Atherosclerosis 243 (2015) 131–137

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Cardiorespiratory fitness and risk of type 2 diabetes mellitus: A 23-year cohort study and a meta-analysis of prospective studies

Francesco Zaccardi [a, *], Gary O'Donovan [a, b], David R. Webb [a], Thomas Yates [a, b], Sudhir Kurl [c], Kamlesh Khunti [a], Melanie J. Davies [a], Jari A. Laukkanen [c, d, e]

[a] Diabetes Research Centre, University of Leicester, Leicester, UK
[b] NIHR Leicester-Loughborough Diet, Lifestyle, and Physical Activity Biomedical Research Unit, UK
[c] Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland
[d] Central Finland Hospital, Jyväskylä, Finland
[e] Department of Medicine, University of Helsinki, Helsinki, Finland

ARTICLE INFO

Article history:
Received 1 July 2015
Received in revised form
31 August 2015
Accepted 9 September 2015
Available online 11 September 2015

Keywords:
Cardiorespiratory fitness
Diabetes mellitus
Type 2
Physical activity
Cohort study
Observational study
Meta-analysis
Systematic review

ABSTRACT

Aims: To investigate the association between cardiorespiratory fitness (CRF) and type 2 diabetes mellitus (T2DM) in a cohort of middle-age Finnish men and to summarise the current evidence in a meta-analysis of prospective studies.

Methods: CRF was measured at baseline in a random population-based sample of 2520 subjects by assessing oxygen uptake during maximal exercise. Cox regression analysis was used to estimate the association between CRF, expressed as metabolic equivalents (METs), and the risk of T2DM adjusted for potential confounders; this estimate was then pooled with the results of other prospective studies in a meta-analysis.

Results: Mean (SD) baseline age and CRF were 53 (5) years and 8.7 (2.1) METs, respectively. During 23 years of follow-up, 153 (6.1%) participants developed T2DM. The hazard ratio per 1-MET higher CRF, adjusted for age, body mass index, systolic blood pressure, serum HDL-cholesterol, and family history of T2DM, was 0.93 (95% confidence interval (CI): 0.84, 1.02; $p = 0.109$); further adjustment for smoking, education, and socioeconomic status did not materially change the estimate. In a random-effects meta-analysis of eight studies (92,992 participants and 8564 T2DM cases) combining maximally adjusted estimates, the pooled risk ratio of T2DM per 1-MET higher CRF level was 0.95 (95% CI: 0.93, 0.98; $p = 0.003$; $I^2 = 81\%$), corresponding to 23 fewer cases per 100,000 person-years based on the assumption of a causal link between CRF and T2DM.

Conclusions: These data suggest that there is an inverse relationship between CRF and T2DM that is largely independent of other risk factors.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder approximately doubling the risk of a wide range of vascular diseases [1–3]. Amongst the risk factors associated with T2DM, overweight/obesity, physical inactivity, and low cardiorespiratory fitness (CRF) have a major role [4,5].

CRF reflects the ability of the lungs and cardiovascular system to transport oxygen and the ability of the tissues and organs to extract and use oxygen during sustained exercise [6]. Aerobic exercise training improves CRF in most adults [7], although the extent of adaptation may be partially influenced by genetics [8]. Published studies suggest an inverse association between CRF and incident T2DM [9–27]. These studies have mainly included American and Asian people and have assessed the relationship between CRF and risk of T2DM adjusting for several, well-known cardiometabolic risk factors. Moreover, some of these studies have reported associations in the same population for different follow-up times.

Abbreviations: CI, confidence interval; CRF, cardiorespiratory fitness; CRP, serum C-reactive protein; HR, hazard ratio; KIHD, Kuopio Ischaemic Heart Disease; METs, metabolic equivalents; NOS, Newcastle-Ottawa Scale; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; VO2 max, maximal oxygen uptake.

* Corresponding author. Diabetes Research Centre, Leicester General Hospital, Leicester, UK.
E-mail address: frazac@fastwebnet.it (F. Zaccardi).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.09.016

However, they use different definitions of CRF and the associations between CRF and T2DM are estimated in inconsistent ways, thus complicating attempts to quantify the magnitude of any relationship.

In a previous meta-analysis Kodama and colleagues estimated the extent to which CRF was inversely associated with the risk of cardiovascular disease and all-cause mortality [28]. Although a similar relationship between CRF and risk of T2DM is expected combining available evidence, the degree of such relationship is not well defined, thus limiting the possibility to comparatively assess the relevance of CRF on the risk of cardiovascular disease and T2DM. The aims of this study were twofold. First, we examined the relationship between CRF and incident T2DM in a population-based sample of men from Eastern Finland. Second, we conducted a systematic review and meta-analysis to estimate the magnitude of the association between CRF and T2DM and quantify the potential impact of CRF improvement on T2DM prevention.

2. Methods

2.1. The Kuopio Ischaemic Heart Disease study

The Kuopio Ischaemic Heart Disease (KIHD) risk factor study was designed to investigate risk factors for atherosclerotic cardiovascular outcomes in a population-based sample of men from Eastern Finland. The subjects were a randomly selected sample of 3433 men 42–60 years of age resident in the town of Kuopio or its surrounding rural communities. The study is described in detail elsewhere [29]. Briefly, baseline examinations were conducted between March 1984 and December 1989. Of those invited, 2682 (78.1%) participated. In the present study, 162 subjects with diagnosed diabetes at baseline, defined as either having regular treatment with an oral hypoglycaemic agent, insulin therapy, or having treatment only with diet while also having a fasting plasma glucose level $\geq$7.0 mmol/l, were excluded; therefore, 2520 participants remained for the analyses. Incident cases of T2DM were defined by a self-reported physician-set diagnosis, or by fasting plasma glucose $\geq$7.0 mmol/l or 2-h oral glucose tolerance test plasma glucose $\geq$11.1 mmol/l at re-examination rounds (4, 11, and 20 years) after baseline, or by record linkage to the national hospital discharge registry and to the Social Insurance Institution of Finland register for reimbursement of medicine expenses. Prior to attendance at the baseline appointment, participants were instructed to abstain from drinking alcohol for a minimum of 3 days and from smoking for at least 12 h. Fasting blood samples were taken following a 30-min rest period in the supine position and collected using vacuum tubes (Terumo Venoject; Terumo, Tokyo, Japan). CRF was assessed by using a respiratory gas exchange analyser during a maximal symptom-limited exercise tolerance test with an electrically braked cycle ergometer [30]. The standardized testing protocol comprised a 3 min warm-up at 50 W followed by a step-by-step increase in the workload by 20 W/min with the direct analyses of respiratory gases (Medical Graphics, St. Paul, MN, USA). A detailed description of the measurement of the testing protocol has been given elsewhere [30]. The VO2 max was defined as the highest value for or the plateau of oxygen uptake and expressed in metabolic equivalents (METs) of oxygen consumption. One MET corresponds to an oxygen uptake of 3.5 mL/kg/min and it is a standard scale for expressing exercise capacity according to Metabolic Calculation Handbook by the American College of Sports Medicine [31]. Maximal exercise workload was defined as the highest workload achieved during the exercise test. Resting blood pressure was measured with a random-zero sphygmomanometer (Hawksley, Lancing England) by two trained nurses. A total of six measurements (3 supine, 1 standing, and 2 sitting) were taken following a 5 min supine rest and blood pressure was taken as the mean of all six measurements. Baseline medical history, smoking habits, family history of T2DM (defined as positive if a first-degree relative of the subject had T2DM history), years of education (from the age of seven year-old), and socioeconomic status were assessed by self-administered questionnaires [30]. The diagnosis of chronic diseases was checked during a medical examination by the internist. Body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in meters. The cholesterol contents of lipoprotein fractions and serum triacylglycerols were measured enzymatically (Boehringer Mannheim, Mannheim Germany). High-density lipoprotein (HDL) was separated from fresh samples by ultracentrifugation and precipitation. Serum C-reactive protein (CRP) was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA).

KIHD was approved by the research ethics committee of the University of Eastern Finland, Kuopio, Finland. Each participant gave written informed consent.

2.2. Literature-based meta-analysis: data sources and searches and study selection

Prospective studies reporting associations between CRF and incident risk of T2DM were sought using the databases PubMed, Web of Science, and Scopus by two independent investigators. The search strategy combined keywords related to the exposure ("cardiorespiratory" or "fitness" or "exercise tolerance" or "exercise test" or "physical fitness" or "oxygen consumption"), outcome ("diabetes" or "NIDDM") and study design ("cohort" or "prospective" or "longitudinal" or "hazard" or "risk" or "odds") and included articles published before August 30th, 2015 without language restrictions (Supplementary Material). Reference lists of retrieved articles were also manually scanned for all relevant additional studies and reviews. Prospective studies were included if CRF was either reported or could be estimated from data as VO_2 max or METs.

2.3. Data extraction and quality assessment

Standardized, pre-defined forms for data extraction and quality assessment were used. Data were abstracted on author, year of journal publication, study location and follow-up, population age, source and gender distribution, total participants and number of cases, exposure definition and assessment, endpoint definition and ascertainment, risk comparison and measurement, and adjustment level. Study quality was assessed by two authors using the nine-star Newcastle-Ottawa Scale (NOS) [32] and discrepancies were resolved by consensus.

2.4. Data synthesis and analysis

All analyses were performed with Stata 13 (Stata Corp, College Station, TX, USA) and two-sided *P*-value <0.05 was considered statistically significant. Results are reported following the recommendations by the STROBE and MOOSE guidelines [33].

In the analysis of the cohort study, natural logarithm transformed values of non-normal distributed variables were used and descriptive data are presented as means and standard deviation (SD) for continuous variables and percentages for categorical ones; their differences were estimated with ANOVA and χ^2 test, respectively. Correlation coefficients were calculated to assess the correlation between CRF levels and other continuous variables, whereas mean differences between groups were calculated for categorical factors. Analyses of the associations between CRF and incident