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Original Article

The Interplay of Type 2 Diabetes Status, Cardiorespiratory Fitness Level, and Sudden Cardiac Death: A Prospective Cohort Study

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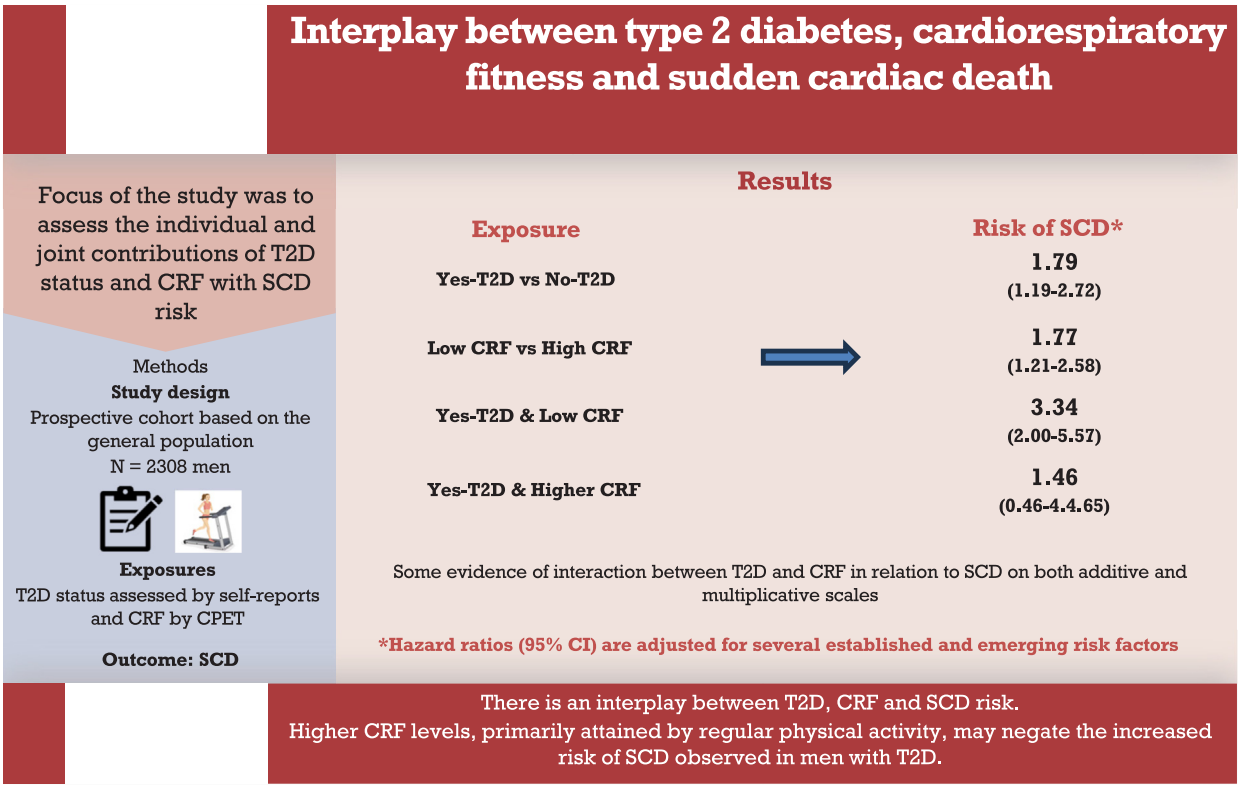

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ABSTRACT

Background: To evaluate the individual and joint effects of type 2 diabetes (T2D) status and cardiorespiratory fitness (CRF) level with sudden cardiac death (SCD) risk.

Methods: Prevalent T2D was defined based on guideline recommendations, and CRF level was assessed using a respiratory gas-exchange analyzer during exercise testing at baseline, in 2308 men aged 42-61 years. T2D status was classified as either "Yes" or "No," and CRF level was classified as low, medium, or high. Cox regression analysis was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for SCD.

Results: A total of 264 SCDs occurred during a median follow-up of 28.1 years. Comparing Yes vs No history of T2D, the multivariable-adjusted HR (95% CI) for SCD was 1.79 (1.19-2.72). Comparing low vs high CRF levels, the corresponding adjusted HR (95% CI) for SCD was 1.77 (1.21-2.58). The HRs persisted when T2D status was further adjusted for CRF level, and vice versa. Compared with No-T2D & medium-high CRF level, men with No-T2D & low CRF and those with Yes-T2D & low CRF had an increased SCD risk: (HR = 1.87, 95% CI, 1.38-2.55) and (HR = 3.34, 95% CI, 2.00-5.57), respectively. No significant association occurred between men with Yes-T2D & medium-high CRF and SCD risk (HR = 1.46, 95% CI, 0.46-4.65). Modest evidence indicated the presence of additive and multiplicative interactions between T2D status and CRF level, in relation to SCD.

Conclusions: An interplay exists between T2D status, CRF level, and SCD risk in middle-aged and older men. Higher CRF levels may mitigate the increased SCD risk observed in men with T2D.

RÉSUMÉ

Contexte : Évaluation des effets individuels et conjoints du statut du diabète de type 2 (DT2) et du niveau d'aptitude cardiorespiratoire (ACR) sur le risque de mort subite cardiaque (MSC).

Méthodes : La prévalence du DT2 a été définie sur la base des recommandations des lignes directrices, et le niveau d'ACR a été évalué à l'aide d'un système d'analyse d'échange gazeux respiratoire lors d'un test d'exercice au départ, chez 2 308 hommes âgés de 42 à 61 ans. Le statut du DT2 a été classé comme "oui" ou "non", et le niveau d'ACR a été classé comme faible, moyen ou élevé. L'analyse de régression de Cox a été utilisée pour estimer les rapports de risque (RR) avec des intervalles de confiance (IC) à 95 % pour la MSC.

Résultats : Au total, 264 MSC sont survenues au cours d'un suivi médian de 28.1 ans. En comparant le statut d'antécédents de DT2 (Oui vs Non), le RR ajusté multivarié (IC à 95 %) pour la MSC était de 1,79 (1,19-2,72). En comparant les niveaux d'ACR faibles *versus* élevés, le RR ajusté correspondant (IC à 95 %) pour la MSC était de 1,77 (1,21-2,58). Les RR ont persisté lorsque le statut de DT2 a été ajusté en fonction du niveau d'ACR, et vice versa. Par rapport à l'absence de DT2 et pour un niveau moyen-élevé d'ACR, les hommes sans DT2 et avec un faible niveau d'ACR et ceux avec un DT2 et un faible niveau d'ACR présentaient un risque accru de MSC : (RR = 1,87, IC à 95 %, 1,38-2,55) et (RR = 3,34, IC à 95 %, 2,00-5,57), respectivement. Aucune association significative n'a été observée entre les hommes présentant un DT2 (Oui) avec une ACR moyenne-élevée et le risque de décès par accident vasculaire cérébral (RR = 1,46, IC à 95 %, 0,46-4,65). Des preuves modestes ont indiqué la présence d'interactions additives et multiplicatives entre le statut DT2 et le niveau d'ACR, en relation avec la MSC.

Conclusions : Il existe une interaction entre le statut DT2, le niveau d'ACR et le risque de MSC chez les hommes d'âge moyen et plus âgés. Des niveaux plus élevés d'ACR peuvent atténuer le risque accru de MSC observé chez les hommes atteints de DT2.

Sudden cardiac death (SCD) represents a significant public health burden, accounting for approximately 15%-20% of all deaths globally.[1] SCD often is precipitated by sudden and unexpected cardiac arrest, typically due to underlying cardiovascular conditions. Coronary artery disease is documented to be the most common pathologic condition underlying SCD in the general population.[1] Established risk factors for SCD include coronary artery disease, heart failure, prior myocardial infarction, type 2 diabetes (T2D), certain genetic predispositions, and modifiable lifestyle risk factors, including smoking and low physical-activity level.[2] However, these factors do not fully account for all incident cases of SCD, leaving a residual risk that possibly suggests that an interplay of these factors occurs (interaction and effect modification), or that additional risk factors may be at play. Interaction and effect modification are 2 related, but distinct, concepts used in epidemiology and statistics to describe the combined effects of 2 exposures on an outcome.[3] Interaction is often assessed to help clarify whether 2 (or more) exposures jointly influence the outcome more (or less) than expected, based on their individual effects.[3,4] Two types of interactions can occur—additive and multiplicative. In an additive interaction, the combined effect of 2 exposures is equal to the sum of their individual effects. In a multiplicative interaction, the combined effect of 2 exposures differs from the product of their individual effects.[3,4] Effect modification, also known as heterogeneity of effects, occurs when the effect of one exposure on an outcome varies across the levels or strata of another variable. This concept is used to identify subgroups within the population for which the exposure—outcome relationship differs.[3,4] Both approaches are important to gain a comprehensive understanding of how multiple risk factors together influence health outcomes.

T2D is a well-recognized risk factor for adverse CVD outcomes, including SCD.[5,6] Individuals who have T2D are at a substantially higher risk of developing CVDs, due to such factors as chronic hyperglycemia, insulin resistance, and

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associated metabolic disturbances.[6] Engaging in regular physical activity is a well-established method to reduce the risk of adverse cardiovascular outcomes, including SCD.[7,8] Concurrently, lack of cardiorespiratory fitness (CRF), largely determined by the level of aerobic physical activity, is a major risk factor for and predictor of adverse cardiovascular outcomes, including SCD.[9-11] Evidence suggests that CRF is such a strong protective risk factor that higher levels can counteract the negative impact of various risk factors. Notably, our research group has shown previously that higher CRF levels can mitigate the adverse effects of low socioeconomic status (SES), elevated levels of inflammatory markers, such as high-sensitivity C-reactive protein (CRP), and elevated systolic blood pressure on the risk of cardiovascular outcomes, including SCD.[12-14] Higher CRF levels also have been shown to potentiate the beneficial effects of protective lifestyle factors, such as frequent sessions in a sauna.[15-17] These observations highlight the potential of higher CRF levels to serve as a powerful protective factor in the context of cardiovascular health.

Given the existing evidence, we hypothesized that prevalent T2D and lower CRF levels would each be associated independently with an increased risk of SCD, and that higher CRF levels could attenuate the increased risk of SCD associated with T2D. To test this new hypothesis, we utilized a population-based prospective study of middle-aged and older men, aiming to assess the individual and joint effects of T2D status and CRF level on SCD risk. Using well-known measures of interaction, we assessed whether their combination has an additive or multiplicative effect on SCD. In our study, we focused on evaluating the joint effects of T2D status and CRF level on SCD risk, as opposed to examining effect modification. We used this approach because our intent was to assess the combined impact of both modifiable exposures (T2D status and CRF level), to better understand their interplay and cumulative risk. This approach is particularly relevant given the modifiable nature of CRF and its potential to mitigate the adverse effects of T2D.

Methods

Study design and participants

This study adheres to the STROBE (**St**rengthening the **R**eporting of **Ob**servational Studies in **E**pidemiology) guidelines for reporting observational studies (Supplemental Table S1). Data were utilized from the Kuopio Ischemic Heart Disease (KIHD) prospective cohort study, an ongoing investigation involving a representative sample of men aged 42-61 years, recruited from the Kuopio region in eastern Finland. The KIHD study was designed primarily to assess risk factors for atherosclerotic CVD and related outcomes. Between March 1984 and December 1989, a total of 3433 men were invited for screening for potential inclusion in the study. Among these men, 3235 were deemed to be eligible, and 2682 of these eligible men voluntarily agreed to participate in the study and underwent baseline assessments. For this analysis, individuals with missing data on the exposures or potential confounding variables (n = 374) were excluded (Supplemental Table S2), leaving 2308 men with complete information on prevalent T2D status, CRF, relevant confounders, and SCD outcome data (Supplemental Fig. S1). The Research Ethics Committee of the University of Eastern Finland approved the study (reference #:143/97), which was conducted in accordance with the Declaration of Helsinki. Additionally, written informed consent was obtained from all participants included in the study.

Assessment of exposures

CRF level, assessed via peak oxygen uptake (VO_{2peak}), was measured directly through gas-exchange analysis, using a computerized metabolic measurement system (Medical Graphics, St. Paul, MN) during a maximal symptom-limited exercise test on an electrically braked cycle ergometer, as described previously.[18,19] The standardized testing protocol included a 3-minute warm-up at 50 W (1 W = 6.12 kgm/min). This protocol was followed by workload increases of 20 W per minute, with direct analyses of expired respiratory gases. Respiratory gas exchange was measured by the breath-by-breath method, which involved breath-sample collection via a face mask. The respiratory-gas analyzer expressed VO_{2peak} as an average value recorded over a period of 8 seconds. VO_{2peak} was defined as the highest or peak attained value for oxygen consumption, expressed as mL/kg/min. Prevalent T2D was identified based on guideline fasting plasma glucose levels or a clinical diagnosis of T2D requiring dietary, oral, or insulin treatment.[20]

Assessment of covariates and outcomes

The methods used for recruiting participants and assessing risk markers have been described in prior publications.[18] Participants were instructed to fast overnight, avoid alcohol for at least 3 days, and refrain from smoking before undergoing assessments, including blood-sample collection between 8 AM and 10 AM. Fasting plasma glucose levels were measured using fresh samples, utilizing the glucose dehydrogenase method (Merck, Darmstadt, Germany) after protein precipitation with trichloroacetic acid. Resting blood pressure was measured between 8 AM and 10 AM, using a random-zero sphygmomanometer. Blood pressure was measured 3 times, each time after the participants rested in a supine position for 5 minutes—once in a standing position, and twice while sitting, with 5-minute intervals between each measurement. The mean of these measurements was calculated. Self-administered questionnaires gathered information on SES, smoking habits, alcohol consumption, and baseline comorbidities. SES was evaluated using a questionnaire that covered the topics of income, education, occupational prestige, material standard of living, and housing conditions, with a composite SES index ranging from 0 to 25, with higher scores indicating a lower SES.[21] A history of coronary heart disease (CHD) was defined by previous occurrence of myocardial infarction, angina pectoris, regular nitroglycerin use for chest discomfort at least once a week, or reported chest pain. All SCDs occurring from study entry to 2017 were included, with diagnoses based on symptoms, electrocardiographic findings, cardiac enzyme-level elevations, autopsy results (available for 80% of cardiac deaths), and CHD history (per Statistics Finland, TK/782/07.03.00/2021).[22]

Statistical analysis

Baseline data were summarized using descriptive statistics, presenting continuous variables as mean ± standard deviation

Table 1. Baseline participant characteristics, overall, and by categories of the combination of type 2 diabetes (T2D) and cardiorespiratory fitness (CRF)

Characteristics	Overall (N = 2308)	No T2D & Med-High CRF (N = 1122)	No T2D & Low CRF (N = 1072)	Yes T2D & Med-High CRF (N = 32)	Yes T2D & Low CRF (N = 82)	*P*
CRF, mL/kg/min	30.3 (± 8.0)	36.6 (± 5.4)	24.2 (± 4.4)	34.6 (± 3.9)	20.7 (± 5.3)	< 0.001
Age, y	53 (± 5)	51 (± 5)	54 (± 4)	51 (± 5)	55 (± 4)	< 0.001
Alcohol consumption, g/wk	31.9 (6.4, 92.4)	30.8 (6.4, 87.7)	32.3 (6.0, 96.0)	22.2 (5.9, 133.3)	40.2 (9.7, 139.4)	0.26
SES	8.44 (± 4.24)	7.71 (± 4.35)	9.12 (± 4.02)	7.91 (± 3.29)	9.63 (± 4.27)	< 0.001
T2D status						< 0.001
No	2194 (95.1)	1122 (100.0)	1072 (100.0)	0 (0.0)	0 (0.0)	
Yes	114 (4.9)	0 (0.0)	0 (0.0)	32 (100.0)	82 (100.0)	
Smoker						< 0.001
No	1583 (68.6)	817 (72.8)	682 (63.6)	26 (81.2)	58 (70.7)	
Yes	725 (31.4)	305 (27.2)	390 (36.4)	6 (18.8)		
History of hypertension						< 0.001
No	1618 (70.1)	905 (80.7)	661 (61.7)	19 (59.4)	33 (40.2)	
Yes	690 (29.9)	217 (19.3)	411 (38.3)	13 (40.6)	49 (59.8)	
History of CHD						< 0.001
No	1762 (76.3)	995 (88.7)	696 (64.9)	27 (84.4)	44 (53.7)	
Yes	546 (23.7)	127 (11.3)	376 (35.1)	5 (15.6)	38 (46.3)	
Body mass index, kg/m^2	26.9 (± 3.5)	25.8 (± 2.8)	27.8 (± 3.7)	27.0 (± 3.0)	30.2 (± 4.0)	< 0.001
SBP, mm Hg	134 (± 17)	132 (± 15)	136 (± 18)	137 (± 17)	145 (± 20)	< 0.001
DBP, mm Hg	89 (± 10)	88 (± 10)	90 (± 11)	87 (± 10)	93 (± 11)	< 0.001
Total cholesterol, mmol/L	5.91 (± 1.07)	5.84 (± 1.06)	5.99 (± 1.08)	5.81 (± 0.92)	5.86 (± 1.10)	0.011
HDL-C, mmol/L	1.29 (± 0.30)	1.35 (± 0.30)	1.24 (± 0.30)	1.30 (± 0.33)	1.14 (± 0.23)	< 0.001

Values are mean (± standard deviation), median (interquartile range), or n (%), unless otherwise indicated.

CHD, coronary heart disease; CRF, cardiorespiratory fitness; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; SES, socioeconomic status.

(SD), or median (interquartile range), and categorical variables as counts (percentages). Cox proportional hazards models were utilized to estimate hazard ratios (HRs), with 95% confidence intervals (CIs), for SCD, adjusting for potential confounders. The following 3 models were used for confounder adjustment: (i) model 1 was adjusted for age; (ii) model 2 included the variable in model 1, plus total cholesterol level, high-density lipoprotein cholesterol (HDL-C) level, systolic blood pressure (SBP), body mass index (BMI), smoking status, prevalent CHD and hypertension, alcohol consumption, and SES; and (iii) model 3 included all variables in model 2, with mutual adjustment for each exposure. These covariates were chosen based on their established roles as risk factors for SCD, their documented associations with SCD in the KIHD study,[12,13,16,22] and their potential as confounders, given their known associations with SCD, and observed associations with the exposures using available data.[23] To maintain consistency with previous reports[12,13] and based on the available data, prevalent T2D status was categorized as "Yes" or "No," and CRF was divided into low, medium, and high levels; CRF was classified further into low and medium-high levels for the evaluation of joint associations. For the joint-impact assessment of T2D status and CRF level on SCD risk, participants were categorized into 4 groups, as follows[24,25]: No-T2D & medium-high CRF (reference comparison); No-T2D & low CRF; Yes-T2D & medium-high CRF; and Yes-T2D & low CRF. Additive and multiplicative 2-way interactions were evaluated between T2D status and CRF level, in relation to SCD risk. Additive interactions were evaluated using the "relative excess risk due to interaction" (RERI), which is estimated for binary variables as $RERI_{HR} = HR_{11} - HR_{10} - HR_{01} + 1$,[26] where HR_{11} is the HR of the outcome (ie, SCD) if both risk factors (Yes-T2D and low CRF) are present; HR_{10} is the HR of the outcome if 1 risk factor is present and the other is absent, with HR_{01} being the reverse. Although RERI is considered the best measure of additivity in a proportional hazards model,[26] the following additional measures of additive interaction were estimated: attributable proportion (AP) = (RERI/ HR_{11}) and synergy index (S) = $[(HR_{11} - 1)/(HR_{10} - 1) + (HR_{01} - 1)]$. The Stata code -ic- (StataCorp, College Station, TX), following the procedure described by Hosmer and Lemeshow,[27] was used to generate these measures, along with their 95% Cis, and 2-tailed tests for no interaction. Multiplicative interactions were evaluated using the ratio of HRs = $HR_{11}/(HR_{10} \times HR_{01})$.[26] In the absence of interaction, RERI and AP = 0, S = 1, and the ratio of HRs = 1. All statistical analyses were performed using Stata, version MP 18 (StataCorp).

Results

Table 1 summarizes the baseline characteristics of the 2308 participants, overall, and by categories of the combination of T2D status and CRF level. Overall, the mean ± SD age and CRF level at baseline were 53 ± 5 years and 30.3 ± 8.0 mL/kg/min, respectively. A total of 114 men (4.9%) had prevalent T2D at study entry. Men with a history of T2D and low CRF levels were older, had a higher alcohol consumption level, and had lower SES. They had a higher prevalence of other comorbidities (hypertension and CHD), higher BMI and blood pressure, and lower HDL-C levels. A comparison of baseline characteristics between the included population and those with missing data on CRF, which accounted for most of the missing data, showed that the baseline characteristics were similar between these groups (Supplemental Table S3).

After a median (interquartile range) follow-up duration of 28.1 years (19.0, 30.6), 264 SCDs occurred. Compared with those who had no history of T2D, men with a history of T2D had an increased risk of SCD, in analysis adjusted for age

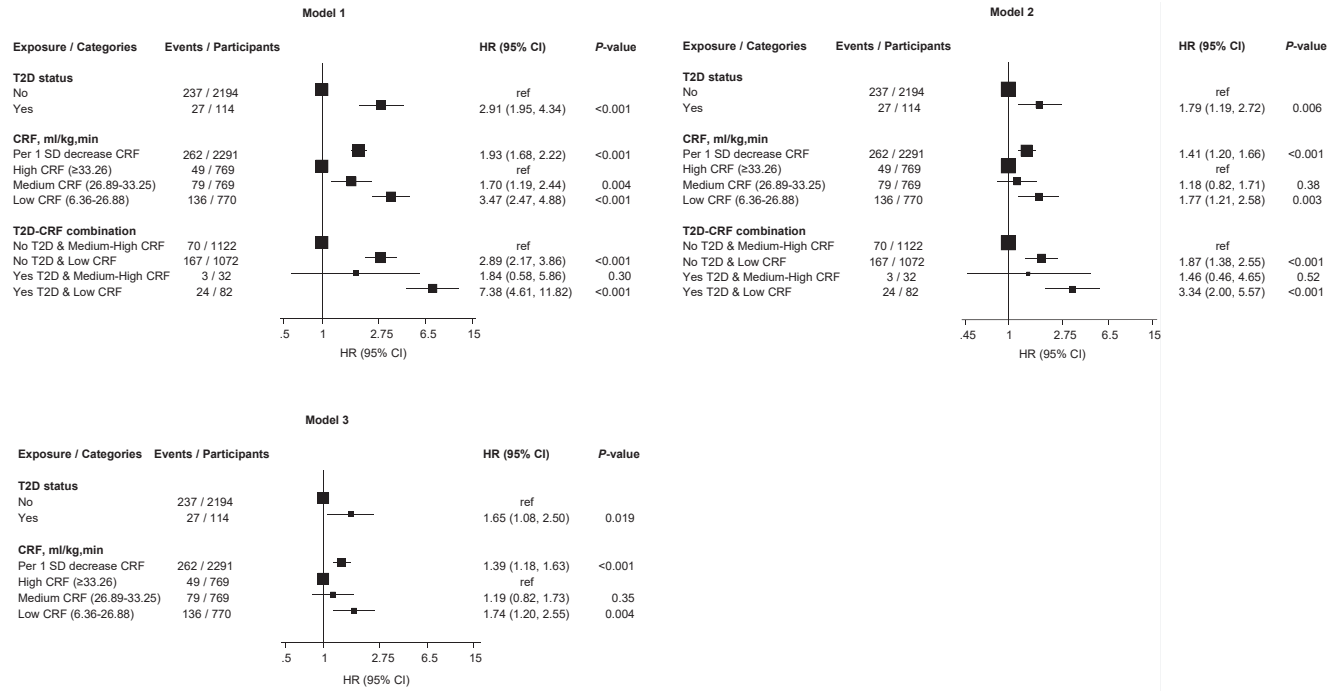

Figure 1. Separate and combined associations of type 2 diabetes (T2D) and cardiorespiratory fitness (CRF) with sudden cardiac death. Model 1: adjusted for age; model 2: model 1 plus total cholesterol, high-density lipoprotein cholesterol, body mass index, smoking status, prevalent history of T2D, coronary heart disease and hypertension, alcohol consumption level, and socioeconomic status. Model 3: model 2 plus mutual adjustment for each exposure. CI, confidence interval; HR, hazard ratio; ref, reference; SD, standard deviation.

(HR = 2.91, 95% CI, 1.95-4.34; Fig. 1—model 1), which was attenuated to HR = 1.79 (95% CI, 1.19-2.72) following further adjustment for total cholesterol level, HDL-C level, SBP, BMI, smoking status, prevalent CHD and hypertension, alcohol consumption level, and SES (Fig. 1—model 2). Following adjustment for the covariates in models 1 and 2, respectively, low vs high CRF level was associated with an increased risk of SCD, as follows: (HR = 3.47, 95% CI, 2.47-4.88) and (HR = 1.77, 95% CI, 1.21-2.58), respectively (Fig. 1—models 1 and 2). A significant association remained when CRF was modeled per 1-SD decrease. The HRs remained similar when T2D status was further adjusted for CRF level, and CRF level was further adjusted for T2D status (Fig. 1—model 3).

Compared with No-T2D & medium-high CRF, men with No-T2D & low CRF, and those with Yes-T2D & low CRF, had an increased risk of SCD, as follows: (HR = 1.87, 95% CI, 1.38-2.55) and (HR = 3.34, 95% CI, 2.00-5.57), respectively. The association between men with Yes-T2D & medium-high CRF and SCD risk was attenuated (HR = 1.46, 95% CI, 0.46-4.65; Fig. 1—model 2). Comparing the HRs for Yes-T2D & low CRF and Yes-T2D & medium-high CRF, an 80% attenuation occurred in the HR, changing it from 3.34 to 1.46 (assuming the association between Yes-T2D & medium-high CRF and SCD risk was statistically significant). Modest evidence indicated that interactions occurred on both the additive and multiplicative scales, as suggested by the following estimates: RERI = 1.00 (95% CI: −1.19, 3.20; P =.37); AP = 0.30 (95% CI: −0.28, 0.89; P = 0.31); SI = 1.75 (95% CI: 0.43, 7.17; P = 0.44); and the ratio of HRs = 1.22 (95% CI: −0.29, 2.72; P = 0.53).

Discussion

In this population-based prospective cohort study of middle-aged and older men, a history of T2D and low CRF levels were each associated independently with an increased risk of SCD. These associations persisted after adjusting for several established risk factors and were minimally attenuated following mutual adjustment for each exposure. New clinically important findings, based on the joint impact of T2D status and CRF levels, showed that men with both a history of T2D and low CRF levels had a nearly 3-fold higher risk of SCD, compared to the risk for men with no history of T2D and medium-high CRF levels. However, this elevated SCD risk was offset in men who had a history of T2D but maintained medium-high CRF levels; on the assumption that the increased risk of SCD was significant in this group (given an HR of 1.46), the percent attenuation in risk is still substantially high, at 80%. Interaction analyses indicated that the combined effect of a history of T2D and low CRF level on SCD risk might be greater than the sum or product of their individual effects. This finding suggests that a synergistic interaction occurs in which the presence of both modifiable risk factors substantially amplifies the risk of SCD, beyond that generated by their individual contributions.

The observed increased risk of SCD associated with a history of T2D or low CRF levels is consistent with findings in the literature. Prior research has established T2D as a

significant risk factor for adverse cardiovascular outcomes, including SCD.[5,6] Similarly, CRF level has been documented extensively as an indicator of elevated cardiovascular risk, including of SCD.[9,10] Our current findings of the interplay among T2D status, CRF level, and SCD risk are novel results; hence, they cannot be compared directly with those of previous studies. However, an emergent literature indicates that higher CRF levels may have a protective effect, and may potentially mitigate the adverse cardiovascular effects of other common risk factors. For instance, evidence has been shown that higher CRF levels may offset the following: (i) the increased risk of SCD in individuals with elevated SBP[13]; (ii) the increased risk of heart failure in individuals with elevated SBP[28]; and (iii) the increased risk of SCD in individuals with increased inflammation (as measured using high-sensitivity CRP level).[12]

The risk of adverse cardiovascular outcomes, including SCD, is significantly higher in individuals with T2D, compared to the risk in those without T2D, often because of the cumulative effects of chronic hyperglycemia, insulin resistance, dyslipidemia, and associated metabolic disturbances.[6] These factors contribute to endothelial dysfunction, increased arterial stiffness, and accelerated atherosclerosis, all of which can elevate the risk of SCD.[1] Additionally, T2D is associated with autonomic neuropathy, which can disrupt normal cardiac autonomic regulation and increase susceptibility to fatal arrhythmias.[29] CRF level is enhanced primarily through regular physical activity and exercise training; the cardioprotective mechanisms of a high CRF level are multifaceted, and they occur mainly via the effects of physical activity. Regular physical activity has antiatherogenic effects, reducing the progression of atherosclerosis and improving lipid profiles[30]; it also exerts anti-inflammatory actions, lowering systemic inflammation markers, such as CRP level.[31] Moreover, physical activity improves endothelial function and causes beneficial modulation of cardiovascular markers, such as glucose level, body weight, blood pressure, natriuretic peptide levels, and cardiac troponin T level.[32] These changes collectively enhance cardiovascular health. Furthermore, physical activity favourably modulates cardiac autonomic function, reducing the risk of fatal arrhythmias by stabilizing the abnormal electrical activity of the heart.[33] The synergistic interaction between a history of T2D and a low CRF level that amplifies the risk of SCD, beyond that attributable to their individual contributions, can be explained by several mechanisms. T2D and a low CRF level each independently exacerbate cardiovascular risk through distinct, yet overlapping, pathways. When combined, these factors can have a compounding effect. For instance, T2D-related metabolic disturbances can exacerbate the impact of a low CRF level on cardiovascular health, leading to more-severe endothelial dysfunction, greater arterial stiffness, thrombosis, and heightened inflammation. Additionally, the autonomic dysfunction associated with T2D can be aggravated further by a low CRF level, increasing the risk of arrhythmias and SCD.

These novel findings add to the emergent literature on the protective effects of a higher CRF level, and its potential to mitigate the adverse cardiovascular effects of other risk factors. Achieving or maintaining higher levels of CRF is essential in delaying or preventing many adverse cardiovascular outcomes, including unexpected SCD events. The most effective strategy to increase or maintain a high CRF level is through regular physical-activity and/or exercise training. Research indicates that individuals who adhere to physical-activity guidelines of 150-300 minutes per week of at least moderate-intensity exercise[34] are more likely to achieve a moderate-to-high CRF level (> 8 metabolic equivalents [METs]),[35] fitness levels that are known to be associated with risk reduction for adverse cardiovascular outcomes.[36] Despite the benefits of physical activity, global adherence to recommended levels remains low,[37] highlighting the need for enhanced education on the health benefits of physical activity, especially its potential to mitigate the risk of death associated with other risk factors, such as T2D. Common barriers to achieving recommended physical-activity levels include limited access and lack of time. Efforts should focus on widening access to physical-activity facilities and promoting simple, yet effective activities, such as walking, which requires no special facilities and can be done at any time.[38] Additionally, adopting a "weekend warrior" physical-activity pattern, in which the recommended physical activity is concentrated into 1 or 2 sessions per week, may be beneficial for those with busy lifestyles.[39] Emerging evidence suggests that several strategies may further enhance CRF level. These strategies include the following: nutritional supplements, such as amino acids, n-3 polyunsaturated fatty acids, and L-carnosine; dietary patterns, such as hypocaloric diets, the Dietary Approaches to Stop Hypertension (DASH) diet, and Mediterranean diets[40]; pharmacologic therapies, such as renin-angiotensin-aldosterone system inhibitors, hydralazine, and digoxin, particularly in populations with impaired CRF, such as heart failure patients[41]; and passive heat therapies, such as Finnish saunas.[19] Additionally, addressing modifiable factors, including via smoking cessation, improvement of body composition, and weight management, which strongly influence CRF level, can provide a more comprehensive approach to enhancing CRF level.[42]

Strengths and limitations

The study's evaluation of the joint impact of T2D status and CRF level on SCD risk is a novel contribution to the existing literature on risk evaluation for SCD in the general population. Other strengths include the use of a prospective cohort design, based on a relatively large, general population—based sample of middle-aged and older Finnish men, with long-term follow-up. This prospective study design allows for temporal relationships to be established between relevant but undefined exposures and outcome, reducing recall bias and providing robust data on the natural history of SCD. The use of an objective gold-standard measure of CRF level, specifically direct oxygen-uptake assessments during exercise, and comprehensive analyses that include multivariable adjustments and the exploration of interactive effects, strengthens the findings.

Several limitations must be considered when interpreting our findings. First, the relatively low event rate of SCD in the general population may have reduced the statistical power for some exposure categories (T2D status and CRF level). Additionally, we could not account for the duration of T2D, and our findings may not be generalizable beyond the study

population of middle-aged and older Finnish men. Another limitation is the potential for CRF level to act as a mediator of T2D, rather than as a contributor to joint exposure, as both CRF level and T2D status were measured cross-sectionally at baseline. Plausibly, T2D could have led to side effects that limit the ability to exercise, thus resulting in lower CRF levels. Also, the study carries the potential for collider stratification bias, due to conditioning the sample on survival to old age, and restricting it to men, which could lead to an underestimated measure of association because of unmeasured common causes, such as lifestyle factors.[43] The study carries the potential for selection bias, given the apparent exclusion of about 14% of the eligible population, owing to missing information on exposures and potential confounders. However, for the majority of the variables, < 1% of data were missing; and CRF level accounted for most of the missing data. A comparison of baseline characteristics between the included population and those with missing data on CRF level showed that the baseline characteristics were similar for these groups, which suggest that the impact of selection bias on our study results is likely to be minimal.

Finally, the observational design of the study is inherently susceptible to biases, such as residual confounding and regression dilution. Despite these limitations, a population-based cohort study remains an ideal context for investigating new and undefined exposures and their combined effects on SCD risk.

Conclusion

An interplay occurs between T2D status, CRF level, and risk of SCD. The risk of SCD is 3-fold higher in men who have a history of both T2D and low CRF levels; however, this elevated risk is offset in men who had a history of T2D but maintained higher CRF levels. The interplay between these risk factors highlights the importance of achieving or maintaining high CRF levels, especially in individuals with T2D, to mitigate the heightened risk of SCD.

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Data Availability

Restrictions apply to the availability of the outcome data, due to recent Finnish legislation concerning the use of national social and health registers in research.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Research Ethics Committee of the University of Eastern Finland approved the study (reference #:143/97).

Patient Consent

Written informed consent was obtained from all participants included in the study.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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