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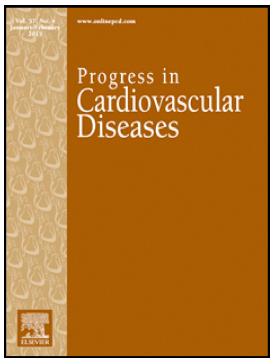

The role of cardiorespiratory fitness on the risk of sudden cardiac death at the population level: A systematic review and meta-analysis of the available evidence

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Title: The Role of Cardiorespiratory Fitness on the Risk of Sudden Cardiac Death at the Population Level: a Systematic Review and Meta-Analysis of the Available Evidence.

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ABSTRACT

Cardiorespiratory fitness (CRF) has been widely studied as a powerful and independent predictor of all-cause and disease-specific mortality. Sudden cardiac death (SCD) is recognized as a significant cause of mortality among the general population, including the general population without previous symptoms of any coronary heart disease (CHD). Consequently, SCD is an important public health problem, which constitutes a clinical challenge. Thus, prevention of SCD by detecting early risk factors could be a useful tool, contributing to the American Heart Association's goal of decreasing the incidence of SCD at the population level. The identification of these risk factors for CVD would facilitate the large-scale screening of those participants at higher risk of SCD. This systematic review collects information about the role of CRF on the risk of SCD at the available evidence, and analyzes the long-term influence of CRF as a risk factor and independent predictor of SCD.

Key words: Cardiorespiratory fitness; Sudden Cardiac Death; large cohorts; coronary heart disease; risk factors.

Alphabetical List of Abbreviations:

ACLS= Aerobics Center Longitudinal Study

AHA= American Heart Association

BMI= body mass index

BP= blood pressure

CHD= coronary heart disease

CRF= Cardiorespiratory fitness

CV= cardiovascular

CVD= cardiovascular disease

ECP= exercise cardiac power

eCRF= estimated-CRF

HTN= hypertension

ICD= the International Classification of Diseases

KIHD= Kuopio Ischemic Heart Disease

LQTS= long QT syndrome

LVEF= left ventricular ejection fraction

MET= metabolic equivalent

peO2p= peak exercise oxygen pulse

PRSIMA= Preferred Reporting Items for Systematic Reviews and Meta-Analysis

SCD= Sudden cardiac death

VAs= ventricular arrhythmias

VO_{2max}= maximal oxygen consumption

INTRODUCTION

Definition and Relevance of Sudden Cardiac Death

Sudden cardiac death (SCD) is recognized as an important cause of mortality, with a significant incidence among the general population, including the general population without previous symptoms of any coronary heart disease (CHD)[1-3]. The concept of SCD is generally defined as death within 1 h of symptom onset or during sleep in a patient who was previously stable[4]. Although most of the total incidence of SCD has been reported to occur in men (70-90%), this cause of mortality has been documented in both sexes in individuals with a history of CHD or other major cardiovascular (CV) disease (CVD) risk factors and in those without a history of CHD or CVD[2,5]. Consequently, SCD is an important public health problem, which constitutes a clinical challenge.

One of the American Heart Association's (AHA) 2020 Impact Goals[6] is to decrease CVD mortality. Thus, prevention of SCD by detecting early risk factors[7] could be a useful tool contributing to the AHA's goal through decreasing the incidence of SCD. The identification of risk factors for CVD would facilitate the large-scale screening of those participants at higher risk of SCD. In line with this, the best-known predictor of death is depressed left ventricular ejection fraction (LVEF), which has been associated with a dramatically increased risk of SCD[8]. Nonetheless, LVEF is limited by low sensitivity, as the majority of people who suffer from SCD have a preserved LVEF[9]. Moreover, several studies analyzed the effect of specific risk factors, such as QRS duration, QT interval and dispersion, signal-averaged electrocardiography, short- and long-term heart rate variability[9], systemic blood pressure (BP) and hypertension (HTN)[10] and asymptomatic ST-segment depression[11] in men or a cluster of lifestyle

factors in women[12], on the risk of SCD. However, although numerous studies[13-15] have attempted to identify those factors associated with higher SCD risk for the general population, conclusive evidence on this point remains somewhat elusive.

On the other hand, genetic background is known to partially explain SCD events[16]. Particularly, recent studies of rare genetic arrhythmic disorders provided information on mechanisms and risk factors associated with the risk of SCD in patients without structural heart disease[16]. Although data on the risk associated with QT prolongation were derived from long-term genotype–phenotype studies of patients with the congenital long QT syndrome (LQTS), importantly, these studies of LQTS have also increased the understanding of SCD in the general population. In addition, the association between QT interval prolongation and SCD has also been reported in individuals without known genetic predisposition[17], and highlight the fact that the focus for risk assessment for SCD at the population level should be not only focused on the overall QT interval but also on its individual components[16].

Definition and Importance of Assessing Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF) can be defined, briefly, as the body's ability to capture and utilize oxygen to perform any movement, physical activity, or exercise. But in particular, the level of CRF requires the involvement of numerous organs and systems among which are the respiratory, circulatory, CV, muscular, and nervous systems. Thus, CRF represents the integrated functional capacity of the human body in response to a stressful physiological stimulus, such as physical exercise. Consequently, the quantification of this capacity (CRF) can be an indicator of total body health[18]. Moreover, it is well-known that roughly half of the variance in CRF is attributable to heritable factors[19]; on the other hand, the rest of the variance depends on the contribution of behavioral patterns. Therefore, having the possibility to influence half of

the variance in CRF by modifiable factors makes it very interesting to investigate the potential role of CRF on health status. In fact, since the 1950s the relationship of CRF with several health outcomes has been studied, but particularly during the past 20 years there has been an exponential increase in the number of studies published analyzing the role of CRF on mortality and health[18,20-24]. In summary, it has been reported[18] that CRF is a strong and independent indicator of risk for CVD- and all-cause mortality, even to be a more powerful predictor of mortality risk than traditional CVD risk factors, such as HTN, smoking, obesity, hyperlipidemia, and type 2 diabetes. Therefore, CRF has been shown to be a more powerful predictor of risk than other exercise testing variables, including ST-segment depression, symptoms, and hemodynamic responses[18]. Most of these studies express CRF in the context of survival benefit per metabolic equivalent (MET), showing that each 1-MET increase in CRF was associated with considerable improvement in survival, ranging from 10% to 25%[18].

Despite the considerable evidence that CRF is associated with many health outcomes and types of mortality, few investigations have been done on how CRF is related with just one particular type of mortality, such as SCD[25,26]. There is no clear consensus on the role of CRF in SCD, neither on its power as a predictor of SCD nor compared with other risk factors or exercise test variables used to assess CVD. In addition, an assessment of the potential influence that each 1-MET increase in CRF has on the risk of SCD is needed, similar to the relationship between CRF and CVD events, CVD-mortality, and all-cause mortality[18].

On the other hand, although CRF is now recognized as an important marker of CV health and all-cause mortality, it has been highlighted that it is currently the only major risk factor not routinely assessed in clinical practice[18]. Thus, summarizing the evidence

in relation to CRF and SCD at the population level would also help to support this international call for assessing CRF in clinical practice.

METHODOLOGY AND SEARCH STRATEGY

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[27] and was registered through the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42019130259).

Search Strategy

A literature search was conducted in PubMed, EBSCOhost (Sportdiscus) and Scopus from their inception to March 11th, 2019. The search terms used to perform the present study were the following: "cardiorespiratory fitness" OR "aerobic capacity" OR "maximal oxygen consumption (VO_{2max})" AND "sudden cardiac death". The reference lists of the retrieved studies were reviewed to identify additional studies.

Selection Criteria

The inclusion criteria were: (i) type of study (longitudinal and prospective studies; at least 5 years follow-up), (ii) the use of CRF or proxy measure as independent or combined predictor of SCD, (iii) endpoint including SCD events or direct risk factor for SCD. There were no restrictions on age, gender, or health status. The exclusion criteria were (i) not longitudinal studies or follow-up shorter than 5 years, (ii) studies written in languages other than English or Spanish, (iii) studies published in non-peer-reviewed journals, (iv) reviews/letters, and, (v) studies in animal models and (vi) not achieving inclusion criteria.

Data Extraction

The following data were collected from each included study: 1) study/year; 2) cohort and design (cohort, follow-up, analysis); 3) participants [sample size, location, health condition, age, sex and BMI]; 4); CRF or proxy measure [test type and protocol, test maximal parameters (maximal oxygen consumption [VO_{2max}], METs, total time, workload, heart rate)]; 5) Combined factors with CRF (systolic BP, ST depression, sauna bathing, etc); 6) SCD information (Sources, Codes, Number of events, proxy measure of risk SCD); 7) Role of CRF on SCD.

Meta-Analysis

In order to quantify the independent role of CRF on SCD, we performed a meta-analysis using the two prospective cohorts analysed in this review. For this purpose, we extracted the hazard ratio and its 95% CI from each included study. Therefore, pooled hazard ratio estimates were obtained for the risk of SCD using a random model due to the greater heterogeneity evaluated by the I^2 statistics.

RESULTS

Overall Results

Figure 1 presents the PRISMA consort diagram for the search strategy. The initial search retrieved 245 articles, and 11 manuscripts were finally included after applying the inclusion and exclusion criteria. The first study regarding the role of CRF on SCD was in 2010[25]. After that, 9 studies were published between 2015 and 2018 [26,28-35], whereas 1 additional study was published in 2019[36] focusing on serious ventricular arrhythmias (VAs) as risk factor for SCD.

The predictive role of CRF has been analyzed by two different cohorts[25,26] (Table 1) accumulating a total of 57,824 participants (96% United States). The other 9 studies[28-36] analyzed the role of both the independent influence of CRF or proxy and combined with other physiological CV parameters on the risk of SCD (Table 2).

The Two Population Cohorts Followed to Assess the Independent Role of Maximal CRF on SCD

The characteristics of the only 2 population cohorts[25,26] available analyzed in the systematic review are shown in Table 1. The first prospective cohort analyzing the relevance of CRF as a predictive marker of SCD was the Kuopio Ischemic Heart Disease (KIHD) risk factor study in 2010[25] with a sample of 2,368 Caucasian men from Europe followed for 17.6 years. Six years later, Jiménez-Pavón et al.[26] reported the influence of CRF on the risk of SCD in 55,456 American men and women from the Aerobics Center Longitudinal Study (ACLS) who were followed for 14.7 years. These are the only two published epidemiologic cohorts analyzing this relationship; thus, their similarities and differences need to be considered in order to better understand the final findings. In this sense, the first cohort studied accounts for only 4% of the total number of participants and was focused in European men, while the second cohort analyzed a mixed population of men and women from the United States accounting for the remaining 96% of total participants. However, the mean difference for age among the cohorts was less than 9 years and only approximately 1 kg/m^2 for BMI.

Another very important difference among these two studies was the methodology used to assess or estimate CRF level. In fact, the European cohort[25] used a maximal cycle ergometer test with direct analyses of respiratory gases providing a precise information of VO_{2max}, while the ACLS cohort[26] used a maximal treadmill test (modified Balke protocol) to estimate the maximal metabolic equivalents (METs; 1 MET=3.5 mL oxygen uptake/kg per minute) from exercise duration and treadmill speed and incline, using standard algorithms. Using these measurements, the difference between the mean

CRF levels of both cohorts was 2.5 METs. These are two well-known and valid aerobic modalities for incremental testing, with different strengths and limitations. The use of cycle ergometer is the most controlled way to perform exercise testing in relation to physiological response of variables, low risk of falls and being safe during the final steps. However, the treadmill test is the most widely used means of assessing exercise capacity in the United States and also recreates the natural skill if walking/running is used as a tool for population-based screenings.

On the other hand, in relation to SCD, the sources used for identifying the events and for definition were similar, being based on the International Classification of Diseases (ICD) codes in both studies. The number of SCD events were 146[25] and 109[26] for the European and American cohorts, respectively, which in relative terms implicates a much higher incidence among the European population.

Regarding the main finding about the role of CRF on SCD, both studies consistently reported an inverse and independent association after controlling for other CVD risk factors[25,26]. Moreover, the European cohort found that the risk of SCD decreased by 22% per 1 MET increase, while the American Cohort showed a risk decrease of 14% per 1 MET increase. The difference in the estimated risk decrease per 1 MET increase among studies could be partially affected by the higher incidence of SCD events reported in the European population[25]. However, other differences between studies, such as sample size, gender, CRF test protocols or location, and associated behaviors could hamper a weighted or equilibrated comparison and interpretation of the real effect of CRF level on SCD.

The two studies provided additional findings specific for their population cohorts. In this line, the study of Laukkanen et al.[25] analyzed the role of reclassification as a measure of CRF. The numbers of men reclassified because of assessment of CRF was

an important additional measure with an almost equal number of case subjects had reclassification upward rather than downward by the addition of CRF to the risk model (11 vs. 12), although more control subjects had their risk reclassified upward than downward (103 vs. 73). Moreover, Laukkanen et al.[25] studied the CRF levels according to health status and reported mean VO_{2max} values of 32.5 ml/kg/min and 27.3 ml/kg/min for healthy and unhealthy men, respectively. They found that an increase in VO_{2max} of 1 MET was related to a 20% risk reduction for healthy men and a 25% risk reduction for men with previously known disease.

In the case of the study performed by Jiménez-Pavón et al.[26], the risk of SCD across CRF levels by the presence or absence of HTN, normal weight or overweight or obese, and healthy or unhealthy groups was reported. They found inverse trends in the risk of SCD across CRF levels in all subgroups, but only reaching statistical significance in HTN (and the normotensive group with high CRF levels), overweight or obese, and healthy or unhealthy (moderate CRF levels) groups. Therefore, those participants identified with HTN and with moderate or high CRF levels had 65% and 72% lower risk of SCD, respectively, than did those with low CRF levels. Similarly, the risk of SCD was 58% and 64% lower in overweight or obese participants with moderate or high CRF levels, respectively. Finally, the authors reported in the unhealthy group that those participants with moderate CRF levels had 69% lower risk of SCD, whereas participants classified in the healthy group and with moderate or high CRF levels had 47 and 65%, respectively, lower risk of SCD than did those with low CRF levels.

Meta-Analysis of the Influence of CRF on SCD in Two Different Cohorts

To provide more evidence about the direct influence of CRF on SCD, and despite the availability of the only 2 cohorts[25,26] reporting these data, we performed a meta-analysis

of these studies. The results of the meta-analysis for the independent effect of CRF on SCD showed a significant difference in favour of CRF on the risk of SCD (Hazard ratio = 0.813, 95% CI: 0.740, 0.894, $p < 0.001$, $I^2 = 47.5\%$, total N = 57,824) (Figure 2). The meta-analysis suggests that despite the methodological and design disparities among the studies, the influence of CRF is constant and relevant across at least two continents.

The Combined Role of Maximal CRF or Sub-maximal CRF on the Risk of SCD

Since 2010, 10 additional studies have been identified that meet the criteria of this systematic review, and 9 out of 10 (90%) belong to the first cohort of European men[28-36] (Table 2). Most of these studies analyzed the role of maximal CRF combined with several physiological parameters to predict the risk of SCD[28,29,32-35], while 2 studies described the predictive validity of sub-maximal CRF values (corresponding to anaerobic threshold and ventilatory threshold) as independent predictors of SCD risk[30,31]. Moreover, 1 recent work focused on the direct association of maximal CRF with VAs as a closely related risk factor of SCD[36].

The 6 studies[28,29,32-35] from the European cohort showing the combined role of CRF on the risk of SCD had follow-ups ranging from 20 to 26 years. The principal extra value of these works is related to the new quantification of the preventive character of CRF when combined with several physiological and CV variables. In this regard, CRF level was studied in combination with maximal systolic BP (Exercise cardiac power-ECP, calculated as ratio of measured VO_{2max} with peak SBP)[28], exercise-induced ST segment depression[29], frequency of sauna bathing[32], maximum exercise heart rate (peak exercise oxygen pulse-peO2p)[33], body weight categories[34] and leisure time physical activity[35]. The combined influence of these parameters reported a change in the risk of SCD ranging from 46% to 380% depending on the parameters included (Figure 3), with the

highest change in the risk of SCD attributed to the combination of CRF with the presence or absence of exercise-induced ST segment depression[29].

Sub-maximal CRF level indicators, such as the oxygen uptake at aerobic threshold and ventilatory threshold (both ml/min) have been also studied[30,31]. The authors found that both are sub-maximal indicators of reduction in the risk of SCD, with 52% (aerobic threshold)[30] and 63% (ventilatory threshold)[31] differences in the risk of SCD when comparing the highest and lowest quartiles. These findings regarding submaximal CRF indicators are quite similar to those reported for the same cohort with maximal CRF when comparing low CRF versus high CRF (risk increase of 1.6-fold)[29].

Finally, Table 2 includes a recent study on the European cohort[36] showing the inverse association of maximal CRF with the incidence of VAs which is considered a principal risk factor of SCD. Particularly, 1 standard deviation increase in CRF was associated with decreased risk of VAs by 36%, and being in the highest CRF group (top tertile) predicted a 71% lower risk of VAs.

DISCUSSION

Main Findings

The studies included in this systematic review were based on the only 2 cohorts available reporting this relationship. We found 11 studies[25,26,28-36] showing association between CRF or its proxy and the risk of SCD, but only 2 large prospective studies[25,26] reported the independent and direct role of maximal CRF level on risk of SCD, each one from one continent (Europe and North America). Consequently, our additional meta-analysis, based only on these 2 different cohorts, showed a significant difference in favour of higher CRF in the risk of SCD, suggesting that despite the methodological and design disparities among studies, the influence of CRF is constant and relevant

across continents, and their findings support and complement each other. In fact, our meta-analysis reported an overall decreased risk of SCD of ~19% per each MET increase, which is in line with that suggested in the original studies from both cohorts (14% and 22%, respectively)[25,26] and among the range of improvement in survival for mortality previously reported[18].

In addition, we found that the combination of maximal CRF with several physiological parameters derived from an exercise test (e.g, systolic BP and maximal test heart rate) or some behaviors (e.g., sauna bathing or leisure time physical activity) also constituted very good predictors of the risk of SCD, in some cases being even better predictors than CRF alone. On the other hand, the use of only CRF at sub-maximal intensity provides similar estimation of the risk decrease for SCD.

Recommendations for CRF Assessment in the Screening of Risk for SCD

The overall importance to periodically obtain a directly measured VO_{2max} has been recently highlighted[18], although CRF estimated from the peak work rate achieved on a treadmill or a cycle ergometer or from non-exercise algorithms was also recognized as relevant, necessary and possibly more cost-effective. From the findings of the current systematic review, the capacity of both measured VO_{2max} and estimated CRF from peak workload showed good sensitivity as risk factor of SCD using cycle ergometer[25] and treadmill[26], respectively. Particularly, one of the cohorts[25] reported that the ability of CRF to improve discrimination and risk classification of SCD did not significantly change when using directly or estimated CRF[37]. Thus, the main recommendation for assessing CRF would be to use one of these methods (estimated from workload or even non-exercise equations) as directly measured VO_{2max} may not be feasible or cost-effective in large populations or in routine clinical practices. In fact, assessing

estimated-CRF (eCRF) from readily available clinical or research data base information has been suggested as a good alternative to objective CRF measurement,[18,38] as it can be quickly and easily collected in epidemiological studies with good correlations with measured CRF and favorable predictive value for CVD events and mortality. Unfortunately, specific data on the ability of eCRF to discriminate the risk of SCD have not yet been published, therefore such data could not be included in our systematic review. However, based on the currently reviewed data and on the utility previously noted for eCRF in relation to other health outcomes and mortality types[38-40], it would be expected that future studies will also corroborate its utility in relation to SCD.

Additionally, when maximal exercise testing is not possible for reasons of safety, health, or cost, the utility of sub-maximal parameters, such as aerobic or ventilatory thresholds, have been analyzed in relation to SCD;[30,31] and these parameters could be an alternative to full exercise testing with overall similar results. However, to highlight the fact that the parameters used as indicators of aerobic threshold and ventilatory threshold were oxygen uptake, gas exchange analysis would still be required. Future studies should add the estimation of hazard-ratio not only for the direct value of oxygen uptake at aerobic or ventilatory thresholds, but also the equivalent of percentage of heart rate reserve, exercise time or workload in order to provide evidence regarding other parameters that can be assessed without the necessity of gas exchange analysis.

Another important recommendation is to consider, when possible, the combination of CRF with other predictors which have been shown to provide extra or additional predictive value (Figure 3). Particularly, the combination of CRF with exercise-induced ST depression[29] or with maximal systolic BP (ECP)[28] reported even better assessment of the risk of SCD. These will be of great interest for those projects in which electrocardiogram or BP could be properly recorded during the maximal exercise test.

However, an alternative combination for large epidemiological studies not able to include more precise technology would be to add the physical activity level as behavior combined with CRF that substantially increase the prediction level of the risk of SCD[35]. In general, it seems possible that a combined panel of measurements, including CRF and physiological/behavioral measures will have substantially improved degrees of discrimination and reclassification.

Limitations and Strengths

This study presents several limitations. First, although two major cohorts were identified with consistent data about the topic of interest, the lack of availability of other cohorts or population studies addressing this relationship hampers the extrapolation, partially, of the current findings. Second, the natural differences among the 2 cohorts[25,26] included in this systematic review, such as number of participants, gender, cycle ergometer versus treadmill or direct assessment versus MET estimation, certainly would require more studies to clarify some issues. Third, the fact that many of the results and conclusions are derived from studies based on the same prospective cohort could imply a methodological bias; therefore, more studies from different populations are needed to confirm part of the findings demonstrated in this review. Additionally, the longitudinal design of the included studies does not allow one to establish a direct causality of increasing CRF on decreasing risk of SCD versus merely an association, and this would require intervention studies for further clarification.

Despite these limitations, to the best of our knowledge, this is the first systematic review with additional meta-analysis which focused on the role of CRF level and the risk of SCD, as well as showing data from 2 representative continents. The additional meta-analysis performed should be acknowledged as, despite the inclusion of only 2

studies, the output confirms a similar trend within these quite different prospective cohorts. Moreover, the constellation of data that we reviewed suggest a powerful association and potential role of higher CRF to markedly reduce the risk of SCD.

Conclusion

Our systematic review provides evidence, on the long-term influence of CRF as a risk factor of SCD. Few studies have assessed the relevance of CRF as an independent predictor of SCD at the population level, but the message from these studies is consistent. The independent ability of higher CRF to predict lower risk of SCD has been confirmed, but the ability of CRF to predict SCD is improved further when combined with some other behavioral or physiological parameters (most significantly, ST-segment depression on exercise testing).

Collectively, from a clinical perspective, our review supports the use of CRF as part of the early and initial screening in adult life for assessing the risk of SCD, in line with recommendations for prediction of CVD- and all-cause mortality. Moreover, from a public health point of view, promoting the increase of CRF early in life and throughout adolescence and adult life to enhance long-term survival is important. However, additional research is needed to add novel insights on the specific role of CRF in women, different population cohorts, and lower-upper threshold values in order to improve the early risk stratification for SCD.

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Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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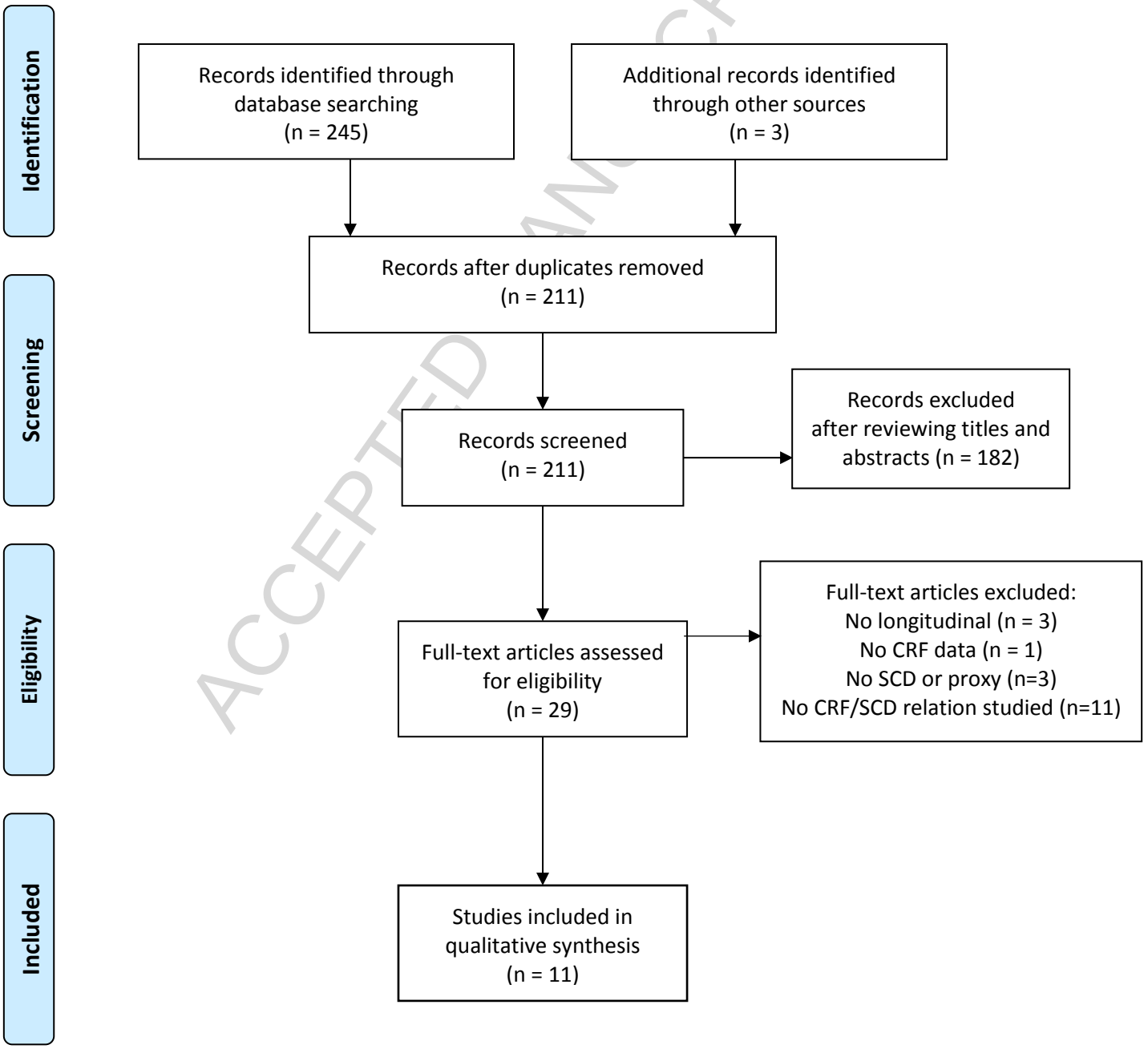

Figure 1. Flow diagram of the literature search and studies selection according PRISMA.

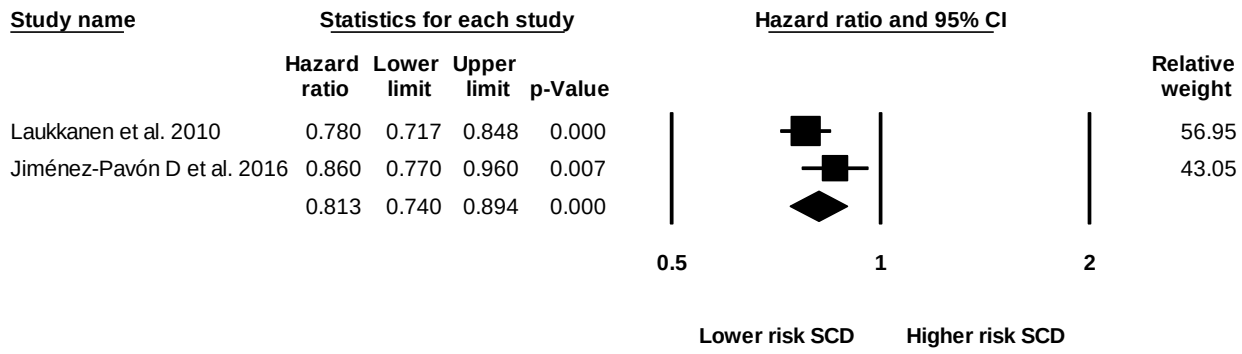

Figure 2. Forest plot of the risk of SCD by CRF measured as 1-MET increase. CI: Confidence Intervals.

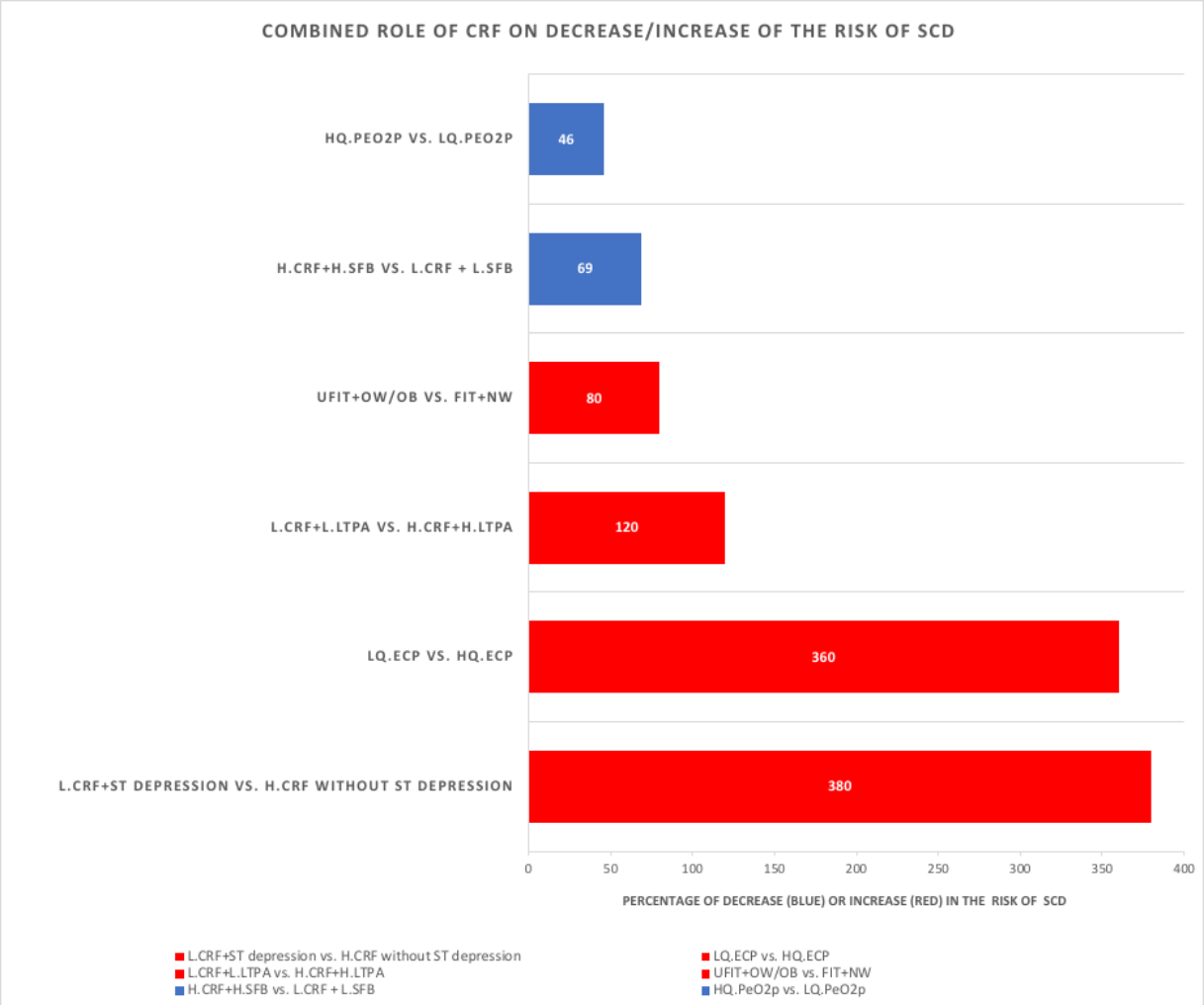

Figure 3. Combined role of CRF on decrease/increase of the risk of SCD where blue bars indicates decreased risk and red bars indicates increased risk (H.CRF, high CRF; H.FSB, high frequency of sauna bathing; HQ.ECP, high quartile exercise cardiac power; HQ.PeO2p, high quartile peak exercise oxygen pulse; H.LTPA, high leisure time physical activity; FIT.NW, Fit and normal weight; L.CRF, Low cardiorespiratory fitness; L.FSB, low frequency of sauna bathing; LQ.ECP, Low Quartile exercise cardiac power; LQ.PeO2p, low quartile peak exercise oxygen pulse; L.LTPA, low leisure time physical activity; UFIT.OW/OB, unfit and overweight-obese).

Table 1.- Characteristics of the two population cohorts followed to assess the independent role of CRF on SCD.

Study/Year	Cohort and Design	Participants	Maximal CRF assessment	SCD Events	Role of CRF on SCD
Laukkanen et al.[25]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD) risk factor study. **Follow-Up:** 17.6 years **Analysis:** Cox proportional hazards regression (Hazard ratios-HRs)	**Sample:** n=2,368 men; **Location:** Caucasian-Europe; **Health Condition:** General population **Age:** 52.9 years **BMI:**26.9 kg/m^2	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal heart rate; 220-age). **CRF:** mean VO_{2max} 30.2 ml/kg/min (8.6 METs). Mean Maximal Workload=181W.	**Source:** Hospital documents, wards of health centers, death certificates, autopsy and medicolegal reports. **Codes and definition:** ICD with codes 978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 146	-Inverse association -Risk of SCD decrease by 22% per 1 MET increase. -CRF ≥12 METs no SCD events.
Jiménez-Pavón et al.[26]	**Prospective Cohort:** Aerobics Center Longitudinal Study (ACLS). **Follow-Up:** 14.7 years **Analysis:** Cox proportional hazards regression (Hazard ratios-HRs)	**Sample:** n=55,456 (13,507 women) **Location:** United States of America **Health Condition:** General Population and sub-analyses for hypertensive, overweight and unhealthy individuals. **Age:** 44.2 years **BMI:** 25.7	**Test Type:** Maximal treadmill test. **Protocol:** Modified balke protocol using maximal heart rate (220-age). **Mean CRF:** 11.1 METs. **L.CRF/total time:** 8.2 METs/10.5min **M.CRF/total time:**10.2 METs/14.9min **H.CRF/total time:**12.9	**Source:** National death index and death certificates. **Codes and definition:** ICD with codes 978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 109.	-Inverse association. -M.CRF-H.CRF provide 44-48% lower risk. -In hypertensive, overweight and unhealthy individuals M.CRF-H.CRF provide 58-72% lower risk. -Risk of SCD

	kg/m^2	METs/20.5min		decrease by 14% per 1 MET increase.

BMI, body mass index; CRF, cardiorespiratory fitness; H.CRF, high CRF; ICD, International Classification of Diseases; L.CRF, Low CRF; M.CRF, moderate CRF; MET, metabolic equivalent (1 MET=3.5 ml/kg/min); SCD, sudden cardiac death; VO_{2max}, maximal oxygen uptake; W, watts.

Table 2.- The combined role of maximal CRF or sub-maximal CRF on the risk of SCD.

Study/Year	Cohort and Design	Participants	Independent/combined Predictors	SCD Events	Role of CRF on SCD
Kurl et al.[28]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD) risk factor study. **Follow-Up:** 20 years **Analysis:**	**Sample:** n=2,358 men; **Location:** Caucasian-Europe **Health Condition:** General population **Age:** 52.8	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal heart rate; 220-age). **Combined Predictors:** **ECP***: mean ECP 11.9 mL/mm Hg. **LQ.ECP:** <8.2 mL/mm Hg **HQ.ECP:** >16.1	**Source:** Hospital documents, wards of health centers, death certificates, autopsy and medicolegal reports. **Codes and definition:** ICD with codes	- Inverse independent and combined association - 1 SD increase in ECP and VO_{2max} (3.6 mL/mm Hg and 635.9 mL/min) decreased risks of SCD by 36% and

	Cox proportional hazards regression (Hazard ratios-HRs)	years **BMI:**26.6 kg/m^2	mL/mm Hg	978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 205	33%. - Risk of SCD was 4.6 fold higher in participants in LQ.ECP compared with those with HQ.ECP
Hagnäs et al.[29]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD) risk factor study. **Follow-Up:** 20.9 years **Analysis:** Cox proportional hazards regression (Hazard ratios-HRs)	**Sample:** n=2,328 men; **Location:** Caucasian -Europe **Health Condition:** General population **Age:** 52.8 years **BMI:**26.8 kg/m^2	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal heart rate; 220-age). **Independent/combined Predictors:** **CRF:** mean 8.6 METs **L.CRF:** ≤8 METs **H.CRF:** ≥8 METs Exercise-induced ST depression: 10.3% (n=239)	**Source:** Hospital documents, wards of health centers, death certificates, autopsy and medicolegal reports. **Codes and definition:** ICD with codes 978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 156	- Inverse independent and combined association - Risk of SCD was 1.6 fold higher in participants with L.CRF compared with those with H.CRF - Risk of SCD was 2.3 fold higher in participants with exercise-induced ST segment depression compared with those without. -Men with L.CRF and ST depression had 4.8 fold higher risk of SCD than

					men with H.CRF and without ST depression.
Kunutsor et al.[30]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD) risk factor study. **Follow-Up:** 25.6 years **Analysis:** Cox proportional hazards regression (Hazard ratios-HRs)	**Sample:** n=1,663 men **Location:** Caucasian -Europe **Health Condition:** General population **Age:** 52.2 years **BMI:**27 kg/m^2	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal heart rate; 220-age). **CRF:** mean VO_{2max} 2,496 ml/min. **Independent Predictor:** oxygen uptake at AT.	**Source:** Hospital documents, wards of health centers, death certificates, autopsy and medicolegal reports. **Codes and definition:** ICD with codes 978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 138	- Inverse association - 1 SD increase in oxygen uptake at AT (ml/min) decreased risks of SCD by 30%. -Higher quartile of oxygen uptake at AT (ml/min) provide 52% lower risk of SCD.
Kunutsor et al.[31]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD) risk factor study. **Follow-Up:** 25.6 years **Analysis:**	**Sample:** n=1,639 men **Location:** Caucasian -Europe **Health Condition:** General population **Age:** 52.2	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal heart rate; 220-age). **Independent Predictor:** Mean VO_2 at VT 23.72 ml/kg/min (6.78 METs).	**Source:** Hospital documents, wards of health centers, death certificates, autopsy and medicolegal reports. **Codes and definition:** ICD with codes	- Inverse association - Risk of SCD decrease by 19% per 1 MET increase. - Higher quartile of oxygen uptake at VT (ml/min) provide 63%

	Cox proportional hazards regression (Hazard ratios-HRs)	years **BMI:**26.9 kg/m^2		978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 121	lower risk of SCD.
Laukkanen et al.[32]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD) risk factor study. **Follow-Up:** 26.1 years **Analysis:** Cox proportional hazards regression (Hazard ratios-HRs)	**Sample:** n=2,291 men **Location:** Caucasian -Europe **Health Condition:** General population **Age:** 53 years **BMI:**26.9 kg/m^2	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal heart rate; 220-age). **CRF:** mean VO_{2max} 30.3 ml/kg/min **Combined Predictors:** **L.CRF:** ≤ 30.02 ml/kg/min **H.CRF:** ≥ 30.03 ml/kg/min **L.FSB:** ≤ 2 sessions/week **H.FSB:** 3-7 sessions/week	**Source:** Hospital documents, wards of health centers, death certificates, autopsy and medicolegal reports. **Codes and definition:** ICD with codes 978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 226	- Inverse independent and combined association - H.CRF provide 52% lower risk of SCD. -H.FSB provide 33% lower risk of SCD. -Men with H.CRF and H.FSB had 69% lower risk of SCD than men with L.CRF and L.FSB.
Laukkanen et al.[33]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD) risk factor study. **Follow-Up:** 26.1	**Sample:** n=2,227 men; **Location:** Caucasian -Europe **Health Condition:** General	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal heart rate; 220-age). **Combined**	**Source:** Hospital documents, wards of health centers, death certificates, autopsy and medicolegal reports.	- Inverse independent and combined association - 1 SD increase in relative peak exercise oxygen pulse was

	years **Analysis:** Cox proportional hazards regression (Hazard ratios-HRs)	population **Age:** 53 years **BMI:**26.9 kg/m^2	**Predictors:** Peak exercise oxygen pulse(peO2p)**: 15.5 mL/beats	**Codes and definition:** ICD with codes 978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 220	associated with decreased risks of SCD by 24%. - Higher quartile of relative peak exercise oxygen pulse provides 46% lower risk of SCD.
Jae et al.[34]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD) risk factor study. **Follow-Up:** 22 years **Analysis:** Cox proportional hazards regression (Hazard ratios-HRs)	**Sample:** n=2,357 men **Location:** Caucasian-Europe **Health Condition:** General population **Age:** 52.7 years **BMI:**26.7 kg/m^2	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal heart rate; 220-age). **CRF:** mean VO_{2max} 30.3 ml/kg/min **Combined Predictors:** **FIT.NW:** ≥8.6 METs, <26.5 kg/m^2 **UFIT.OW/OB:** <8.6 METs, ≥26.5 kg/m^2	**Source:** Hospital documents, wards of health centers, death certificates, autopsy and medicolegal reports. **Codes and definition:** ICD with codes 978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 253	- Inverse independent and combined association. - Risk of SCD was 1.80-fold higher in participants in UFIT.OW/OB compared with those in FIT.NW.
Hagnäs et al.[35]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD)	**Sample:** n=2,656 men **Location:** Caucasian-Europe	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal	**Source:** Hospital documents, wards of health centers, death	- Inverse independent and combined association. - Risk of

	risk factor study. **Follow-Up:** 19 years **Analysis:** Cox proportional hazards regression (Hazard ratios-HRs)	**Health Condition:** General population **Age:** 53 years **BMI:**26.9 kg/m^2	heart rate; 220-age). **CRF:** mean VO_{2max} 30.1 ml/kg/min (8.6 METs). **Combined Predictors:** **H.CRF-H.LTPA:** 9.9 METs **L.CRF-L.LTPA:** 6.4 METs	certificates, autopsy and medicolegal reports. **Codes and definition:** ICD with codes 978.1 and 146 from 9th and 10th revision. **Number of SCD events:** 205	SCD decrease by 18% per 1 MET increase. - Risk of SCD was 1.6 and 1.4 folds higher in participants with L.CRF and L.LTPA (respectively) compared with those with H.CRF and H.LTPA. - Risk of SCD was 2.2 fold higher in participants in L.CRF-L.LTPA compared with those with H.CRF-H.LTPA.
Laukkanen et al.[36]	**Prospective Cohort:** Kuopio Ischemic Heart Disease (KIHD) risk factor study. **Follow-Up:** 25.3 years **Analysis:** Cox proportional hazards	**Sample:** n=2,299 men **Location:** Caucasian-Europe **Health Condition:** General population **Age:** 53 years	**Test Type:** Maximal cycle ergometer test. **Protocol:** 3min warm-up 50w+ step-by-step increase of 20W/min (maximal heart rate; 220-age). **Independent Predictor:** **CRF:** mean VO_{2max} 30.3 ml/kg/min.	**Source:** National Hospital Discharge Register. **Codes and definition:** VAs defined by ICD with codes 427.41 and 147.2-149.0 from 9th and 10th revision,	- Inverse association. - 1 SD increase in CRF was associated with decreased risks of VAs by 36%. - High CRF (top tertile) provide 71% lower risk of VAs.

	regression (Hazard ratios-HRs)	**BMI:**26.9 kg/m^2	respectively. **Number of VAs events:** 73 serious VAs.

AT, aerobic threshold; VT, ventilatory threshold; BMI, body mass index; CRF, cardiorespiratory fitness; ECP, Exercise cardiac power; H.CRF, high CRF; H.FSB, high frequency of sauna bathing; HQ.ECP, high quartile ECP; H.LTPA, high leisure time physical activity; ICD, International Classification of Diseases; FIT.NW, Fit and normal weight; L.CRF, Low CRF; L.FSB, low frequency of sauna bathing; LQ.ECP, Low Quartile ECP; L.LTPA, low leisure time physical activity; MET, metabolic equivalent (1 MET=3.5 ml/kg/min); SCD, sudden cardiac death; SD, standard deviation; UFIT.OW/OB, unfit and overweight-obese; VAs, ventricular arrhythmias; VO_{2max}, maximal oxygen uptake; W, watts.* ECP calculated as ratio of measured VO_{2max} with peak SBP; ** Peak exercise oxygen pulse calculated by dividing the measured peak VO2 by the maximum exercise heart rate.