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Addition of estimated cardiorespiratory fitness to the clinical assessment of 10-year coronary heart disease risk in asymptomatic men

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ABSTRACT

The Framingham Risk Score (FRS) was developed to quantify a patient's coronary heart disease (CHD) risk. Non-exercise estimated CRF (e-CRF) may provide a clinically practical method for describing cardiorespiratory fitness. We computed e-CRF and tested its association with the FRS and CHD.

Male participants (n = 29,854) in the Aerobics Center Longitudinal Study (ACLS) who completed a baseline examination between 1979–2002 were followed for 12 years to determine incident CHD defined by self-report of myocardial infarction, revascularization, or CHD mortality. e-CRF was defined from a 7-item scale and categorized using age-specific tertiles. Multivariable survival analysis determined associations between FRS, e-CRF, and CHD. Interaction between e-CRF and FRS was tested by stratified analysis by 'low' and 'moderate or high' 10-year CHD risk.

Men with high e-CRF were significantly (p-value < 0.0001) younger, and less likely to be smokers, compared to men with low e-CRF. Multivariable survival analysis reported men with high e-CRF were 29% (HR = 0.71; 95% 0.56, 0.88) less likely to experience a CHD event compared to men with low e-CRF. Stratified analyses showed men with 'low' 10-year FRS predicted CHD risk and high e-CRF had a 28% (HR = 0.72; 95% CI 0.57, 0.91) lower CHD-mortality risk compared to men with low e-CRF, no association was found in this group and men with moderate e-CRF. Men who were more fit had a decreased risk for CHD compared to men in the lowest third of fitness. Estimated CRF may add clinical value to the FRS and help clinicians better predict long-term CHD risk.

1. Introduction

Despite the decrease in coronary heart disease (CHD) incidence worldwide in the past 30 years (Rodriguez et al., 2006; Bennett et al., 2006). a decrease in age-adjusted CHD mortality in the United States (US) (Xu et al., 2010), and decrease in self-reported CHD (Centers for Disease Control and Prevention, 2011) from 2006 to 2010, CHD remains one of the leading causes of death in the US. (Murphy et al., 2012) CHD risk factors include diabetes (Grossman & Messerli, 1996), hypercholesterolemia (Wijeysundera et al., 2010), hypertension (Strauer, 1979), and smoking (Scheidt, 1997). Accordingly, risk scores have been developed to enable clinicians to quantify these risk factors from their patients' medical histories in order to provide an estimate of CHD risk (Assmann & Schulte, 1988; Wilson et al., 1998).

The Framingham Risk Score (FRS) was reported by physicians to be the most widely used CHD risk score (Sposito et al., 2009; Kannel et al., 1976) The FRS was developed from the Framingham Heart Study (Kannel et al., 1976), and a 1998 version by Wilson et al. (1998) categorized the aforementioned risk factors to determine 10-year CHD risk and provide a score sheet for clinical implementation. The FRS' predictive power has persisted through validation in various populations (Kagan et al., 1975; Stampfer et al., 1991) as well as modifications such as the inclusion of apolipoproteins (Ingelsson et al., 2007), C-reactive protein (Pischon et al., 2007), and involuntary job loss (Gallo et al., 2006).

Few studies have examined the association between FRS and cardiorespiratory fitness (CRF) (Gander et al., 2015). The protective effect of CRF on CHD (Chong et al., 1999; Ekelund et al., 1988), and other adverse events has been well documented (Blair et al., 1989a; Sui et al., 2007; Sui et al., 2008; Sieverdes et al., 2010; Gander et al., 2011). Our recent study examining the association between CRF and 10-year CHD risk showed that men with high CRF had a 26% (HR = 0.75; 95% CI 0.56–

Abbreviations: CRF, cardiorespiratory fitness; e-CRF, estimated cardiorespiratory fitness; CHD, coronary heart disease.

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0.98) lower risk of CHD compared to men with low CRF, while controlling for an individual's FRS-predicted risk (Gander et al., 2015). A clinical limitation to CRF, however, is the methodologic rigor and associated high costs required to determine an individual's CRF, traditionally determined via a maximal exercise test. For these reasons, researchers have developed methods for estimating a patient's CRF (Nes et al., 2014; Jackson et al., 2012; Coleman et al., 2012). Recently, a 7-item, non-exercise, scale estimating CRF (e-CRF) (Jackson et al., 2012) was developed that incorporates sex, age, body mass index (BMI), waist circumference (WC), resting heart rate (RHR), smoking status, and physical activity (PA). No study has investigated the association between e-CRF and CHD independently or in addition to a CHD risk score, such as the FRS. This study was designed to expand on previous literature by determining the relationship between e-CRF and CHD. A second aim was to evaluate the potential for the e-CRF to add clinical value to the FRS by testing for improvement in predicting 10-year CHD risk.

2. Methods

2.1. Study population

This study focused on men from the Aerobics Center Longitudinal Study (ACLS) prospective cohort. The ACLS participants were recruited from patients attending the Cooper Clinic in Dallas, TX for a preventive medical examination and health behavior counseling. The participants completed a baseline examination at the Cooper Clinic from January 1, 1979 through December 31, 2002. Women were excluded from analyses due to a low number of CHD events ($n = 45$). The five inclusion criteria for men were 1) age at baseline was between 30 and 74 years, 2) BMI ≥ 18.5 kg/m^2, 3) free of a previous CHD, cancer, or stroke diagnosis at baseline, 4) reached an age-predicted maximal exercise heart rate ≥ 85% at each visit, and 5) had complete data with a minimum of 1 year of follow-up. The Cooper Clinic Institutional Review Board reviewed and approved the ACLS protocol annually. Fig. 1 displays the inclusion and exclusion criteria for this study.

2.2. Clinical examination

Standardized protocols were followed by trained technicians at every clinical exam. Personal and family medical histories were taken during the baseline examination. Other clinical baseline measures included a 12-hour fasting cholesterol and glucose measurement, blood pressure assessment, electrocardiogram, anthropometric measurements, and a maximal exercise test (Blair et al., 1989b; Blair et al., 1995; Blair et al., 1996). A standardized questionnaire was used to capture an individual's current smoking status and medical history.

2.3. Measures

2.3.1. Definition of outcome

CHD was defined either by self-reported myocardial infarction, bypass surgery, coronary balloon, angioplasty, or stent placement, or by CHD mortality. Self-reported history of CHD was collected through a mail-back survey administered in 1982, 1986, 1990, 1995, 1999, and 2004 and this method of event identification has been described before (Sui et al., 2007). The aggregate survey response rate across all survey periods in the ACLS is approximately 65%. Nonresponse bias is a concern in epidemiologic surveillance, and this issue has been investigated previously (Macera et al., 1990). CHD-specific mortality was determined through linking the ACLS cohort with the National Center for Health Statistic's National Death Index. The primary cause of death was determined by International Classification of Disease Ninth (ICD-9) and Tenth (ICD-10) revisions. CHD mortality was classified with ICD-9 codes 410.0–414.0 and ICD-10 codes I20-I25. In accordance with FRS's follow-up definition, the cut-off for maximum follow-up time for CHD event was 12 years.

2.3.2. Primary exposure

Estimated CRF (e-CRF) was expressed in metabolic equivalent of task (MET) units, which were estimated using a 7-item algorithm (Artero et al., 2014). The sex-specific scale is composed of a participant's age, BMI, WC, RHR, two-level PA, and smoking status (smoke). Details on PA were captured through a medical history questionnaire in which participants reported their regular PA for the past 3 months (Kampert et al., 1996; Cheng et al., 2000), and dichotomized in to two levels: none or low, vs. moderate or high physical activity. The accuracy of the developed algorithm was determine by computing the random intercept's square root of the sum and the residual variances (Jackson et al., 2012; O'Connor et al., 2010). These

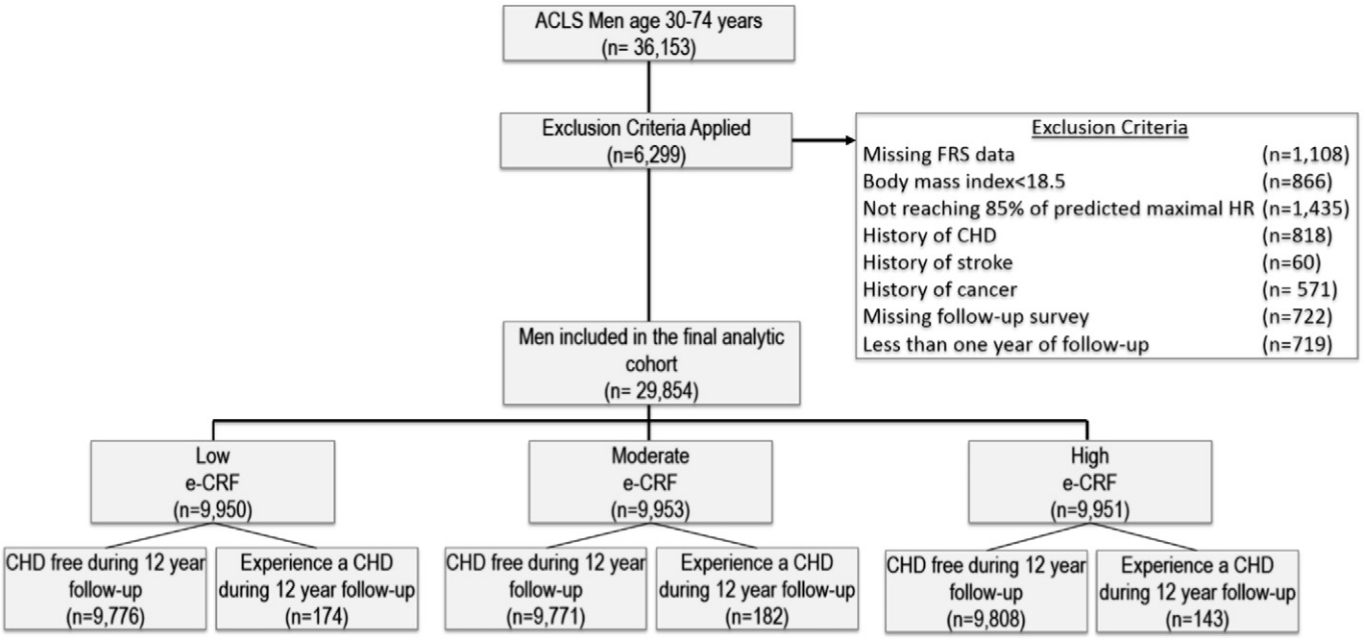

Fig. 1. Aerobics Center Longitudinal Study participants flow diagram. FRS, Framingham Risk score; CHD, coronary heart disease; HR, heart rate.