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Original Investigation

Percentage of age-predicted cardiorespiratory fitness may be a stronger risk indicator for incident type 2 diabetes than absolute levels of cardiorespiratory fitness

Setor K. Kunutsor, PhD[1,2,3], Hassan Khan, PhD[4], Samuel Seidu, MD[3], Jari A. Laukkanen, PhD[5,6,7]

[1] *National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, UK*

[2] *Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, UK*

[3]*Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4WP, UK*

[4]*Leon H. Charney Division of Cardiology, New York University Langone Health, New York, NY, USA*

[5] *Central Finland Health Care District Hospital District, Department of Medicine, Jyväskylä, Finland District, Jyväskylä, Finland*

[6] *Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland*

[7] *Institute of Clinical Medicine, Department of Medicine, University of Eastern Finland, Kuopio, Finland*

Running title: Percentage of age-predicted cardiorespiratory fitness and type 2 diabetes

Correspondence: *Setor K. Kunutsor, Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK; Phone: +44-7539589186; Fax: +44-1174147924; Email: skk31@cantab.net*

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Abstract

Purpose: There are inverse and independent associations between cardiorespiratory fitness (CRF) and several adverse cardiometabolic outcomes. The percentage of age-predicted CRF (%age-predicted CRF) is comparable to absolute CRF as a risk indicator for some of these outcomes, but the association between %age-predicted CRF and risk of type 2 diabetes (T2D) has not been previously investigated. We aimed to assess the association between %age-predicted CRF and T2D in a prospective cohort study.

Methods: Cardiorespiratory fitness, as measured directly by peak oxygen uptake, was assessed in 1901 men aged 42-60 yr who underwent cardiopulmonary exercise testing**.** The age-predicted CRF estimated from a regression equation for age was converted to %age-predicted CRF using (achieved CRF/age-predicted CRF)*100. Hazard ratios (HRs) (95% confidence intervals, CIs) were estimated for T2D.

Results: During a median follow-up of 26.8 yr, 227 T2D cases were recorded. The risk of T2D decreased continuously with increasing %age-predicted CRF (*P*-value for non-linearity=.30). A 1 SD increase in %age-predicted CRF was associated with a decreased risk of T2D in analysis adjusted for established risk factors (HR=0.68: 95% CI, 0.59–0.79). The corresponding adjusted risk was (HR=0.51: 95% CI, 0.35-0.75) comparing extreme tertiles of %age-predicted CRF. The respective estimates for the association between absolute CRF and T2D were (HR=0.71: 95% CI, 0.60-0.83) and (HR=0.64: 95% CI, 0.44-0.95).

Conclusions: Percentage of age-predicted CRF is linearly, inversely and independently associated with the risk of incident T2D and may be a stronger risk indicator for T2D compared to absolute CRF in a general population of middle-aged and older men.

Diabetes, of which type 2 diabetes (T2D) accounts for more than 90% of cases, is a leading cause of morbidity, mortality and associated with substantial economic burden on healthcare and global systems.[1, 2] Major risk factors for T2D constitute older age, non-white ethnicity, obesity, family history of T2D, poor diet, smoking, excessive alcohol consumption and physical inactivity.[3] Despite increasing knowledge on the epidemiology of T2D and development of successful preventive strategies, its prevalence and incidence are not on the decrease. There is documented evidence on the role of regular physical activity (PA) in reducing the risk of adverse cardiometabolic outcomes including T2D.[4, 5] Cardiorespiratory fitness (CRF), a cardiopulmonary exercise testing (CPX) parameter and one of the best measures for assessing cardiovascular fitness and aerobic capacity, can be increased through increased PA and exercise training.[6] A wide variation of methods are used to assess CRF and these range from directly measured maximal oxygen uptake (VO_{2max}) or peak oxygen uptake (VO_{2peak}) during CPX,[6, 7] to estimation from exercise tests and non-exercise prediction equations. Like PA, several observational studies have shown that CRF, either directly measured or estimated from exercise tests, is inversely and independently associated with cardiovascular outcomes[8-13] as well as T2D.[14] In addition to the fact that about half of the variation in CRF is heritable,[15] CRF is strongly influenced by age;[16] hence, CRF can be expressed as a percentage of the value predicted on the basis of age (percentage of age-predicted CRF, %age-predicted CRF). Some observational prospective studies have shown that %age-predicted CRF is inversely associated with cardiovascular outcomes such as cardiovascular disease (CVD), coronary heart disease (CHD), sudden cardiac death (SCD), hypertension as well as mortality.[6, 17-21] However, the association between %age-predicted CRF and T2D, a major risk factor for vascular disease, has not been previously investigated. The primary aim of this study was to evaluate the nature, magnitude and specificity of the association between %age-predicted CRF and risk of incident T2D in a population-based cohort of apparently healthy middle-aged and older men from eastern Finland. To put the strength of the association of %age-predicted CRF with the risk of future T2D into

context, a comparison was made with the association between absolute CRF levels and T2D risk in the same sample of study participants.

METHODS

Study design and population

The current study adhered to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (Supplementary Digital Content 1).[22] We employed data from the Kuopio Ischaemic Heart Disease (KIHD) risk factor study, a population-based prospective cohort study that was designed to investigate established and emerging risk factors for atherosclerotic cardiovascular outcomes in Eastern Finland. Participants included in the KIHD study comprised a representative sample of men aged 42 to 60 yr living in the city of Kuopio and its surrounding rural communities in eastern Finland. Invitations were sent to potential study participants during the recruitment phase. Of the representative sample of 3,433 potentially eligible men who were invited for screening examinations between March 1984 and December 1989, 3,235 were found to be eligible. Of this number, 2682 (83%) volunteered to participate and 553 did not respond to the invitation or declined to give informed consent. For this analysis, men with a prevalent history of T2D (n=112) and those with missing data on the exposure and potential confounders (n=669) were excluded. The current analysis included 1,901 men with complete information on %age-predicted CRF, absolute CRF, relevant risk markers, and incident T2D events (Supplementary Digital Content 2). The Research Ethics Committee of the University of Eastern Kuopio, Finland approved the study which was conducted in accordance with the Declaration of Helsinki. Each participant provided written informed consent.

Assessment of CRF, %age-predicted CRF, covariates and T2D

Peak oxygen uptake, used as a measure of CRF, was directly assessed using a computerized metabolic measurement system (Medical Graphics, USA) during a maximal symptom-limited

exercise-tolerance test on an electrically braked cycle ergometer which was conducted between 8:00 am and 10:00 am.[23] Repeat measurements of CRF were performed 11 yr after baseline in a random subset of the study participants.[12, 24, 25] The standardized testing protocol included a 3-min warm-up at 50 watts (W; 1W = 6.12 kgm/min), followed by 20 W/min increases in workload with direct analyses of expired respiratory gases. The respiratory gas analyzer expressed VO_{2peak} as an average value recorded over 8 seconds. Peak oxygen uptake was defined as the highest or peak attained value for oxygen consumption, expressed as ml/kg/min; VO_{2peak} was also expressed in metabolic equivalents (METs) (1 MET corresponding to an oxygen uptake of 3.5 mL/kg/min). The respiratory exchange ratio (RER), defined as the ratio between respiratory gases ($\dot{V}CO_2$ and VO_2,) was obtained exclusively from ventilatory expired gas analysis. Maximal effort was defined as RER greater than or equal to 1.1.[16] Peak oxygen uptake expressed in METs was incorporated into a regression equation [18.4-(0.15 x age)], which was used to estimate age-predicted CRF.[26] The %age-predicted CRF was then calculated from the formula: achieved CRF/age-predicted CRF)*100.[21, 26] Given the strong influence of age on CRF and the need to assess if %age-predicted CRF was a stronger risk indicator than absolute levels of CRF, the regression equation for age by Morris and colleague CRF[26] was the most appropriate equation to use rather than equations that took into account multiple factors.[27] Furthermore, we used this approach to maintain consistency with previous reports.[18-21] An experienced physician and nurse supervised all exercise tests to ensure safety. Electrocardiographic indices, blood pressure, and heart rate were measured during exercise testing.

The assessment of lifestyle characteristics and medical history, collection of blood specimens and measurement of blood biomarkers, and physical examinations have been described in previous reports.[28, 29] Briefly, self-administered questionnaires were used to assess sociodemographic characteristics, lifestyle characteristics such as smoking and alcohol consumption, existing medical conditions and use of medication.[28] Prevalent T2D was defined as a fasting blood glucose level ≥7.0 mmol/L or clinical diagnosis of diabetes with dietary, oral, or insulin treatment. The cholesterol

content of lipoprotein fractions were measured enzymatically (Boehringer Mannheim, Germany).[30] Adulthood socioeconomic status (SES) was assessed as a summary index of the combination of income, education, occupation, occupational prestige, material standard of living, and housing conditions. The composite SES index ranged from 0 to 25, with higher values indicating lower SES.[31] Smoking status was categorised into smokers and non-smokers. A participant was defined as a smoker if he had ever smoked regularly and had smoked cigarettes, cigars, or a pipe within the past 30 dy. Alcohol consumption reported in g/week was assessed using the Nordic Alcohol Consumption Inventory. Resting blood pressure was measured between 8:00 and 10:00 AM with a random-zero sphygmomanometer using a standardised protocol. After a supine rest of 5-min, blood pressure was measured three times in supine position, once in standing position, and twice in sitting position with 5-min intervals, and the arithmetic mean of all available measurements was taken. Leisure-time PA was assessed from a 12-mo PA history questionnaire modified from the Minnesota Leisure-Time Physical Activity Questionnaire.[32]

We included all T2D cases that occurred from study enrollment through to 2018. An incident T2D case was defined as a fasting plasma glucose (FPG) ≥ 7.0 mmol/L, a 2 h glucose tolerance test plasma glucose ≥ 11.1 mmol/L, or use of glucose-lowering medication according to self-report at re-examination and by record linkage to the national hospital discharge registry and to the Social Insurance Institution of Finland register for reimbursement of medicine expenses. There were no losses to follow-up.

Statistical analysis

Variables with skewed distributions (i.e., alcohol consumption, physical activity) were natural log transformed to achieve approximately symmetrical distributions. Descriptive statistics were used to summarise baseline data: mean ±SD or median (IQR) for continuous variables and counts (percentages) for categorical variables. To assess the cross-sectional associations of %age-predicted

CRF with various risk markers, Pearson's correlation coefficients were estimated using linear regression models adjusted for age. Hazard ratios (HRs) with 95% CIs for incident T2D were estimated using Cox proportional hazard models, after confirming no major departure from the assumptions of proportionality of hazards using Schoenfeld residuals.[33] To explore a potential nonlinear dose-response relationship between %age-predicted CRF and T2D risk, we constructed a restricted cubic spline with knots at the 5th, 35th, 65th and 95th percentiles of the distribution of %age-predicted CRF in a multivariable adjusted model. We modelled %age-predicted CRF as both continuous [per SD increase] and categorical (quartiles) variables. Adjustment for confounders was made using two models: (Model 1) systolic blood pressure (SBP), smoking status, total cholesterol, HDL-C, FPG, family history of T2D and history of hypertension and (Model 2) model 1 plus alcohol consumption, SES and physical activity. To quantify and correct for within-person variability (regression dilution bias) in CRF levels, which is, the extent to which an individual's CRF measurements vary around the long-term average exposure levels ("usual levels"),[34] adjusted regression dilution ratios (RDRs) were calculated by regressing available repeat measurements of CRF on baseline values.[35] The estimated disease association was then divided (log hazard ratio and its 95% CIs) by the RDR. Given that %age-predicted CRF was estimated from CRF values, the association of "usual levels" of %age-predicted CRF with T2D risk was estimated using the RDR derived from repeat measurements of CRF. We used formal tests of interaction tests to assess statistical evidence of effect modification by individual characteristics, such as age and other clinically relevant characteristics. To minimize any bias due to reverse causation, sensitivity analysis involved excluding the first five yr of follow-up. Direct comparisons were made to the association of absolute CRF with incident T2D risk in the same sample of participants. All statistical analyses were conducted using Stata MP version 16 (Stata Corp, College Station, Texas).

RESULTS

The mean ±SD age, %age-predicted CRF, absolute CRF and RER at baseline was 53 ±5 yr, 87.0 ±21.3%, 30.6 ±7.9 mL/kg/min and 1.09 ±0.14, respectively (Table 1). Men who developed T2D had lower values of %age-predicted CRF and HDL-C and higher values of BMI and blood pressure at baseline. They were also more likely to have a history of hypertension and a family history of T2D (Table 1).

Repeat measurements of CRF taken at 11 yr after baseline were available in a random sample of 505 men. The overall age-adjusted RDR of CRF was 0.58: 95% CI, 0.52-0.64, suggesting that using single baseline measurements of the exposures could under-estimate the associations of %age-predicted CRF and absolute CRF with risk of T2D by [(1/0.58)-1]*100 = 72.4%.

During a median (IQR) follow-up of 26.8 (17.7-31.1) yr (45,182 person-yr at risk), 227 cases of T2D (annual rate 5.02/1000 person-yr at risk, 95% CI, 4.41-5.72) were recorded. A multivariable restricted cubic spline curve showed the risk of T2D decreased linearly with increasing %age-predicted CRF across the range 71-190 (*P*-value for non-linearity=.30) (Figure 1). In analysis adjusted for SBP, smoking status, total cholesterol, HDL-C, fasting plasma glucose, family history of T2D and history of hypertension, the HR (95% CI) per 1 SD increase in %age-predicted CRF for incident T2D was 0.67 (0.58-0.78), which persisted 0.68 (0.59-0.79) after further adjustment for alcohol consumption, SES and PA. Alternatively, comparing the top versus bottom tertiles of %age-predicted CRF, the corresponding adjusted HRs (95% CIs) for incident T2D were 0.49 (0.34-0.71) and 0.51 (0.35-0.75), respectively (Table 2**).** The risk estimates were stronger on correction for regression dilution bias (Table 2). The association between %age-predicted CRF and T2D risk did not vary significantly by levels or categories of several clinically relevant characteristics (Figure 2). The inverse relationship between %age-predicted CRF and T2D risk persisted in analyses that excluded the first five yr of follow-up in the whole population (Supplementary Digital Content 3).

In analyses that assessed the association of absolute CRF with incident T2D risk in the same set

of study participants with consistent adjustment for confounders (including age), the HRs (95% CIs) were 0.71 (0.60-0.83) for a 1 SD increase in CRF and 0.64 (0.44-0.95) comparing the top versus bottom tertiles of CRF (Table 3). The risk estimates were stronger on correction for regression dilution bias (Table 3).

DISCUSSION

In this population-based cohort study of Caucasian men without a history of T2D at baseline, higher %age-predicted CRF was associated with a lower risk of incident T2D, which was independent of several established risk factors and consistent with a linear dose-response relationship. The association of %age-predicted CRF with incident T2D risk did not differ by several clinically relevant subgroups and in sensitivity analysis that excluded the first five yr of follow-up. Further analyses in the same sample of participants showed significant evidence of an association between absolute CRF and T2D risk; but the risk estimates were more extreme for %age-predicted CRF and T2D risk, suggesting that %age-predicted CRF might be a stronger risk indicator for T2D than absolute CRF. In an analysis that corrected for within-person variability in CRF values, we also observed that using only single baseline measurements of %age-predicted CRF to assess the association may underestimate the strength of the association by 72%.

Though CRF is determined by many unmodifiable factors such as age, sex, and genetic factors, the most established ways of increasing CRF are through increased habitual PA and exercise training.[6] Apart from habitual PA and exercise training, other related determinants of CRF include baseline health and fitness status of the individual, type, duration, and intensity of PA. It has been reported that 1 MET gain in CRF levels may be achieved through structured exercise for 4-5 mo irrespective of age, sex, weight-status and previous history of PA.[6, 36] The beneficial effects of %age-predicted CRF on T2D risk may be via the effects of PA or exercise training. Indeed, it has been reported that most different types of PA (eg, total PA, leisure-time activity, resistance exercise, occupational activity, walking) are associated with a 25-40% reduction in the relative risk of T2D.[4] Physical activity and exercise training may contribute to a reduction in the risk of T2D via improvement in energy balance, reduction in adiposity[37] and inflammatory markers such as interleukin-19 and C-reactive protein,[38, 39] improvement in glucose homeostasis,[40] insulin sensitivity, glycaemic control and the metabolic profile,[41, 42] transformation of muscle fibres, increased

mitochondrial activity and content, and increases in GLUT4 protein expression.[40] The improvements in insulin sensitivity and blood glucose reductions have been reported to be related to the duration and intensity of exercise, with greater effects attributed to more prolonged and intense PA than for non-vigorous PA.[42] This is consistent with the results from our restricted cubic spline curve, which showed no threshold effect, suggesting that the risk of T2D decreases continuously with increase in levels of %age-predicted CRF from low to high. Furthermore, the preventative cardioprotective effects of CRF has been suggested to be partly explained by healthy vascular aging, which confers higher CRF.[43]

There is limited data on the potential clinical application of %age-predicted CRF as a useful exercise test parameter. Only a few studies including some of ours have evaluated associations between %age-predicted CRF and outcomes such as CVD mortality, sudden cardiac death, hypertension, and all-cause mortality.[18-21] Majority of studies evaluating CPX parameters have focused on absolute CRF values. So far, the evidence seems to suggest that %age-predicted CRF (i.e., values of CRF which take into account the influence of age) is comparable or may be superior to absolute CRF as a risk indicator or predictor for adverse cardiometabolic outcomes.[18-20] The strong and graded nature of the relationship between %age-predicted CRF and T2D risk suggests that %age-predicted CRF may be potentially suitable for population-level risk assessment. There have been continued calls for research into the clinical utility of CPX parameters across all patient populations.[44] These findings should stimulate more research into the use of %age-predicted CRF, which may be a more reliable risk factor for chronic disease outcomes, including T2D.

Strengths and limitations

This is the first evaluation of the association of %age-predicted CRF with the risk of incident T2D as well as comparison of the association with that of absolute CRF and T2D risk in the same sample of study participants. Other strengths included the use of the gold standard objective approach of

assessing CRF, the relatively large population-based cohort which was also representative of a general population of middle-aged and older Finnish men, exclusion of men with prevalent T2D at baseline, adjustment for several potential confounders, and further association analyses including evaluating the nature of the dose-response relationship, assessing effect modification by clinically relevant characteristics, and minimising reverse causation by conducting sensitivity analyses which involved excluding the first five yr of follow-up. Repeat measurements of CRF made within a random subset of individuals over time after baseline were available, which enabled correction for the extent of within-person variability in CRF values over the long period of follow-up. Corrections could only be done using the RDR and not a time-varying analysis, because repeat measurements were only available in a random subset of participants. The limitations were mostly inherent to the study design and included (i) potential biases in observational studies such as residual confounding due to errors in risk marker measurements and unmeasured confounding; (ii) the possibility that lifestyle habits may have changed during follow-up due to probable changes in health habits or other incident diseases occurring over the long period of time; and (iii) inability to generalise the findings to women and other populations and age-groups. The exposure - age-predicted CRF - was estimated from an age-based prediction equation. It is acknowledged that nonexercise prediction equations have inherent limitations such as inability to account for well-established genetic influence on CRF, influence of social desirability biases on self-reported aspects of some of the equations, and underestimation and overestimation of CRF at the top and bottom ends of the distribution, respectively.[6, 45-47] However, it is also well known that most of these nonexercise-based algorithms can conveniently estimate CRF in a rapid, inexpensive and reasonably accurate way when used for large population settings.[6]

CONCLUSIONS

Percentage of age-predicted CRF is inversely and independently associated with risk of incident T2D in middle-aged and older men, consistent with a linear dose-response relationship. Furthermore, %age-predicted CRF may be a stronger risk indicator for T2D than absolute CRF.

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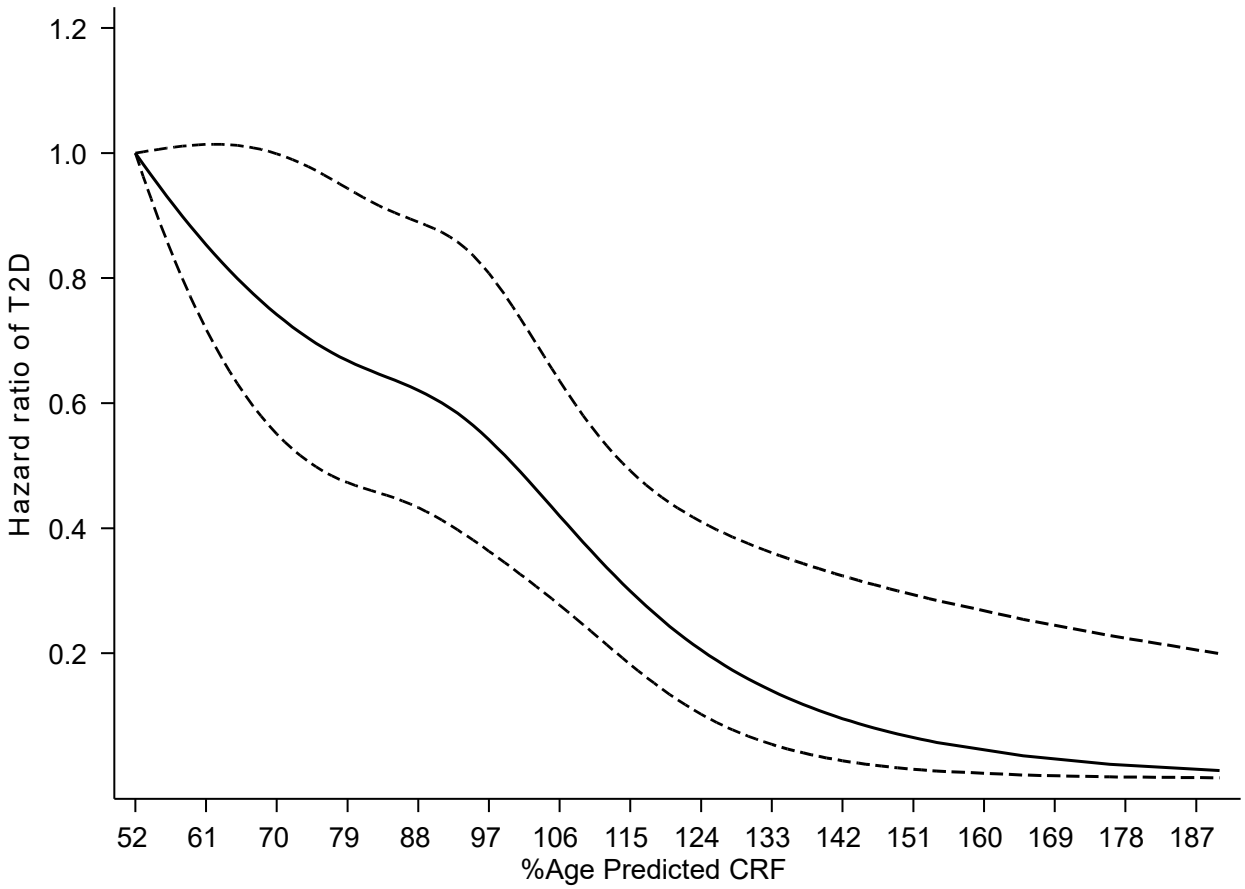
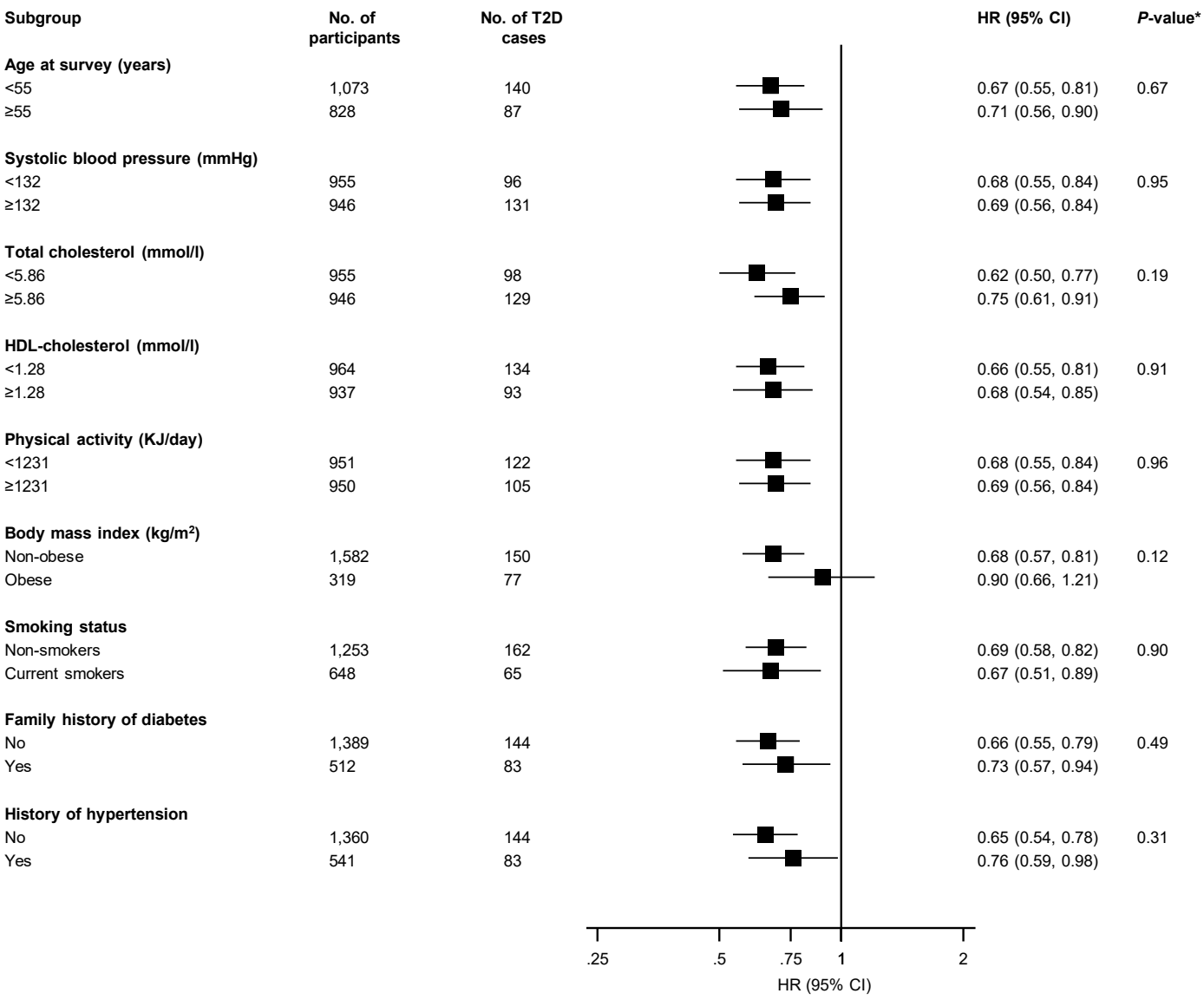
Figure Legends

Figure 1. Restricted cubic splines of the hazard ratios of incident type 2 diabetes with %age-predicted CRF



CRF, cardiorespiratory fitness; T2D, type 2 diabetes; Reference value for %age-predicted CRF is 52; dashed lines represent the 95% confidence intervals for the spline model (solid line) Models were adjusted for systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, family history of type 2 diabetes, history of hypertension, alcohol consumption, socioeconomic status and physical activity

Figure 2. Association of %age-predicted CRF with incident type 2 diabetes in clinically relevant subgroups



Hazard ratios were adjusted for systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, family history of type 2 diabetes, history of hypertension, alcohol consumption, socioeconomic status and physical activity; CI, confidence interval; CRF, cardiorespiratory fitness; HDL, high-density lipoprotein; HR, hazard ratio; T2D, type 2 diabetes; *, *P*-value for interaction; cut-offs used for age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol; and physical activity are median values.

Table 1. Baseline participant characteristics

	Overall (N=1901) Mean ±SD, median (IQR), or %	**Did not develop T2D (N=1674) Mean ±SD, median (IQR), or %**	**Developed T2D (N=227) Mean ±SD, median (IQR), or %**	***P*-value**
Exercise testing measures				
Percentage of age-predicted CRF	87.0 ±21.3	87.8 ±21.5	80.7 ±18.6	<.001
Absolute CRF (mL/kg/min)	30.6 ±7.9	30.9 ±8.0	28.7 ±7.2	<.001
Metabolic equivalents	8.74 ±2.27	8.82 ±2.29	8.20 ±2.06	<.001
Peak respiratory gas exchange ratio	1.09 (0.14)	1.10 (0.14)	1.08 (0.13)	0.08
Questionnaire/Prevalent conditions				
Age at survey (yr)	53 ±5	53 ±5	52 ±5	.20
Alcohol consumption (g/week)	42.5 (12.4-103.2)	42.4 (12.4-101.6)	44.7 (12.1-120.0)	.95
Socioeconomic status	8.18 ±4.26	8.18 ±4.28	8.18 ±4.16	<.99
Smoking status				.065
No	1253 (65.9)	1091 (65.2)	162 (71.4)	
Current	648 (34.1)	583 (34.8)	65 (28.6)	
Family history of T2D				<.001
No	1389 (73.1)	1245 (74.4)	144 (63.4)	
Yes	512 (26.9)	429 (25.6)	83 (36.6)	
History of hypertension				.004
No	1360 (71.5)	1216 (72.6)	144 (63.4)	
Yes	541 (28.5)	458 (27.4)	83 (36.6)	
Physical measurements				
BMI (kg/m^2)	26.8 ±3.4	26.5 ±3.3	28.8 ±3.6	<.001
SBP (mmHg)	134 ±16	133 ±16	137 ±17	.003
DBP (mmHg)	89 ±10	88 ±10	92 ±9	<.001
Physical activity (KJ/day)	1231 (662-2000)	1245 (680-1992)	1094 (534-2111)	.059
Blood-based markers				
Total cholesterol (mmol/L)	5.94 ±1.07	5.93 ±1.06	6.02 ±1.13	.25
HDL-C (mmol/L)	1.30 ±0.31	1.31 ±0.31	1.22 ±0.27	<.001
Fasting plasma glucose (mmol/L)	5.22 ±0.85	5.12 ±0.61	5.97 ±1.64	<.001

BMI, body mass index; CI, confidence interval; CRF, cardiorespiratory fitness; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure; T2D, type 2 diabetes
*, One metabolic equivalent corresponds to an oxygen uptake of 3.5 ml/kg/min during maximal exercise test

Table 2. Association between percentage of age-predicted CRF and risk of type 2 diabetes

Percentage of age-predicted CRF	**Events/ Total**	**Model 1**		**Model 2**	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline %age-predicted CRF					
Per 1 SD increase	227 / 1,901	0.67 (0.58-0.78)	<.001	0.68 (0.59-0.79)	<.001
Tertile 1 (16.95-78.06)	94 / 634	ref		ref	
Tertile 2 (78.07-94.78)	85 / 634	0.88 (0.65-1.20)	.43	0.91 (0.67-1.23)	.53
Tertile 3 (>94.78)	48 / 633	0.49 (0.34-0.71)	<.001	0.51 (0.35-0.75)	.001
Usual %age-predicted CRF*					
Per 1 SD increase	227 / 1,901	0.50 (0.39-0.65)	<.001	0.52 (0.40-0.67)	<.001
Tertile 1 (16.95-78.06)	94 / 634	ref		ref	
Tertile 2 (78.07-94.78)	85 / 634	0.81 (0.6548-1.37)	.43	0.84 (0.50-1.43)	.53
Tertile 3 (>94.78)	48 / 633	0.29 (0.15-0.55)	<.001	0.32 (0.17-0.60)	.001

*, indicates correction for within-person variability in values of CRF, that is, the extent to which an individual's CRF measurements vary around a long-term average value ("usual CRF values")

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; %age-predicted CRF, percentage of age-predicted cardiorespiratory fitness; SD, standard deviation

Model 1: Adjusted for systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, family history of type 2 diabetes and history of hypertension

Model 2: Model 1 plus alcohol consumption, socioeconomic status and physical activity

Table 3. Association between absolute CRF and risk of incident type 2 diabetes

Absolute CRF (mL/kg/min)	**Events/ Total**	**Model 1**		**Model 2**	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
		Baseline CRF			
Per 1 SD increase	227 / 1,901	0.69 (0.59-0.81)	<.001	0.71 (0.60-0.83)	<.001
Tertile 1 (6.36-27.13)	86 / 634	ref		ref	
Tertile 2 (27.14-33.62)	86 / 634	1.01 (0.74-1.39)	.94	1.05 (0.76-1.44)	.79
Tertile 3 (>33.62)	55 / 633	0.61 (0.41-0.89)	.01	0.64 (0.44-0.95)	.025
		Usual CRF*			
Per 1 SD increase	227 / 1,901	0.53 (0.40-0.70)	<.001	0.55 (0.42-0.73)	<.001
Tertile 1 (6.36-27.13)	86 / 634	ref		ref	
Tertile 2 (27.14-33.62)	86 / 634	1.02 (0.59-1.77)	.94	1.08 (0.62-1.87)	.79
Tertile 3 (>33.62)	55 / 633	0.42 (0.22-0.81)	.01	0.47 (0.24-0.91)	.025

*, indicates correction for within-person variability in values of CRF, that is, the extent to which an individual's CRF measurements vary around a long-term average value ("usual CRF values")

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; SD, standard deviation

Model 1: Adjusted for age, systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, family history of type 2 diabetes and history of hypertension

Model 2: Model 1 plus alcohol consumption, socioeconomic status and physical activity

SUPPLEMENTARY MATERIAL

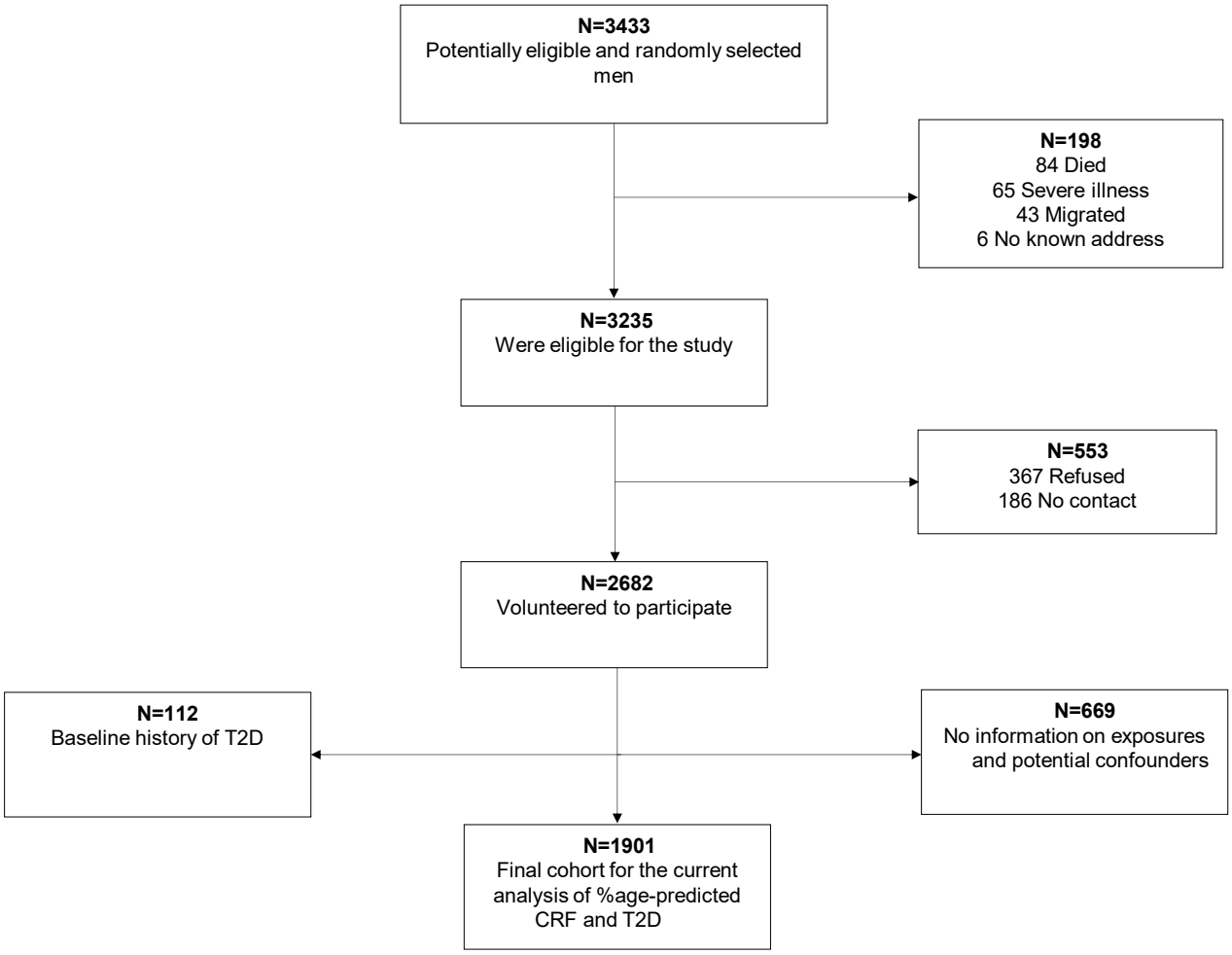
Supplementary Digital Content 1	STROBE Statement
Supplementary Digital Content 2	Participant flow through the study
Supplementary Digital Content 3	Association between percentage of age-predicted CRF and risk of type 2 diabetes, on excluding the first 5 years of follow-up

Supplementary Digital Content 1. STROBE Statement

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	Page 3-4
Methods			
Study design	4	Present key elements of study design early in the paper	Study population
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Study population
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Study population
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Statistical analyses
Study size	10	Explain how the study size was arrived at	Statistical analyses
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analyses
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analyses
		(*b*) Describe any methods used to examine subgroups and interactions	Statistical analyses
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Statistical analyses

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Study population
		(b) Give reasons for non-participation at each stage	Study population
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	Results
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results; Tables 2-3; Figures 1-2
		(*b*) Report category boundaries when continuous variables were categorized	Results; Tables 2-3; Figures 1-2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results; Figure 2; Supplementary Digital Content 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion - Summary of main findings
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

Supplementary Digital Content 2. Participant flow through the study



CRF, cardiorespiratory fitness; T2D, type 2 diabetes

Supplementary Digital Content 3. Association between percentage of age-predicted CRF and incident type 2 diabetes, on excluding the first 5 years of follow-up

Percentage of age-predicted CRF	Events/ Total	Model 1		Model 2	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD increase	215 / 1,808	0.67 (0.58-0.78)	<.001	0.69 (0.59-0.80)	<.001
Tertile 1 (16.95-78.87)	90 / 603	ref		ref	
Tertile 2 (78.88-95.31)	80 / 603	0.91 (0.66-1.24)	.54	0.94 (0.68-1.28)	.69
Tertile 3 (>95.31)	45 / 602	0.49 (0.33-0.71)	<.001	0.52 (0.35-0.76)	.001

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; SD, standard deviation

Model 1: Adjusted for systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, family history of type 2 diabetes and history of hypertension

Model 2: Model 1 plus alcohol consumption, socioeconomic status and physical activity