Cardiorespiratory fitness as a predictor of short-term and lifetime estimated cardiovascular disease risk

Running title: Normative fitness thresholds and CVD risk

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Abstract

Development of cardiovascular disease (CVD) remains a public health concern for young-to-middle-aged adults, now exacerbated by the increasing prevalence of obesity and sedentary lifestyles. Cardiorespiratory fitness (CRF) improves the reclassification of short-term (10-year) CVD risk, but has not been uniformly defined across studies. This study evaluated cross-sectional differences in short-term and lifetime CVD risk scores, across both absolute metabolic equivalent (MET), sex- and age-standardised CRF categories in 805 healthy apparently healthy young-to-middle aged adults (68% male; 47.4 ± 7.2 years). CVD risk factors were evaluated, and estimated cardiorespiratory fitness (CRF) measurements (METS and peak VO_2) were derived from a submaximal Bruce treadmill test. CRF measures also included post-exercise heart rate recovery (HRR) data. Consistent trends showing more favorable risk factor profiles and lower short-term CVD (QRISK2), and CVD mortality (SCORE) scores, associated with higher levels of CRF were evident in both sexes. Lifetime CVD risk (Q-Lifetime) was highest in the lowest CRF categories. Peak VO_2 and HRR following submaximal exercise testing contributed to the variability in short-term and lifetime CVD risk. Global CVD risk predictions were examined across different contemporary CRF classifications with inconsistent findings. Recommended absolute MET and sex- and age-standardised CRF categories were significantly associated with both short-term and lifetime risk of CVD outcomes. However, compared to internationally-derived normative CRF standards, cohort-specific CRF categories resulted in markedly different proportion of individuals classified in the “poor” CRF category at higher CVD risk.

KEY WORDS: peak VO_2; heart rate recovery; aerobic capacity

Introduction

Physical activity habits and notably cardiorespiratory fitness (CRF) are important and increasingly recognised CVD risk factors, but do not contribute directly to most current global CVD risk prediction models used in clinical practice. There is growing interest and evidence to support the implementation of a CRF measure (directly-determined or estimated peak VO_2, or its metabolic equivalents (METS)), into CVD risk estimation (1,2). In the large UK Biobank study (3), significant increases in CVD risk with decreasing physical activity were only evident in those with the lowest CRF (7.12±1.5 METS). This study further emphasised the relevance of reducing CVD or mortality outcomes among individuals who exhibit a 'low fitness profile' (i.e. physically inactive plus low CRF).

Ross *et al.* (1) provided the scientific justification for CRF as an independent CVD risk factor and clinical vital sign. Notably, CRF significantly improves the reclassification of risk for short-term CVD risk. A progressive and dose-dependent reduction in short-term CVD risk has typically been observed with cohort stratification into CRF categories. Accordingly, Kokkinos *et al* (4) cited several studies that have reported that fitter individuals have as much as an 80% reduction in CVD risk compared with the least fit individuals, regardless of age, sex, body composition, or other cardiovascular risk factors. CRF has been reported to be a characteristic of the metabolically healthy but obese phenotype (5), plus low fitness in mid-life has been associated with likelihood of metabolic syndrome (6) and with higher lifetime risk for CVD death in a well-characterized cohort with long-term follow-up (7). These findings, reinforce the need to assess, monitor and improve CRF and associated surrogate fitness measures, such as post-exercise heart rate recovery (HRR), within younger adults to encourage positive future health outcomes.

The CVD risk associated with different levels of CRF has varied considerably, even within contemporary cohort studies. This is likely related to participant differences and the methodologies used to measure and subsequently categorise CRF (typically based on tertile-, quartile- or quintile-based categories of directly determined or mostly estimated peak VO_2/METs) within the prospective cohorts. To ameliorate these methodological limitations, standardised methods to uniformly define

CRF categories and more accurately quantify the impact of CRF on CVD risk have been advocated (1). Several investigators have proposed a sex- and age-adjusted analytical approach to CRF categorization (4), (using either peak VO_2 expressed in millilitres per kilogram per minute, or METs) and/or the utilisation of comprehensive published normative datasets for CRF. Furthermore, low CRF combined with poor HRR following exercise testing has also been independently associated with increased all-cause and cardiovascular mortality (8). Despite this, simple surrogate measures of cardiac autonomic function, such as post-exercise HRR, are not considered in most global CVD risk scores, or routinely applied in clinical practice.

UK clinical practice is now routinely adopting the QRISK prediction model, a UK-specific and validated predictor of 10-year CVD risk in representative cohorts (9), but European alternative risk algorithms (SCORE) are also advised (10). A major change in the most recent Joint British Society (JBS) guidelines on CVD prevention was the recommendation that CVD risk estimation based not only on short-term (10-year) risk, but also consider lifetime risk (11). Consideration of a lifetime risk approach, particularly within younger adults, may further support appropriate CVD risk stratification/management and lifestyle changes. The QRISK lifetime risk model uses a competing risks analysis, producing both summary CVD risk, up to 95 years of age, and showing the cumulative risk of a CVD event (12). Likewise, the JBS3 CVD risk algorithm provides CVD event-free survival, together with 10-year risk scores. Few cross-sectional studies have evaluated associations of CRF with lifetime CVD risk.

The purpose of our study was to examine CVD risk factors, both short-term (10-year) and lifetime risk of CVD in a cross-sectional study of males and females presenting for routine preventive health assessments. We examined associations of CRF and CVD risk using separate fitness classification methods, including absolute (METS-based) categories and CRF categories based on internationally derived sex- and age-standardised normative data. Further, we evaluated if contemporary CRF indices (including predicted peak VO_2 and HRR) contributed significant to 10-year and lifetime global CVD risk estimation in our cohort of healthy young to middle-aged males and females.

Materials and Methods

Participants: A cross-sectional analysis of males and females, free from any cardiovascular and/or metabolic conditions, who attended preventive health screening assessments at Nuffield Health in Manchester, UK over a 2-year period. These assessments for employed participants were mostly funded (in-full, or in-part) through corporate wellness schemes, but a small proportion were self-funded. All testing was completed in clinical practice where routine non-gold standard measures were used. Prior to the testing, informed consent was obtained from each participant and the study conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the local human research and ethical committee. Each participant completed a comprehensive medical and lifestyle questionnaire, which comprised key information for global CVD risk predictions (sex, age, smoking status, medical history/medications and family history of myocardial infarction (MI) under 60 years). For descriptive purposes, self-reported ratings of physical activity status were sought from each participant. Information about weekly frequency and duration of light (<3METS), moderate (3-6METS) and vigorous (>6METS) physical activity (PA) was requested with the help of examples provided from the updated PA compendium (13).

Test procedures:

Fasting (12-hour) venous blood samples were obtained from the anticubital fossa using the BD Vacutainer® system (New Jersey, USA). For the purpose of CVD risk scores, fasting blood glucose (FBG) and lipid profiles including total cholesterol (TC), low-density lipoprotein (LDL-c), high-density lipoprotein (HDL-c) and triglyceride (TG) levels were analysed using a point of care Piccolo analyser (Abaxis, USA). Resting blood pressure (BP) was measured using a manual sphygmomanometer and stethoscope. A second measurement was taken if a blood pressure (BP) >140 mmHg systolic or >90 mmHg diastolic was recorded (14).

Body mass was measured to the nearest 0.1kg using digital scales (Marsden, UK) and stature measured to the nearest 0.1cm using a stadiometer (Seca, Hamburg, Germany), enabling

subsequent calculation of BMI. Body fat content (BF%) was determined using the BodyStat 1500 whole-body bioelectrical impedance analyser (BodyStat Limited, UK), which minimised the inter-tester variability associated with other measures of BF%. Waist circumference (WC) was measured at the midway point between the lowest rib and iliac crest, and waist-to-hip ratio (WHR) was calculated by dividing WC by the hip circumference measured at the level of the greater trochanter (15). In addition, waist-to-height ratio (WHtR) was calculated by WC divided by height (16).

Prior to the exercise test, resting heart rate (RHR) was determined by supine 12-lead electrocardiography (ECG; Marquette CASE System, GE Healthcare, UK). A submaximal Bruce treadmill test was performed (90 ± 5% and 89 ± 3% of age-predicted maximum heart rate (APMHR), in males and females respectively). Any participants that displayed abnormal ECG responses during and/or post exercise were excluded from the study. Due to the submaximal nature of the test and no respiratory gas analysis available in the clinic for objective assessment of oxygen consumption, total treadmill time was recorded (17,18). Validated prediction equations for the Bruce treadmill protocol were used to calculate peak VO_2 in males (19) and females (20), which were also converted into METS [$VO_{2\,peak}$ divided by 3.5] for CRF categorisation purposes. Once a target HR of 85-90% APMHR was achieved, participants adopted a supine position and HRR data was collected at one and two minutes post-exercise. HRR was recorded as a delta value calculated from the submaximal peak exercise HR achieved (ΔHRR_{60} and ΔHRR_{120}).

QRISK2 (21) and JBS3 (22) were calculated to determine 10-year global CVD risk using an online calculator that required age, sex, smoking status, family history of MI <60 years, TC, HDL-c, BMI and BP. The European Heart SCORE online calculator (23) was used to generate 10-year CVD mortality risk, based on the work of Conroy *et al.* (10). In order to report lifetime CV risk, further online calculators were used for Q-Lifetime to determine % risk at 95 years of age (24), and JBS provided a predicted Survival Age and Heart Age based on the inputted CVD risk factors.

Statistical analysis: IBM SPSS Version 24 was used for all analyses (Armonk, NY: IBM Corporation). Prior to any statistical analysis, data was checked for normality. Most variables were not normally distributed using Kolmogorov-Smirnov tests ($P<0.05$) but given the sample size adequate power existed to avoid performing log-transformations. On visual examination of histograms and stem-and-leaf plots, there were some outliers at the upper-end but no notable skewness was observed. It was deemed not appropriate to remove these data points as it was a true reflection of the distribution in this wide age group. All data were reported as mean, standard deviation (SD) and/or 95% confidence intervals (CI). Student's independent t-tests were performed to compare the mean values between males and females for age, anthropometric measures, CVD risk factors, CRF measures and CVD risk scores. Non-parametric tests were performed to identify the difference of lifestyle characteristics including smoking and familial history across both sexes and CRF groups. Effect size estimations were noted to identify meaningfulness of difference between males and females, and across CRF groups.

For the identification of individuals in the lower CRF groups and implicitly at higher CVD risk, three distinct methods were adopted to classify CRF, a) absolute MET-based categories; b) tertiles of estimated peak VO_2, based on the cohort distribution; c) categories of CRF based on internationally derived sex- and age-standardised thresholds. The 3 methods used to categorise the CRF results are outlined in detail in the supplementary files.

Separate unadjusted analysis of variance (ANOVA) models with Bonferroni post-hoc calculations were performed on male and females to determine differences in age, anthropometric measures, CVD risk factors and HRR across the CRF groups. Models were subsequently adjusted for age and smoking status. Within ANOVA models, the CVD risk scores were not adjusted as age and smoking status were already accounted for in the risk estimations. To evaluate the CRF and other predictors of both short-term and lifetime CVD risk in males and females, backward stepwise linear regression

models were run for each CVD risk score. Initially, the regression models were adjusted for age to highlight the contribution of this major risk factor (Model[1]). As age is already accounted for in the CVD risk algorithms, each model was also run without age-adjustment (Model[2]). The independent variables entered into the regression models included both CRF predictors (predicted $VO_{2\ peak}$ and ΔHRR_{60}), and anthropometric variables (BF% and WC). Given, potential collinearity, and given BMI is included in all the algorithms for CVD risk a final regression model was run without body fat content. Model[1] and model[2] both incorporate the standard predicted peak VO_2 and ΔHRR_{60} as the fitness predictors. Model[1] was age-adjusted, whereas model[2] was not age-adjusted due to the inclusion of "age" as a factor in the prediction algorithms. Statistical significance was set at $P<0.05$.

Results

Physiological and anthropometric characteristics of the 805 participants (551 males; 254 females) are presented in **Table 3**. Males displayed significantly higher values for most anthropometric measures. BMI distribution for normal-weight, overweight and obesity differed between males (28.1%, 49.5% and 22.3% respectively) and females (57.9%, 27.6% and 13.8% respectively). Males had higher values for standard CVD risk factors (except HDL-c). Males had significantly higher 10-year risk of CVD events (+3.6% QRISK2) and risk of hard CVD events (+1.2% SCORE) compared to females. Longer-term CVD risk estimations also showed males had significantly higher Q-lifetime CVD risk (+13.5%) and lower JBS3 survival age (-4.6 years). JBS3 estimated a significantly higher mean heart age (1.9 years older for females; 6.1 years older for males) compared to chronological age. Similar proportions of males and females were current smokers (29.5 % and 28.3% respectively), reported familial hypertension, type 2 diabetes and CVD. (Table S1).

Males exhibited significantly lower resting heart rates and longer treadmill exercise time, but there were no significant differences in predicted peak VO_2/METS using standard Bruce protocol equations. Females displayed more favourable exercise cardiac autonomic function measures, exhibiting similar peak exercise heart rates but more rapid post-exercise HRR at 1 and 2 minutes (**Table 4**).

Cardiorespiratory fitness (CRF) Classifications

As outlined in the supplementary methods section, **Table 1 and 2** illustrates the cohort distribution for the 3 different methods used to classify CRF. Table 1a shows the CRF results based on the AHA MET-based classification (1). The largest proportion of participants (42.6% male, 52.8% female) were categorised as exhibiting higher levels of CRF based on these absolute MET groups.

Lifestyle factors across CRF groups

The distribution of several lifestyle factors were examined across the three absolute MET-based groups. No significant differences in smoking prevalence or alcohol consumption was evident across any of the CRF classifications in males and females. As expected, there was a significantly higher frequency of moderate and vigorous exercise sessions in the higher CRF groups in both males and females ($P<0.001$ and $P=0.002$ respectively). In both sexes, the higher absolute CRF groups were undertaking a mean of 3.8 ± 2.5 moderate and vigorous exercise sessions per week. Typically, higher fitness groups were undertaking 3-4 moderate and vigorous weekly exercise sessions. The high CRF groups showed clear trends in the reported frequency of vigorous exercise (all $P<0.001$). The pattern was similar across CRF^{std} and CRF^{wm} groups.

Associations of CRF with CVD risk factors, fatness, and cardiac autonomic function.

Table 5 provides unadjusted values for CVD risk factors, anthropometric and cardiac autonomic function measures across the absolute CRF groups. As expected, there was a significant difference in the age profile across the CRF groups in males and females, with younger mean ages in the higher CRF groups. This age disparity was more evident in females ($\eta^2=0.139$) compared to males ($\eta^2=0.034$). Following adjustment for age and smoking status, anthropometric measures of body fat content/distribution and cardiac autonomic function following exercise did not differ across CRF groups in both sexes.

As expected, all anthropometric/fatness measures reduced with higher CRF levels (BMI, WC, BF%, WHR, WHtR), with the largest differences evident between low CRF and high CRF (all P<0.001). These differences represented small-to-medium effect sizes in males (η^2=0.57-0.90) and females (η^2=0.09-0.12), following adjustment for age and smoking status (Table S2). **Table 6** Similar analyses were performed across the CRF^{std} and CRF^{wm} (Table S3 and S4), showing body fatness measures remain significantly different across the groups, but most notably when comparing the low CRF^{std} group with the two higher groups. Effect sizes for CRF were marginally larger in females (η^2=0.05-0.13) than males (η^2=0.05-0.08). The age-specific CRF^{wm} groups showed the high fitness group had lower levels of fatness (Table S4), however this trend was clearer for females.

All post-exercise cardiac autonomic function measures (Table S2) were more favourable with higher CRF groups, yet small effect sizes (η^2=0.028-0.046). Although still highly significant with medium effect sizes, the female associations were slightly weakened for RHR (P=0.009), ΔHRR_{60} (P=0.008) and ΔHRR_{120} (P=0.003), but possibly because of smaller sample size (n=254). Higher CRF was associated with a lower RHR but this was a more meaningful difference across CRF groups in males than females (η^2=0.122 compared to η^2=0.037). In CRF^{std} and CRF^{wm} analyses, the autonomic measures followed the same trend with a lower RHR and quicker HRR at both time-points in the higher CRF groups (Table S3 and S4).

Most standard CVD risk factors, except LDL-c, HDL-c and blood glucose concentrations showed significant differences between the CRF groups, with the largest difference evident between low CRF and high CRF (Table S2-S4).

Global CVD risk scores

Table 5 highlights the observed trend towards differences in estimated 10-year CVD risk across CRF groups in both sexes. These analyses demonstrated higher fitness is associated with lower 10-year CVD risk, with small-to-medium effect sizes evident for QRISK2 (unadjusted η^2=0.05_{male}, 0.10_{female}). Reduced short-term risk of CV mortality (SCORE) with higher fitness was found across the CRF

groups in both sexes. This trend was also observed across CRF^{std} groups and female CRF^{wm} groups. Male CRF^{wm} groups did not present a clear downward trend across the three CRF^{wm} groups with moderate CRF group showing lower 10-year risk, which could be explained by a larger moderate CRF group. However, there was no trend or notable difference in SCORE across male CRF^{wm} groups. Lifetime CVD risk (Q-Lifetime), was lower in the highest CRF categories. However, the trend is less distinct between lower CRF groups. There was no difference in JBS3 CVD survival age across the CRF groups determined by the different CRF thresholds utilised.

Table 6 provides results from stepwise linear regression to identify the main CRF (and fatness predictors) of the selected global CVD risk scores in both males and females. In the age-adjusted models, 55% and 57% of the variance in estimated short-term CVD risk (QRISK2 score) was explained in males and females respectively. Age and waist circumference were the main predictors ($P<0.001$) with either peak VO_2 and/ or ΔHRR_{60} being included in the model. Within model^2, 20% and 28% of the variance in QRISK2 score was explained by the main predictors, in males and females respectively. Amongst CRF variables, post-exercise HRR was the most predictive of QRISK2 in females. The outcome was similar for SCORE 10-year mortality risk in both regression models. Interestingly, when overall BF% was not included as a predictor variable, WC and CRF measures were similarly predictive of short-term CVD. Waist circumference was the strongest predictor of lifetime risk, with either CRF variable contributing to the model.

Table Legends

Table 1: Distribution of participants across three a) absolute MET-based CRF categories and b) pooled CRF^{wm} categories

Table 2: Distributional tertile CRF cut-points for $VO_{2\ peak}$ across 3 age bands in the Nuffield cohort

Table 3: Physiological and anthropometric characteristics for all participants

Table 4: Submaximal exercise test and cardiac autonomic function results in all participants

Table 5: CVD risk scores across the CRF groups determined by three classification methods in males and females

Table 6: Overall predictors of global short and lifetime CVD risk in healthy, young to middle-aged male and females.

Supplementary files

Table S1: Lifestyle characteristics for all participants

Table S2: Unadjusted CVD risk factors and anthropometric profiles across absolute MET-based CRF categories

Table S3: Unadjusted CVD risk factors across sex and age-specific tertiles of CRF (CRF^{std})

Table S4: Unadjusted CVD risk factors across age-standardised normative CRF (CRF^{wm}) pooled categories

Table S5: Overall predictors (standardized Beta coefficient) of global short and lifetime CVD risk in healthy, young to middle-aged male and females.

Discussion

This study shows favourable trends for lower estimated 10-year CVD risk and 10-year CVD mortality risk with higher CRF levels in a predominantly low risk cohort of young-to-middle-aged adults attending a preventive medical assessment. Lifetime risk of CVD was also

significantly higher with lower levels of CRF. As expected, less pronounced differences in short-term and lifetime CVD risk were evident across the sex- and age-specific CRF categories compared to the absolute CRF definitions (MET-based thresholds referred to within the AHA scientific statement). Further, the CRF categories based on internationally derived normative data (CRF^{wm} groups) showed similar trends for lower 10-year and lifetime CVD risk associated with higher CRF fitness.

Our findings are consistent with the HUNT Fitness Study, which provided the largest database of directly-measured peak VO_2 with standard cardiovascular risk factors and self-reported physical activity in healthy women and men across a wide range (26). We also demonstrate concordance with prospective cohort studies that have shown associations between CRF and CVD event outcomes are graded across the CRF distribution. The meta-analysis of Kodama et al. (28) examined associations of CRF with CVD outcomes within 24 prospective cohort studies recruiting over 84,000 participants. Using various methods to quantify cardiorespiratory fitness (CRF), the studies collectively reported associations of CRF with 4485 CHD/CVD index events. The risk of cardiovascular events/ mortality was 15% lower for each 1-MET increase in exercise capacity (28). Within a categorical analysis, individuals with low CRF (<7.9 METs) had a substantially higher risk of all-cause mortality and CHD/CVD compared with those with intermediate and high CRF (7.9-10.8 and ≥10.9 METs, respectively). These are consistent with our findings of lower CVD risk across the AHA CRF metabolic equivalents (MET) categories for exercise capacity (1). The Kodama meta-analysis included only 10 studies employing standardised maximal exercise testing procedures, including the Kuopio Ischaemic Heart Disease Risk Factor Study. In that study peak VO_2 , measured directly with respiratory gas exchange, was predictive of non-fatal and fatal cardiac events among a representative randomly selected sample of 1294 healthy men during a 13-year follow-up (29). Within participants (with various combinations of risk factors), a one-MET increment in CRF amounted to an average decrease of 17-29% in non-fatal and 28-51% in fatal cardiac events, after adjustment for age. The age-adjusted risk of fatal cardiac events

was more than 4.5-fold higher in healthy individuals with a VO_{2max} in the lowest quartile (below 27.6 ml O_2/kg/min; 8 METS) compared to the highest aerobic fitness quartile (VO_{2max} above 37.1 ml O_2/kg/min; 10.6 METS).

The CVD risk associated with different CRF classifications has varied considerably between previously published prospective cohort studies. This is likely related to participant differences and the methodologies used to measure and classify CRF (typically quartile- or quintile-based categories of peak VO_2/ METs) within the cohorts. A recent report from the large UK Biobank study, utilised age- and sex-specific tertiles of peak VO_2 derived from submaximal cycle exercise testing to examine prospective associations with CVD outcomes (3). The association between physical activity and mortality was stronger among those in the lowest tertile of CRF (HR:1.13 [1.02–1.26]) than those in the highest (HR:1.03 [0.91–1.16]). The pattern for physical activity and CRF with CVD events was reported by the authors to be comparable.

We have explored standardised methods to uniformly examine CRF categories. In particular, we have incorporated normative reference data from several representative reports to more accurately quantify the impact of CRF on predicted short and long-term CVD. The differences in these primary studies and there normative results have been described in detail elsewhere (1,26,27). We applied a weighted mean approach, combining the sex- and age-specific quintiles (20% cut-points) from these 3 large-scale, representative US, and two northern European cross-sectional epidemiological studies all employing maximal treadmill testing and incorporating respiratory gas analysis. CRF categories based on this normative data showed favourable trends to short-term and lifetime CVD risk reduction with higher fitness in all adults in the present cohort. Few prospective studies have examined associations of CRF with lifetime CVD risk. In an analysis from the Aerobic Center Longitudinal study (ACLS), low CRF fitness, obtained from a single measurement of exercise capacity, was associated with marked differences in the lifetime risks for CVD death >30 years later (7).

We examined the predictive role of CRF variables on estimated short-term and lifetime CVD risk. Our multivariate regression analyses indicated that CRF and body fatness variables, especially waist circumference, were significant predictors of both short- and longer-term CVD risk in both males and females. Whilst, age and waist circumference were the strongest independent predictors of short and lifetime CVD risk, either peak VO_2 and/or HRR were retained within the final regression models. Amongst CRF variables, post-exercise HRR was the most predictive of QRISK2 in females. It is increasingly appreciated that CRF and measures of cardiac autonomic function are interlinked and associated with CVD. Mora and colleagues (27) reported that the routine inclusion of both CRF and post-exercise heart rate recovery (HRR) measurements enhanced risk prediction using the Framingham 10-year risk score in asymptomatic middle-aged adults in the United States. These findings provide further support for the potential value of cardiac autonomic function measurements within preventative health settings. A recent meta-analysis (30) confirmed associations of post-exercise heart rate recovery with cardiovascular events in middle-aged adults. Within five prospective cohort studies examining cardiovascular events, enrolling 1061 cases from 34 267 participants, the pooled hazard ratios associated with attenuated HRR (referent) compared to rapid HRR after exercise testing was 1.69 (95% CI 1.05-2.71) for cardiovascular events. Supplementary analyses indicated that the associations of attenuated HRR and increased risk of fatal cardiovascular events were independent of traditional CVD risk factors. Our study provides complimentary, albeit indirect evidence that CVD risk assessment /CRF assessments should consider the inclusion of a simple measure of post-exercise cardiac autonomic function (HRR) to enhance risk predictions in apparently healthy, young-to-middle-aged adults. The inclusion of CRF, determined by METS from maximal exercise, enhances Framingham risk predictions (31), and improves short and long-term risk for CVD mortality when added to traditional risk factors (2). To our knowledge, Mora and co-workers are the only others to have investigated the inclusion of a HRR measure with global 10-year risk (31). In over 6 000 asymptomatic individuals with Framingham risk scores <20%, they reported an

enhanced CVD risk prediction with the addition of ΔHRR_{120} and METS to Framingham equations.

Our findings support recommendations to reduce global CVD risk in apparently healthy young-to-middle-aged adults, a focus should be initially placed on lifestyle factors within young- and middle-aged adults exhibiting poor CRF. This involves improving peak CRF and parasympathetic activity by weight loss and/or regular moderate-to-vigorous exercise training interventions (32). We also supports the recommendations for preventive health centres to routinely measure and classify both CRF and HRR as clinical vital signs in cardiovascular health (33). However, our findings provide evidence of inconsistencies in the classification of the “low fitness phenotype” within younger- and middle-aged adults. To illustrate this issue, we have presented analyses using several different methods of classifying CRF, including in absolute exercise capacity values recommended by an expert consensus (1) and CRF sex- and age-specific cut-points based on distributional tertiles within our cohort, and CRF categories based on normative reference data from three representative studies.

Within our cohort, it appears that using AHA recommended MET-based thresholds for exercise capacity (Table 1) leads to a disproportionately lower number of participants assigned to the “low CRF phenotype” compared to either cohort specific,. or normative CRF reference data approaches. Our weighted mean CRF cut-points established from studies employing “gold-standard “ treadmill cardiopulmonary exercise testing- were similar in males, but slightly lower in females by comparison to the widely applied ACSM CRF classifications (14). The ACSM fitness thresholds were devised from the Aerobics Centre Longitudinal Study cohort using estimated peak VO_2 from the Balke treadmill protocol. They were approximately midway between two of the reference norms derived from gold-standard CRF testing methods (25,27), but the HUNT norms (26) were evidently higher in both sexes. These were compared to cohort-specific cut-points for low, moderate, and high CRF, consistent with epidemiological approaches. The differences evident in our CVD findings across the retrospective aerobic

fitness categorisations require further consideration and a standardised approach across studies would be useful to reduce these inherent limitation and interpretation within the literature examining such associations.

Consistent with other reports, the most obvious limitation is the cross-sectional study design that, in principle, does not allow causal inferences between peak VO_2 and the prevalence of unfavorable levels of CVD risk factors and predicted short- and long-term CVD risk. Participants were recruited from a preventive health-screening centre primarily recruiting the employees of corporate clients and are likely to be more representative of higher socioeconomic groups. The QRISK and JBS3 risk algorithms employed for CVD risk estimation both include a measure of socioeconomic status. Future studies should employ similar methodological approaches to cohorts with a wider socioeconomic demographic. Submaximal exercise testing with prediction of peak VO_2 was applied in this study, this approach certainly has its limitations. However, this methodology for determining CRF has been widely applied in prospective and cross-sectional epidemiological studies of short-term CVD risk. Submaximal methodologies accommodate most population groups in terms of ability to complete the test and to minimise safety concerns associated with maximal exercise testing. By comparison, with regard to measures of cardiac autonomic function, submaximal testing has actually been favoured to determine HRR as it reduces the interference by heightened sympathetic activity associated with maximal exercise testing (34). In addition, HRR has been reported to be a reliable measure following submaximal exercise (35). The predictive value of CRF may have increased if the testing had been maximal in nature. However, most exercise testing performed in non-hospital settings in the UK is submaximal. To provide preventive CVD screening to large population groups, it is not always feasible to perform expensive, resource intensive, “gold-standard” maximal tests with respiratory gas analysis. Surrogate submaximal treadmill exercise tests and perhaps non-exercise models for estimating CRF could be more widely implemented.

In conclusion, we have reported that predicted peak VO_2 and post-exercise heart rate recovery (ΔHRR_{60}) derived from submaximal treadmill exercise testing were strong and significant predictors of 10-year and lifetime CVD risk (as measured by the QRISK2, SCORE and related CVD risk algorithms) within apparently healthy, young-to-middle-aged adults. These findings highlight the potential value of routine monitoring of CRF and simple post-exercise testing HRR measures as important contemporary CVD risk indicators. We have shown with relative consistency that CRF groups determined by different classification methods are associated with both short-term and lifetime estimates of CVD risk. Yet, the proportion of individuals with higher CVD risk based on lower CRF varies considerably with the categorization method adopted. This reinforces the importance for a standardized approach to CRF categorization in order to support its implementation in future risk stratification and clinical practice.

Perspective

Cardiorespiratory fitness is increasingly recognised as a clinical vital sign and viewed as complimentary to the established global CVD risk prediction algorithms applied in primary prevention settings. However, there is a need to adopt more standardised approaches to CRF classification for identification of individuals exhibiting “low CRF” and implicitly at higher CVD risk. The aim of this study was to examine short-term (10-year) and lifetime risk of CVD using establish CVD algorithms (QRISK, European SCORE) associated with CRF; but applying different methods to classify CRF (including absolute METS and across levels of estimated maximum oxygen uptake ($VO_{2\,max}$) based on cohort distributional cut-points, or internationally derived sex- and age-standardised thresholds). As expected, younger and middle-aged participants with higher levels of CRF demonstrated significantly lower estimated short and lifetime CVD risks compared to their lower fitness counterparts . However, we highlight that using absolute thresholds based on METS leads to a disproportionately fewer participants assigned to the lower CRF groups compared to cohort specific or normative reference approaches. Accordingly, our findings highlight the inconsistencies evident with different

methodological approaches to CRF classification and reinforce recent recommendations to implement more standardised approaches to CRF categorization, to support their wider implementation into risk stratification within clinical practice.

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