

Is Diabetes Mellitus a Coronary Heart Disease Equivalent? Results of a Meta-Analysis of Prospective Studies

José Miguel González-Clemente,^a Silvia Palma,^b Jaume Arroyo,^a Carme Vilardell,^a Assumpta Caixàs,^a Olga Giménez-Palop,^a and Miguel Delgado-Rodríguez^b

^aServicio de Diabetes, Endocrinología y Nutrición, Hospital de Sabadell, Sabadell, Barcelona, Spain

^bDepartamento de Medicina Preventiva y Salud Pública, Universidad de Jaén, Jaén, Spain

Introduction and objectives. Several guidelines on the treatment of cardiovascular risk factors base their recommendations on the assertion that diabetes mellitus (DM) is a coronary heart disease (CHD) or cardiovascular disease (CVD) risk equivalent. To date, no systematic review of studies substantiating this assertion has been carried out.

Methods. A systematic search of the PubMed database up to February 2006 was performed to identify prospective studies meeting the following criteria: a) follow-up was >5 years; b) groups of subjects with DM and without CHD (ie, DM+CHD-), without DM and with CHD (DM-CHD+), and without either DM or CHD (DM-CHD-) were all included; and c) data on CHD or CVD mortality was reported. The characteristics of the studies were assessed, and data were combined separately for men and women using a random effects model and taking the DM-CHD- group as a reference.

Results. In total, 13 studies met the inclusion criteria. Overall, CHD mortality was non-significantly lower in DM+CHD- men than in DM-CHD+ men, hazard ratio [HR] (95% confidence interval [CI]), 3.06 (2.45-3.83) versus 4.28 (3.24-5.66), respectively ($P=0.066$); as was CVD mortality, HR (95% CI), 2.55 (2.00-3.26) versus 3.61 (2.81-4.62), respectively ($P=0.051$). In women, there was no significant difference between the DM+CHD- and DM-CHD+ groups with regard to either CHD mortality, HR (95% CI), 4.68 (3.40-6.45) versus 3.51 (1.75-7.04), respectively ($P=0.42$), or CVD mortality, HR (95% CI), 4.70 (4.23-5.22) versus 3.39 (1.51-9.02), respectively ($P=0.59$).

Conclusions. The findings of this meta-analysis support the view that women in the DM+CHD- group have similar CHD and CVD mortality to those in the

DM-CHD+ group, whereas men in the DM+CHD- group demonstrated a non-significant trend towards lower CHD and CVD mortality than those in the DM-CHD+ group.

Key words: *Coronary heart disease. Cardiovascular disease. Diabetes mellitus. Meta-analysis. Coronary heart disease equivalent.*

¿La diabetes mellitus es un equivalente de riesgo coronario? Resultados de un metaanálisis de estudios prospectivos

Introducción y objetivos. Varias guías sobre el tratamiento de los factores de riesgo cardiovascular basan sus recomendaciones en el concepto de que la diabetes mellitus (DM) es un equivalente de riesgo coronario o de riesgo cardiovascular. Hasta el presente no se ha realizado ninguna revisión sistemática sobre los estudios en los que se sustenta dicho concepto.

Métodos. Se ha realizado una búsqueda sistemática en PubMed hasta febrero de 2006 para localizar los estudios prospectivos que cumplían los siguientes criterios: a) período de seguimiento > 5 años; b) incluir un grupo de pacientes con DM y sin enfermedad coronaria (DM+EC-), otro sin DM y con enfermedad coronaria (DM-EC+), y otro sin ninguno de los 2 factores de riesgo (DM-EC-), y c) proporcionar datos sobre mortalidad coronaria o cardiovascular. Se ha evaluado las características de los estudios y se las ha combinado separadamente, según el sexo, con un modelo de efectos aleatorios, y tomando el grupo DM-EC- como de referencia.

Resultados. Trece estudios han cumplido los criterios de inclusión. Los varones del grupo DM+EC- presentan una menor mortalidad coronaria y cardiovascular que los del grupo DM-EC+, pero las diferencias no son significativas (*hazard ratio* [intervalo de confianza del 95%]: mortalidad coronaria, 3,06 [2,45-3,83] frente a 4,28 [3,24-5,66], respectivamente, $p = 0,066$; mortalidad cardiovascular, 2,55 [2-3,26] frente a 3,61 [2,81-4,62], respectivamente, $p = 0,051$). Las mujeres no presentan diferencias significativas entre los dos grupos DM+EC- y DM-EC+ en relación con la mortalidad coronaria (4,68 [3,40-6,45] frente a 3,51 [1,75-7,04], respectivamente; $p = 0,42$) y la cardiovascular (4,70 [4,23-5,22] frente a 3,39 [1,51-9,02], respectivamente; $p = 0,59$).

Conclusiones. Este metaanálisis apoya la idea de que las mujeres del grupo DM+EC- tienen una mortalidad coronaria y cardiovascular similar a la de las mujeres en el

The authors have received grants from the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Fondo de Investigaciones Sanitarias: RGDM 03/212 and PI 050626.

Correspondence: Dr. J.M. González-Clemente. Servicio de Diabetes, Endocrinología y Nutrición. Hospital de Sabadell. Parc Taulí, s/n. 08208 Sabadell. Barcelona. España. E-mail: gonclem@yahoo.es

Received February 2, 2007.

Accepted for publication July 11, 2007.

grupo DM–EC+, mientras que los varones del grupo DM+EC– tienen una tendencia no estadísticamente significativa a presentar una menor mortalidad coronaria y cardiovascular que los varones en el grupo DM–EC+.

Palabras clave: *Enfermedad coronaria. Enfermedad cardiovascular. Diabetes mellitus. Metaanálisis. Equivalente de riesgo coronario.*

ABBREVIATIONS

CHD: coronary heart disease
 CI: confidence interval
 CVD: cardiovascular disease
 DM: diabetes mellitus
 DM2: type 2 diabetes mellitus
 HR: hazard ratio
 MI: myocardial infarction
 STROBE: Strengthening the Reporting of
 Observational studies in Epidemiology

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a well-known risk factor for cardiovascular disease (CVD).^{1,2} A cohort study carried out in 1998 found that patients with DM2 but no history of myocardial infarction (MI) had a similar CHD mortality to that of persons without diabetes mellitus but with a prior history of MI,³ leading to the conclusion that DM2 was a coronary risk equivalent. This concept was included in the Third Report of the National Cholesterol Education Program⁴ and in the European guidelines on the prevention of CVD.^{5,6} These guidelines focus on the prevention of CVD rather than the prevention of coronary heart disease (CHD), and classify persons with DM2 in the same category of a high risk for a fatal cardiovascular event as persons with established CVD.⁵ However, over recent years several studies have examined this subject, but with contradicting results. Thus, some studies have found that CHD mortality was the same⁷⁻⁹ or even greater^{10,11} in persons with diabetes mellitus without CHD (DM+CHD–) as in persons without DM but with CHD (DM–CHD+), whereas other studies have found that DM confers a lower risk for complications than CHD.¹²⁻¹⁷ Furthermore, yet other studies indicate that men and women could react differently in this aspect.¹⁸⁻²⁰

Determining whether DM2 is or is not a coronary risk equivalent may be important in order to improve the current recommendations on the treatment of cardiovascular risk factors, although to date no systematic review has been undertaken. In this study we carry out a systematic review whose main aim is to assess whether DM+CHD– persons have the same risk

for CHD and CVD mortality as DM–CHD+ persons, although we recognize that the terms DM and CHD cover a wide spectrum of clinical situations that may differ greatly.

METHODS

Inclusion Criteria

Studies were included if they fulfilled the following criteria: *a)* they were prospective and had a follow-up of at least 5 years; *b)* they included at least the following 3 groups of subjects: DM+CHD–, DM–CHD+, and DM–CHD– (subjects without DM and without CHD); and *c)* they presented data on CHD or CVD death separately for men and women. If a study led to publication of more than one article, then the most recent article was analyzed.

Bibliographic Search and Identification of the Primary Studies

We undertook a search in PubMed for studies in human subjects, with no restriction on language, up to February 28, 2006. The following search strategy was used, with these medical subject headings: (“diabetes mellitus”) AND (“follow-up studies” OR “longitudinal studies” OR “prospective studies” OR “case-control studies” OR “cohort studies,” OR “comparative study”) AND (“coronary disease/complications” OR “coronary disease/mortality”), OR (“cardiovascular diseases/complications” OR “cardiovascular diseases/mortality”) OR (“myocardial infarction/complications” OR “myocardial infarction/mortality”). In order to detect possible clinical trials that had not been found with the previous strategy, we also carried out the following search (studies in humans, with no restriction on language up to February 28, 2006): (“diabetes mellitus”) AND (“clinical trials”) AND (“coronary disease/complications” OR “coronary disease/mortality”) OR (“cardiovascular diseases/complications” OR “cardiovascular diseases/mortality”), OR (“myocardial infarction/complications” OR “myocardial infarction/mortality”). Two independent reviewers obtained the full-text article of all those considered to be potentially relevant for the review. In order to detect any other articles that might fulfill the inclusion criteria we also analyzed all the references of the full-text articles retrieved and consulted with experts in the subject. All possible discrepancies between the 2 reviewers were resolved by consensus agreement between them.

Data Extraction

The following information was collected for each of the articles selected: design, characteristics of the study population (number of persons, age, sex, race), country,

years of follow-up, losses during the follow-up, type of DM, duration of the DM, diagnostic criteria for DM and CHD, method used to determine death, study groups with their estimations of adjusted odds ratios (OR) or hazard ratios (HR), with their respective 95% confidence intervals (CI), for each of the events recorded in each study. None of the authors of any of the studies was contacted concerning the data analyzed. When the same article referring to the same event included different estimations of OR or HR, we always used that which had been adjusted for more confounding factors. As many studies report the HR instead of the OR and considering that both terms represent very similar concepts, we shall use the term HR from here on. Two independent reviewers analyzed the quality of the studies according to the criteria of the STROBE report (Strengthening the Reporting of Observational studies in Epidemiology).²¹ Possible discrepancies were resolved by mutual agreement between the reviewers.

Data Analysis

Subjects in the DM–CHD– group were used as the reference group (this was done in most of the studies analyzed) and compared against the DM+CHD– and the DM–CHD+ groups and the group of patients with DM and with CHD (DM+CHD+). The estimations of the HR were combined, weighting for the inverse of the variance with a random effects model.²² This model was chosen because it functions better than the fixed effects model when the number of studies to be combined is less than 20,^{23,24} and it also takes into account the variation between the studies.^{25,26} The HR of the different categories (DM+CHD– vs DM–CHD+, etc) were compared using their standard errors.²⁷ The possible publication bias was studied in comparison with the greatest number of studies (ie, CHD mortality in men) by means of the method of Egger et al²⁸ and the regression of the funnel plot.²⁹ All the analyses were performed with the statistical program Stata 8-SE (College Station, Texas, United States).

RESULTS

The bibliographic search retrieved 4233 articles with the first strategy and 655 with the second (designed to specifically detect clinical trials). After reviewing the titles and abstracts of all these, 22 full-text articles were selected. A further 2 articles were obtained after reviewing the references for these 22 articles.^{18,30} Of these 24 articles, 11 were excluded for the following reasons: *a*) they did not include persons from the DM+CHD– or DM–CHD+ groups³¹; *b*) they lacked data on CHD or CVD death stratified according to sex^{12,15,32-34}; *c*) data were presented in a more recent article³; and *d*) similar data were presented in another publication but with no relevant new data.³⁵

Thus, 12 studies finally fulfilled the inclusion criteria totally.^{7-11,13,14,16,17,19,20,30} An additional study was included because, although it grouped subjects according to CVD instead of CHD,¹⁸ we considered CHD to be the most important clinical manifestation of CVD, bearing in mind the age and origin of the persons studied. Analysis of the impact of this study on the final results of the meta-analysis was done by a sensitivity analysis, excluding this study from the analysis. Notably, the study by Haffner et al³ was not included in the meta-analysis because it included that of Juutilainen et al,¹¹ which is based on the same cohort of subjects, and was published more recently with data from a longer-term follow-up (13 years rather than 7).

The 13 articles analyzed included data from over 15 000 persons in the DM+CHD– group and over 21 000 in the DM–CHD+ group, and who were followed up from 5 to more than 20 years. Table 1 summarizes the main characteristics of these studies, ordered by year of publication. They were all published over the last 6 years and carried out in Europe or America; 7 of them provide information about the race of the participants.^{8,13,16-19,30} With regard to the design of the studies, only 1 of them was a randomized clinical trial,¹³ 11 were cohort studies,^{7,8,10,11,14,16-20,30} and the remainder were derived from the results of 2 population-based registries.⁹

Twelve of the studies provided data on men and just 9 on women. Most of the studies provided no information on the type of DM or its duration, and diagnosis of persons with CHD, CVD, or DM was done in the most part from information provided by the patients themselves. All the studies except one¹⁸ give information about CHD mortality, whereas 7 give information about CVD mortality. Additionally, 2 studies provide information about mortality due to stroke.^{17,20} We considered all those studies that had an acceptable quality in accordance with the STROBE report.

Table 2 shows the estimations of the HR with their respective 95% CI resulting from the combination of the corresponding HR of the studies evaluated. These estimations were calculated for CHD and CVD mortality, with the DM–CHD– group used as the reference group and stratifying the results by sex. Figure 1 shows the different HR in men in relation to CHD and CVD mortality, comparing the DM+CHD– and DM–CHD+ groups with the reference group (DM–CHD–). After combining the results of the 11 studies, the men in the DM+CHD– group had a lower CHD mortality than in the DM–CHD+ group, though the difference was not statistically significant ($P=.066$) (Table 2). For the women, 8 studies were combined to provide data on CHD mortality. The women in the DM+CHD– group experienced greater CHD mortality than those in the DM–CHD+ group, though again the difference was not statistically significant ($P=.42$) (Table 2).

Concerning the men, after combining the results of the 5 studies that provided information about CVD

TABLE 1. Characteristics of the Prospective Studies Included in this Systematic Review

Study	n	Design/Country. Duration of Follow-up	Criteria for MI/CHD	Criteria for DM	Sex	Study Groups	RR or HR for CHD Mortality (Adjusted)	Adjustment Variables
Lotufo et al ¹³	91 285	Randomized clinical trial (Physicians' Health study)/ United States. Follow-up: 5 years	CHD (patient report)	Patient report	Men	DM-/CHD- DM+/CHD- DM-/CHD+ DM+/CHD+	1 2.90 (2.30-3.70) 5.40 (4.70-6.20) 10.60 (8.60-13.10)	Age, BMI, smoking, vigorous physical exercise, alcohol intake
Hu et al ¹⁴	114 472	Prospective cohort study (Nurses' Health Study)/ United States. Follow-up: 5 years	CHD (patient report)	Patient report	Women	DM-/CHD- DM+/CHD- DM-/CHD+ DM+/CHD+	1 5.65 (4.83-6.60) 10.7 (9.03-12.6) 25.3 (20.6-31.1)	Age, duration, BMI, smoking, menopause, family history of MI
Cho et al ¹⁶	51 316	Prospective cohort study (Health Professionals Follow-up Study)/United States. Follow-up: 10 years	MI (patient report)	Patient report and questionnaire, PG concentrations and treatment with OADA	Men	DM-/CHD- DM+/CHD- DM-/CHD+ DM+/CHD+	1 3.37 (2.72-4.17) 8.39 (7.29-9.65) 14.51 (11.91-17.67)	Age, smoking, BMI, physical activity, alcohol intake, family history of MI, use of vitamin E supplements
Natarajan et al ¹⁹	5243	Combination of 2 prospective cohorts from Framingham/ United States. Follow-up: 20 years	CHD (not indicated)	Framingham Heart Study: 2 PG >150 mg/dL or use of OADA. Framingham Offspring Study: Fasting PG 140 mg/dL or use of OADA	Men	DM-/CHD- DM+/CHD- DM-/CHD+ DM+/CHD+	1 2.1 (1.3-3.3) 4.2 (3.2-5.6) 6.1 (3.4-10.9)	Age, smoking, hypertension, total cholesterolemia, HDL-C, BMI
Becker et al ¹⁸	2461	Population based cohort study/ Netherlands. Follow-up: 11 years	Information on CVD events obtained from patient report	WHO 1985 criteria for DM (oral glucose tolerance test with 75 g)	Men	DM-/CVD- DM+/CVD- DM-/CVD+ DM+/CVD+	1 2.40 (1.50-3.80) ^a 1.20 (0.50-3.10) ^a 2.30 (0.90-6.20) ^a	Age, smoking, hypertension, total cholesterolemia, HDL-C, BMI
Vaccaro et al ¹⁷	332 547	MRFIT study cohort/ United States. Follow-up: 25 years	MI (patient report)	Use of OADA (according to patient report)	Men	DM-/MI- DM+/MI- DM-/MI+ DM+/MI+	1 3.56 (3.35-3.79) ^b 5.46 (5.18-5.75) ^b 7.12 (5.93-8.48) ^b	Age, ethnic group, income, cholesterolemia, systolic blood pressure, smoking
Wannamethee et al ⁷	5934	Prospective cohort study (British Regional Heart Study)/ United Kingdom. Follow-up: 10 years	MI patient report, (registries of primary care physicians)	Patient report and registries of primary care physicians	Men	DM-/CHD- DM+/CHD- DM-/CHD+ DM+/CHD+	1 2.82 (1.85-4.28) 3.14 (2.56-3.81) ^c 8.93 (6.13-12.99)	Age, smoking, social class, BMI, physical activity, alcohol intake

(Continued on following page)

TABLE 1. Characteristics of the Prospective Studies Included in this Systematic Review (Continuation)

Study	n	Design/Country. Duration of Follow-up	Criteria for MI/CHD	Criteria for DM	Sex	Study Groups	RR or HR for CHD Mortality (Adjusted)	Adjustment Variables
Natarajan et al ⁸	10 871	Cohort of the NHANES I Epidemiologic Follow-up Study/ United States. Follow-up: 20 years	MI (patient report)	Patient report	Men	DM-/MI-	1	Initial age, ethnic group, smoking, hypertension, cholesterolemia, BMI
						DMR+/MI- and DML+/MI-	4.76 (2.08-7.37) ^d	
Hu et al ²⁰	51 735	Six independent cohort studies/Finland. Follow-up: 7.2 years	MI (patient report or hospital discharge diagnosis of MI) to obtain OADA free of charge	Patient report, hospital discharge diagnosis of DM or authorization to obtain OADA free of charge	Men	DM-/MI-	1	Initial age, ethnic group, smoking, hypertension, cholesterolemia, BMI
						DMR+/MI- and DML+/MI-	2.99 (2.17-4.10) ^d	
Whiteley et al ¹⁰	15 406	Prospective cohort study (Renfrew and Paisley Survey)/ United Kingdom (Scotland). Follow-up: 25 years	CHD (Rose angina questionnaire, severe chest pain lasting at least 30 min, or various Minnesota codes)	Mainly patient report (in some cases, in addition, casual glycaemia ≥ 11.1 mmol/L)	Men	DM-/MI-	1	Age, year of study, BMI, systolic blood pressure, total cholesterolemia, smoking
						DMR+/MI- and DML+/MI-	4.89 (3.84-6.24)	
Juutilainen et al ¹¹	2432	Population based cohort study/Finland. Follow-up: 17.5 years	CHD (review of hospital registries)	WHO 1985 criteria for DM	Men	DM-/MI-	1	Age, smoking, hypertension, cholesterolemia, BMI, social class
						DMR+/MI- and DML+/MI-	34.40 (12.20-97)	
Pajunen et al ⁹	13 876	FINAMI MI Registry & FINRISK Study Cohort/Finland. Follow-up: 10 years	MI (criteria of the WHO MONICA Project)	FINAMI: physician or OADA reimbursement registries. FINRISK: patient report + reimbursement of OADA	Men	DM-/MI-	1	Age, place of residence, smoking, hypertension, total cholesterolemia, HDL-C, triglycerides
						DMR+/MI- and DML+/MI-	6.20 (2.19-20)	
					Women	DM-/MI-	1	Age
					Women	DM+/MI+	7.56 (5.62-10.17) ^f	
					Women	DM-/MI-	6.20 (4.78-8.03) ^f	

(Continued on following page.)

TABLE 1. Characteristics of the Prospective Studies Included in this Systematic Review (Continuation)

Study	n	Design/Country. Duration of Follow-up	Criteria for MI/CHD	Criteria for DM	Sex	Study Groups	RR or HR for CHD Mortality (Adjusted)	Adjustment Variables
Howard et al ³⁰	4549	Population based cohort study in 13 American Indian tribes or communities (The Strong Heart Study)/ United States. Follow-up: 12.6 years	Electrocardiograms and medical records	Fasting PG >126 mg/dL, use of OADA or insulin, or diagnosis of DM done by a physician	Men	DM-/CHD- DM+/CHD- DM-/CHD+ DM+/CHD+	1 1.60 (1.20-2.10) 2.20 (1.10-4.50) 1.60 (1.00-2.60)	Age
					Women	DM-/CHD- DM+/CHD- DM-/CHD+ DM+/CHD+	1 2.10 (1.30-3.40) 2.70 (0.60-12.70) 4.10 (1.90-8.90)	Age

HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; DM, diabetes mellitus; DML, long-term diabetes mellitus (more than 10 years); DMR, diabetes mellitus of recent onset (less than 10 years); CHD, coronary heart disease; CVD, cardiovascular disease; PG, plasma glycemia; OADA, oral anti-diabetic agents; HR, hazard ratio; MI, myocardial infarction.

³⁰Data on CVD mortality.

²⁷Estimation obtained after weighting for the inverse of the variance of the following 2 groups: angina alone + MI alone.

²⁸Estimation obtained after weighting for the inverse of the variance of the following 2 groups: DMR and DML.

²⁹In the original study the reference group was DM+/CHD-; this reference group was changed and the estimations were made with the unadjusted data and the information from multivariate analyses provided by the authors.²⁷

²⁷Estimation obtained after weighting for the inverse of the variance of the strata of different age groups.

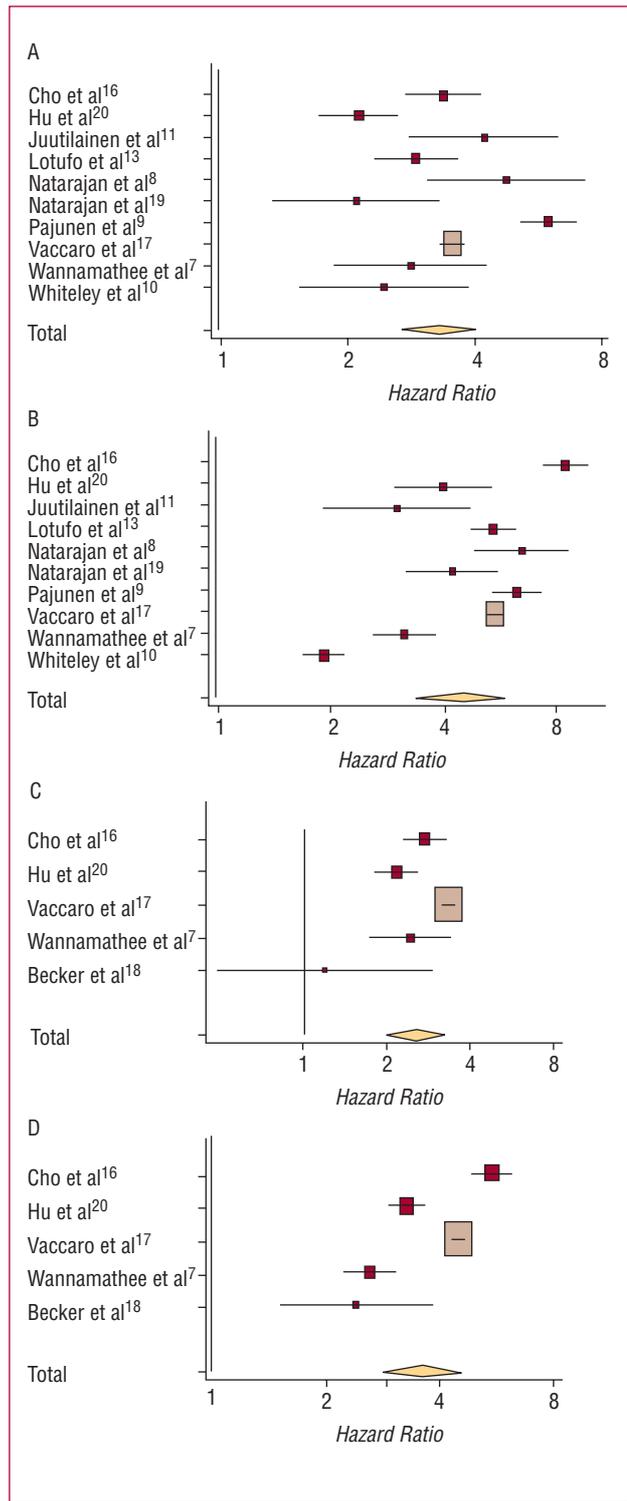


Figure 1. A: funnel plot comparing coronary heart disease mortality between men without diabetes mellitus and without coronary heart disease (DM-/CHD-; reference group) with men without diabetes mellitus but with coronary heart disease (DM+/CHD-). B: funnel plot comparing coronary heart disease mortality between men in the DM-/CHD- group with men in the DM+/CHD+ group. C: funnel plot comparing cardiovascular disease mortality between men in the DM-/CHD- group with men in the DM+/CHD- group. D: funnel plot comparing cardiovascular disease mortality between men in the DM-/CHD- group with men in the DM+/CHD+ group.

TABLE 2. Hazard Ratio (HR) of Coronary Heart Disease and Cardiovascular Disease Mortality in Relation With Diabetes Mellitus (DM) and Coronary Heart Disease (CHD)

	Exposure ^a	HR (95% Confidence Interval)	Combined Studies
CHD mortality	Men	DM+CHD-	7-11,13,16,17,19,20,30
		DM-CHD+	7,11,13,16,17,20,30
		DM+CHD+	7,8,10,11,13,16,17,19,20,30
	Women	DM+CHD-	8-11,14,19,20,30
		DM-CHD+	8-11,14,19,20,30
		DM+CHD+	8,10,11,14,19,20,30
CVD mortality	Men	DM+CHD-	7,16-18,20
		DM-CHD+	7,16-18,20
		DM+CHD+	7,16-18,20
	Women	DM+CHD-	14,18,20
		DM-CHD+	14,18,20
		DM+CHD+	14,18,20

Reference group, DM-CHD-.

mortality, this was found to be lower in persons from the DM+CHD- group than those in the DM-CHD+ group. These results were at the limit of statistical significance ($P=.051$) (Table 2). The results did not change after excluding the study by Becker et al,¹⁸ which grouped persons according to CVD rather than CHD ($HR_{DM+CHD-}=2.67$ [95% CI, 2.11-3.40], $HR_{DM-CHD+}=3.83$ [95% CI, 2.95-4.97], $HR_{DM+CHD+}=6.92$ [95% CI, 5.33-8.99]). For women, it was possible to combine 3 studies to obtain estimations of the HR for mortality due to CVD. No significant differences were found between the DM+CHD- and DM-CHD+ groups ($P=.592$) (Table 2).

These results also remained the same after eliminating the study by Becker et al¹⁸ ($HR_{DM+CHD-}=4.69$ [95% CI, 4.22-5.22], $HR_{DM-CHD+}=4.27$ [95% CI, 1.42-12.82], $HR_{DM+CHD+}=11.61$ [95% CI, 3.82-35.28]).

Comparison of the HR between men and women showed significant differences between the 2 groups of DM+CHD- in CHD mortality (HR in men=3.06 [95% CI, 2.45-3.83]; HR in women=4.68 [95% CI, 3.40-6.45]; $P=.033$), and CVD mortality (HR in men=2.55 [95% CI, 2-3.26]; HR in women=4.70 [95% CI, 4.23-5.22]; $P<.001$). However, no differences were found between men and women for either of the types of mortality (CHD and CVD) or in the DM-CHD+ group or in the DM+CHD+ group (data not shown).

Combination of the 2 studies in men which provided information on mortality due to stroke^{17,20} showed that this was significantly greater in the DM+CHD- group as compared with the DM-CHD+ group (HR=3.07 [95% CI, 2.64-3.57] vs 1.70 [95% CI, 1.40-2.07], respectively, $P<.001$).

In order to study the publication bias we used the method of Egger in the comparison with the greatest number of studies (CHD mortality in men).

The P value of the ordinate in the origin was .778 in the DM+CHD- group. Similar results were obtained in the DM-CHD+ group ($P=.352$) and the DM+CHD+ group ($P=.617$). The results of the regression in the funnel plot were also non-significant.

DISCUSSION

This review confirms that both DM and CHD significantly increase the risk for CHD and CVD mortality. Additionally, it shows that comparison of persons who are DM+CHD- with those who are DM-CHD+ gives a relative risk of CHD and CVD mortality that varies between men and women. The men in the DM+CHD- group had a non-significant trend towards lower CHD and CVD mortality as compared with the men in the DM-CHD+ group. No differences were found for the women in CHD or CVD mortality between the DM+CHD- and the DM-CHD+ groups. It would probably have been better to compare directly persons who were DM+CHD- with those who were DM-CHD+, but all the studies except for one use DM-CHD- as the reference group.

Coronary Heart Disease Mortality and Cardiovascular Disease Mortality in DM+CHD- Men as Compared With DM-CHD+ Men

Coronary heart disease mortality in the men was lower in the DM+CHD- group than the DM-CHD+ group, though the difference was not significant.

Although this finding in itself is not sufficient to consider that DM is not a coronary risk equivalent, other results from this systematic review suggest that this could be the case. Firstly, CVD mortality, which basically

includes CHD mortality and mortality due to cerebrovascular disease, was also lower in men from the DM+CHD- group than men from the DM-CHD+ group, in this case reaching the limit of statistical significance ($P=.051$). Moreover, it should be recalled that several studies adjusted for cholesterol concentrations, which could have led to over-adjusting the risk in the CHD+ persons whilst having no effect on the DM+ persons. It could thus be speculated that without this adjustment for cholesterol figures, the differences would have been even greater than those found between the DM+CHD- and the DM-CHD+ groups.

Coronary Heart Disease Mortality and Cardiovascular Disease Mortality in DM+CHD- Women as Compared With DM-CHD+ Women

As opposed to what was found for the men, the DM+CHD- women had a greater risk for CHD and CVD mortality than the DM-CHD+ women, although the difference was not statistically significant. In this case the following reflections can be made. Firstly, the statistical power of the sample of women was lower than that for the sample of men, as fewer studies were combined and, additionally, the total number of women was much lower (the cohort in the MRFIT study is much larger than any of the other studies included, and this study only included men). Secondly, if the data had not been adjusted for cholesterol concentrations, the differences between the 2 groups, DM+CHD- and DM-CHD+, might have been even greater. These facts support the idea that DM in women confers a similar risk for CHD and CVD mortality to CHD itself, although the information that we were able to obtain from the data with women was less than that for the men.

These results, therefore, all indicate that men and women with DM could behave differently concerning the risk for CHD and CVD mortality. In fact, comparison of the DM+CHD- and the DM-CHD+ groups in relation to the risks for CHD and CVD mortality showed that the risks were significantly greater in the women as compared to the men. To this extent, our results are in agreement with earlier studies that show that DM increases the risk for CVD to a greater degree in women than in men.³⁶⁻³⁸ This increased risk for women conferred by DM may even occur in pre-diabetes states and is only partly explained by an increase in the traditional cardiovascular risk factors.³⁹

Limitations

This review has certain limitations. Firstly, most of the studies involved in our review included the diagnosis of CHD/CVD and DM based on information provided by the patients themselves, which may have led to

errors in the classification of subjects within the various groups. Moreover, it should be recalled that the terms "CHD" and "DM" each include diverse nosologic situations. Generally speaking, one can consider that using the information provided by the patients in order to classify them as having CHD/CVD may be a relatively reliable way of doing so. However, in the case of DM this strategy may have led to "milder cases" of DM being excluded from those persons with the disease.⁹ Furthermore, none of the studies used the current criteria for the diagnosis of DM, which use lower blood glucose figures than the previous classification in order to define the presence of DM. It therefore seems quite likely that the persons with DM included in most of the studies analyzed correspond to what could be considered a well-established clinical disease. Thus, some persons in the groups classified as not having DM could have been reclassified as having DM, according to the current criteria for the diagnosis of DM. The extrapolation of our results to all persons who currently fulfill the criteria for DM is therefore complex.

Secondly, this review did not examine the effects of the duration of DM on the risk for CHD and CVD mortality, because these data were lacking in most of the studies included. Nevertheless, some of these studies found that as the duration of DM increases, the greater the risk of CHD mortality, both in men¹⁶ and in women.^{8,14} In fact, the duration of DM could be a factor that explains the differences in CHD mortality between the various studies carried out in order to determine whether DM is or is not a coronary risk equivalent.¹⁵ Finally, the HR for CHD and CVD mortality may vary considerably according to race,⁴⁰ and even within similar ethnic populations.⁴¹ In this case, the lack of sufficient relevant data in the studies analyzed prevents us undertaking an analysis of the impact of race on CHD and CVD mortality.

CONCLUSIONS

This is the first systematic review to evaluate studies comparing CHD and CVD mortality in persons who were DM+CHD- and DM-CHD+. The men in the DM+CHD- group tended to have a lower CVD mortality than the men in the DM-CHD+ group, whereas the DM+CHD- women tended to have greater CHD and CVD mortality. Nonetheless, with the studies available at the present time, neither of these two trends was statistically significant. Further studies are required to determine whether these trends can in fact be confirmed.

ACKNOWLEDGEMENTS

The authors are grateful to Neil Hossack for the English language version of the manuscript.

REFERENCES

- Folsom AR, Szklo M, Stevens J, Liao F, Smith R, Eckfeldt JH. A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes. The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care*. 1997;20:935-42.
- Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI, et al. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Diabetes Care*. 1999;22:1077-83.
- Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-34.
- Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-97.
- de Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2003;24:1601-10.
- Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, De Boer MJ, et al. Guías de práctica clínica sobre diabetes, prediabetes y enfermedades cardiovasculares. *Rev Esp Cardiol*. 2007;60:525.e1-e64.
- Wannamethee SG, Shaper AG, Lennon L. Cardiovascular disease incidence and mortality in older men with diabetes and in men with coronary heart disease. *Heart*. 2004;90:1398-403.
- Natarajan S, Liao Y, Sinha D, Cao G, McGee DL, Lipsitz SR. Sex differences in the effect of diabetes duration on coronary heart disease mortality. *Arch Intern Med*. 2005;165:430-5.
- Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Raiha P, Karja-Koskenkari P, et al. Myocardial infarction in diabetic and non-diabetic persons with and without prior myocardial infarction: the FINAMI Study. *Diabetologia*. 2005;48:2519-24.
- Whiteley L, Padmanabhan S, Hole D, Isles C. Should diabetes be considered a coronary heart disease risk equivalent?: results from 25 years of follow-up in the Renfrew and Paisley Survey. *Diabetes Care*. 2005;28:1588-93.
- Juutilainen A, Lehto S, Ronnema T, Pyorala K, Laakso M. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care*. 2005;28:2901-7.
- Simons LA, Simons J. Diabetes and coronary heart disease. *N Engl J Med*. 1998;339:1714-5.
- Lotufo PA, Gaziano JM, Chae CU, Ajani UA, Moreno-John G, Buring JE, et al. Diabetes and all-cause and coronary heart disease mortality among US male physicians. *Arch Intern Med*. 2001;161:242-7.
- Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med*. 2001;161:1717-23.
- Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ*. 2002;324:939-42.
- Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB. The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. *J Am Coll Cardiol*. 2002;40:954-60.
- Vaccaro O, Eberly LE, Neaton JD, Yang L, Riccardi G, Stamler J. Impact of diabetes and previous myocardial infarction on long-term survival: 25-year mortality follow-up of primary screenees of the Multiple Risk Factor Intervention Trial. *Arch Intern Med*. 2004;164:1438-43.
- Becker A, Bos G, de Vegt F, Kostense PJ, Dekker JM, Nijpels G, et al. Cardiovascular events in type 2 diabetes: comparison with nondiabetic individuals without and with prior cardiovascular disease. 10-year follow-up of the Hoorn Study. *Eur Heart J*. 2003;24:1406-13.
- Natarajan S, Liao Y, Cao G, Lipsitz SR, McGee DL. Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. *Arch Intern Med*. 2003;163:1735-40.
- Hu G, Jousilahti P, Qiao Q, Katoh S, Tuomilehto J. Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with or without history of myocardial infarction. *Diabetologia*. 2005;48:856-61.
- STROBE Statement: STrengthening the Reporting of OBServational studies in Epidemiology. Version 3 (update Sep 2005) (cited 18 Oct 2005). Available from: <http://www.strobe-statement.org/Checkliste.html>
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-88.
- Villar J, Mackey ME, Carroli G, Donner A. Meta-analyses in systematic reviews of randomized controlled trials in perinatal medicine: comparison of fixed and random effects models. *Stat Med*. 2001;20:3635-47.
- Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. *Stat Med*. 2001;20:825-40.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-58.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-60.
- Rothman KJ, Greenland S. *Modern epidemiology*. Rothman KJ, Greenland S, editors. 2^a ed. Boston: Lippincott-Raven; 1998. p. 643-74.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-34.
- Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med*. 2001;20:641-54.
- Howard BV, Best LG, Galloway JM, Howard WJ, Jones K, Lee ET, et al. Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. *Diabetes Care*. 2006;29:391-7.
- Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. *Arch Intern Med*. 2005;165:1910-6.
- Casiglia E, Zanette G, Mazza A, Donadon V, Donada C, Pizziol A, et al. Cardiovascular mortality in non-insulin-dependent diabetes mellitus. A controlled study among 683 diabetics and 683 age- and sex-matched normal subjects. *Eur J Epidemiol*. 2000;16:677-84.
- Lee CD, Folsom AR, Pankow JS, Brancati FL. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. *Circulation*. 2004;109:855-60.
- Hackam DG, Tan MK, Honos GN, Leiter LA, Langer A, Goodman SG. How does the prognosis of diabetes compare with that of established vascular disease? Insights from the Canadian Vascular Protection (VP) Registry. *Am Heart J*. 2004;148:1028-33.
- Hu G, Jousilahti P, Qiao Q, Peltonen M, Katoh S, Tuomilehto J. The gender-specific impact of diabetes and myocardial infarction at baseline and during follow-up on mortality from all causes and coronary heart disease. *J Am Coll Cardiol*. 2005;45:1413-8.
- Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA*. 1991;265:627-31.
- Hu G. Gender difference in all-cause and cardiovascular mortality related to hyperglycaemia and newly-diagnosed diabetes. *Diabetologia*. 2003;46:608-17.
- Juutilainen A, Kortelainen S, Lehto S, Ronnema T, Pyorala K, Laakso M. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. *Diabetes Care*. 2004;27:2898-904.

39. Howard BV, Cowan LD, Go O, Welty TK, Robbins DC, Lee ET. Adverse effects of diabetes on multiple cardiovascular disease risk factors in women. The Strong Heart Study. *Diabetes Care*. 1998;21:1258-65.
40. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434-44.
41. Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. *Diabetes Care*. 1997;20:163-9.