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Review

Mortality in diabetes compared with previous cardiovascular disease: A gender-specific meta-analysis

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Abstract

Aims. – Diabetes has been described as a cardiovascular disease (CVD) risk equivalent. There is evidence, however, that its impact may differ between women and men. For this reason, our study aimed to obtain gender-specific hazard ratios (HRs) comparing diabetes and CVD patients in terms of all-cause, CVD and coronary heart disease (CHD) mortality.

Methods. – Individuals with diabetes (without CVD) and those with CVD (without diabetes) were examined through a systematic review of articles that provided gender-specific HRs for mortality. Searches included Medline, Embase and the Cochrane Library database (from January 1998 to December 2009) and exploded MeSH headings [cardiovascular diseases, risk, epidemiologic studies, case-control studies, cohort studies, mortality, outcome assessment (health care), sex factors, survival analysis and diabetes mellitus, type 2]. Two observers selected and reviewed the studies and hierarchical Bayesian random-effects models were used to combine HRs, thereby accommodating any between-study differences through inclusion of a between-study variance in HRs.

Results. – Out of 5425 studies, nine were relevant (0.17%). CVD and CHD mortality in men was lower for diabetes alone (CVD mortality HR: 0.82, 95% CrI: 0.69–0.98; CHD mortality HR: 0.73, 95% CrI: 0.65–0.83). In contrast, rates appeared to be higher in women with diabetes alone (CVD mortality HR: 1.29, 95% CrI: 0.79–2.26; CHD mortality HR: 1.28, 95% CrI: 0.75–2.22), although wide credible intervals precluded any definitive conclusions. All-cause mortality in men was similar for diabetes and previous CVD (HR: 1.02, 95% CrI: 0.93–1.12) whereas, among women, it was at least as high and possibly higher for diabetes alone (HR: 1.25, 95% CrI: 0.89–1.76).

Conclusion. – Compared with previous CVD, diabetes alone leads to lower CVD and CHD mortality risk in men, and similar all-cause mortality. In contrast, although further studies are needed, it is possible that diabetes leads to higher CVD, CHD and all-cause mortality in women.

Keywords: Cardiovascular events; Gender; Diabetes mellitus; Type 2 diabetes; Cohort; Mortality; All-cause mortality; Cardiovascular mortality; Coronary mortality; Epidemiology; Relative risk; Meta-analysis

Résumé

Comparaison du risque de mortalité chez les diabétiques et les patients non-diabétiques avec antécédent de malade cardiovasculaire : méta-analyse selon le sexe.

But. – Le diabète (DM) a été considéré comme un facteur de risque de mortalité équivalent à celui d'un antécédent de maladie cardiovasculaire (MCV). Cependant, des données indiquent que son impact pourrait varier selon le sexe. Notre étude avait pour objet de comparer selon le sexe le risque de mortalité toutes causes confondues, de mortalité liée aux MCV et de mortalité liée aux maladies coronaires (MC) entre diabétiques et patients avec antécédent de MCV.

Méthodes. – Nous avons inclus les données des personnes atteintes de DM (sans maladie cardiovasculaire) et des personnes avec antécédent de MCV (sans diabète) en procédant à un examen systématique des articles qui donnaient le risque de mortalité selon le sexe. Nous avons fait des recherches dans Medline, Embase et Cochrane sur la période janvier 1998 à décembre 2009, avec comme mots clés : maladies cardiovasculaires, risque, études épidémiologiques, études cas–témoin, études par cohortes, mortalité, évaluation des résultats (soins de santé), facteurs liés au sexe,

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analyse de survie, diabète sucré, type 2. Deux observateurs ont évalué la pertinence des études et revu celles-ci. Nous avons utilisé des modèles bayésiens hiérarchiques à effets aléatoires pour combiner les rapports de risques (RR) en vue de tenir compte des différences d'une étude à l'autre par l'inclusion d'un écart de résultats entre les études dans les RR.

Résultats. – Neuf des 5425 études étaient pertinentes (0,17 %). La mortalité liée aux MCV et aux MC chez les hommes était plus faible chez les diabétiques sans antécédent de MCV (mortalité liée aux MCV : RR 0,82 ; IC 95 % 0,69–0,98 ; mortalité liée aux MC : RR 0,73 ; IC 95 % 0,65–0,83). En revanche le risque semblait plus élevé chez les femmes diabétiques (mortalité liée aux MCV : RR 1,29, IC 95 % 0,79–2,26 ; mortalité liée aux MC : RR 1,28, IC 95 % 0,75–2,22), mais l'importance des intervalles de confiance n'a pas permis de conclusion définitive. La mortalité toutes causes confondues chez les hommes était similaire pour le diabète et les antécédents de MCV (RR 1,02 ; IC 95 % 0,93–1,12). Chez les femmes, ces données étaient au moins aussi élevées, avec une tendance en faveur d'une élévation pour le diabète seul (RR 1,25, IC 95 % 0,89–1,76).

Conclusions. – Chez les hommes, par comparaison aux non-diabétiques avec antécédent CV, les diabétiques sans antécédent CV ont un risque de mortalité liée aux MCV et aux MC plus faible et un risque de mortalité toutes causes confondues similaire. En revanche, il existe une tendance en faveur d'un risque plus élevé chez les femmes diabétiques de mortalité liée aux MCV, aux MC et toutes causes confondues que chez les femmes non-diabétiques avec antécédent de MCV. D'autres études sont cependant nécessaires pour affirmer ou infirmer ces données.

Mots clés : Événements cardiovasculaires ; Antécédents, diabète ; Épidémiologie ; Mortalité cardiovasculaire ; Mortalité coronaire ; Mortalité toutes causes confondues ; Sexe ; Méta-analyse

1. Introduction

Over 10 years ago, Haffner and colleagues [1] reported that mortality in diabetes patients was similar to that of patients with previous myocardial infarction (MI). These findings contributed to the concept of diabetes as a cardiovascular disease (CVD) 'risk equivalent' [2–7], and led to more aggressive risk-management strategies in diabetes patients. This was a welcome development, given that diabetes confers a two- to fourfold risk increase for heart disease and stroke [8]. CVD prevention requires careful attention to physical-activity levels, dietary intake and appropriate use of cardioprotective medications [9].

However, diabetes may not only be a CVD risk equivalent in women, but may actually confer greater risk: in an updated analysis of the cohort examined by Haffner and colleagues [10], women with diabetes had higher rates of mortality than women with previous CVD. Although not all other investigators have identified such a gender difference, the updated analysis was consistent with studies suggesting that the relative risk increase for acute MI with diabetes is higher in women than in men [11,12].

A relatively higher mortality for women with diabetes compared with those with prior CVD would suggest inadequate attention to CVD prevention in women with diabetes. While, a study using Framingham data reported declining mortality rates for both women and men with diabetes [13], an analysis of the US National Health and Nutrition Examination Survey (NHANES) data demonstrated declines in all-cause mortality over time for men with diabetes, but not for women [14]. Thus, the latter has highlighted a need to carefully examine gender differences in the effects of diabetes on mortality towards the goal of establishing appropriate preventative strategies in both women and men.

For this reason and returning specifically to the question of gender-specific differences in the context of diabetes and CVD 'equivalence', the present study has examined the totality of evidence through a systematic review and meta-analysis aiming to obtain gender-specific hazard ratios (HRs) by comparing diabetes and CVD patients in terms of all-cause, CVD and coronary heart disease (CHD) mortality.

2. Materials and methods

2.1. Study selection

For our review, observational studies were identified that prospectively examined the mortality rates in individuals with diabetes, but without a prior history of CVD, that were compared directly with mortality in individuals with CVD, but without a previous history of diabetes. Our study also required that outcomes (such as all-cause, CVD and/or CHD mortality) be reported separately for women and/or men.

2.2. Literature search

Searches were performed (C.L.) with a medical librarian's assistance (A.C.), using three citation indices (Medline and Embase through the Ovid interface, and the Cochrane Library database). Our Medline search strategy included both truncated free text and exploded Medical Subject Headings (MeSH). These headings were 'cardiovascular diseases', 'risk', 'epidemiologic studies', 'case-control studies', 'cohort studies', 'morbidity', 'outcome assessment (health care)', 'sex factors', 'survival analysis' and 'diabetes mellitus, type 2'. Non-exploded MeSH included 'odds ratio', 'prognosis', 'disease progression', 'men', 'women' and 'mortality'. Embase was searched using the equivalent search strategy, but with one change: the Embase subject heading equivalent to the MeSH 'diabetes mellitus, type 2' was 'non-insulin-dependent diabetes mellitus'. The study-type headings in Embase were 'cross-sectional study', 'incidence', 'prevalence', 'case-control study' and 'cohort analysis'. In both Embase and Medline, 'odds ratio' considers all comparisons of risk. In the Cochrane database, the terms 'heart', 'myocardial', 'coronary' and 'cardio*' were combined with 'odds ratio' (OR), and further combined by AND with diabetes. Reference libraries were imported into EndNote for the three searches. These were all then merged and any duplicates removed (Endnote X1, The Thomas Corporation, 1988–2007).

In addition, a search through PubMed was made to identify any previous meta-analyses assessing CVD risk in the

context of type 2 diabetes or previous CVD, combining the following exploded MeSH terms with AND: 'cardiovascular diseases', 'diabetes mellitus, type 2' and 'meta-analysis [publication type]'. The reference lists of relevant meta-analyses were examined to identify any relevant articles. Searches were performed for the time period January 1, 1998 to December 13, 2009. No language restrictions were applied. As detailed below, only one relevant non-English (Spanish) publication was identified. The figures and tables of this Spanish publication were examined, and selected text was assessed with the assistance of Google Translate™.

2.3. Data abstraction

Manuscript titles and/or abstracts in the merged EndNote library were independently reviewed by two investigators (C.L. and K.D.) to assess for pertinence to our study purpose. The investigators then met to compare selections, and any differences resolved through discussion and consensus. Full texts of the selected manuscripts were reviewed to assess quality, and data abstraction was performed using a predetermined form. Citation tracking was used (reference lists of relevant manuscripts reviewed) to identify other potentially relevant studies.

The abstraction form included first and last authors; journal; year of publication; study design; sample selection (general population, clinical, men, women); country; sample size; number of years for cohort inception and data collection; age range; gender; attrition rates; inclusion/exclusion of individuals with type 1 diabetes; diabetes definitions; previous CVD definitions; whether diabetes and CVD definitions captured incident disease, prevalent disease, or both; data sources for mortality outcomes; adjusted HRs; and confounders and covariates included in the final models. Based on this information, a final determination of eligibility (see section on study selection above) was made, with assessment of study quality, and the accuracy of data abstraction confirmed. All HRs were recorded as diabetes *vs* previous CVD; when reported as previous CVD *vs* diabetes, reciprocal values of HRs and associated CIs were computed.

2.4. Quantitative data synthesis

All studies retained their reported outcomes as HRs with 95% confidence intervals (CI). These were converted to the best-fitting log-normal distributions, while posterior distributions from each study were combined *via* Bayesian hierarchical meta-analysis models (L.J.). These models are the Bayesian equivalent to random-effects meta-analysis models, thereby accomodating between-study heterogeneity through a between-study variance term. Bayesian hierarchical models account for sample size, with larger sample sizes contributing more information to the final estimates. This is roughly equivalent to the most frequently applied models using weighting. HRs are preferred to ORs because they are somewhat easier to interpret, being simple ratios of probabilities of events, instead of ratios of the odds.

Separate meta-analyses were carried out for each outcome (all-cause, CVD and CHD mortality in men and in women), and point estimates and 95% credible intervals (CrI) were also reported. All analyses were carried out using the confidence profile method, which includes modules for converting HR CIs to the closest-fitting log-normal densities and for combining these densities *via* Bayesian hierarchical models [15].

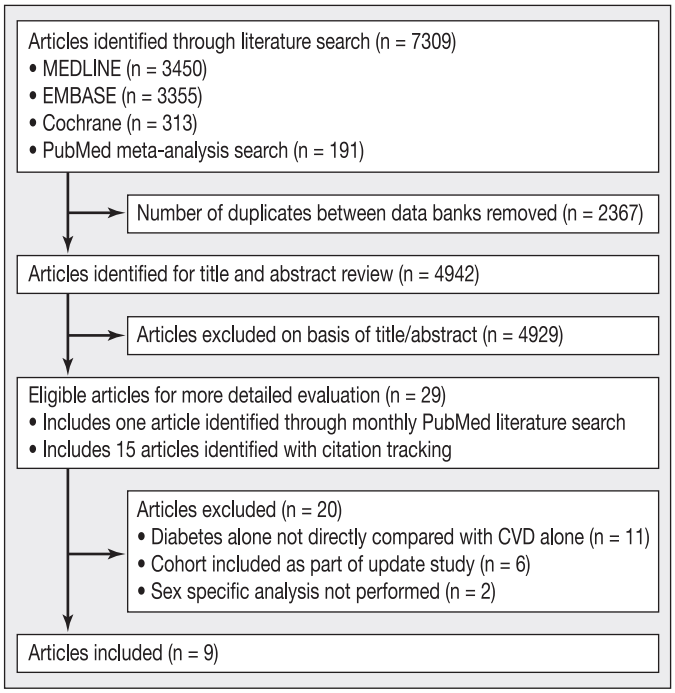

Fig. 1. Graphic representation of the process of study selection and the results.

3. Results

3.1. Trial flow/flow of included studies

Nine studies were examined in detail and included (Fig. 1, Table 1). The PubMed search for previous meta-analyses assessing CVD risk in the context of type 2 diabetes or previous CVD generated 191 titles, among which one was deemed potentially relevant [16]. An updated search (August 1, 2009 to December 13, 2009) did not result in any additional primary research studies for inclusion, but did identify a second potentially relevant meta-analysis [17].

3.2. Previous meta-analyses

One previous meta-analysis [16] was published in Spanish. This study involved only a single database (PubMed, up to February 2006), and subjects with diabetes *vs* previous CVD were not directly compared. Instead, both groups were compared with individuals who did not have diabetes and previous CVD, respectively [16].

The second meta-analysis [17] examined mortality differences between diabetes alone compared with previous CVD without diabetes, but did not include gender-specific meta-analyses. Moreover, in this study, a meta-analysis of HRs was not performed. Instead, the investigators extracted the number of outcomes in the groups of interest, computed the ORs and

Table 1
Characteristics of the nine studies included in the meta-analysis.

Study (first author, year)	Country	Number (with diabetes/CVD)		Age group (years)	Mortality outcome	Adjustments	Diabetes definition	Previous CVD definition
		Men	Women					
Becker, 2003 [22]	Netherlands	63/178	90/156	50–75	CVD	Age, smoking, LDL and HDL cholesterol, triglycerides, hypertension	Fasting blood glucose and 75-g oral glucose tolerance test	Self-reported MI, angina, TIA, stroke, CABG/angioplasty, claudication, nitrate use
Wannamethee, 2004 [20]	England	202/926		52–74	Total, CVD, CHD	Age, smoking, social class, BMI, physical activity, alcohol	Self-report, GP records	MI, angina by self-report or GP records
Vaccaro, 2004 [18]	United States	4809/4625		35–57	Total, CVD, CHD	Age, smoking, race, income, total cholesterol, systolic blood pressure	Self-report of medication	MI by self-report
Whiteley, 2005 [21]	Scotland	74/1402	77/1613	45–64	Total, CHD	Age, smoking, blood pressure, cholesterol, BMI, social class	Self-report, random blood glucose	MI, angina (Rose questionnaire)
Hu, 2005 [23]	Finland	496/982	466/326	25–74	Total, CVD, CHD	Age, smoking, BMI, systolic blood pressure, total cholesterol, study year	Self-report, National Hospital Discharge Register, glucose-lowering medication from National Prescription Register	MI by self-report or National Hospital Discharge Register
Juutilainen, 2005 [10]	Finland	263/138	169/118	45–64	Total, CVD, CHD	Age, smoking, total cholesterol, HDL, triglycerides, hypertension, area of residence	National Drug Reimbursement Register	MI by self-report confirmed by review of hospital records, angina (Rose questionnaire)
Booth, 2006 [8]	Canada			≥ 20	Total	Age	One hospital admission or two physician billing claims for diabetes within a 2-year period (provincial databases)	MI as primary diagnosis on hospital discharge database
Schramm, 2008 [24]	Denmark	33,741/49,357	31,641/23,798	≥ 30	Total, CVD, CHD	Age, co-morbidity, gross income, time[a]	Glucose-lowering medication from National Prescription Registry	MI in National Hospital Discharge Register
Dagenais, 2009 [19]	Canada	137/527		35–64	Total	Age	Self-reported or fasting glucose	MI, unstable angina, stroke by records, including ECG

CVD: cardiovascular disease; CHD: coronary heart disease; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; GP: general practitioner; MI: myocardial infarction; CABG: coronary artery bypass graft surgery; TIA: transient ischaemic attack; BMI: body mass index; ECG: electrocardiography.

[a] Matched according to these characteristics.

performed a meta-analysis of these ORs. As a result, they were not able to account for time to event in their analyses [17]. It was also noted that some of the studies included in this second meta-analysis were not included in our present meta-analysis because they provided no gender-specific mortality data.

3.3. Study characteristics

All nine primary studies retained were peer-reviewed publications reporting longitudinal data (Table 1). Three [8,18,19] were from North America, two [20,21] were from the United Kingdom and four [10,22–24] were from Northern Europe. All reported on men, while six also reported on women. The study by Juutilainen and colleagues [10] was an updated version of the original study by Haffner and colleagues [1].

These studies used different sampling methods. Six [10,19–23] involved community-based random sampling followed by invitation for clinical assessment. Another study [18] involved direct clinical assessment at baseline, but the participants were men screened (but not enrolled) in the Multiple Risk Factor Intervention Trial (MRFIT). The two remaining studies [8,24] relied exclusively on data recorded through administrative health-insurance databases.

There were also differences across studies in the time periods examined. In the studies involving direct clinical assessment, baseline data had been collected during the 1970s in four [18,19,21,23], and during the late 1970s and/or 1980s in three [10,20,22]. In the two administrative database studies [8,24], cohorts were defined based on data available in the 1990s. Individuals aged less than 35 years at baseline were included in both administrative database studies [8,24] and in one [23] of the other seven studies.

Reporting of ethnocultural background and socioeconomic status was also varied. One (Northern European/Dutch) study [22] was restricted to Europids. Only one other study [18] provided information on the ethnocultural background of participants: in this US study, 7.5% of those with previous CVD (defined as previous MI) and 16.9% of those with diabetes were reported to be of non-Europid background. Four studies [18–21] provided some description of socioeconomic status of their study subjects. In one North American (Quebec, Canada) study [19], both those with diabetes and those with previous CVD had attended school for approximately 10 years. In one UK study [20], approximately 56% of those with diabetes and 60% of those with prior MI were manual labourers.

3.3.1. Diabetes definitions

Most of the nine studies focused on prevalent diabetes, although one study [19] included only incident diabetes (self-reported and/or high levels of fasting glucose). Diabetes was defined through physicians' billing claims and hospital discharge data in one administrative database study [8] (Table 1), and through medication reimbursement data in the other [24]. Of the other studies, two [10,23] also used medication reimbursement data, one [22] used blood glucose testing exclusively and the remaining studies used self-reporting in combination with blood tests or review of the medical records. Three reports [19,22,23] indicated that individuals with type 1 diabetes were specifically excluded.

3.3.2. Previous cardiovascular disease

Previous CVD was exclusively defined as previous MI in four studies [8,18,23,24] (Table 1). The five others [10,19–22] included both MI and angina; of these, one [22] also included stroke and transient ischaemic attacks. Three [8,23,24] relied on hospital discharge database information (MI), while the remainder used some combination of self-reporting with or without confirmation (medical records; Table 1).

3.3.3. Outcome assessment

National death registers were used to identify mortality outcomes. CVD mortality was defined by International Classification of Diseases (ICD) codes 390–459. CHD mortality was defined by ICD codes 410–414, and the code for sudden cardiac death (ICD 798) [25] was also included in one study [22].

3.4. Quantitative data synthesis

The planned meta-analysis proceeded on the basis that:

- although case definitions differed somewhat across studies, the definitions used for diabetes and previous CVD were reasonably specific for these conditions;
- mortality outcomes were derived from national registers/death certificates with cause-specific classification by ICD codes;
- although loss to follow-up was not reported in every study, the use of national registers for mortality outcomes arguably mitigated this shortcoming to some degree;
- while it is acknowledged that the studies were conducted in different countries/regions/populations with potential differences in health beliefs and behaviours that could affect dietary and physical-activity habits, there have been clear reductions in physical activity and increases in obesity in most regions of the world.

For this reason, it is also acknowledged that there were differences in the variables for which HRs were adjusted across studies; however, the hierarchical model used in our present study can accommodate study differences by the inclusion of a between-study variance in the HRs.

Thus, according to our meta-analysis, all-cause mortality rates for men with diabetes alone were similar to those with previous CVD without diabetes (HR: 1.02, 95% CI: 0.93–1.12; Fig. 2A). The HR was centred at approximately 1.0 with a narrow CrI. In women, all-cause mortality rates with diabetes alone were similar or higher than those with previous CVD without diabetes (HR: 1.25, 95% CI: 0.89–1.76; Fig. 2B)—that is, the HR was centred at greater than 1.0 and the lower limit of the CrI was close to 1.0. In terms of CVD mortality among men, this was lower with diabetes alone compared with previous CVD without diabetes (HR: 0.82, 95% CI: 0.69–0.98;

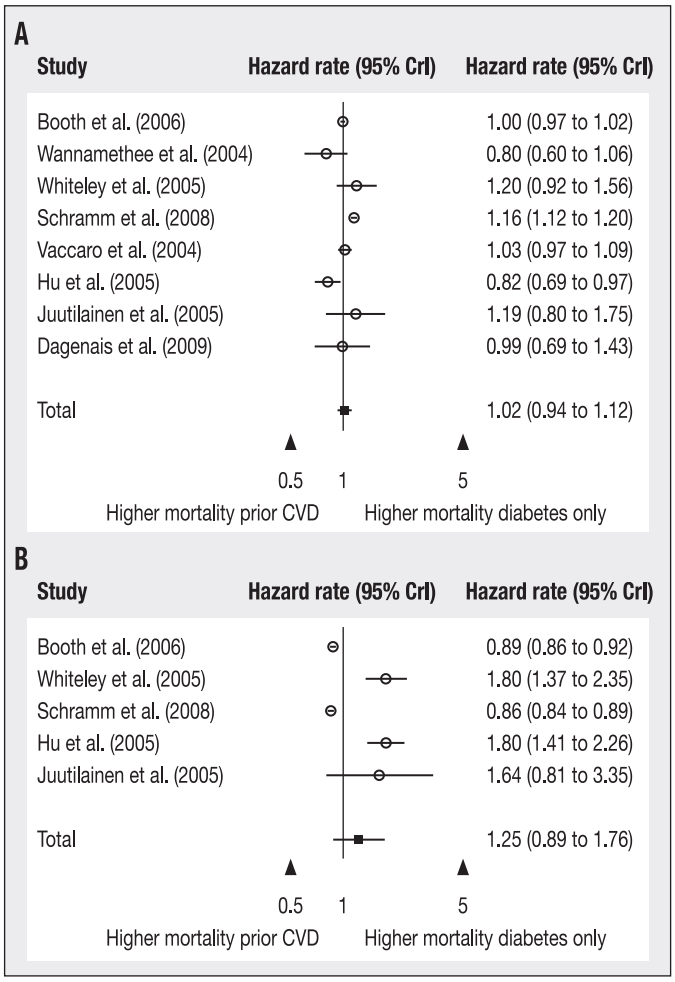

Fig. 2. Hazard ratios for all-cause mortality in diabetes *vs* mortality in those with previous cardiovascular disease (CVD), but no diabetes history, by gender: (A) men; and (B) women. CrI: credible interval.

Fig. S1A; see supplementary material associated with this article online). Among women, wide CrIs precluded any definitive conclusions regarding differences in CVD mortality (HR: 1.29, 95% CrI: 0.79–2.26; Fig. S1B; see supplementary material associated with this article online), but the point estimate was greater than 1.0. The findings for CHD mortality (Fig. S2; see supplementary material associated with this article online) were similar to those for CVD mortality: the HR for CHD mortality in men was 0.73 (95% CrI: 0.65–0.83) *vs* 1.28 (95% CrI: 0.75–2.22) in women.

In our sensitivity analysis excluding studies that included angina and transient ischaemic attacks in the previous CVD definition, the results for comparisons of diabetes alone *vs* previous CVD in men were similar to those when these studies were retained: all-cause mortality HR: 1.02, 95% CrI: 0.90–1.15 (four studies); CVD mortality HR: 0.85, 95% CrI: 0.67–1.05 (three studies); and CHD mortality HR: 0.70, 95% CrI: 0.60–0.83 (three studies). In women, the CrIs were widened even further and the point estimates were closer to 1.0: all-cause mortality HR: 1.08, 95% CrI: 0.72–1.63 (three studies); CVD mortality HR: 1.02, 95% CrI: 0.52–2.05 (two studies); and CHD mortality HR: 1.01, 95% CrI: 0.44–2.33 (two studies).

4. Discussion

The present findings confirm that, in men, CVD and CHD mortality is lower with diabetes alone compared with previous CVD (CVD mortality HR: 0.82, 95% CrI: 0.69–0.98; CHD mortality HR: 0.73, 95% CrI: 0.65–0.83), while the all-cause mortality was similar with diabetes and previous CVD (HR: 1.02, 95% CrI: 0.93–1.12). In women, the paucity of studies has limited firm conclusions, but there is an indication that CVD, CHD and all-cause mortality may be higher with diabetes alone compared with previous CVD (CVD mortality HR: 1.29, 95% CrI: 0.79–2.26; CHD mortality HR: 1.28, 95% CrI: 0.75–2.22; all-cause mortality HR: 1.25, 95% CrI: 0.89–1.76). In particular, for all-cause mortality in women, the lower limit of the 95% CrI was close to 1.0, suggesting that diabetes indeed confers a risk of all-cause mortality in women that is at least close to that of previous CVD.

Both biological and social explanations are possible for the potentially higher mortality rates among women with diabetes compared with women with previous CVD. In terms of potential biological explanations, women with diabetes may be more susceptible to the insidious development of diffuse small-vessel disease. Diabetic cardiomyopathy is seen more frequently in both women and in diabetes patients [26,27]. It is therefore possible that, in the years prior to the occurrence of MI, for example, diffuse asymptomatic small-vessel disease has already developed along with heart failure. Thus, when a CVD event arises, the impact may be greater, thereby increasing the likelihood of death, for example. Interestingly, blood glucose levels have been demonstrated to be higher in women than in men at the time of MI [28], and there is evidence that higher glucose levels at the time of MI may be associated with lower survival, although this association was more evident in individuals without diabetes. For this reason, it is possible that a greater relative impact of diabetes on mortality risk in women might be partly attributed to higher glucose responses to stressful events such as MI. In addition to higher glucose levels, the older postmenopausal woman may be particularly vulnerable to the impact of diabetes because of a general deterioration in CVD risk profile in terms of lipid [29] and blood pressure levels [30]. This may contribute to both myocardial damage prior to the first MI in women with diabetes as well as to lower rates of survival thereafter.

In terms of possible social explanations, material deprivation in women with diabetes appears to increase mortality more than in men with diabetes [31]. Other studies have demonstrated social gradients in diabetes prevalence that again appear to be more pronounced in women than in men [32–34]. This was also confirmed by a recent European review [35], and was consistent with our own analyses of Canadian Community Health Survey data [36,37]. Thus, there is a possibility that the mortality impact of diabetes may in part stem from the socioeconomic disadvantages associated with diabetes, which could potentially have an impact on motivation and/or opportunity/access to cardiovascular risk-management strategies (such as more physical activity, healthier dietary practices, smoking cessation and use of appropriate medication). Indeed, there is evidence that higher-quality healthcare services can attenuate socioeconomic status

(SES)-related differences in diabetes outcomes: for example, an Italian study indicated a greater impact of low levels of education on mortality in individuals without diabetes than in those with diabetes [38], which the investigators attributed to the high-quality health services for diabetes patients that could have potentially attenuated SES effects. Thus, there may be a particular need to ensure high-quality management for women with diabetes.

In a previous meta-analysis that also examined diabetes *vs* previous CVD in terms of mortality, Bulugahapitiya et al. [17] reported that adults with diabetes and no previous MI had a 43% lower risk for fatal and non-fatal CHD events (composite endpoint) compared with adults with previous MI and no history of diabetes (OR: 0.56, 95% CI: 0.53–0.60). As already discussed, however, rather than performing a meta-analysis of HRs as in our present meta-analysis, those investigators did a meta-analysis of ORs and, thus, were not able to account for time to event in their findings. Their approach also differed from ours by combining fatal and non-fatal CVD events. These differences may account for the lower risk with diabetes that they reported. Furthermore, if gender alters risk, as our present results appear to indicate, then the impact of diabetes on future CVD events would be less pronounced in men, as also suggested by our results. This suggests that a study without a gender-specific analysis that also includes more men is likely to underestimate the impact of diabetes.

However, while our present meta-analysis generated fairly precise results for men, our estimates for women were less precise because of the smaller number of studies including women. The number of studies could have been increased by opting for indirect comparisons of risk in diabetes subjects without previous CVD and in those with CVD without diabetes (comparing each to the absence of diabetes and CVD, respectively), but such indirect comparisons would not have satisfactorily addressed the issue of risk equivalence. In addition, our selected studies failed to consistently report time since diagnosis of diabetes or CVD, which was unfortunate, given that disease duration can impact mortality risk. Indeed, at least one study indicated that, compared with previous CVD, diabetes was associated with lower mortality earlier on, but had similar mortality with longer disease duration [18]. In another study, diabetes conferred a lower mortality risk than previous CVD at younger ages, but more similar risk at older ages [8].

This suggests that future studies examining mortality in women with diabetes would do well to separately examine women who are above and below the mean age at which 'risk transition' may occur, such as around the mean age for natural menopause (approximately 50 years of age). In addition, it would be useful to examine these issues in different ethnocultural groups, given that some groups are more susceptible to the development of diabetes itself and its complications.

Despite the limitations of the current literature and, thus, our present meta-analysis, our findings indicate that, compared with previous CVD, diabetes is associated with lower rates of CVD and CHD mortality, but similar all-cause mortality in men. In women, however, comparisons between previous CVD and diabetes were not conclusive for CVD and CHD mortality, but there was a strong indication that diabetes confers a similar or higher risk for all-cause mortality. Having a first MI is generally sufficiently symptomatic and disruptive to convince both patients and practitioners to engage in secondary preventative strategies. In contrast, a diagnosis of diabetes is often made on the basis of blood tests and may or may not be symptomatic. Thus, the need for definitive action may be less apparent to patients and practitioners, irrespective of treatment practice guidelines and health-promotion efforts [39]. More important, taking action includes not only pharmacological therapies (such as lipid-lowering agents, antihyperglycaemics and antihypertensives), but also higher physical-activity levels and more prudent dietary intakes. Indeed, our present synthesis of the available evidence may help practitioners to convince their diabetes patients of the importance of paying careful attention to risk-factor control, particularly in women. This work could also stimulate the development of gender-tailored strategies to reduce CVD risk in diabetes, particularly gender-specific interventions to optimize dietary and physical-activity habits.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary material (Figs. S1 and S2) associated with this article can be found at http://www.sciencedirect.com, at http://dx.doi.org/10.1016/j.diabet.2012.04.002.

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