Aim: Recent studies have suggested that non-high-density lipoprotein cholesterol (non-HDL-C) may be a good marker of coronary heart disease and cardiovascular disease risk. Therefore, we investigated the relationship between cardiorespiratory fitness (CRF) and non-HDL-C.

Methods: We evaluated CRF and the incidence of high level of non-HDL-C in 4,067 Japanese men without dyslipidemia. The participants were given a submaximal exercise test, a medical examination, and questionnaires on their health habits in 1986. A cycle ergometer was used to measure the CRF and maximal oxygen uptake was estimated. The incidence of a high level of non-HDL-C (≥170 mg/dL) from 1986 to 2006 was ascertained based on the fasting blood levels. A high level of non-HDL-C was found in 1,482 participants during the follow-up. Cox proportional hazard models were used to obtain the hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of a high level of non-HDL-C.

Results: Following age adjustment, and using the lowest CRF group (quartile 1) as reference, the HRs and 95% CIs for quartiles II through IV were: 1.00 (95% CI: 0.87–1.15), 0.87 (95% CI: 0.76–1.00), and 0.70 (95% CI: 0.60–0.81), respectively (P for trend <0.001). After additional adjustment for body mass index, systolic blood pressure, smoking, alcohol intake, and family history of dyslipidemia, the HRs and 95% CIs were: 1.05 (95% CI: 0.92–1.21), 0.94 (95% CI: 0.81–1.08), and 0.79 (95% CI: 0.67–0.92), respectively (P for trend =0.001).

Conclusions: These results suggest that there is an inverse relationship between CRF levels and the incidence of a high level of non-HDL-C in Japanese men.
protein cholesterol (non-HDL-C)²⁻⁵, predict the risks of developing coronary heart disease (CHD) and cardiovascular disease (CVD). Non-HDL-C refers to TC minus HDL-C, and includes cholesterol of potentially atherogenic lipoprotein particles such as LDL. Furthermore, non-HDL cholesterol includes cholesterol of triglyceride-rich lipoproteins (e.g., chylomicron, very-low-density lipoprotein) and that of remnants which are known to promote the development of atherosclerosis; thus, it represents atherogenic lipoprotein profiles that cannot be measured solely as LDL-C². Recent studies have suggested that the use of non-HDL-C may be superior to that of LDL-C in predicting the risk of developing CHD²⁻⁶. Thus, the adequate control of non-HDL-C may be critical to prevent the development of dyslipidemia, a risk factor of atherosclerotic diseases.

Many randomized controlled trials (RCTs) have examined the association between aerobic exercise (AE) and the serum lipid profile, and several review studies have performed the meta-analyses of the RCT reported in the literature. Some of the meta-analyses of studies examining TC and HDL-C in relation to AE have demonstrated that AE lowers TC and increases HDL-C⁸⁻⁹. However, other review studies performed meta-analyses and demonstrated that AE does not have a clear influence on TC or HDL-C¹⁰⁻¹². Thus, there is no consensus on how AE influences TC or HDL-C. Similarly, two studies that performed meta-analyses of RCTs examining the association between AE and non-HDL-C reported inconsistent results¹³, ¹⁴. A meta-analysis examining the relationship between the levels of non-HDL-C and walking, a moderate intensity AE, reported that AE lowers non-HDL-C levels¹³. On the other hand, another meta-analysis of RCT investigating the influence of AE and diet on non-HDL-C levels indicated that there is no significant correlation between the levels of non-HDL-C and AE alone¹⁴. There is also no consensus on the relationship between AE and non-HDL-C. Thus, further evidence is required to determine whether AE can prevent a high level of non-HDL-C. Therefore, we used a cohort study in Japanese men to examine the relationship between the incidence of a high level of non-HDL-C and AE, using cardiorespiratory fitness (CRF) as an objective indicator of AE¹⁵.

Methods

Study Participants

The aim of this prospective cohort analysis¹⁶, ¹⁷ was to assess the relationship between CRF levels and health outcomes of Japanese men who are employees of a natural gas company in the Tokyo area in Japan. This company conducts health examinations and exercise tests annually to maintain the health of employees in accordance with the Japanese Industrial Safety and Health Law and related laws.

The study cohort included 9,221 men who underwent annual health examinations and exercise tests between April 1986 and March 2006. To conduct appropriate analyses, the exclusion criteria included not having a blood test performed (n = 385) and a diagnosis of dyslipidemia already reported at the baseline (n = 3,909), as defined by the diagnostic criteria of the Japan Atherosclerosis Society¹⁸, ¹⁹ (i.e., HDL-C < 40 mg/dL, LDL-C ≥ 140 mg/dL, triglyceride (TG) ≥ 150 mg/dL, or non-HDL-C ≥ 170 mg/dL). Furthermore, individuals for whom CRF levels could not be accurately measured because of their inability to carry out the exercise test for at least 4 min because of abnormal findings on their electrocardiogram (ECG) or their poor physical condition were excluded (n = 12). Women were also excluded because of their small number (n = 487). Of the remaining 4,428 participants, another 282 with missing data on potential confounders were excluded. Finally, an individual who underwent only one blood test during the follow-up was excluded (n = 79). The final cohort consisted of 4,067 men aged 19 to 60 years who were followed up till 2006.

The Research Ethics Committee of the National Institutes of Biomedical Innovation, Health and Nutrition approved this study (20120821-02, August 21 2012).

Baseline Examination

The height, body weight, and blood pressure at rest of all the participants were measured during health examinations conducted in 1986. A scale was used to measure the body weight with the participants in light clothing and with shoes removed. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Blood pressure at rest was measured using an automated sphygmomanometer with the participants seated in a chair. The participants aged 35 to 40 years underwent blood tests annually to maintain the health of employees. In 1994 and after, blood tests were conducted on the participants aged 25, 30, 35, and ≥ 40 years. All the participants were instructed to fast for 12 h prior to blood testing. The results of the blood test in the first year were used as the baseline values. Standard laboratory procedures were used to measure the levels of TC, HDL-C, TG, and glucose. Enzymatic methods were used to measure the concentration of lipids and glucose. The non-HDL-C levels were calculated by subtracting HDL-C from TC. The Friedewald equation was used to calculate the levels of LDL-C²⁰. Furthermore, a self-administered questionnaire was used to collect information on potential
confounders related to CRF and non-HDL-C, including alcohol intake (non-drinker, 1–45 g/day, ≥46 g/day), smoking habit (non-smoker, 1 to 20 cigarettes/day, ≥21 cigarettes/day), and family history of dyslipidemia (yes, no). Family history of dyslipidemia was determined by a positive response at least once in the questionnaires completed during annual health examinations conducted between 1986 and 2006.

Assessment of Cardiorespiratory Fitness

A submaximal exercise test on a cycle ergometer (Monark Exercise AB, Vansbro, Sweden) was used to measure the estimated maximal oxygen uptake, an index of CRF. The exercise test was composed of a maximum of three steps, each lasting 4 min, with increased resistance in each step. The loads for the participants in the 19 to 29, 30 to 39, 40 to 49, and 50 to 60 year age groups were 98, 86, 74, and 61 W, respectively. The heart rate was measured based on the R-R interval on an ECG. The target heart rate was set as 85% of the maximum heart rate estimated according to the 220 minus age (years). The exercise test was interrupted when abnormal ECG findings occurred or when the participants indicated that they did not feel well during the test. The maximum oxygen uptake was estimated using the Åstrand-Ryhming nomogram\(^21\) and Åstrand age-correction factors\(^22\).

Determination of a High Level of Non-HDL-C

We used fasting blood levels to diagnose high levels of non-HDL-C based on the Japan Atherosclerosis Society published in 2012 (non-HDL-C of ≥170 mg/dL)\(^{18,19}\). Follow-up was discontinued for participants confirmed to have started dyslipidemia treatment before the incidence of a high level of non-HDL-C in the self-administered questionnaires at health examinations between 1986 and 2006.

Statistical Analysis

The participants were categorized into quartiles by age group (≤24, 25 to 29, 30 to 34, 35 to 39, 40 to 44, 45 to 49, and ≥50 years) based on CRF, and these were then combined into four groups (Q\(_1\), Q\(_2\), Q\(_3\), Q\(_4\)) to compare physical characteristics at the baseline (1986). The continuous variables are expressed as mean, standard deviation (SD) and categorical variable are expressed as percentages, respectively. We performed an analysis of variance to compare multiple group means.

Then, Cox proportional hazards model analysis was performed with the presence or absence of a high level of non-HDL-C as the dependent variable and each potential confounder as independent variables to assess the relationship between a high level of non-HDL-C and the potential confounders of BMI, systolic blood pressure, smoking habit, alcohol intake, and family history of dyslipidemia. Next, multivariable adjusted hazard ratios (HRs) adjusted for other potential confounders and 95% confidence intervals (CI) were calculated.

Further analyses were performed to examine the relationship between the level of CRF and the incidence of a high level of non-HDL-C with the presence or absence of a high level of non-HDL-C as the dependent variable and CRF categories (quartiles) as the independent variables. Then, the age-adjusted HRs and 95% CIs were calculated. The multivariable adjusted HRs and 95% CIs were calculated further adjusting for the potential confounders of BMI (continuous variable), systolic blood pressure (continuous variable), smoking habit (3 categories), alcohol intake (3 categories), and family history of dyslipidemia (yes, no) at the baseline. To assess whether the proportional hazard hypothesis was valid, a log-minus-log plot was visually checked.

Furthermore, the relationship between the level of CRF and the incidence of a high level of non-HDL-C was assessed by sensitivity analysis with a high level of non-HDL-C defined as a non-HDL-C of ≥140 mg/dL. In addition, a sensitivity analysis that excluded populations who developed a high level of non-HDL-C within 2 years of starting follow-up was performed, because it is also possible that dyslipidemia already present at the baseline affected the values of the baseline CRF. Furthermore, we divided the participants into two groups of over 40 and under 40 years, and analyzed them. Finally, the presence of a potential effect modification was verified by including potential confounders of CRF, such as age, BMI, systolic blood pressure, alcohol intake, smoking habit, and family history of dyslipidemia, into the model to verify the presence of interactions.

SPSS Statistics version 23 (IBM-SPSS, Inc., Chicago, IL, USA) was used to perform all the statistical analyses. A two-tailed probability value of <0.05 was considered statistically significant.

Results

The mean age of the participants at the time of starting the follow-up was 36.8 (SD: 9.8) years. During the follow-up period of 48,300 man-years (median, 13 years; maximum, 20 years), high levels of non-HDL-C was observed in 1,482 participants (incidence of 30.7 cases per 1,000 man-years).

Table 1 shows the physical characteristics and lifestyle habits at the baseline in the four groups by the CRF categories. A higher CRF level tended to be associated with a lower BMI, systolic blood pressure, diastolic blood pressure, smoking habit, and the baseline
lipid levels. However, there were no clear differences in the alcohol intake or family history of dyslipidemia among the CRF categories.

Table 2 shows the adjusted multivariable HRs adjusted for incidence of a high level of non-HDL-C and 95% CIs assessed by potential confounders. There was a positive dose-response relationship between the incidence of a high level of non-HDL-C and BMI and a negative dose-response relationship with the amount of alcohol consumed. The participants with a family history of dyslipidemia had higher HRs for the incidence of a high level of non-HDL-C. In contrast, there was no clear relationship between the incidence of a high level of non-HDL-C and age, systolic blood pressure, or smoking habit.

Table 3 shows the multivariable adjusted HRs and 95% CIs of the incidence of high levels of non-HDL-C by CRF levels categorized by quartile. There was a significant negative dose-response relationship between the adjusted multivariable HRs of Q2, Q3, and Q4 CRF based on Q1. We further adjusted for HDL-C and TG because the baseline lipid levels were different between the CRF categories.

Thus, we adjusted HDL-C and TG. As we expected, further adjustment for HDL-C and TG at the baseline examination substantially attenuated the HRs. The multivariable hazard ratio was Q1 = 1.00, Q2 = 1.06 (95% CI, 0.92-1.22), Q3 = 1.01 (95% CI, 0.99-1.14), Q4 = 0.86 (95% CI, 0.73-1.00), (p for trend = 0.040). HDL-C and TG are likely to be intermediate factors for CRF; thus, this result may not indicate the effect of CRF accurately. Furthermore, the optimal management goal of non-HDL-C has been discussed23-25); the same results as those in the main analysis were obtained by sensitivity analysis that examined the relationship between CRF levels and the incidence of a high level of non-HDL-C within 2 years of the baseline (p = 0.014). Finally, no significant interactions were observed between the CRF levels and age, BMI, systolic blood pressure, alcohol intake, smok-
ship between the intensity of exercise and levels of non-HDL-C reduction. In agreement with this study, we demonstrated a significant inverse dose-response relationship between CRF and the incidence of a high level of non-HDL-C. Collectively, these results suggest that moderate intensity AE such as walking may prevent a high level of non-HDL-C, and that AE at a higher intensity may be more effective for its prevention. However, another study by Kelly et al.14), involving a meta-analysis of 6 RCTs that examined the association between the levels of non-HDL-C and either AE, diet, or their combination, demonstrated that AE alone does not reduce the levels of non-HDL-C. The result may have been influenced by the fact that the study participants in the “AE alone” group for each RCT included those with lower non-HDL-C levels at the baseline compared with those in the “diet alone” and “diet + AE” groups. Thus, further studies are warranted to determine whether AE can prevent a high level of non-HDL-C.

A few plausible mechanisms may explain the results of the present study. First, physical activity activates AMP-activated protein kinase in the skeletal muscle and promotes the expression of lipoprotein lipase (LPL), an enzyme degrading TG into free fatty acids and glycerol by increasing PPARγ1 levels.27) Accordingly, the increase in LPL activity following exercise increases the

### Discussion

In the present study, we examined the association between CRF, an indicator of AE15), and the incidence of a high level of non-HDL-C in a cohort of Japanese men who were followed for a period of 13 years (median). Our results demonstrated that Japanese men with a high CRF level at the baseline had a lower incidence rate of a high level of non-HDL-C. This suggests that habitual AE may reduce the risk of having a high level of non-HDL-C.

To our knowledge, no study has investigated the association between CRF and the incidence of a high level of non-HDL-C. However, many RCTs have investigated the effect of AE on the serum lipid profile, and these studies have been examined collectively in meta-analyses. Kelly et al.13) reviewed 22 RCTs that examined the influence of walking, a moderate intensity AE, on the levels of TC and HDL-C, and demonstrated that AE reduces non-HDL-C levels by 4%. This study suggests that moderate intensity AE may prevent a high level of non-HDL-C. An RCT by O’Donovan et al.26) investigated the effect of moderate and high-intensity AE on the levels of non-HDL-C in sedentary men, and demonstrated a significant dose-response relationship between the intensity of exercise and levels of non-HDL-C reduction. In agreement with this study, we demonstrated a significant inverse dose-response relationship between CRF and the incidence of a high level of non-HDL-C. Collectively, these results suggest that moderate intensity AE such as walking may prevent a high level of non-HDL-C, and that AE at a higher intensity may be more effective for its prevention. However, another study by Kelly et al.14), involving a meta-analysis of 6 RCTs that examined the association between the levels of non-HDL-C and either AE, diet, or their combination, demonstrated that AE alone does not reduce the levels of non-HDL-C. The result may have been influenced by the fact that the study participants in the “AE alone” group for each RCT included those with lower non-HDL-C levels at the baseline compared with those in the “diet alone” and “diet + AE” groups. Thus, further studies are warranted to determine whether AE can prevent a high level of non-HDL-C.

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| Table 2. Multivariable adjusted hazard ratios for incidence of a high level of non-HDL-C by potential risk factors |
|-----------------|-------------|-------------|-------------|-----------------|-------------|-------------|
| **Potential risk factors** | **Participants** | **Number of cases** | **Incidence rate** | **Hazard ratio (95% CI)** | **p value** |
| Age (single year) | 4,067 | 1,482 | 30.7 | 1.01 (1.00–1.01) | 0.015 |
| Body mass index | 1st tertile (Low) | 1,362 | 412 | 23.4 | 1.00 (Reference) | – |
| | 2nd tertile (Middle) | 1,357 | 498 | 30.4 | 1.27 (1.11–1.45) | <0.001 |
| | 3rd tertile (High) | 1,348 | 572 | 39.9 | 1.58 (1.38–1.80) | <0.001 |
| Systolic blood pressure | < 140 mmHg | 3,474 | 1,264 | 29.9 | 1.00 (Reference) | – |
| | ≥ 140 mmHg | 593 | 218 | 35.9 | 1.06 (0.92–1.23) | 0.425 |
| Smoking status | None | 1,600 | 592 | 32.0 | 1.00 (Reference) | – |
| | 1-20 cigarettes/day | 1,453 | 506 | 28.7 | 0.96 (0.85–1.09) | 0.524 |
| | ≥ 21 cigarettes/day | 1,014 | 384 | 31.6 | 1.02 (0.90–1.16) | 0.754 |
| Alcohol intake | None | 1,187 | 440 | 30.7 | 1.00 (Reference) | – |
| | 1-45 g/day | 2,672 | 971 | 30.8 | 0.95 (0.85–1.07) | 0.424 |
| | ≥ 46 g/day | 208 | 71 | 28.8 | 0.84 (0.65–1.08) | 0.173 |
| Family history of dyslipidemia | No | 3,949 | 1,412 | 30.1 | 1.00 (Reference) | – |
| | Yes | 118 | 70 | 53.3 | 1.85 (1.45–2.35) | <0.001 |

CI, confidence interval
Adjusted for cardiorespiratory fitness level and all items in the table.

\(^{8}\)Incidence rate is presented in cases per 1,000 man-years of observation.
The activation of LPL as, described above, causes TG-rich lipoprotein levels to decrease since LPL hydrolyzes TG in TG-rich lipoprotein particles\(^{29}\). Second, the increase in glucose transporter 4 associated with physical activity may reinforce insulin sensitivity\(^{30}\). Increased insulin sensitivity leads to increased hepatic very-low-density lipoprotein (VLDL) and Apo B secretion, as well as decreased free fatty acids in the liver\(^{28}\). In addition, increased insulin sensitivity suppresses the exchange reaction between TG and cholesterol ester in HDL particles by cholesteryl ester transfer protein and TG-rich lipoprotein particles (VLDL particles, LDL particles). Therefore, VLDL, LDL, and small dense LDL decrease\(^{28}\). Furthermore, exercise reduces the expression of lipoprotein convertase subtilisin/kexin type 9, resulting in increased clearance of LDL-C and thus decreased LDL-C\(^{28}\). Third, increased insulin sensitivity elevates Lecithin cholesterol acyltransferase activity, suppresses cholesteryl ester transfer protein activity, and reduces hepatic triglyceride lipase activity, resulting in increased HDL\(_2\) and decreased HDL\(_3\)\(^{28}\). Additionally, LPL activation leads to increased transport of lipids and lipoproteins into peripheral circulation and the hepatic tissues, resulting in increased HDL-C levels. As a result of these mechanisms, high non-HDL-C values may have occurred less frequently in the high CRF group in this study compared to in the group exhibiting low CRF.

To our knowledge, this is the first study describing the association between non-HDL-C levels and CRF, an objective indicator of AE and an important measure of cardiorespiratory capacity of an individual at a given degree of fitness and oxygen availability\(^{32}\). We focused on non-HDL-C as the primary outcome; since it is not influenced by the level of triglycerides, it is considered a predictive indicator of CHD\(^{3}\). Therefore, our study provides novel evidence to highlight the importance of evaluating CRF to reduce the risks of developing various diseases related to non-HDL-C, including dyslipidemia. While there have been RCTs examining the influence of AE on TC, HDL-C, and non-HDL-C levels, RCTs have been criticized for their low external validity in spite of the high internal validity. The present study is observational in nature and enrolled a large number of participants; thus, while the study design is less rigorous than an RCT is, the results may be more generalizable.

However, the present study has some limitations. First, the CRF in this study is an indirect measurement of maximum oxygen uptake, and may be less accurate than a direct measurement of maximum oxygen uptake. However, the method used in the present study, which relies on the estimation of the maximum oxygen uptake, and may be less accurate but may not reduce the internal validity. Third, we did not have information on diet, which influences lipid levels; therefore, residual confounding by diet may be present. Fourth, the lack of data on insulin resistance and glycemic markers may have biased the results through the potential effects on non-HDL-C. Furthermore, the participants were only men, limiting the generalizability of this study but not its validity. Last, the study participants were restricted to those who resided in the Tokyo area and who were working at a particular company. Therefore, they may not be representative of Japanese men. In spite of this limitation, the participants had various roles within the company, suggesting that they could represent Japanese men to a certain extent. However, further studies are needed to validate the results.

### Table 3. Multivariable adjusted hazard ratios for incidence of a high level of non-HDL-C according to cardiorespiratory fitness levels

| Quartiles of age-adjusted baseline cardiorespiratory fitness levels | \(\beta\) value for trend |
|---|---|
| Q\(_1\) (Lowest) | Q\(_2\) | Q\(_3\) | Q\(_4\) (Highest) |
| Number of participants | 995 | 1,011 | 1,064 | 997 |
| Number of cases | 390 | 404 | 384 | 304 |
| Incidence rate | 34.5 | 34.5 | 30.2 | 24.2 |
| Model 1 hazard ratio (95% CI) | 1.00 (reference) | 1.01 (0.88–1.15) | 0.87 (0.76–1.00) | 0.70 (0.60–0.81) | <0.001 |
| Model 2 hazard ratio (95% CI) | 1.00 (reference) | 1.01 (0.88–1.16) | 0.89 (0.77–1.03) | 0.72 (0.62–0.84) | <0.001 |
| Model 3 hazard ratio (95% CI) | 1.00 (reference) | 1.05 (0.92–1.21) | 0.94 (0.81–1.08) | 0.79 (0.67–0.92) | 0.001 |

CI, confidence interval
Model 1: adjusted for age.
Model 2: Model 1 plus systolic blood pressure, smoking status, alcohol intake, and family history of dyslipidemia.
Model 3: Model 2 plus body mass index.
\(^{\text{a}}\)Incidence rate is presented in cases per 1,000 man-years of observation.
of this study in non-Asian participants with a high proportion of obesity and who have different lifestyles to the Japanese.

Conclusions

In the present study, we demonstrated that Japanese men with high levels of CRF are less likely to have a high level of non-HDL-C. Our findings indicate that habitual AE may prevent a high level of non-HDL-C, a risk factor for CHD.

Acknowledgments

The authors thank the study participants and the physicians and medical staff of Tokyo Gas Company for assisting with the data collection.

Funding Source

This work was supported by the National Institutes of Biomedical Innovation, Health and Nutrition, and a collaborative research grant from the Juntendo University Graduate School of Health and Sports Science and the Institute of Health and Sports Science and Medicine (1521224, NW).

Conflicts of Interests

The authors declare that they have no competing interests.

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**Supplementary Table 1.** Multivariable adjusted hazard ratios for incidence of a high level of non-HDL-C (≥140 mg/dL) according to cardiorespiratory fitness levels

| Quartiles of age-adjusted baseline cardiorespiratory fitness levels | Q₁ (Lowest) | Q₂ | Q₃ | Q₄ (Highest) | p value for trend |
|---|---|---|---|---|---|
| Number of participants | 738 | 770 | 844 | 834 | 0.001 |
| Number of cases | 530 | 556 | 560 | 501 | 0.001 |
| Incidence rate<sup>8</sup> | 90.4 | 87.7 | 77.2 | 64.0 | 0.001 |
| Model 1 hazard ratio (95% CI) | 1.00 (reference) | 0.96 (0.85–1.08) | 0.85 (0.76–0.96) | 0.71 (0.63–0.80) | <0.001 |
| Model 2 hazard ratio (95% CI) | 1.00 (reference) | 0.96 (0.85–1.09) | 0.86 (0.76–0.97) | 0.71 (0.63–0.81) | <0.001 |
| Model 3 hazard ratio (95% CI) | 1.00 (reference) | 1.00 (0.88–1.12) | 0.89 (0.79–1.01) | 0.76 (0.67–0.86) | <0.001 |

CI, confidence interval  
Model 1: adjusted for age.  
Model 2: Model 1 plus systolic blood pressure, smoking status, alcohol intake, and family history of dyslipidemia.  
Model 3: Model 2 plus body mass index.  
<sup>8</sup>Incidence rate is presented in cases per 1,000 man-years of observation.

**Supplementary Table 2.** Multivariable adjusted hazard ratios for incidence of a high level of non-HDL-C according to cardiorespiratory fitness levels excluding those who had a high level of non-HDL-C within 2 years after the start of follow up

| Quartiles of age-adjusted baseline cardiorespiratory fitness levels | Q₁ (Lowest) | Q₂ | Q₃ | Q₄ (Highest) | p value for trend |
|---|---|---|---|---|---|
| Number of participants | 936 | 960 | 1,017 | 975 | 0.001 |
| Number of cases | 331 | 353 | 337 | 282 | 0.001 |
| Incidence rate<sup>8</sup> | 29.5 | 30.3 | 26.6 | 22.5 | 0.001 |
| Model 1 hazard ratio (95% CI) | 1.00 (reference) | 1.03 (0.89–1.19) | 0.90 (0.77–1.04) | 0.76 (0.65–0.89) | <0.001 |
| Model 2 hazard ratio (95% CI) | 1.00 (reference) | 1.04 (0.89–1.20) | 0.91 (0.78–1.06) | 0.77 (0.66–0.91) | <0.001 |
| Model 3 hazard ratio (95% CI) | 1.00 (reference) | 1.08 (0.93–1.26) | 0.96 (0.82–1.12) | 0.84 (0.71–0.99) | 0.014 |

CI, confidence interval  
Model 1: adjusted for age.  
Model 2: Model 1 plus systolic blood pressure, smoking status, alcohol intake, and family history of dyslipidemia.  
Model 3: Model 2 plus body mass index.  
<sup>8</sup>Incidence rate is presented in cases per 1,000 man-years of observation.
**Supplementary Table 3.** Multivariable adjusted hazard ratios for incidence of a high level of non-HDL-C according to cardiorespiratory fitness levels excluding those who had a high level of non-HDL-C (≥40, <40 age at baseline)

| Quartiles of age-adjusted baseline cardiorespiratory fitness levels | Q1 (Lowest) | Q2 | Q3 | Q4 (Highest) | \( p \) value for trend |
|---|---|---|---|---|---|
| **≥ 40 age at baseline** | | | | | | |
| Number of participants | 365 | 349 | 383 | 367 | | |
| Number of cases | 130 | 111 | 125 | 99 | | |
| Incidence rate \( ^8 \) | 39.8 | 33.8 | 36.6 | 26.7 | | |
| Hazard ratio (95% CI) | 1.00 (reference) | 0.85 (0.66–1.10) | 0.94 (0.74–1.21) | 0.73 (0.56–0.95) | 0.053 | |
| **< 40 age at baseline** | | | | | | |
| Number of participants | 630 | 662 | 681 | 630 | | |
| Number of cases | 260 | 293 | 259 | 205 | | |
| Incidence rate \( ^8 \) | 32.4 | 34.8 | 27.8 | 23.2 | | |
| Hazard ratio (95% CI) | 1.00 (reference) | 1.17 (0.99–1.38) | 0.94 (0.79–1.13) | 0.83 (0.68–1.00) | 0.011 | |

CI, confidence interval

Adjusted for age, systolic blood pressure, smoking status, alcohol intake, and family history of dyslipidemia, and body mass index.

\(^8\) Incidence rate is presented in cases per 1,000 man-years of observation.