiles of cardiorespiratory fitness trend, among men categorized by initial (1979) cardiorespiratory fitness level (upper panel) or baseline (1985) BMI (lower panel).

* Adjusted for age, systolic blood pressure, cigarette smoking, alcohol intake, a family history of diabetes and BMI (upper panel) or initial cardiorespiratory fitness level (lower panel).
Figure 1