SUPPLEMENTARY MATERIAL TO THE ARTICLE

DIABETES MELLITUS AND RISK OF SUDDEN CARDIAC DEATH:
A SYSTEMATIC REVIEW AND META-ANALYSIS

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SEARCH STRATEGY

METHODS

2 SUPPLEMENTARY TABLES

3 SUPPLEMENTARY FIGURES

REFERENCES
Search Strategy

We searched PubMed, EMBASE and Web of Science for studies published before June 1st, 2014, without language restriction and reporting associations between diabetes mellitus and incidence of sudden cardiac death/arrest.

**Exposure**

#1 Diabetes  
#2 Glucose  
#3 Glycaemia  
#4 Glycemia  
#5 Hyperglycaemia  
#6 Hyperglycemia  
#7 Diabetes pills  
#8 Insulin  
#9 OR / #1-#9

**Study design**

#17 Cohort  
#18 Prospective  
#19 Case-control  
#20 Cross-sectional  
#21 Observational  
#22 Epidemiologic  
#23 Longitudinal  
#24 Retrospective  
#25 Follow-up study  
#26 Odds  
#27 Risk  
#28 Hazard  
#29 OR / #17-#29

**Outcomes**

#10 Sudden cardiac death  
#11 SCD  
#12 Arrhythmia  
#13 Arrhythmic death  
#14 Sudden cardiac arrest  
#15 Cardiac arrest  
#16 OR / #10-#16

#10 AND #19 AND #36; Filters: Humans
METHODS

This study was conducted following the MOOSE guidelines for meta-analysis of observational studies [29]. Prospective and retrospective studies that have information on diabetes status, recorded SCD events, and published before June 1st, 2014 were identified through electronic searches and supplemented by scanning reference lists of relevant studies. Two authors, with any disagreement solved by a third, used standardized pre-defined forms for data extraction and quality assessment (Newcastle-Ottawa scale); we corresponded with study authors to obtain additional information if not reported in sufficient detail.

Relative risk (RR) and 95% confidence interval was used as a measure of association, assuming that hazard ratios, risk ratios and odds ratio approximate the same measurement of RR for rare events; if RRs were separately calculated by gender and/or prevalent VD, each estimate was used for the subgroup analysis and a fixed-effect summary estimate was computed for the overall estimate. Where studies reported RRs with differing degrees of adjustment, the most adjusted estimate was used. RRs were pooled using a random-effects model and statistical heterogeneity across studies was quantified using the $I^2$ statistics. Random-effects meta-regression using pre-specified study-level characteristics (level of adjustment, duration of follow-up, gender, number of cases recorded, inclusion of individuals with pre-existing VD at baseline) was used for subgroup analysis. Publication bias was assessed through graphical and formal tests. Stata 12 was used for analyses and two-sided p<0.05 was considered statistically significant.
**Studies included in qualitative synthesis**
N = 18

- Not relevant exposures
  - 77
- Not relevant populations
  - 133
- Reviews/Editorials/Comments/Letters/Others
  - 50

**Studies included in quantitative synthesis (meta-analysis)**
N = 14

- Not possible to obtain relevant estimates from the published report or correspondence [25-27]
- One study [28] had a shorter follow-up compared to a later publication [17] on the same population

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**Identification**

10,343 Records identified through database searching on June 1\(^{st}\), 2014
- Pubmed 3,404
- Embase 3,517
- ISI Web of Science 3,422

**Screening**

Full text articles screened
N = 278

260 Full-text articles excluded
- Not relevant exposures
  - 77
- Not relevant populations
  - 133
- Reviews/Editorials/Comments/Letters/Others
  - 50

10,065 Records removed after duplicates exclusion and title/abstract selection

**Eligibility**

Studies included in qualitative synthesis
N = 18

4 Excluded
- Not possible to obtain relevant estimates from the published report or correspondence [25-27]
- One study [28] had a shorter follow-up compared to a later publication [17] on the same population
**eFigure 2**: Forest plot of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Cases</th>
<th>Adjustment Level*</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective Cohort Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albert [11]</td>
<td>244</td>
<td>++</td>
<td>2.93 (2.13, 4.04)</td>
</tr>
<tr>
<td>Balkau [12]</td>
<td>92</td>
<td>++</td>
<td>1.82 (1.04, 3.18)</td>
</tr>
<tr>
<td>Bertoina [13]</td>
<td>418</td>
<td>++</td>
<td>2.00 (1.55, 2.58)</td>
</tr>
<tr>
<td>Curb [15]</td>
<td>347</td>
<td>+++</td>
<td>2.24 (1.19, 4.22)</td>
</tr>
<tr>
<td>Junttila [18]</td>
<td>83</td>
<td>+++</td>
<td>2.30 (1.40, 3.79)</td>
</tr>
<tr>
<td>Kataoka [19]</td>
<td>56</td>
<td>+++</td>
<td>1.86 (1.07, 3.25)</td>
</tr>
<tr>
<td>Kucharska-Newton [20]</td>
<td>209</td>
<td>++</td>
<td>2.11 (1.58, 2.82)</td>
</tr>
<tr>
<td>Laukkanen [21]</td>
<td>175</td>
<td>++</td>
<td>2.86 (1.87, 4.38)</td>
</tr>
<tr>
<td>Wannamethee [23]</td>
<td>117</td>
<td>+++</td>
<td>1.00 (0.22, 4.47)</td>
</tr>
<tr>
<td>Yeung [24]</td>
<td>143</td>
<td>-</td>
<td>1.90 (1.05, 3.44)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>1884</td>
<td></td>
<td>2.22 (1.95, 2.53)</td>
</tr>
<tr>
<td></td>
<td>$I^2=0%$ (95%CI: 0-62), p=0.610</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Case Control Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burke [14]</td>
<td>206</td>
<td>+++</td>
<td>3.18 (1.70, 5.95)</td>
</tr>
<tr>
<td>Escobedo [16]</td>
<td>1415</td>
<td>+</td>
<td>2.47 (1.83, 3.33)</td>
</tr>
<tr>
<td>Jouven [17]</td>
<td>2040</td>
<td>+</td>
<td>1.60 (1.36, 1.89)</td>
</tr>
<tr>
<td>Sexton [22]</td>
<td>102</td>
<td>++</td>
<td>4.22 (1.39, 12.81)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>3763</td>
<td></td>
<td>2.32 (1.57, 3.44)</td>
</tr>
<tr>
<td></td>
<td>$I^2=74%$ (95%CI: 27-91), p=0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>5647</td>
<td></td>
<td>2.18 (1.89, 2.52)</td>
</tr>
<tr>
<td></td>
<td>$I^2=42%$ (95%CI: 0-69), p=0.049</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a*) Adjustment Level:
- adjusted for not specified covariates
+ adjusted for age, sex (when appropriate), 1 or 2 cardiovascular risk factors
++ adjusted for age, sex (when appropriate), 3 cardiovascular risk factors (not left ventricular hypertrophy and/or ECG variables)
+++ adjusted for age, sex (when appropriate), 3 cardiovascular risk factors plus left ventricular hypertrophy and/or ECG variables.

Cardiovascular Risk Factors are reported in eTable 1; CI: Confidence Interval; RR: Relative Risk
eFIGURE 3: Funnel plot of the studies included in the meta-analysis

Funnel plot with pseudo 95% confidence limits

Egger's p=0.116
<table>
<thead>
<tr>
<th>First Author [Ref]</th>
<th>Population Sample</th>
<th>Exposure definition</th>
<th>Exposure assessment</th>
<th>Endpoint definition</th>
<th>Endpoint ascertainment</th>
<th>Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert [11]</td>
<td>30-55 yr-old female registered nurses of the Nurses’ Health Study Cohort (NHS)</td>
<td>Self Reported</td>
<td>Self Reported</td>
<td>Death or cardiac arrest that precipitated the terminal event occurred within 1h of symptom onset</td>
<td>Physicians’ review of medical records and death certificates and next of kin interview</td>
<td>Age, menopausal status, postmenopausal hormone use, prior report of coronary heart disease, BMI, parental history of MI, smoking, dyslipidemia, hypertension</td>
</tr>
<tr>
<td>Balkau [12]</td>
<td>43-52 yr-old native Frenchmen employed by Civil Service (Paris Prospective Study 1)</td>
<td>OGGT cut-off not specified or self-reported</td>
<td>OGGT test or anti-diabetic treatment</td>
<td>Unexpected cardiac death within 1h of onset of symptoms</td>
<td>Physicians’ review of medical records and death certificates</td>
<td>Age, BMI, smoking, heart rate, systolic blood pressure, cholesterol, triglycerides, diabetes, family history of myocardial infarction and for sudden death</td>
</tr>
<tr>
<td>Bertoia [13]</td>
<td>50-79 yr-old post-menopausal women of the observational study within Women’s Health Initiative (WHI) clinical trials</td>
<td>Self-reported or anti-diabetic treatment</td>
<td>Self-reported or anti-diabetic treatment at baseline or during follow-up (non-adjudicated)</td>
<td>Death occurring within 1h of symptom onset or within 1h after the participant was last seen without symptoms; death occurring in the absence of a potentially lethal non-coronary disease process</td>
<td>Physicians’ review of death certificates, autopsy reports, circumstances of death, electrocardiogram and laboratory test results</td>
<td>Age, race, income, smoking, resting pulse, BMI, WHR, white blood cell count, CHD (no MI), MI, heart failure, self-reported atrial fibrillation, carotid artery disease, hypertension</td>
</tr>
<tr>
<td>Burke [14]</td>
<td>Cases and Controls: retrospective evaluation of sudden and non-sudden (natural and non-cardiovascular) deaths in 30-69 yr-old men and women occurred between 1994-99 in the State of Maryland</td>
<td>Subjects with BMI&gt;25, HbA1c&gt;8%, and non-insulin treatment</td>
<td>Medical history and HbA1c</td>
<td>Death (witnessed arrest) with symptoms commencing within 6 hours; death occurring within 24 hours after the victim was last seen alive in his normal state of health</td>
<td>Autopsies for all the cases</td>
<td>Age, sex, smoking, BMI, hypertension, total and HDL cholesterol, left ventricular hypertrophy</td>
</tr>
<tr>
<td>Curb [15]</td>
<td>45-68 yr-old US subjects of Japanese ancestry enrolled in the Honolulu Heart Program</td>
<td>Self-Reported and non-fasting 50g 1hOGTT &gt;225 mg/dL</td>
<td>Self-Reported and non-fasting 50g OGGT</td>
<td>Non-traumatic death occurring suddenly or unexpectedly &lt;1h after the onset of the terminal episode and resulting from CHD or unknown causes</td>
<td>Physicians’ review of medical records, death certificates, autopsy reports, circumstances of death, electrocardiogram and laboratory test results</td>
<td>Age, hypertension, BMI, serum cholesterol, serum triglycerides, smoking, alcohol, left ventricular hypertrophy</td>
</tr>
<tr>
<td>Escobedo [16]</td>
<td>Cases: Stratified, random sample of approximately 1% of all deaths occurred in 1986 among US residents ≥ 25yrs; Controls: multistage probability sample that represents US civilians (1985 National Health Interview Survey)</td>
<td>Self Reported</td>
<td>Self Reported</td>
<td>Sudden coronary heart disease death: death occurring among persons with a history of angina pectoris or heart attack; Unexpected sudden coronary deaths: deaths among persons without a history of angina pectoris or heart attack</td>
<td>Death certificates (ICD-9 code 410-414)</td>
<td>Age, race, sex, education, other (unspecified) CHD risk factors</td>
</tr>
<tr>
<td>Jouven [17]</td>
<td>Cases: Incident, out-of-hospital SCD in a large health maintenance organization; Controls: Stratified random sample; strata defined in cases by age (decade), gender, calendar year, and treatment with digoxin or nitroglycerin (proxy for heart disease)</td>
<td>≥ 7.7 mmol/L (139 mg/dL)</td>
<td>Ambulatory Medical Records</td>
<td>Sudden pulseless condition in the absence of evidence of a non-cardiac condition as the cause of cardiac arrest</td>
<td>Review of the ambulatory medical record identified by emergency medical services databases</td>
<td>Age, smoking, systolic blood pressure and anti-diabetic treatment, [gender stratification]</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Subjects</td>
<td>Eligibility Criteria</td>
<td>Methods</td>
<td>Outcomes</td>
<td>Variables Selected</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Junttila [18]</td>
<td>Subjects enrolled in two post-MI prospective studies</td>
<td>1998 WHO criteria</td>
<td>Blood tests before or at the time of entry in the studies</td>
<td>Witnessed death occurring within 1h from the onset of new symptoms, unless a cause other than cardiac was obvious; unwitnessed death (&lt;24 hours) in the absence of pre-existing, progressive circulatory failure or other cause of death; death during attempted resuscitation</td>
<td>Hospital records, autopsy reports, primary care physicians or event's witnesses</td>
<td>Age, gender, hypertension, prior MI, three-vessel disease, left ventricular hypertrophy, heart rate variability, mean heart rate, and use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blocking agents</td>
</tr>
<tr>
<td>Kataoka [19]</td>
<td>35-69 yr-old Japanese subjects screened with OGTT and 24h-ECG</td>
<td>FPG ≥126 mg/dl and/or 2hOGTT ≥200 mg/dl</td>
<td>FPG and OGTT test if FPG≥100 mg/dl</td>
<td>Unexpected cardiac event within 24 h of onset of acute symptoms</td>
<td>Death certificates (ICD-9 code 410-414 and 428)</td>
<td>Age, gender, BMI, ischemic ECG change, fasting plasma glucose, CVR–R, systolic blood pressure, total cholesterol, triglycerides, smoking</td>
</tr>
<tr>
<td>Kucharska-Newton [20]</td>
<td>45-64 yr-old subjects included in a probability sample prospective cohort (ARIC study)</td>
<td>Self reported or FPG ≥126 mg/dl or non-fasting glucose ≥200 mg/dl</td>
<td>Self reported or blood tests at baseline</td>
<td>Sudden, pulseless condition without a known non-cardiac cause</td>
<td>Physicians' review of medical records and death certificates, informant interviews, physician questionnaires, coroner reports, or hospital discharge summaries</td>
<td>Age, gender, race/ARIC centre, smoking, cigarette years of smoking, systolic blood pressure, antihypertensive medication use, gender-by-systolic blood pressure, HDL-cholesterol</td>
</tr>
<tr>
<td>Laukkanen [21]</td>
<td>42-60 yr-old subjects randomly selected men from Eastern Finland</td>
<td>Self reported or 2012 ADA criteria</td>
<td>Self reported or blood tests at baseline</td>
<td>Death occurred either within 1h after the onset of an abrupt change in symptoms or within 24 h after the onset of symptoms when clinical findings did not reveal a non-cardiac cause of sudden death</td>
<td>Interviews, hospital documents, death certificates, autopsy reports, medico-legal reports</td>
<td>Age, BMI, systolic blood pressure, serum LDL cholesterol, smoking, alcohol consumption, prevalent CHD, family history of CHD</td>
</tr>
<tr>
<td>Sexton [22]</td>
<td>Cases: 25-74 yr-old men with an event between 1/1/87 and 31/12/89; Controls: Selected from electoral rolls using an incidence-density sampling method and invited to participate by letter and follow-up telephone calls</td>
<td>Self reported</td>
<td>Self reported</td>
<td>Death occurring within 1h of the onset of symptoms of myocardial ischemia in a person without any prior overt manifestations of IHD</td>
<td>Death, necropsy and hospital records, family members interview</td>
<td>Age, BMI, smoking, hypertension, hypercholesterolemia, family history of CAD, exercise amount, alcohol use</td>
</tr>
<tr>
<td>Wannamethee [23]</td>
<td>40-59 yr-old men selected from the age-gender registers of GPs</td>
<td>Self reported</td>
<td>Self reported</td>
<td>Death occurring within 1h after the onset of symptoms</td>
<td>UK National Health Service registers</td>
<td>Age, BMI, pre-existing ischemic heart disease, arrhythmia, antihypertensive treatment, physical activity, smoking, heavy drinking, hematocrit, heart rate, systolic blood pressure, blood cholesterol, HDL cholesterol</td>
</tr>
<tr>
<td>Yeung [24]</td>
<td>Single-centre, prospective observational study in post-MI subjects without residual myocardial ischemia</td>
<td>Not specified</td>
<td>Based on medical records or prescription of diabetic medications</td>
<td>Death occurring within 1h of onset of cardiac symptoms in a person without any previous condition explaining the fatality</td>
<td>Medical records and discharge summaries</td>
<td>(Unspecified) Variables selected with a p value ≤0.1 in the univariate analysis</td>
</tr>
</tbody>
</table>
**eTABLE 2:** Newcastle-Ottawa Quality Scores for the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Author [Ref]</th>
<th>Newcastle-Ottawa Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective Cohort Studies</strong></td>
<td>Selection (1-4)</td>
</tr>
<tr>
<td>Balkau [12]</td>
<td>3</td>
</tr>
<tr>
<td>Bertoia [13]</td>
<td>3</td>
</tr>
<tr>
<td>Curb [15]</td>
<td>3</td>
</tr>
<tr>
<td>Junttila [18]</td>
<td>2</td>
</tr>
<tr>
<td>Kataoka [19]</td>
<td>3</td>
</tr>
<tr>
<td>Kucharska-Newton [20]</td>
<td>4</td>
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<tr>
<td>Laukkonen [21]</td>
<td>3</td>
</tr>
<tr>
<td>Wannamethee [23]</td>
<td>2</td>
</tr>
<tr>
<td>Yeung [24]</td>
<td>2</td>
</tr>
<tr>
<td><strong>Case-Control Studies</strong></td>
<td>Selection (1-4)</td>
</tr>
<tr>
<td>Burke [14]</td>
<td>2</td>
</tr>
<tr>
<td>Escobedo [16]</td>
<td>3</td>
</tr>
<tr>
<td>Jouven [17]</td>
<td>3</td>
</tr>
<tr>
<td>Sexton [22]</td>
<td>3</td>
</tr>
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</table>
References
