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

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A B S T R A C T

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; I² = 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.

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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; KIHDS, Kuopio Ischaemic Heart Disease Study; METs, metabolic equivalents; NOS, Newcastle-Ottawa Scale; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; VO2 max, maximal oxygen uptake.

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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 ≥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 ≥7.0 mmol/l or 2-h oral glucose tolerance test plasma glucose ≥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 (Hawkesley, 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 VO2 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 χ2 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
T2DM involved Cox-regression modelling with progressive adjustment for potential confounders selected on the basis of their previously established role as predictive factors. In model 1, we estimated the age-adjusted association. Model 2 included age, BMI, SBP, serum HDL-cholesterol, and family history T2DM; model 3 comprised variables in model 2 plus smoking, education, and socioeconomic status. Hazard ratios (HRs) were calculated per 1-MET change of CRF. The proportional hazards assumption was verified for all variables by inspection of the plots of the Schoenfeld residual for covariates.

In the prospective studies included in the meta-analysis, relative risk (RR) with 95% confidence interval was used as a measure of exposure/outcome association, assuming that HRs, risk ratios, and odds ratio approximate the same measurement of RR. To allow a consistent comparison among studies, reported RRs were transformed into a common scale, i.e. RR per 1-MET increase. For studies reporting RR per 1 standard deviation change of CRF, log ratio estimates were transformed under the assumption of normality of the distribution of CRF and a log-linear association with disease risk by using methods previously described [34]. When studies reported number of cases and total participants (or person-years) across categories of VO2 max, a generalised least-squares trend estimation analysis was used to compute the RR per 1-MET from the correlated logs of the RRs [35]. If studies published more than one adjusted RR, the most adjusted estimate was considered. A within-study summary estimate was computed by fixed effect analysis if RRs were separately reported in males and females. Reported CIs were used to obtain standard errors and RRs were pooled using a random-effects model [36]. Statistical heterogeneity across studies was quantified using the I² statistics; publication bias was estimated with the Egger's test [37]. The number of fewer cases retrieved from US National Surveillance data [39].

Reported CIs were used to obtain standard errors and RRs were pooled using a random-effects model [36]. Statistical heterogeneity across studies was quantified using the I² statistics; publication bias was estimated with the Egger's test [37]. The number of fewer cases retrieved from US National Surveillance data [39].

### 3. Results

#### 3.1. Cardiorespiratory fitness and incident type 2 diabetes mellitus

Baseline characteristics of the study population and correlation coefficients are reported in Table 1 and Supplementary Table S1, respectively. Baseline mean age and CRF were 53 years (SD, 5) and 8.7 METs (SD, 2.1), respectively; CRF levels were moderately correlated with other risk factors.

During a median follow-up to incident T2DM or the end of follow-up of 23 years (interquartile range: 18–25 years), a total of 153 (6.1%) new cases of T2DM were recorded. In an analysis adjusted for age, BMI, SBP, serum HDL-cholesterol, and family history T2DM, the HR of T2DM per 1-MET higher baseline CRF resulted 0.93 (95% confidence interval (CI): 0.84, 1.02; p = 0.109; Table 2). Further adjustment for smoking, education, and socioeconomic status did not materially change the estimate (Table 2).

#### 3.2. Meta-analysis

After screening of title/abstract and exclusion of duplicates, 141 articles remained for further evaluation (Supplementary Fig. S1). Following detailed assessments, 19 articles were selected for qualitative evaluation and seven included in the quantitative analysis; studies excluded and reasons of exclusion are reported in Supplementary Table S2. Together with KIH, eight prospective studies were available for the meta-analysis: their characteristics and the NOS scores are provided in Supplementary Table S3 and S4, respectively. Overall, information from the seven studies was available on 92,992 males and females participants and 8564 incident T2DM events. In all but two study [10,12], the mean (or median) duration of follow-up was more than 15 years. CRF was expressed as VO2 max in six studies [9,11–15] and as METs in one study [10]; Carnethon and colleagues [10] instead reported treadmill time, and VO2 max was calculated using previously published formulae [40,41]. Diagnosis of diabetes was based on biochemical measurements or self-reported and all studies adjusted for age and sex (when appropriate) (Supplementary Table S3). Finally, studies had a NOS score ≥7 (Supplementary Table S4).

The random-effects meta-analysis combining maximally adjusted RR of T2DM was 0.95 (95% CI: 0.93, 0.98; p = 0.003) per 1-MET higher baseline CRF, with heterogeneity across studies (I² = 88% (95% CI: 79, 93); p < 0.001 (Fig. 1). There was no evidence of publication bias (p = 0.566). In a sensitivity analysis, the exclusion of one study with outlying RR [11] did not change the overall estimate. On the assumption of a causal relationship between CRF and T2DM, with a T2DM incidence of 5 per 1000 person-year 1-MET increase would prevent 23 cases of diabetes per 100,000 people per year (Fig. 2).

### Table 1

Baseline characteristics of the study population (N = 2520) according to incident (Yes) and non-incident (No) cases of type 2 diabetes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 2367)</th>
<th>Type 2 diabetes mellitus (N = 153)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.0</td>
<td>53.4</td>
<td>0.339</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.7</td>
<td>29.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134</td>
<td>135</td>
<td>0.227</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.30</td>
<td>1.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerols (mmol/l)</td>
<td>1.11</td>
<td>1.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>1.28</td>
<td>1.70</td>
<td>0.017</td>
</tr>
<tr>
<td>Education (years)</td>
<td>8.63</td>
<td>8.25</td>
<td>0.153</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>12.3</td>
<td>13.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Smoking (yes)</td>
<td>33%</td>
<td>33%</td>
<td>0.846</td>
</tr>
<tr>
<td>Family history of diabetes (yes)</td>
<td>27%</td>
<td>29%</td>
<td>0.546</td>
</tr>
<tr>
<td>METs (ml kg⁻¹ min⁻¹)</td>
<td>8.72</td>
<td>8.14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed means/standard deviations or percentages.

a Difference Yes vs No.

b Data reported as median and interquartile range.

c Socio-economic status is a summary index combining measures of income, occupation, occupational prestige, material standard of living, and housing conditions (all assessed with self-reported questionnaires).
4. Discussion

In the present study, we did not find a statistically significant association between CRF and incident T2DM in a randomly selected population cohort of middle-age Finnish men. Notwithstanding, in a pooled analysis of published reports from eight prospective cohort studies, each 1-MET increment in CRF was associated with a 5% (95% CI: 2, 7) relative reduction in T2DM risk. One MET equates to a relatively small difference in absolute fitness levels. For example, it has consistently been shown to be less than a 0.5 mile-per-hour difference in walking or running speed [42]. In addition, considering the average level of fitness in the meta-analysis was 10.3 METs, 1-MET is equivalent to a 10% difference in fitness. A change in fitness of greater than this magnitude is achieved by most individuals after traditional exercise training interventions consistent with minimum recommendations for health, including in diseased populations [43–45].

In a recently published literature-based meta-analysis, Aune and colleagues investigated the association between physical activity and T2DM risk [46]. In their study, the Authors also reported a 35% reduction of T2DM risk comparing “high” vs “low” CRF (six studies) and a 26% reduction per 5.7-MET CRF increase (four studies). To quantify the precise magnitude of the association between CRF and T2DM, we standardised the reported risk across studies to a consistent comparison, i.e. per 1-MET increase; moreover, we reported a longer follow-up analysis of the KIHD and included further studies in the meta-analysis. The standardised estimation of the CRF/T2DM relationship also allows a comparison with the association between CRF and cardiovascular disease. Indeed, Kodama and colleagues [28], reviewing the literature to December 2008, included 33 studies with 4485 cases in a meta-analysis and reported that each 1-MET increase in CRF was associated with a 15% reduction in cardiovascular disease events (95% CI: 12, 18). We reviewed the literature to August 2015, included eight studies with 8564 cases in the meta-analysis, and found that each 1-MET increase in CRF was associated with a 5% reduction in diabetes events. It is not surprising that the association between CRF and cardiovascular disease is stronger than the association between CRF and diabetes because CRF is a direct reflection of heart and lung function [6]. The association between CRF and diabetes may be a reflection of indirect mechanisms, such as physical activity, inflammation, insulin resistance, and obesity [47-49]. It is reasonable to assume that CRF is a reflection of habitual activity in large prospective studies because most fit people are active [50]. Although CRF has a genetic component [8] and there are high and low responders to exercise training [43], data from 633 participants in the HERITAGE Family Study suggest exercise training increases CRF by around 20% regardless of age, gender, race and initial fitness level (participants cycled three times per week for 20 weeks, progressing from 30 min per session at 55% of VO2 max to 50 min per

<table>
<thead>
<tr>
<th>Model</th>
<th>Adjustment</th>
<th>Hazard ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>0.81 (0.74, 0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>Age, BMI, systolic blood pressure, serum HDL-cholesterol, and family history of T2DM</td>
<td>0.93 (0.84, 1.02)</td>
<td>0.109</td>
</tr>
<tr>
<td>3</td>
<td>Model 2 + Smoking, education, and socioeconomic status</td>
<td>0.95 (0.86, 1.04)</td>
<td>0.270</td>
</tr>
</tbody>
</table>

CI: Confidence interval; BMI: Body mass index; HDL: High-density lipoprotein; T2DM: type 2 diabetes mellitus.
The results of this meta-analysis suggest a wide range in the strength of association between CRF and T2DM, from 65% reduction to 5% increase of T2DM risk per 1-MET increase (Fig. 1). Such a heterogeneity could be related to a true difference, owing to the inherent dissimilar characteristics of the study populations in terms of age, sex, race, or genetic background; or due to the ascertainment of outcomes; or associated to statistical planning and analysis; or a combination of all these. Of note, a critical point in analyses assessing the relationship between CRF and incident diabetes is the adjustment for covariates. As CRF reflects a combination of physiologically interconnected factors (i.e., physical activity, body composition, intermediate risk factors, lung and heart function), adjustment is of crucial importance in trying to explore a potential independent role of CRF on risk of T2DM. In particular, in recent years there has been a growing interest on the combined contribution of CRF and fatness to health. Although controversial, extensive evidence would indicate that fitness could counterbalance the negative effects of several cardiovascular disease risk factors (i.e., overweight/obesity, T2DM, and hypertension) on the risk of cardiovascular events [51]. However, it has not been clearly demonstrated whether CRF modifies the risk of T2DM in obese subjects. Thus, we analyse the majority of studies adjusted for baseline BMI, although in three studies [10–12] this measure was not taken into account (Supplementary Table 3). Further studies could help clarify in more detail the inter-relationship between fitness, fatness, and risk of T2DM, and elucidate whether CRF modifies the association between obesity (ideally measured as fat distribution) and risk of T2DM.

A clearer understanding of the interplay between CRF, T2DM, and obesity (as well as other cardiometabolic risk factor) is also essential to better quantify the impact CRF changes as a preventive strategy to reduce the incidence of T2DM. Our estimations (Fig. 2) are based on associations independent of several T2DM risk factors. As the improvement in CRF achieved by exercise results also in an overall better cardiometabolic profile, the “real-world” impact of 1-MET increase in CRF is likely to be greater. Moderate-intensity activity is the emphasis of prevailing physical activity guidelines [52,53], and it would seem that the objective is to get the least active and the least fit to achieve a moderate level of activity and a moderate level of fitness. The present study suggests that greater emphasis should be placed on the importance of vigorous-intensity activity and cardiorespiratory fitness. Of note, this could also explain the discrepancy between prospective cohort studies and interventions: while cardiorespiratory fitness reflects time spent in vigorous-intensity physical activity [54], moderate-intensity physical activity is recommended or emphasized in interventions [55,56].

A more precise estimate of the association between CRF and T2DM might have been also possible if studies had reported multiple measurements during the follow-up. Unfortunately, only two previous studies [9,22] have this specific design, with two measurements apart of CRF and both showing an inverse association between changes in CRF and incident cases of T2DM. These studies would support a causal association between CRF and T2DM, with an estimated random-effects overall of ~15% risk reduction per 1-MET increase over time. However, given the small number of studies, it is not possible to derive definitive conclusions. Moreover, it is challenging to adjust these estimates for factor(s) affecting both the risk of diabetes and CRF within the interval of two measurements, as they could act as confounding variables.

We should acknowledge some limitations of this study. First, to some extent subjects enrolled, exposure and outcome definition and assessment, and follow-up durations differed among studies included in the meta-analysis. This could explain the statistical heterogeneity over the relationship between CRF and T2DM risk. To help interpret the results, however, we have collected and reported comprehensively the characteristics of the included studies. Second, the small number of studies included limited our ability to conduct more detailed investigations (i.e., extensive subgroup analyses and identification of sources of heterogeneity). Third, the present evidence is limited to observational prospective studies in adult populations. More detailed data would help clarify whether age, gender, and/or ethnicity could modify the CRF/T2DM relationship. Fourth, because KIHD and the majority of other prospective studies reported CRF only at baseline, we could not correct for a possible regression dilution bias [57] or estimate the effects of CRF changes on T2DM risk. Indeed, an inverse association has been shown between CRF changes over time and risk of T2DM [9,22] and all-cause mortality [58,59]. On the other hand, KIHD has several strengths. This cohort included a large and homogenous community-based sample of people from the general population (i.e., subjects not included on the basis of specific characteristics) with a recruitment process using national registers and a response rate ~80%. Rigorous measurement of baseline risk factors and assessment of T2DM, with no losses to follow-up over 23 years, allowed the exclusion of all individuals with baseline T2DM (thus reducing the risk of reverse causation bias) and the estimation of independent associations adjusted for a large panel of well-established risk markers for T2DM, including obesity measures. Furthermore, we selected studies from a wide search to estimate in a consistent way the impact of CRF improvement on the risk of T2DM also from a public health perspective.

In conclusion, our findings suggest an inverse association between CRF and risk of T2DM independent of several common T2DM risk factors. Additional research, ideally summarised in an individual participant data meta-analysis, will further help clarify the role of CRF as a confounder or effect-modifier in the association between BMI/fatness and risk of T2DM and quantify the potential ability of CRF, on top of well-established risk factors, in the prediction of T2DM.

Author contribution

FZ study idea and design, data analysis and collection, manuscript draft.

GO, DRW, TY, KK, MJD study critical revision, manuscript draft.

SK data collection, manuscript draft.

JAL study design, critical revision, manuscript draft.

All authors provided final approval of the version to publish. FZ is the study guarantor.

Ethics

The study was approved by the Research Ethics Committee of the University of Eastern Finland.

Conflict of interest

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme. KK has received funds for research, honoraria for speaking at meetings and has served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk.

MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Novo Nordisk, Dohme, Boehringer Ingelheim, AstraZeneca, Lilly and Merck Sharp & Dohme.
speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly.

All other Authors have no conflicts of interests to disclose.

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**Appendix A. Supplementary data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.09.016.

**References**


1770–1776.


