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Sex-Specific Differential in Risk of Diabetes-Related Macrovascular Outcomes

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Abstract

Reports from recent studies suggest that diabetes confers a higher risk of cardiovascular disease in women compared to men. Larger studies, including meta-analyses, report that women with diabetes have a 44% greater risk of incident coronary heart disease and a 27% greater risk of incident stroke compared to men with diabetes. In this article, we summarize results from longitudinal studies that examine sex differences in risk factors for and rates of macrovascular complications from diabetes. We also discuss possible mechanisms for increased cardiovascular risk associated with diabetes in women compared to men, including the clustering of hypertension, obesity, and elevated triglycerides, the possible contribution of hormonal differences, and sex differences in the prescription of and adherence to pharmacologic treatment. In conclusion, diabetes is associated with a slightly higher risk of cardiovascular disease in women compared to

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Amanda Lyon, Elizabeth A. Jackson, Rita R. Kalyani, Dhananjay Vaidya, and Catherine Kim declare that they have no conflict of interest.

men. Future studies should further explore the reasons underlying imperfect use of medications that lower cardiovascular risk in both women and men with diabetes.

Keywords

diabetes; cardiovascular; sex; coronary heart disease; stroke

Introduction

In this review, we describe the literature regarding sex differences in the associations between type 2 diabetes and CVD. Diabetes confers increased risk of microvascular and macrovascular events in both men and women (1). However, women with type 2 diabetes have been reported to have significantly higher risks of both fatal and non-fatal coronary heart disease (CHD) and stroke than men with diabetes (2–4). A key to these sex differences includes the CVD risk factors that often accompany diabetes. The presence of these risk factors has been labeled "metabolic syndrome" (MetS), which is variably defined across studies (5). Definitions of both MetS and diabetes are shown in Table 1; of note, epidemiologic studies that examine sex differences rely primarily on older definitions of diabetes which do not incorporate elevations in hemoglobin A1c levels.

CHD events comprise fatal or nonfatal myocardial infarction (MI) and sudden cardiac death as typical “hard” endpoints (6), and stable and unstable angina, heart failure, coronary artery bypass grafting, and percutaneous coronary interventions for measurement of “total” events (6). The World Health Organization (WHO) defines cerebrovascular disease as “a general term encompassing different disturbances of the vascularization of the brain (7).” More specifically, stroke is defined as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin” (7). This includes subcortical strokes, which occurs more frequently in type 2 diabetes compared to other types of ischemic strokes (8; 9). Although ischemic stroke is distinct from hemorrhagic stroke, the majority of studies which report upon diabetes and sex differences do not distinguish between subtypes of stroke. Cerebrovascular disease also includes transient ischemic attack, defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (10).

In the following paragraphs, we summarize the evidence from prospective studies examining sex differences in macrovascular complications from diabetes. We review possible mechanisms for the increased CVD risk observed in women with diabetes as compared to men with diabetes. Finally, we conclude with a summary of research examining sex differences in the pharmacologic management of CVD risk in persons with diabetes.

Recent systematic reviews

In 2014 and 2015, several reports summarized the extensive literature on sex differences in the impact of diabetes upon CVD risk (2–4; 11; 12). Peters *et al.* conducted a meta-analysis which included data from 64 cohorts of 858,507 individuals 20–107 years of age (2).

Baseline data was collected from 1960 to 1997 (2) and follow-up ranged between 5 to 30 years. The authors included prospective population- based studies that provided relative risks (RR) or equivalents for the association between diabetes and CHD in both men and women. This meta-analysis noted that individuals with diabetes have greater CHD risk compared to those without diabetes, and the difference in the magnitude of this risk was greater in women compared to men [RR 2.82, 95% CI (2.35, 3.38)] vs. women [RR 2.16, 95% CI (1.82, 2.56)] (2). Women with diabetes had a 44% greater risk for CHD than men with diabetes [RR 1.44, 95% CI (1.27, 1.63)] (2). This relationship reached statistical significance mainly in studies with a larger number of participants. More specifically, in the 21 studies that were included in this review, 5 showed statistically significant higher RRs in women as compared to men, accounting for more than 43% weight in the overall RR ratio. Ethnicity, geographical location, year of data collection, and duration of follow up did not appear to influence the risk in women compared to men (2).

In another meta-analysis of studies among healthy young and middle-aged adult population without CHD, Kalyani *et al.* also examined sex differences in diabetes and CHD risk (11). This report included participants in the Gene Study of Atherosclerosis Risk in Families (GeneSTAR) (n=1448, follow up of 12 years), the Multi-Ethnicity Study of Atherosclerosis (MESA) (n=3,072, follow up 7 years), and the Nutrition Health and Nutrition Examination Survey III (n=6,997, follow up 15 years) (11). After adjustment for age, body mass index, smoking, hypertension, lipid levels, anti-hypertensive and cholesterol lowering medications, men without diabetes had an increased risk of CHD compared to women without diabetes [hazard ratio (HR) 2.43, 95% CI (1.76, 3.35)]. However, CHD rates were similar between men and women who had diabetes [HR 0.89, 95% CI (0.43, 1.83)]. These findings suggest that among younger adults when women are expected to have lower rates, diabetes equalizes the risk of CHD between the sexes.

Peters *et al.* also conducted a similar systematic review with stroke as the primary outcome (3). The resulting meta-analysis examined 64 cohorts and included 775,385 individuals with 12,539 fatal and non-fatal strokes (3). The year of baseline data collection ranged from 1961-2002, with duration of follow up between 5 and 32 years. Compared to individuals without diabetes, the RR of stroke in individuals with diabetes was 2.28 (95% CI 1.93, 2.69) in women and 1.83 (95% CI 1.60, 2.08) in men (3). The pooled risk ratio for stroke in women compared to men was 1.27 (95% CI 1.10, 1.46), suggesting a 27% greater risk for stroke in women with diabetes than in men with diabetes. Similar to the meta- analysis that examined CHD as an outcome, this association was not statistically significant in individual studies but only reached significance in the pooled analysis. The exception was in the Atherosclerosis Risk in Communities (ARIC) Study (13), which had a large number of participants.

Updated literature review

For the purposes of this report, we also performed a literature review to determine if additional studies with primary data had been published after the 3 reports noted above (2; 3; 11). Although we were also interested in the impact of sex differences in the impact of diabetes upon peripheral arterial disease, a PubMed search using key words of diabetes

AND peripheral vascular disease AND sex yielded 929 articles, none of which were prospective studies that reported on incident peripheral vascular disease in women and men who have diabetes.

A search using the key words of diabetes AND coronary heart disease AND sex with the publication dates between January 2013 and February 2015 yielded 676 articles. Inclusion criteria were that the analyses be prospective and note sex-specific risk; publications not in English were excluded. One (22) of the 676 studies met inclusion criteria (Table 2). A search using the key words of diabetes AND stroke AND sex with the publication dates between January 2013 and February 2015 and in English yielded 591 articles. Two of the 591 studies met inclusion criteria (Table 2) (14; 15). A final search was done in an attempt to capture any studies meeting our inclusion criteria that may have been missed in the recent meta-analyses or previously described searches. In this search we used the key words of prospective AND diabetes AND cardiovascular AND sex which yielded 1869 articles. The majority of prospective studies examining incident stroke and CHD were captured in the previously described searches. However, we found 4 reports which examined CHD and stroke as a summary measure and these are included in Table 2 (16–19).

Coronary heart disease

Hadaegh *et al.* (20) analyzed data from a cohort of 8071 individuals age >30 years participating in the prospective, population based Tehran Lipid and Glucose Study and selected from a district in Tehran using a multistage cluster random sampling method. Men (n=2267) and women (n=2931) were categorized by diabetes status and CHD at baseline and followed for a mean period of 7.6 years. Baseline and outcome CHD data were elicited through self-report and verified with medical record review; death and cause of death was ascertained using death certificate data. Women with previously undiagnosed diabetes [HR 3.1 (95% CI 1.8, 5.6)] and previously diagnosed diabetes [HR 6.2 (95% CI 3.6, 10.6)] had a greater risk of CHD compared to women without diabetes. In contrast, men with previously undiagnosed diabetes [HR 1.7 (95% CI 1.1, 2.7)] had relatively smaller magnitude of CHD risk compared to men without diabetes; men with previously diagnosed diabetes had a similar point estimate for risk but the difference was not statistically significant compared to men without diabetes[HR 1.7 95% CI (0.9, 3.3)] Of note, the the majority of the individuals were free from diabetes and CHD at baseline including 1726 (or 76%) of total men and 2184 (or 75%) of total women. The number of individuals with “new or known” diabetes according to CHD status was relatively few, with only 313 men and 462 women fitting into this category. This may account for the insignificant relationship observed between men with known diabetes and the RR of CHD, particularly after adjustment for other CVD risk factors including age, hypertension, and smoking. Furthermore, this study largely relied on self-report for CHD screening, which may have led to incomplete ascertainment of CHD and biased results to the null (21; 22).

Stroke

Zhao *et al.* (14) examined whether values of HbA1c predicted incident stroke risk among 10,876 men and 19,278 women with newly diagnosed diabetes participating in the Louisiana State University Hospital Based Longitudinal Health Study who were followed for a mean

period of 6.7 years. Baseline and follow up data were extracted from the electronic health records, which may ascertain more severe strokes. In men, HbA1c level was not associated with stroke risk [HR 1.01, 95% CI (0.99, 1.04)]. In contrast, among women, the age-adjusted HR for each 1% increase in HbA1c was 1.06 (95% CI 1.04, 1.08) (14). This suggests that level of glycemia is related to stroke risk in women but not men, although a direct comparison between men and women was not performed.

CHD or Stroke

Guzder *et al.* (16) analyzed data from a nested case control study of 736 individuals with diabetes and non-diabetic age- and sex-matched controls. This population was derived from the Poole Diabetes Study, a community-based prospective study, recruited from primary care practices in the UK Poole Hospital catchment area. The average length of follow-up was 5.25 years, with the primary outcome of CVD and non-CVD mortality, ascertained from medical record review, hospital discharge data, and death certificates. Although diabetes was associated with increased CVD mortality in both sexes, the magnitude of risk was greater among women [odds ratio (OR) 2.36, 95% CI (1.13, 4.78)] compared to men [(OR) 1.93, 95% CI (1.10, 3.68)] (16). Models adjusting for other CVD risk factors were not reported.

Mak *et al.* (15) grouped 3,414 individuals participating in the Singaporean National Health Survey of 1992 who were aged 18–69 years and without CVD. The primary outcome was a hospital discharge diagnosis of CHD, stroke, or CVD mortality, which again may capture more severe events and events with “typical” as opposed to atypical presentations. Over a 10-year follow-up, the annual unadjusted CVD event rate (per 1,000 person years) in women with diabetes and MetS was 21.5, but only 5.3 in women with diabetes but without MetS. These data suggest that women with diabetes and MetS have a much greater risk of CVD than women with diabetes without MetS(15). Among men, the annual unadjusted CVD events rate (per 1,000 person years) in men with diabetes and MetS was 21.4, and 22.5 in men with diabetes but without MetS (15). This suggests that diabetes has a large impact on CVD risk in men, but the risk is similarly increased regardless of MetS status. Even though CVD events occurred more commonly among men than women without MetS [HR 6.04, 95% CI (1.43, 25.6)], the risk was similar in men and women with type 2 diabetes and MetS [HR 0.98, 95% CI (0.48, 1.99)].

Schottker *et al.* (17) followed 8,365 individuals who presented for health maintenance examinations for about 8 years and examined the incidence of MI, stroke, or CVD death ascertained by death certificate and self-report with verification by medical review. Unadjusted analysis showed that diabetes was associated with an increased CVD risk in men [HR 2.36 (95% CI 1.81, 3.09)] and women [HR 2.64 (95% CI 1.96, 3.55)]. After adjustment for CVD risk factors, diabetes was associated with a similar increased CVD risk in men [HR 2.09 (95% CI 1.61, 2.71)], while in women, the risk of CVD associated with diabetes dropped to a much greater extent 1.71 (95% CI 1.25, 2.35). While men and women were not compared directly, this report, as well as the report by Mak *et al.* (15), suggest that the CVD risk factors that accompany diabetes are key to the elevated CVD risk observed in diabetic women.

Using an administrative database, Baviera *et al.* (18) reported that among 158,426 individuals with newly diagnosed diabetes followed for a mean of 33 months, men and women had similar incidences of hospitalization for CVD. They also reported a 19% higher risk of total mortality in women with diabetes compared to men [HR 1.19 (95% CI 1.13–1.24)]. The investigators also noted that women were less likely than men to be prescribed lipid-lowering and antiplatelet medications, despite their diagnoses of diabetes. It is possible that inclusion of persons with recent diabetes diagnoses, short follow-up, and reliance on only discharge data may have limited their ability to draw conclusions regarding diabetes of longer duration, as well as less severe presentations of CVD. However, these findings suggest that differences in treatment may contribute to increased CVD risk in women with diabetes.

In The Korean Heart Study (19), Kim *et al.* followed 408,022 individuals undergoing voluntary private health exams in 17 centers in South Korea for a 10 year period. They found that diabetes posed a similar risk for CVD in men [HR 1.52 (95% CI 1.46, 1.58)] compared to women [HR 1.45 (95% CI 1.38, 1.53)](19). It is possible that the nature of individuals who chose to undergo screening, the low CVD event rate, and the methods of ascertainment that relied upon hospital discharge data contributed to a lack of sex- differential. Alternatively, it is possible that in this particular racial/ethnic group, sex differentials are not as pronounced as noted in the non-Asian populations studies summarized above. Of note, we found few studies that examined the impact of gender, diabetes, and race interactions in cardiovascular disease outcomes.

Potential mechanisms

In the following section, we discuss possible mechanisms through which diabetes may increase risk of CVD in women as opposed to men. These mechanisms include the increased likelihood that CVD risk factors are more strongly associated with diabetes in women than in men, the possible role of sex hormones, and sex differences in the effectiveness of pharmacologic therapies and the prescription of such therapies.

Risk factor clustering

Several reports have suggested that the traditional cardiovascular risk factors cluster to a greater extent in women than in men. This was first illustrated in the Rancho Bernardo study, a cohort based in southern California (23; 24). The proportion of study participants with diabetes who clustered in the 90^{th} percentile of smoking, obesity, blood pressure, and triglycerides was almost twice as high in women compared to men (23; 24). Specifically, a meta-analysis which included the Rancho Bernardo cohort as well as 6 other cohorts noted a large and statistically significant difference in diabetes-associated CHD risk in women [HR 3.42, 95% CI (2.55, 4.59)] compared to men [HR 2.07, 95% CI (1.39, 3.08)] prior to adjustment for hypertension, elevated triglycerides, smoking, and obesity (25). After adjusting for these risk factors, the dramatic difference in CHD risk associated with diabetes between sexes nearly disappeared, with adjusted RR of 2.9 in women and 2.3 in men (25). This clustering of risk factors in women compared to men was also suggested by the

previously mentioned report by Mak *et al.* (15), where adjustment for MetS factors had a greater impact on women's than men's CVD risk.

The meta-analysis by Peters *et al.* suggest that clustering of risk factors may not account for sex differentials in the impact of diabetes upon stroke as opposed to CHD (3). In that meta-analysis, as mentioned earlier, the age adjusted RR was 2.46 for women and 1.96 in men, decreasing to 2.37 in women and 1.90 for men after adjusting for other cardiovascular risk factors (3). This is a similar degree of attenuation of less than 10% in both sexes (3). Thus, while explanations are speculative, it is possible that the mechanisms for sex-specific differentials differ by vascular bed, including the differential prescription of CVD risk-lowering medications for women vs. men (26).

Sex hormone profile

Sex hormones may have dimorphic effects regarding CVD risk and CVD in men and women, i.e. androgenic environments may be more favorable in men compared to women (27). We note, however, that this is not necessarily true for other types of metabolic outcomes and sarcopenia; for the purposes of this review, we limit ourselves primarily to descriptions of CHD risk.

The natural cardioprotection observed in women when compared to men has been well recognized and has been largely attributed to differences in endogenous sex steroids (28). Thus, when we observe that women with diabetes appear to have an increased risk of CHD compared to men with diabetes (29), it is reasonable to postulate that diabetes itself may be associated with changes in endogenous sex steroids. Previous reports suggest that testosterone may be associated with diabetes in men and women. Men with diabetes have lower levels of testosterone compared to men without diabetes (30; 31). In contrast, women with diabetes have higher levels of testosterone compared to women without diabetes (30). Along similar lines, a number of studies suggest that low levels of testosterone in men predict incident coronary events, while extremes of bioavailable testosterone may have negative effects on CHD risk in women (32; 33). However, it is not known whether sex steroids act independently from other risk factors for diabetes, particularly visceral and hepatic adiposity (34) and exercise capacity (35), due to the difficulty of accurately quantifying the volumes of adipose tissue depots and sex steroid concentrations and accurate measures of fitness in prospective studies that are adequately powered to examine incident diabetes.

Statins, aspirin, and hypertensive therapies

Another potential explanation for the greater impact of diabetes upon CVD risk in women than in men is less intensive pharmacologic therapy in women and men. Several reports have noted that women are less likely to receive statins than men despite having similar risk (18; 36–38). Women are also more likely to discontinue statin therapy than men secondary to side effects (39). It is also possible that the relative underrepresentation of women in randomized trials of statin therapy for prevention contribute to perceptions of lower CVD risk in women, despite a diabetes diagnosis. However, evidence for the benefits of statins is substantial in men and women, including a meta-analysis which showed 20% reduction in

overall CVD risk across primary and secondary prevention trials. Women (n=2,625) had a 17% reduction compared to men (n=10,765) who had a 23% reduction (40). Therefore, the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend statins for use in intermediate as well as high-risk adults (41).

Women with diabetes have reported aspirin use less often than men, even in cohorts such as the United Kingdom Prospective Diabetes Study, a randomized trial, in which macrovascular events were a primary outcome (42). Whether this is related to patient or provider factors remains unclear. While the Antithrombotic Trialists' Collaboration demonstrated clear evidence for secondary prevention of myocardial infarction (MI) in women with aspirin therapy (43), a large meta-analysis showed that aspirin reduced the MI risk in men with diabetes [RR 0.57, 95% CI (0.34, 0.94)] but not in women with diabetes [RR 1.01, 95% CI (0.71, 1.65)] (44). Aspirin use was also not associated with a statistically significant decrease in stroke risk in men [RR 1.11, 95% CI (0.75, 1.64)] or women (RR 0.75, 95% CI (0.37, 1.53) with diabetes (44). Thus, perceptions of reduced benefit in women with diabetes without a macrovascular event may be contributing to differences in aspirin use. However, specifically regarding men and women with diabetes, current consensus guidelines released in 2010 by the AHA and the ADA recommend consideration of aspirin for primary prevention in adults with an intermediate risk of CVD (10-year CVD risk of 5–10%) (45).

Sex differentials in the benefits of glycemic therapy and hypertensive therapy have not been reported, and to our knowledge, studies reporting differences in pharmacologic therapy between men and women with diabetes for these therapies do not exist. Although prospective epidemiologic studies have demonstrated a graded relationship between the degree of hyperglycemia and the risk of microvascular events (46), strict glycemic control has not been conclusively demonstrated to reduce the risk of incident macrovascular events in randomized trials (47–50). Similarly, while achieving moderate targets of blood pressure does reduce CVD risk among persons with diabetes (51; 52), sex disparities in degree of blood pressure control have not been reported. Among persons with type 1 diabetes, angiotensin-converting enzyme inhibitors are prescribed less often in women than in men, but it is unclear how much of this disparity was due to men's higher blood pressure levels (52).

Conclusion

The risk for CHD and stroke associated with diabetes may be higher in women compared to men, particularly in younger populations. However, sex differences are observed primarily in large cohorts, suggesting that the magnitude of the difference is relatively modest. Accordingly, it is important to consider aggressive screening and risk factor modification in both men and women with diabetes. Since the increased CVD risk observed in women compared to men with diabetes may be due to the presence of other CVD risk factor abnormalities besides hyperglycemia, it is important to address elevations in blood pressure and statin use in women. Further investigation is needed to determine the reasons for potential underuse of pharmacologic therapies that may benefit persons with diabetes and the margin of benefit for such therapies as aspirin.

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•• Of major importance

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Table 1

Definitions of Type 2 Diabetes and Metabolic Syndrome (MetS)

Type 2 Diabetes
American Diabetes Association (ADA)
Hemoglobin A1c ≥6.5%, OR
Fasting plasma glucose ≥ 126 mg/dl, OR
2-hour plasma glucose ≥ 200 mg/dl, OR
Random plasma glucose ≥ 200 mg/dl, in the presence of symptoms of hyperglycemia
Former World Health Organization (WHO) (53)
Fasting plasma glucose ≥ 140 mg/dl, OR
2-hour plasma glucose ≥ 200 mg/dl, OR
Random plasma glucose ≥ 200 mg/dl, in the presences of symptoms of hyperglycemia
MetS
Adult Treatment Panel III (54) classifies individuals as having MetS if ≥ 3 of the following are present:
1) abdominal obesity, indicated by waist circumference ≥102 cm in men or ≥88 cm in women
2) hypertriglyceridemia, indicated by triglyceride level ≥ 150 mg/dL (1.70 mmol/L)
3) low high-density lipoprotein cholesterol, indicated by a level <40 mg/dL (1 mmol/L) in men or <50 (1.30 mmol/L) in women
4) blood pressure ≥ 130/85 mm Hg or drug treatment for hypertension
5) fasting plasma glucose ≥ 100 mg/dL (5.6 mmol/L) or a pre-existing diagnosis of diabetes
While the exact criteria vary across organizations, definitions often include a combination of lipid abnormalities, blood pressure elevations, central obesity, and glucose elevations (54–56). Comparisons of these slightly different MetS definitions have demonstrated that they are generally equally predictive of incident CVD (5).

Table 2

Longitudinal studies examining the impact of diabetes (DM) upon cardiovascular disease (CVD) outcomes in men vs. women.

Reference	Country	Year	Study participants, (n) duration of follow up	Outcome definition	Results, Risks are adjusted unless explicitly noted otherwise
Baviera et al(18)	Italy	2002–2006	158,426 followed for 33 months	First hospital admission diagnosis of coronary heart disease (CHD), myocardial infarction (MI), heart failure (HF), CVD, stroke, and death	Risk of CHD in women with DM vs. men with DM, HR 1.10, (95% CI 1.01–1.19) Risk of MI in women with DM vs. men with DM, HR 1.13, (95% CI 1.00–1.27) Risk of CVD in women with DM vs. men with DM, HR 1.01, (95% CI 0.94–1.10) Risk of stroke in women with DM vs men with DM, HR 1.04, (95% CI 0.93–1.16) Risk of HF in women with DM vs. women without DM, HR 1.11, (95% CI 1.01–1.22) Risk of total mortality in women with DM vs. men with DM, HR 1.19, (95% CI 1.13–1.24)
Guzder(16)	United Kingdom	1996–1998	736 followed for 5.25 years	CVD mortality by death certificate	Risk of CVD mortality in men with diabetes vs. men with normal glucose, OR 1.93 (95% CI 1.01–3.68) Risk of CVD mortality in women with diabetes vs. women with normal glucose, OR 2.36 (95% CI 1.13–4.78)
Hadaegh et al(20)	Tehran	1999–2001	5,198 grouped based on the presence of new or known DM and CHD at baseline followed for 7.6 years	Self-report of CHD with medical review, death certificate CHD = MI, USA, angiographic evidence, CHD death	Risk of CHD event in men with newly diagnosed DM and no baseline CHD, HR 1.7 (95% CI 1.1–2.7) Risk of CHD event in men with known DM and no baseline CHD, HR 1.7 (95% CI 0.9–3.3) Risk of CHD event in women with newly diagnosed DM and no baseline CHD, HR 3.1 (95% CI 1.8–5.6) Risk of CHD event in women with known DM and no baseline CHD, HR 6.2 (95% CI 3.6–10.6)
Kim et al (19)	South Korea	1996–2004	408,022 followed for 10 years	Discharge diagnosis of CHD, ischemic stroke, and total CVD	Risk of CVD in men with DM vs men with normal glucose, HR 1.52 (95% CI 1.46–1.58) Risk of CVD in women with DM vs women with normal glucose HR of 1.45 (95% CI 1.38–1.53) Risk of CHD in men with DM vs men with normal glucose, HR 1.71 (95% 1.61–1.82)

Reference	Country	Year	Study participants, (n) duration of follow up	Outcome definition	Results, Risks are adjusted unless explicitly noted otherwise
					Risk of CHD in women DM vs women with normal glucose, HR of 1.67 (95% 1.52–1.84) Risk of stroke in men with DM vs men with normal glucose, HR 1.87 (95% 1.70–2.06) Risk of stroke in women with DM vs women with normal glucose, HR 1.82 (95% 1.59, 2.07)
Mak (15)	Singapore	1992	3,414 grouped according to DM and MetS status followed for 10 years	Discharge diagnosis of CHD, stroke, CVD death	Annual CVD event rates (per 1,000 person-years) Incidence of CVD event in men without DM and without MetS: 3.0 Incidence of CVD event in men with DM and without MetS: 22.5 Incidence of CVD event in men without DM and with MetS: 15.9 Incidence of CVD event in men with DM and with MetS: 21.4 Incidence of CVD event in women without DM and without MetS: 0.9 Incidence of CVD event in women with DM and without MetS: 5.3 Incidence of CVD event in women without DM and with MetS: 3.7 Incidence of CVD event in women with DM and with MetS: 21.5
Schottker et al(17)	Germany	2000–2002	8,365 followed for 8 years	Self-report with medical review, death certificate MI, stroke, or CVD death	CVD risk in men with DM vs. men without DM, HR 1.86 (95% CI 1.48–2.32) CVD risk in women with DM vs. women without DM, HR 1.74 (95% CI, 1.32–2.28) CVD risk in men with DM vs men with normal glucose levels, HR 2.09 (95% CI, 1.61–2.71) CVD risk in women with DM vs women with normal glucose levels, HR 1.71 (95% CI 1.25, 2.35) CVD risk in men with DM vs. men without DM, crude HR 2.36 (95% CI 1.81, 3.09) CVD risk in women with DM vs. women without DM, crude HR 2.64 (95% CI 1.96, 3.55)

Reference	Country	Year	Study participants, (n) duration of follow up	Outcome definition	Results, Risks are adjusted unless explicitly noted otherwise
Zhao et al(14)	USA	1999–2009	30,154 followed for 6.7 years	Discharge diagnosis, stroke	Increase in risk of stroke in men with DM associated with each 1% increase in A1c , HR of 1.01 (95% CI 0.99, 1.04) Increase in risk of stroke in women with DM associated with each 1% increase in A1c, HR 1.05 (95% CI 1.02, 1.07)