DOI: 10.1111/j.1464-5491.2008.02640.x

Original Article: Epidemiology

Is diabetes a coronary risk equivalent? Systematic review and meta-analysis

U. Bulugahapitiya, S. Siyambalapitiya, J. Sithole* and I. Idris

Sherwood Forest Hospitals Foundation Trust and Academic Unit of Diabetes, Endocrinology and Metabolism, University of Sheffield, Sheffield and *Trent RDSU, University of Nottingham, Nottingham, UK

Accepted 25 November 2008

Abstract

Aims To determine whether patients with diabetes without prior myocardial infarction (MI) have the same risk of total coronary heart disease (CHD) events as non-diabetic patients with previous myocardial infarction.

Methods Using MEDLINE, EMBASE, Cochrane and MeSH in this systematic review and meta-analysis, extensive searching was carried out by cross-referencing from original articles and reviews. The study consisted of cohort or observational studies with hard clinical endpoints, including total CHD events (fatal or non-fatal myocardial infarction), stratified for patients with diabetes but no previous myocardial infarction, and patients without diabetes but with previous myocardial infarction. Studies with less than 100 subjects, follow-up of less than 4 years and/or without provisions for calculating CHD event rates were excluded. The review of articles and data extraction was performed by two independent authors, with any disagreements resolved by consensus.

Results Thirteen studies were included involving 45 108 patients. The duration of follow-up was 5–25 years (mean 13.4 years) and the age range was 25–84 years. Patients with diabetes without prior myocardial infarction have a 43% lower risk of developing total CHD events compared with patients without diabetes with previous myocardial infarction (summary odds ratio 0.56, 95% confidence interval 0.53–0.60).

Conclusion This meta-analysis did not support the hypothesis that diabetes is a 'coronary heart disease equivalent'. Public health decisions to initiate cardio-protective drugs in patients with diabetes for primary CHD prevention should therefore be based on appropriate patients' CHD risk estimates rather than a 'blanket' approach of treatment.

Diabet. Med. 26, 142–148 (2009)

Keywords coronary risk equivalent, diabetes, meta-analysis

Abbreviations CHD, coronary heart disease; CI, confidence interval

Introduction

Increased cardiovascular morbidity and mortality in patients with Type 2 diabetes is well established; diabetes is associated with twice the risk of incident coronary heart disease (CHD) and ischaemic stroke and 2–4 times increased risk of CHD and stroke mortality compared with patients without diabetes [1–3]. As more than 65% of deaths in patients with diabetes are from cardiovascular causes [4], the management of diabetes mellitus has shifted from a glucocentric approach to an aggressive multifactorial strategy to identify and target patients' cardiovascular risk factors.

Correspondence to: Dr Iskandar Idris DM FRCP, John Pease Diabetes Centre, Sherwood Forest Hospitals Foundation Trust, Mansfield Road, Sutton in Ashfield, UK, E-mail: iidris@aol.com

The widely quoted study by Haffner and colleagues has suggested that people with diabetes without prior myocardial infarction have a similar risk of CHD to those without diabetes who have had a myocardial infarction [5]. The study suggests that patients with diabetes should be treated as if they had existing CHD. This observational study, performed in a Finnish population cohort had some weaknesses, such as the lack of power to detect differences between two groups of patients. In addition, patients in this study were self-selected rather than derived from a population-based cohort. Despite these limitations, the concept of diabetes as a coronary risk equivalent, introduced by this study, has led to significant widespread changes in how clinicians approach primary CHD prevention in this population. The enthusiasm for this elegant concept is driven by the availabilities of therapeutic agents such as statins and aspirins, which lower CHD events irrespective of

individual CHD risk factors [6–8]. Consequently, some clinicians have argued for more aggressive treatment for CHD risk factors, including the widespread use of statins in all patients with Type 2 diabetes for primary CHD prevention irrespective of their cholesterol levels. Recent guidelines from the National Cholesterol Education Programme and the American Diabetes Association have also advocated lower low-density lipoprotein cholesterol targets in all patients with diabetes [9]. Following the findings by Haffner and colleague, large observational studies performed in other population groups, however, have provided contradictory results, with some studies supporting the concept of coronary risk equivalent [10–13] and others not [14–17]. As the issue is of considerable clinical importance, particularly for public health strategies aimed at reducing CHD, we undertook a systematic review and performed a meta-analysis of studies to compare the risk of total CHD events between two group of participants: (i) patients with diabetes without previous myocardial infarction and (ii) patients without diabetes but with previous myocardial infarction.

Methods

Search strategy

We identified relevant studies through a literature search using MEDLINE (1966 to April 2007), EMBASE (1980 to April 2007) and MeSH (from 1990) using a combined text word and MeSH heading search strategy of the term 'diabetes, myocardial infarction', 'no diabetes or non-diabetic, myocardial infarction' present within titles, keywords or abstracts. This search strategy was derived following a pilot single item search; 'diabetes', 'coronary heart disease' cardiovascular disease' (first 1000 results). We also searched the clinical trials registry of the Cochrane Library (Oxford, UK) to ensure that we did not miss any preliminary or follow-up observational arm of randomized control studies that are not included in MEDLINE and performed extensive searches using cross references from original articles and reviews.

Selection of studies and data extractions

Two reviewers (UB and SS) independently reviewed the title and abstract of all identified studies based on clearly stated a priori specification, with the following inclusion criteria: cohort studies or observational studies with hard clinical endpoints which included total CHD events (fatal or non-fatal myocardial infarction) stratified for (i) patients with diabetes but no previous myocardial infarction and (ii) patients without diabetes but with previous myocardial infarction. Screened citations were downloaded from the electronic searches to obtain full copies of potentially suitable reports for further assessment. We excluded studies with less than 100 subjects, studies with follow-up of less than 4 years and studies with no provision for calculating event rates. Studies with a mixture of cardiovascular events where the results could not be distinguished for specific CHD event rates were excluded. We did not assess the methodological criteria of the studies because of the uncertainties of the merit of scoring in meta-analysis of observational studies [18] and the limitations of suitable studies. Study details such as patients' clinical characteristics, demographics, definition of outcomes, inclusion and exclusion criteria and extraction of eligible data were obtained independently between UB and SS, ascribed on to standardized proforma and cross-checked for accuracy. Any disagreements were resolved by consensus based on a predefined agreed protocol for the meta-analysis, which sets out its objectives, hypothesis, scope, methods and design. Completed proforma was independently reviewed by a third reviewer (II) before a formal statistical analysis was performed with the help of a statistician with experience in meta-analysis design and analysis (JS). Our main outcome was a composite of major coronary events defined as fatal or non-fatal myocardial infarction (binary outcome data) in patients with diabetes without previous myocardial infarction compared with patients without diabetes but with previous myocardial infarction.

Data analysis

For each sub-study, odds ratios with their corresponding 95% confidence intervals (CIs) were calculated from the summary data provided. We calculated a weighted average of odds ratio, with weights being the inverse of variance of odds ratio. Using the fixed effects technique, the bigger the study the more weighting it received. For the random effects technique, because it took into account the heterogeneity in the data, a more equal weighting was applied. Forest plots of the sub-study outcomes were examined visually and we analysed heterogeneity between studies using the I^2 test and a value > 70% represents significant heterogeniety. As we detected heterogeneity between studies, we used and present the random effects model as the primary analysis here. The use of both fixed and random effect techniques, the latter because of the presence of significant heterogeneity, also forms the sensitivity analysis in our meta-analysis. Results are displayed as summary odds ratios and 95% CIs for achieving outcome measures of total CHD events.

Results

Literature search

Our search strategy yielded a total of 8322 studies, of which 334 included primary data. We further excluded 289 articles because they did not have outcome of interest or they reported duplicate data. A further 32 papers were excluded as a result of the lack of 'acute myocardial infarction with no diabetes' cohort at baseline (20 articles) or the lack of 'diabetes with no prior myocardial infarction' cohort at baseline (12 articles). The remaining 13 articles were eligible for inclusion in our meta-analysis [5, 10–17,19–22]. Table 1 shows the characteristics of these studies. A total of 45 108 patients were involved in these studies. Duration of follow-up varied from 5 to 25 years (mean 13.4 years) and the age range was 25–84 years. Five studies provided data for males and females separately [10–12,14,17], one was a female-only study [13] and two were male-only studies [15,16]. The other studies provided combined data for males and females together

Table 1 Characteristics of included study

Authors	Year	Country	Type of study	Age range (years)	Follow-up duration (years)	*n*	Gender	Adjustment	End points	Ascertainment of diabetes status	Ascertainment of MI status (baseline, ascertainment)
Lee *et al.* [19]	2004	USA	Cohort	45–64	9	1743	M/F	Age, sex, race, study centre, smoking, exercise, cholesterol, BP, BP treatments	Fatal and non-fatal MI (WHO criteria, ICD9)	Fasting or random glucose > 7.0 and > 11.1 mmol/l, glucose-lowering agents, self	ECG/self report, medical records/death certificates
Evans *et al.* [14]*	2002	UK	Register	45–64	8	2502	M/F	Age, sex	Fatal and non-fatal MI ICD9 410.9)	Validated registry record linked to medical records	Validated registry record linked to medical records
Haffner *et al.* [5]	1998	Finland	Cohort	45–64	7	959	M/F	Age, sex, cholesterol, BP, smoking	Fatal and non-fatal MI		
Hu FB *et al.* [13]	2001	USA	Cohort	45–64	20	5007	F	Age, BMI, smoking, menopausal status, parenteral history	Fatal CHD ICD9, (410–414)	Validated self-reported questionnaire	Self-reported MI, death certificates/medical records/autopsy
Lotufo *et al.* [15]	2001	USA	Cohort	40–84	5	8223	M	Age, BMI, smoking, exercise, alcohol	CHD mortality (ICD9 410–414)	Self-reported diagnosis	Self report, death certificates
Eberly *et al.* [22]	2003	USA	Cohort	35–57	18	1780	M/F	Age, race, smoking, alcohol, BMI, cholesterol, parenteral history, proteinuria, heart rate, Qt interval	Fatal CHD (ICD9 410–414, 429.2 and ICD10 120–125)	Self-reported use of glucose-lowering therapy/fasting glucose > 7.0 mmol/l	Self-report history of MI/ECG evidence of previous MI, death certification
Hu G *et al.* [17]	2005	USA	Survey	25–64	12	2270	M/F	Age, BMI, BP, cholesterol, smoking	Fatal and non-fatal MI (ICD9 410–414, 120–125)	Validated self report	Self report, register linkage
Cho *et al.* [20]	2002	US	Cohort	40–75	10	3323	M/F	Age, smoking, BMI, activity, parental history, alcohol, vitamin E supplement	Fatal CHD (ICD9, 410–414)	Validated self report	Validated self report, search of National death index/death certificates
Wannamathe *et al.* [21]	2004	UK	Cohort	54–74	10	4925	M/F	Age, smoking, social class, activity, alcohol	Fatal and non-fatal MI (ICD9 410–414), WHO criteria	Self report of physician diagnosed diabetes	Self report, patients notes/GP reports/ questionnaires
Natarajan *et al.* [11]	2003	USA	Cohort	35–74	20	478	M/F	Age, BP, smoking, cholesterol, BMI	CHD mortality	Two random glucose or use of glucose-lowering agents	Self reported, review of records
Natarajan *et al.* [12]	2005	USA	Cohort					Age, race, BP, smoking, cholesterol, BMI	CHD mortality (ICD9 410–414)	Self report of physician diagnosed Diabetes	Self report of physician diagnosed MI, death certificates
Vacarro *et al.* [16]	2004	USA	Cohort	35–57	25	9434	M	Age, race, income, cholesterol, BP, smoking	CHD mortality (ICD9, 410, 411–414, 429.2)	Self-reported use of glucose-lowering agent(s)	Self reported, death certification
Pajunen *et al.* [10]	2005	Finland	Survey	45–74	10	1085	M/F	Age, sex	Fatal and non-fatal CHD events	Self-reported and record linkage	Record linkage, death certificates/medical records/autopsy rep.

*Data for Evans *et al.* represents cross-sectional study.
BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; ECG, electrocardiogram; F, female; GP, general practitioner; ICD9, International Classification of Diseases 9; M, male; MI, myocardial infarction; WHO, World Health Organization.

[19–22]. Hence, the odds ratio for coronary risk equivalent in our study was analysed for males and females together. Two studies [14,22] followed patients from the time of diagnosis of acute myocardial infarction and diabetes, while others followed patients from a cross-sectional time point. The study by Evans *et al.* [14] provided outcome data for both. We excluded the important study by Booth *et al.* [23] because results were expressed in number of events per 1000 person-years and no separate data were available for the absolute number of patients achieving main outcomes stratified for the two baseline groups. We also excluded the important study by Juutilainen *et al.* [24] because they reported the same population group as the study by Haffner *et al.*, albeit at a longer follow-up duration and stratified for men and women. We chose the latter study because the Haffner study was the original landmark study that forms the reference point of this meta-analysis.

Main results

The study reports the total CHD events (fatal and non-fatal myocardial infarction) from 13 studies involved in the meta-analysis. There were 2603 total CHD events in the diabetes without prior myocardial infarction group and 3927 in the non-diabetic with prior myocardial infarction group. Figure 1 shows the forest plots of individual and total odds ratio for developing total CHD events (fatal or non-fatal myocardial infarction) in patients with diabetes without prior myocardial infarction compared with non-diabetic individuals with prior myocardial infarction. Across the age range studied in the meta-analysis, patients with diabetes without prior myocardial infarction had a significant 43% lower risk for total CHD events compared with non-diabetic subjects with prior myocardial infarction (summary odds ratio 0.56, 95% CI 0.53–0.60). To distinguish between studies which followed patients from the diagnosis of myocardial infarction and diabetes with studies which followed patients from a cross-sectional time point, we performed a separate meta-analysis for these two types of studies. For both types of studies, patients with diabetes without prior myocardial infarction had a lower risk for total CHD events compared with non-diabetic subjects with prior myocardial infarction (summary odds ratio 0.37, 95% CI 0.32–0.43 and 0.57, 95% CI 0.54–0.61 for the first and second types of study, respectively) (Figs 2 and 3). We carried out sensitivity analysis on the 13 studies included in this meta-analysis by calculating odds ratio according to fixed effects or random effects models. Results are similar between

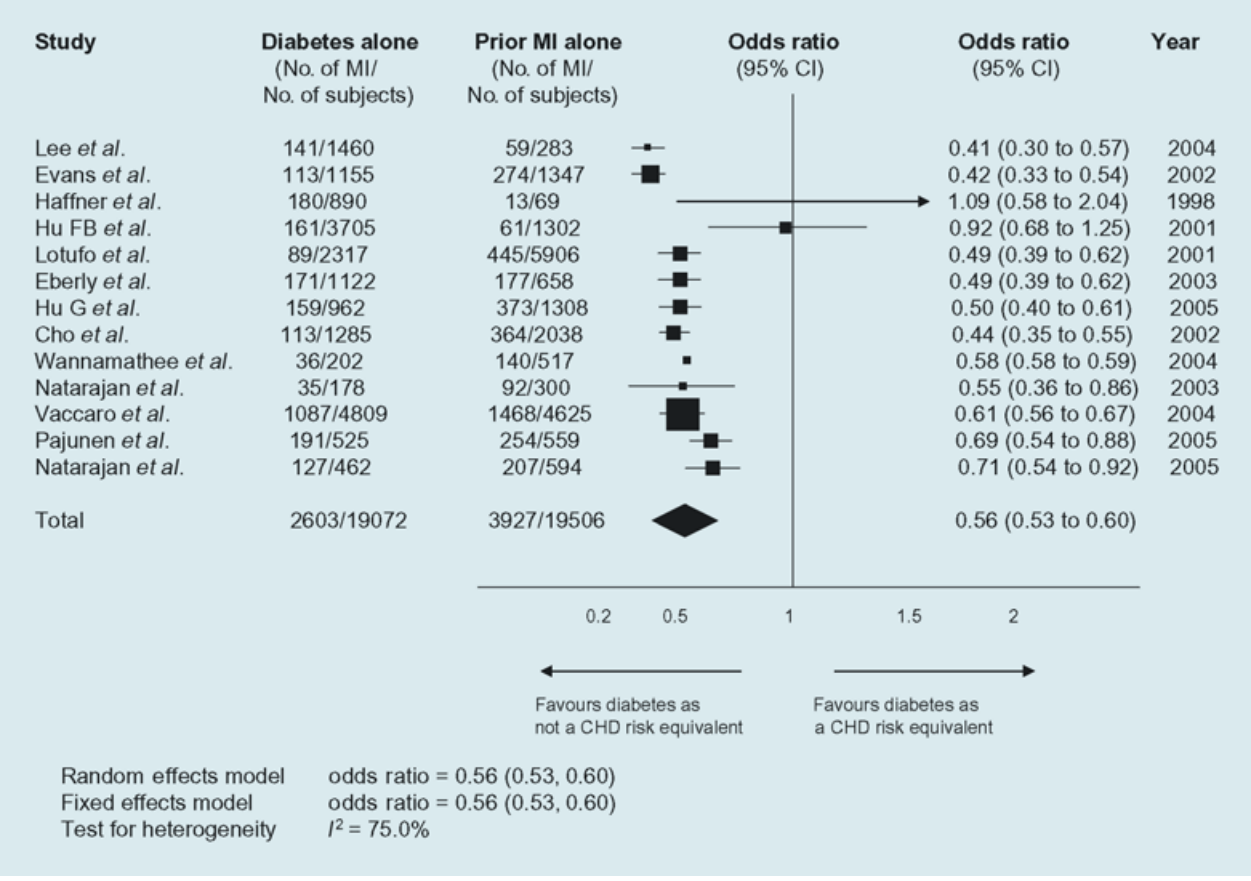

FIGURE 1 Effects of diabetes alone compared with prior myocardial infarction alone on odds of developing fatal or non-fatal myocardial infarction. CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.

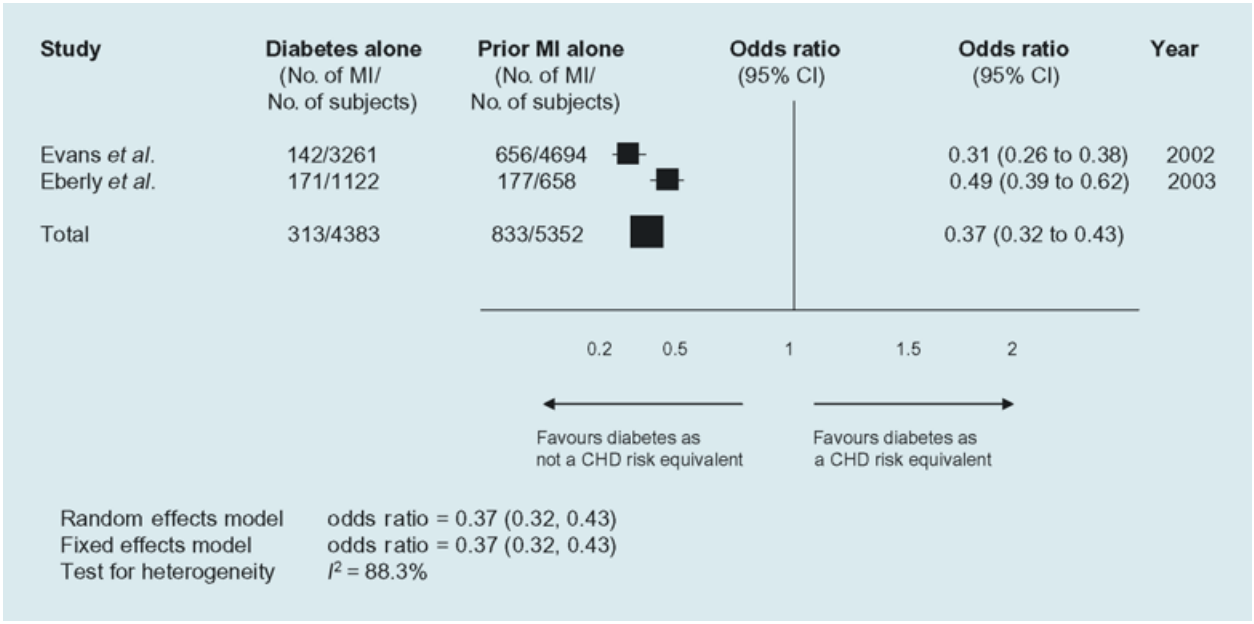

FIGURE 2 Effects of diabetes alone compared with prior myocardial infarction alone on odds of developing fatal or non-fatal myocardial infarction for studies which followed patients from their first diagnosis of myocardial infarction or diabetes. CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.

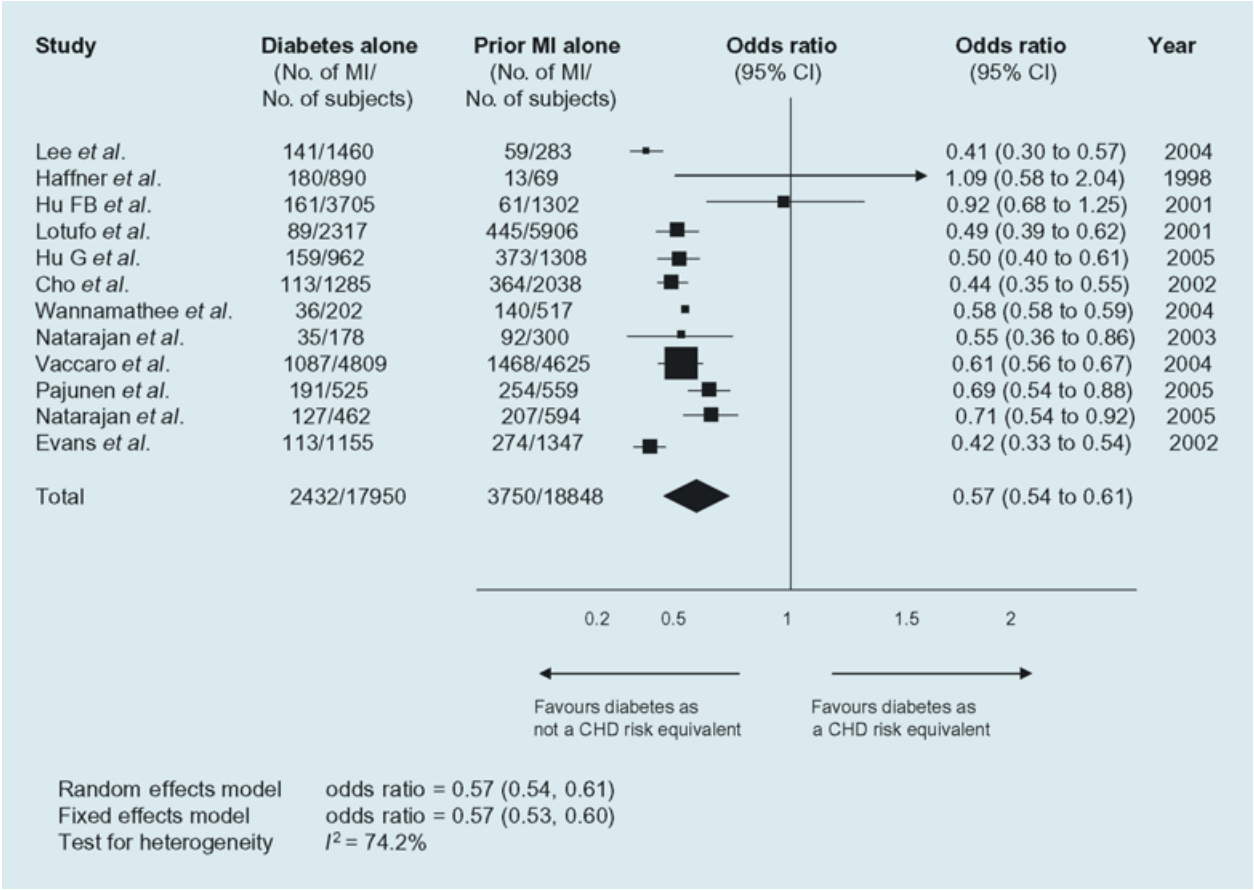

FIGURE 3 Effects of diabetes alone compared with prior myocardial infarction alone on odds of developing fatal or non-fatal myocardial infarction for studies which followed patients with diagnosis of myocardial infarction or diabetes from a cross-sectional time point. CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.

the two models. As there was significant heterogeneity in all our meta-analysis, results are presented based on the random effects model (Figs 1–3).

Discussion

The results of this meta-analysis indicate that patients with diabetes were at a lower risk of developing total CHD events compared with patients without diabetes with established CHD. This suggests that diabetes is not a coronary risk equivalent when the criterion for CHD is prior myocardial infarction applied across all age groups and did not support the notion that all patients with diabetes should be treated as secondary prevention. However, we recognized the importance of diabetes as a major risk factor for cardiovascular disease and that aggressive intervention in high-risk individuals is important in order to reduce cardiovascular mortality in patients with diabetes.

Following the original study by Haffner *et al.*, various studies from different population cohorts have provided varying conclusions on the validity of the concept of coronary risk equivalent in patients with diabetes. Differences in sample size, follow-up duration, selection criteria and population characteristics may explain these discrepancies. By using the random effects model and study weighting, our meta-analysis where possible took into account some of these confounders. However, the fact that calculated odds ratios were similar in the different studies despite variation in the follow-up period suggests that our result is generalizable. We were unable to use secondary outcome measures of total mortality or total cardiovascular events because the number of eligible studies that presented these outcome measures was too small.

Our findings suggest that individual risk assessment remains necessary when determining risks in patients with diabetes. This is particularly important within healthcare services with limited resources. Treating all patients with diabetes as secondary prevention irrespective of their cardiovascular risk may potentially limit the resources available to treat high-risk patients without diabetes. In a study of the general population in the UK, diabetes accounted for only 20% of all subsequent fatal cardiovascular disease [25]. The total risk of cardiovascular disease for any value of glycated haemoglobin (HbA_{1c}) was further determined by the presence of other factors such as smoking, hypertension or dyslipidaemia. Thus, focusing cardiovascular disease prevention solely on the presence of diabetes will have a limited impact on improving the population health as only one-fifth of cardiovascular events in the population are attributed to diabetes per se.

Some limitations to our analysis merit discussion. In view of the difficulty in finding studies with more homogenous patient profiles, the population of patients included in this study was quite heterogenous. However, the results obtained using the random effects technique are similar to the results calculated using the fixed effects technique method which do not take heterogeneity into account. As we did not have access to individual patient's data, we were unable to adjust for differences in sex, age and other confounders across the studies. However, the individual odds ratios for the studies were already adjusted for these relevant confounders. We also cannot exclude publication or language bias as a potential confounder to this study. By the same token, the findings from this study may not be easily extrapolated to high-risk ethnic group populations, such as south Asians, as we were not able to obtain individual studies from such populations that fulfilled the inclusion criteria of this meta-analysis. In addition, only a limited number of studies presented data for men and women separately. We therefore had to present our analysis based on total men and women together. In practical terms, this approach is probably more clinically applicable based on the assumption that coronary risk equivalent is assumed to apply equally in men and women. However, some studies have suggested that diabetes might be a coronary risk equivalent for women, but not men [12] and, thus, further clarification on gender-related difference is required.

Importantly, studies included in this meta-analysis determine short-term risk and may not take into account patients' total lifetime risk of cardiovascular disease. For example, a middle-aged person who was found to have diabetes during childhood may have a higher lifetime cardiovascular burden compared with another person of the same age who was only recently diagnosed to have diabetes [26]. It is interesting to note that the result of our meta-analysis, which included studies that followed patients up from diagnosis of diabetes or myocardial infarction, gave a much lower odds ratio for developing a future myocardial infarction compared with studies which determined risk from a cross-sectional time point. While this may suggest that the concept of 'diabetes being a coronary risk equivalent' is less true if risk assessment is determined from the outset of diagnosis of diabetes or first myocardial infarction, this did not take into account patients' duration of diabetes, duration of follow-up of these patients as well as their lifetime risk. In addition, both studies included in this sub-meta-analysis did not include patients below the age of 35 years [14,22].

In conclusion, the results of this meta-analysis suggest that diabetes is not a coronary risk equivalent. The important implication of our finding is that primary prevention strategy to prevent cardiovascular disease in patients with diabetes should still be based on patient's absolute risk of developing cardiovascular events rather than a 'blanket' approach to treatment irrespective of patients' absolute CHD risk. The latter may confer little clinical benefit in many patients with diabetes [26] and will expose patients at lower CVD risk to lifelong treatment with attendant adverse effects, lack of compliance and polypharmacy at the expense of high cost to the healthcare provider. Consideration should therefore be given to the most cost-effective strategy to reduce cardiovascular risk, one that would identify the least number of individuals but would prevent the largest amount of cardiovascular events. Further studies are required to clarify the nature of such strategy.

Authors' contributions

UB and SS were involved in the study concept and design, data acquisition and data analysis, JS was involved in the study concept and design, data acquisition and led data analysis and interpretation. II conceived the study, was involved in the study concept and design and wrote the first draft the manuscript. All authors read, contributed towards and approved the final manuscript.

Competing interests

Nothing to declare.

References

1 Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis in Ontario, Canada 1996/97. *Diabetes Care* 2004; **27**: 407–414.

2 Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the US population, 1971–1993. *Diabetes Care* 1998; **21**: 1138–1145.

3 Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 1979; **2**: 120–126.

4 American Diabetes Association. Complications of diabetes in the United States. Available at http://www.diabetes.org/diabetesstatistics/complications.jsp Last accessed 14 September 2007.

5 Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with Type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction *N Engl J Med* 1998; **339**: 229–234.

6 Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**: 2005–2016.

7 Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ *et al.* Primary prevention of cardiovascular disease with atorvastatin in Type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**: 685–696.

8 Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid-lowering drug treatment for diabetes and non-diabetic patients: meta-analysis of randomized controlled trials. *Br Med J* 2006; **332**: 1115–1124.

9 JBS-2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005, **91**: v1–v52.

10 Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Räihä P, Kärjä-Koskenkari P *et al.* Myocardial infarction in diabetic and non-diabetic persons with and without prior myocardial infarction: the FINAMI Study *Diabetologia* 2005; **48**: 2519–2524.

11 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**: 1735–1740.

12 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**: 430–435.

13 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 mortality in women: 20 years of follow-up. *Arch Intern Med* 2001; **161**: 1717–1723.

14 Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with Type 2 diabetes and those who had myocardial infarction: cross-sectional and cohort studies. *Br Med J* 2002; **324**: 939–942.

15 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**: 242–247.

16 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 screeners of the Multiple Risk Factor Intervention Trial. *Arch Intern Med* 2004; **164**: 1438–1443.

17 Hu G, Jousilahti P, Qiao Q, Katoh S, Tuomilehto J. Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with and without history of myocardial infarction. *Diabetologia* 2005; **48**: 656–661.

18 Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *J Am Med Assoc* 1999; **282**: 1054–1060.

19 Lee CD, Folsom AR, Pankow JS, Brancati FL; Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular events in diabetic and non-diabetic adults with or without history of myocardial infarction. *Circulation* 2004; **109**: 855–860.

20 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**: 954–960.

21 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**: 1398–1403.

22 Eberly LE, Cohen JD, Prineas R, Yang L; Intervention Trial Research group. Impact of incident diabetes and incident non-fatal cardiovascular disease on 18-year mortality: the multiple risk factor intervention trial experience. *Diabetes Care* 2003; **26**: 848–854.

23 Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet* 2006; **368**: 29–36.

24 Juutilainen A, Lehto S, Rönnemaa T, Pyörälä 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**: 2901–2907.

25 Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A *et al.* Glycated haemoglobin, diabetes and mortality in men in Norfolk, cohort of European prospective investigation of cancer and nutrition. (EPIC Norfolk). *Br Med J* 2001; **322**: 15–18.

26 Robins SJ. Cardiovascular disease with diabetes or the metabolic syndrome: should statins or fibrates be first line lipid therapy? *Curr Opin Lipidol* 2003; **14**: 575–583.

