



Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia

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OBJECTIVE

Type 2 diabetes confers a greater excess risk of cardiovascular disease in women than in men. Diabetes is also a risk factor for dementia, but whether the association is similar in women and men remains unknown. We performed a meta-analysis of unpublished data to estimate the sex-specific relationship between women and men with diabetes with incident dementia.

RESEARCH DESIGN AND METHODS

A systematic search identified studies published prior to November 2014 that had reported on the prospective association between diabetes and dementia. Study authors contributed unpublished sex-specific relative risks (RRs) and 95% CIs on the association between diabetes and all dementia and its subtypes. Sex-specific RRs and the women-to-men ratio of RRs (RRRs) were pooled using random-effects meta-analyses.

RESULTS

Study-level data from 14 studies, 2,310,330 individuals, and 102,174 dementia case patients were included. In multiple-adjusted analyses, diabetes was associated with a 60% increased risk of any dementia in both sexes (women: pooled RR 1.62 [95% CI 1.45–1.80]; men: pooled RR 1.58 [95% CI 1.38–1.81]). The diabetes-associated RRs for vascular dementia were 2.34 (95% CI 1.86–2.94) in women and 1.73 (95% CI 1.61–1.85) in men, and for nonvascular dementia, the RRs were 1.53 (95% CI 1.35–1.73) in women and 1.49 (95% CI 1.31–1.69) in men. Overall, women with diabetes had a 19% greater risk for the development of vascular dementia than men (multiple-adjusted RRR 1.19 [95% CI 1.08–1.30]; $P < 0.001$).

CONCLUSIONS

Individuals with type 2 diabetes are at ~60% greater risk for the development of dementia compared with those without diabetes. For vascular dementia, but not for nonvascular dementia, the additional risk is greater in women.

Dementia is a multifaceted syndrome that lays claim to a growing burden of global disease: the most recent estimates suggest that there are ~44 million affected individuals worldwide and a further 7.7 million new cases annually (1,2). Underpinned by a shifting demographic and associated epidemiological profile worldwide,

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the prevalence of dementia is forecast to nearly double by 2030 and to triple by 2050 and is set to create a significant economic, social, and public health burden particularly in resource-poor countries (1,2).

Nonvascular dementia, which mainly constitutes Alzheimer disease (AD), and vascular dementia are the two most common forms of dementia, accounting for ~70% (25 million) and 20% (7 million) of all dementia cases, respectively (2). Lifestyle risk factors, including type 2 diabetes, cigarette smoking, and obesity, are associated with an increased risk for the development of both vascular dementia and nonvascular dementia in later life (3). For example, a review (4) that included information on ~15,000 cases of dementia found that, compared with nonaffected individuals, those with diabetes had an ~70% greater risk for the development of dementia.

While of value, that review (4) has some important limitations: >73% of dementia cases were derived from two large Asian cohorts (5,6) and the influence of these studies on the overall summary estimates was not examined. Moreover, information on dementia subtypes was not universally available, including the single study (5) that provided information on >50% of all dementia cases. Finally, because the analyses were not sex specific, it was not possible to determine whether the magnitude of the association between diabetes and incident dementia and its main subtypes differed in women and men. This is of interest given the substantial amount of evidence suggesting that diabetes confers a significantly greater additional vascular hazard in women compared with men, which potentially has ramifications for the clinical management of diabetes and vascular disease in women (7–9).

To overcome the substantial methodological limitations of past reviews, we requested individual study investigators

to contribute unpublished results to a pooled analysis. In line with the current evidence base, which suggests that diabetes poses more of a vascular hazard in women compared with men, our hypothesis was that diabetes confers a greater excess risk of vascular dementia in women than in men, but that the impact of diabetes on the risk for nonvascular dementia is similar between the sexes.

RESEARCH DESIGN AND METHODS

Search Strategy and Selection Criteria

We used PubMed MEDLINE (www.ncbi.nlm.nih.gov) and Ovid MEDLINE for the period from January 2011 to November 2014 to identify studies that had reported on the association between diabetes and dementia in men and women from a general population. The search strategy combined the following text and MeSH terms: “dementia,” “vascular dementia,” “delirium,” “cognitive disorders,” “amnesic disorders,” “frontotemporal dementia,” “multi-infarct dementia,” “Alzheimer disease,” “Lewy body,” “type 2 diabetes mellitus,” “diabetes mellitus,” “DM,” “diabetes complications,” “blood glucose,” “impaired glucose tolerance,” “glycosylated hemoglobin,” and “prediabetes.” Studies prior to 2011 were identified from previous systematic reviews (4,10,11). Data from randomized trials were excluded because of the nongeneralizable nature of trials to the general population. Two authors (S.C. and S.A.E.P.) conducted the literature search. Uncertainties regarding the identification of studies were discussed and resolved by mutual consent. Because most studies did not publish estimates of relative risk (RR) separately for men and women or for dementia subtypes and varied by which factors were included in adjusted models, we contacted the authors of all of the selected studies and asked them to provide additional results adjusted, where possible, for the same set of confounders: blood

pressure, cigarette smoking, BMI, and total cholesterol level. On a specifically designed form, contributing authors provided summary results for the age-adjusted and multiple-adjusted RRs and 95% CIs for any dementia and, if available, for vascular dementia and nonvascular dementia segregated by sex.

Data Extraction and Statistical Analysis

The primary end points were incident all-cause dementia, vascular dementia, and nonvascular dementia (as defined by the study investigators; see Supplementary Table 1). The primary metrics were the pooled multiple-adjusted RRs for dementia associated with diabetes and the women-to-men ratio of the RRs (RRR). Covariates that were included in the multiple-adjusted model were reported differently between studies and are shown in Table 1. Age-adjusted estimates were used in a secondary analysis. From each study, we obtained the previously unpublished sex-specific RRs with accompanying 95% CIs for individuals with versus without diabetes. We also requested information on the number of person-years of follow-up to calculate sex-specific incidence rates in individuals with and without diabetes. We log transformed these RRs and pooled them across studies using random-effects meta-analysis with inverse variance weighting and then exponentiated these values to obtain the pooled RR separately for women and men. We used similar methods to pool women-to-men RRRs. For each study, we obtained the SE of the log RRR by taking the square root of the sum of the variance of the two sex-specific log RRs. We used the I^2 statistic to estimate the percentage of variability across studies due to between-study heterogeneity. In sensitivity analyses, we excluded estimates from two large cohort studies (6,12) from Taiwan and Korea that had a large influence on the summary estimates. We also examined whether restricting the analysis to those

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Table 1—Characteristics of included studies

Cohort	Country	Baseline study (years)	Mean FU (years)	Age range (years)	N (% w)	N diabetes (% w)	N dementia (% w)	N VaD (% w)	N non-VaD (% w)	Ascertainment of diabetes	Ascertainment of dementia	Maximum adjustment available
ACT Study (18)	U.S.	1994–1996	7	65+	2,067 (59)	232 (52)	524 (62)	67 (61)	457 (62)	Measured	Cognitive Abilities Screening Instrument, DSM, NINCDS/ADRDA	Age, sbp, smoking, BMI
ARIC (15)	U.S.	1990–1992	14	46–70	11,151 (57)	1,445 (55)	203 (57)	NA	NA	Measured or SR	ICD-9 codes	Age, race, sbp, smoking, BMI, tc
CCMS (20)	U.S.	1995	5	65+	3,260 (58)	343 (53)	141 (71)	37 (65)	104 (73)	SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, hypertension, BMI, high cholesterol
English and Scottish Health Surveys (16)	U.K.	1998–2008	8	16–102	154,844 (52)	12,267 (48)	1,242 (54)	NA	NA	SR	ICD-9, ICD-10 codes	Age, sbp, smoking, BMI, tc
Framingham Study (14)	U.S.	1976–1978	13	NR	2,609 (56)	363 (43)	234 (61)	51 (61)	183 (61)	Measured	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, BMI, tc
Hisayama Study (23)	Japan	1985–1988	15	60+	1,017 (57)	150 (55)	232 (66)	65 (51)	167 (72)	Measured	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, BMI, tc
KAME Project (17)	U.S.	1992–1994	6	65+	1,709 (55)	290 (44)	140 (59)	45 (58)	112 (63)	SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, BMI
Kungsholmen Project (25)	Sweden	1987–1989	9	75+	1,301 (75)	104 (75)	350 (81)	49 (71)	301 (83)	SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, BMI
MHAS (22)	Mexico	2001–2003	3	60+	5,398 (54)	749 (61)	306 (60)	54 (63)	230 (61)	SR	CCCE, IQCODE	Age, hypertension, smoking, obesity
NHI, Taiwan (12)	Taiwan	2000–2008	9	NR	1,229,747 (52)	614,876 (52)	95,087 (57)	8,300 (52)	86,757 (57)	Measured	ICD-9 codes	Age, insurance premium, region, urbanization, cbvd, cvd, hypertension, hyperlipidemia
NHIC, Korea (6)	Korea	1992–1995	14	40–95	848,505 (42)	51,611 (35)	2,914 (55)	516 (47)	1,669 (57)	Measured	DSM and medical examination	Age, alcohol
Norwegian Counties Study (24)	Norway	1974–1978	35	35–50	46,231 (51)	613 (34)	460 (53)	NA	NA	Measured or SR	ICD-9 codes	Age, sbp, smoking, BMI, tc
OCTO-Twin Study (19,21)	Sweden	1991–1999	9	80+	702 (67)	122 (67)	225 (70)	57 (58)	163 (73)	Measured	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, BMI, tc
SALSA Study (21)	U.S.	1998–1999	10	60+	1,789 (58)	797 (56)	116 (66)	12 (50)	90 (71)	Measured or SR	DSM, NINCDS/ADRDA, NINDS-AIREN	Age, sbp, smoking, BMI, tc

ACT, Adult Changes in Thought; ARIC, Atherosclerosis Risk in Communities Study; cbvd, cerebrovascular disease; CCCE, Cross-Cultural Cognitive Examination; CCMS, Cache County Study on Memory Health and Aging; cvd, cardiovascular disease; FU, follow-up; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MHAS, Mexican Health and Aging Study; NA, not available; NHI, National Health Insurance; NHIC, National Health Insurance Corporation; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; Alzheimer's criteria; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria; NR, not reported; OCTO-Twin, Origins of Variance in the Old-Old; Octogenarian Twins study; SALSA, Sacramento Area Latino Study on Aging; sbp, systolic blood pressure; SR, self-report diabetes; tc, total cholesterol; VaD, vascular dementia; % w, percent women.

studies that used higher-quality research criteria for dementia diagnosis (e.g., the Cross-Cultural Cognitive Examination and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's criteria) affected the main results. We explored whether the background rate of dementia in the study population influenced the sex-specific associations by meta-regression analyses of the log RRR versus the difference in incidence rate between women with and without diabetes minus the equivalent estimate in men (i.e., the difference of the difference). We assessed the methodological quality of the studies using the Newcastle-Ottawa Scale (Supplementary Data) (13). All analyses were performed using Stata version 12.0.

RESULTS

The systematic search identified 1,495 unique articles that were subsequently examined on title and abstract (Supplementary Fig. 1). Overall, 1,425 articles were excluded for one or more reasons including lack of primary data, single-sex population, animal study, non-prospective study design, and randomized trial of a high-risk population. Of the remaining articles, 70 articles qualified for full-text evaluation. Of these, 28 studies had relevant data on the relationship between diabetes and risk of dementia, and the authors were contacted and asked to contribute additional estimates to those in the published reports. Authors from 13 studies (response 48%) contributed unpublished summary data (12,14–25), and for 1 study (6) we extracted the necessary data from its published report. The 14 noncontributing studies comprised 30,900 individuals and 2,300 cases of dementia (Supplementary References), and the baseline characteristics are described in Table 1. Overall, data were available on 2,310,330 individuals (48% women) and 102,174 incident cases of dementia, including 9,253 cases of vascular dementia (52% women) and 90,233 cases of nonvascular dementia (58% women). Three cohorts were from Asia (90% of the individuals) (6,12,23), four were from Europe (9%) (16,19,24,25), and seven were from the Americas (1%) (14,15,17,18,20–22). The mean age of study participants ranged from 43 to

83 years, and the mean study duration ranged from 2 to 35 years across studies. The included studies were generally of good to very good quality (Supplementary Table 1). There was variation in the incidence rates for dementia among populations (Supplementary Table 2).

Compared with not having diabetes, diabetes was significantly associated with ~60% increased risk of any dementia in both sexes; the multiple-adjusted pooled RR for any dementia associated with diabetes was 1.68 (95% CI 1.64–1.71) in women and 1.61 (95% CI 1.42–1.83) in men (Figs. 1 and 2). There was moderate heterogeneity between studies in both women ($I^2 = 40%$, $P = 0.065$) and men ($I^2 = 48%$, $P = 0.048$). The size of the associations in women and men remained robust after excluding data, in turn, from the two large Asian cohorts (Supplementary Fig. 2). Results from the age-adjusted analyses were not materially different (RR 1.58 [95% CI 1.41–1.78] in women, RR 1.65 [95% CI 1.46–1.87] in men). Restricting the analysis to studies that used higher-quality research criteria to diagnose dementia had little effect on the summary estimates (RR 1.65 [95% CI 1.42–1.91] in women, RR 1.49 [95% CI 1.19–1.87] in men).

Diabetes was associated with a significantly increased risk of vascular dementia in both women and men; the multiple-adjusted pooled RR was 2.34 (95% CI 1.86–2.94) in women and 1.73 (95% CI 1.61–1.85) in men (Figs. 1 and 2). Between-study heterogeneity was moderate for women ($I^2 = 34%$, $P = 0.14$) and was absent for men ($I^2 = 0%$, $P = 0.86$). Excluding data from either of the large Asian cohorts had no discernible impact on the results (Supplementary Fig. 2). The age-adjusted estimates were 2.23 (95% CI 1.72–2.90) in women and 2.02 (95% CI 1.90–2.16) in men. The summary estimates from those studies that used the higher-quality research criteria for the diagnosis of dementia did not differ appreciably from the multiple-adjusted estimates (2.43 [95% CI 1.67–3.54] and 1.86 [95% CI 1.25–2.76]).

Individuals with diabetes also had a 50% increased risk for the development of nonvascular dementia compared with unaffected people: the multiple-adjusted pooled RR was 1.53 (95% CI 1.35–1.73) in women and 1.49 (95% CI 1.31–1.69) in men (Figs. 1 and 2). Between-study heterogeneity was low-

moderate in both sexes ($I^2 = 30%$, $P = 0.16$ in women; 19%, $P = 0.27$ in men). These estimates were largely unaffected after the exclusion of data from the two largest studies (Supplementary Fig. 2). The age-adjusted estimates were weaker in both women and men (1.44 [95% CI 1.26–1.65] and 1.34 [95% CI 1.05–1.70], respectively). Restricting the search to studies that used research criteria for the diagnosis of dementia did not materially affect the summary estimates (1.47 [95% CI 1.20–1.81] in women and 1.34 [95% CI 0.99–1.80] in men).

Diabetes conferred a significantly greater excess risk for the development of dementia in women, but this was confined to vascular dementia (Fig. 3). Women with diabetes had a 19% (95% CI 8–30%, $P < 0.001$) greater excess risk for vascular dementia compared with men with diabetes, with no evidence of significant between-study heterogeneity ($I^2 = 0%$, $P = 0.58$). This effect remained following the exclusion of data from the Korean study (RRR 1.18 [95% CI 1.07–1.30]) (6) and the Taiwanese study (12), although it was then no longer statistically significant (RRR 1.33 [95% CI 0.94–1.88]) (Supplementary Fig. 2). In the age-adjusted analysis, there was no significant sex difference in the association between diabetes and vascular dementia (RRR 1.10 [95% CI 0.84–1.45], $P = 0.49$). For nonvascular dementia, there was no evidence of a sex difference in the effect of diabetes from either the multiple-adjusted estimate (Fig. 3) or the age-adjusted estimate (RRR 1.05 [95% CI 0.81–1.36]). The results did not change appreciably after excluding data from the Taiwanese (12) or Korean (6) studies (Supplementary Fig. 2). Restricting the analysis to those studies that used the research criteria for the diagnosis of dementia produced a similar pattern of results, although the sex difference with vascular dementia was no longer statistically significant (RRR 1.24 [95% CI 0.73–2.11]).

Given the substantial variation in background rates of dementia and its major subtypes across the studies, we examined what impact such heterogeneity may have had on the RRR estimate through meta-regression analysis. The overall estimate of the RRR was robust to between-study differences in diabetes incident rates because there was no

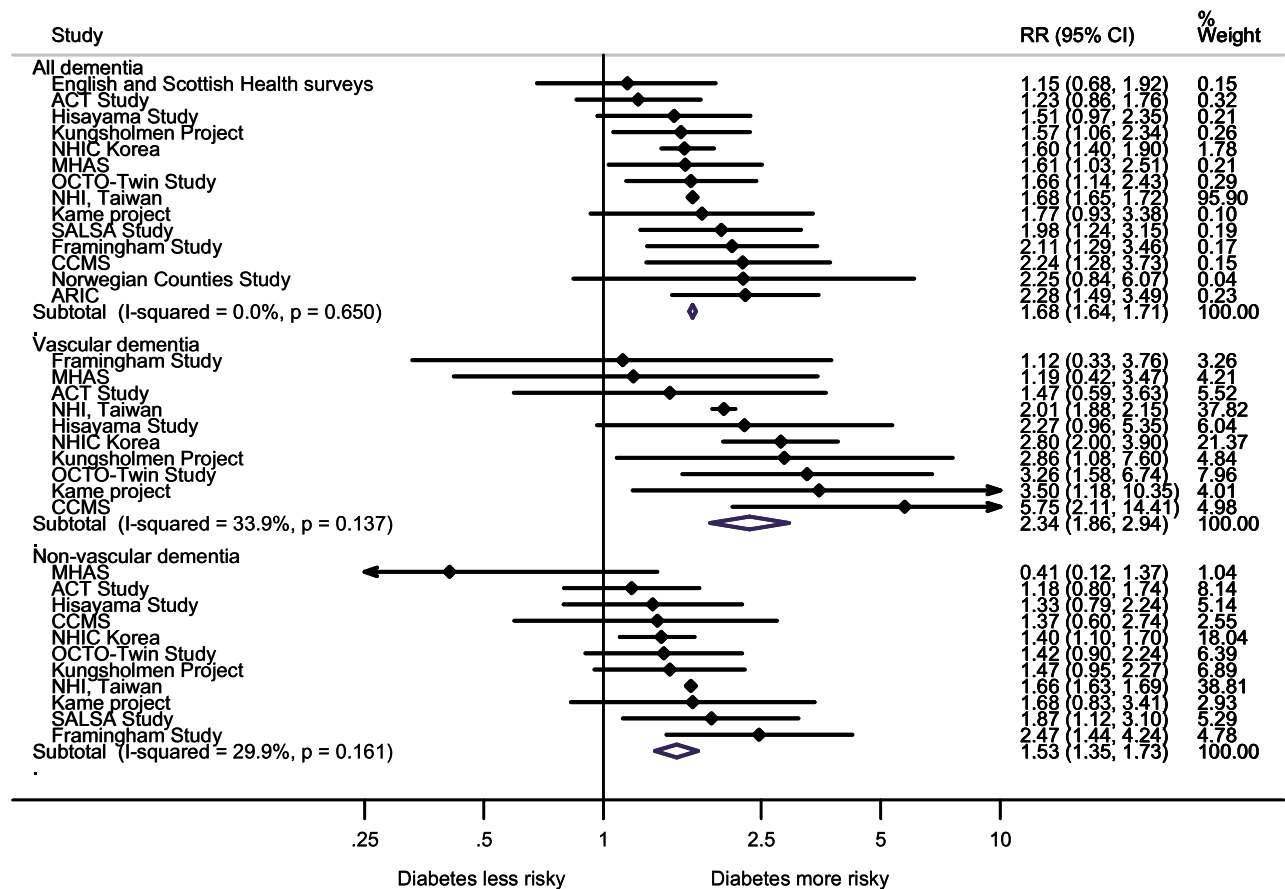


Figure 1—Multiple-adjusted RR for any dementia, vascular dementia, and nonvascular dementia in women, comparing individuals with diabetes to those without diabetes. Horizontal bars represent 95% CIs.

significant evidence that differences in background rates materially influenced the RRR estimate for either vascular dementia ($P_{\text{for heterogeneity}} = 0.22$) or nonvascular dementia ($P_{\text{for heterogeneity}} = 0.30$)

CONCLUSIONS

This pooled analysis of 14 studies combined largely unpublished data from >2.3 million individuals and information on >102,000 incident cases of dementia—more than seven times the amount of information as in previous reviews of the same topic (4,10,11). Our findings offer support for a role of diabetes in the etiology of dementia, although the magnitude of the relationship differs according to subtype overall, diabetes was associated with an ~60% increased risk of all-cause dementia and a 40% risk of nonvascular dementia in both women and men, independent of important confounders. For vascular dementia, the association was stronger, with evidence of a stronger effect in women than in men. Compared with people with no diabetes, after

adjusting for possible confounders, women with diabetes had a 120% greater risk for the development of vascular dementia compared with a 70% greater risk in men, which equated to an 18% significantly greater excess risk in women with diabetes compared with similarly affected men. These results were largely robust to the exclusion of data from two large cohorts that together comprised 96% of all incident cases of dementia (6,12).

The recorded excess RR of vascular dementia in women might be an artifact of the data driven by higher absolute rates for incident dementia in men than in women in the background population. If this were true, then the relative effect of diabetes on incident dementia would be greater in women than in men in populations in which the absolute incident rate is higher in men than in women, but should converge when the rates are similar between the sexes. However, our present findings show evidence to the contrary, with a trend toward higher incident rate

ratios (indicating a greater excess risk in women than in men) in studies in which the background incident rates for dementia were higher in women than in men.

Previous reviews (4,10,11) of the association between diabetes and risk of dementia reported slightly larger estimates, but were still compatible with those presented here. Moreover, because these reviews were reliant on published data, they were largely unable to examine the effect of diabetes on dementia subtypes and the impact of confounding or to perform sex-specific comparisons. In contrast, by sourcing previously unpublished study-level estimates, we were largely able to overcome these limitations. Moreover, by standardizing the level of adjustment for other major vascular risk factors across studies (as far as possible), we not only lessened the possible effect of residual confounding on study estimates, but we could also examine whether adjustment had a similar effect on the age-adjusted estimates for women and men. Our findings indicated that adjustment

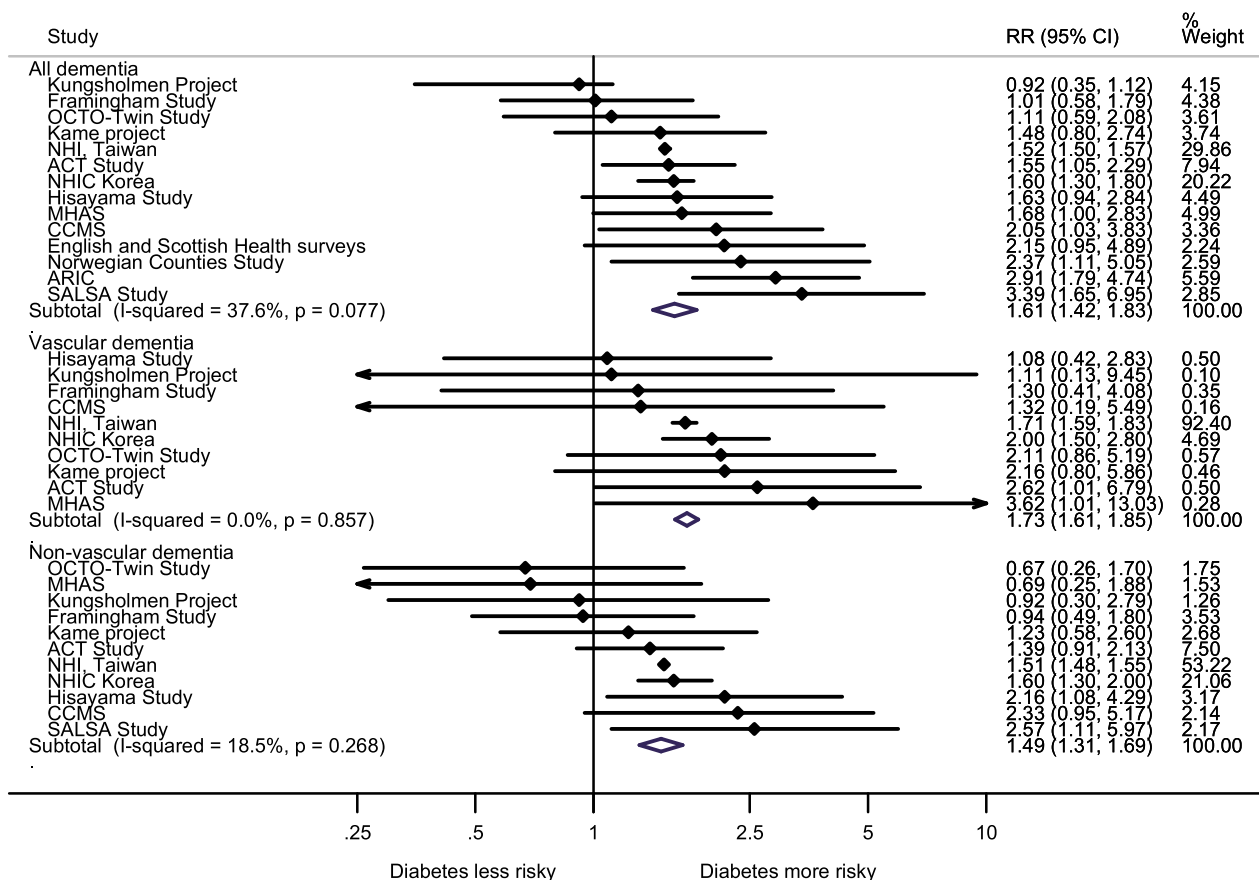


Figure 2—Multiple-adjusted RR for any dementia, vascular dementia, and nonvascular dementia in men, comparing individuals with diabetes to those without diabetes. Horizontal bars represent 95% CIs.

for other vascular risk factors on the association between diabetes and risk of vascular dementia had opposing effects

in women and men: in women, adjustment tended to strengthen the association (by ~7%), whereas in men the association

was somewhat weakened (by 14%), which would explain the lack of an observed sex difference in the risk of diabetes for

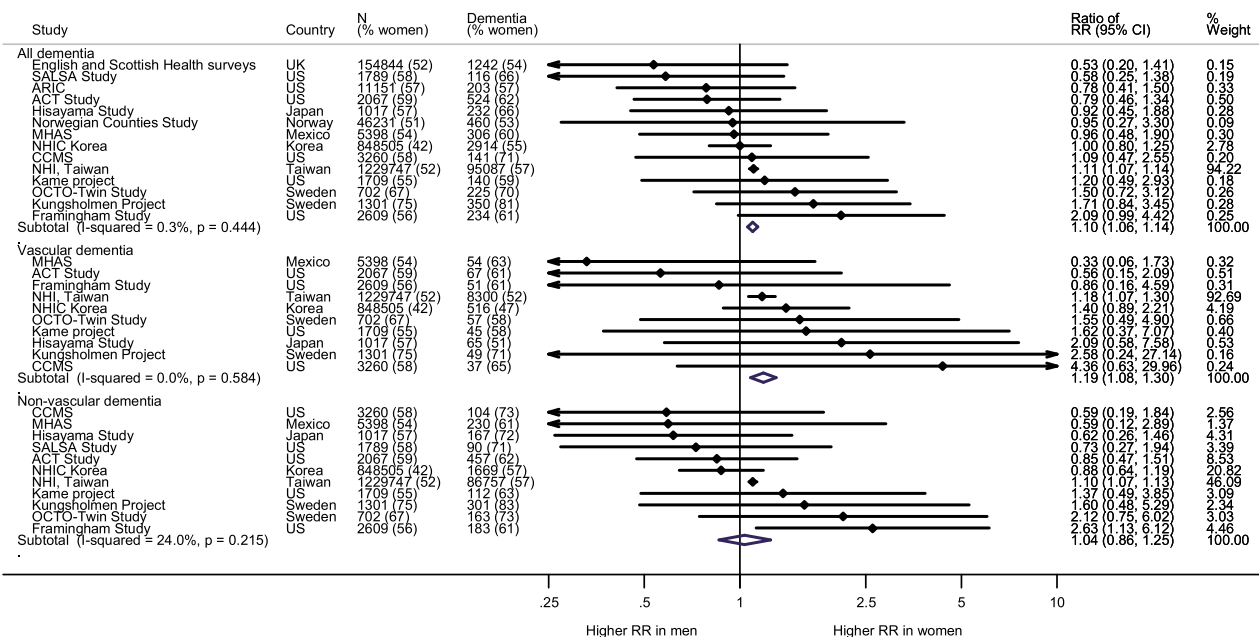


Figure 3—Multiple-adjusted women-to-men RRRs for any dementia, vascular dementia, and nonvascular dementia, comparing individuals with diabetes to those without diabetes. Horizontal bars represent 95% CIs.

vascular dementia in the age-adjusted estimate.

Whereas several processes are thought to promote the onset of dementia in individuals with diabetes, the biological basis of this relationship is still uncertain. Findings from a recent study (26) that examined the genetic susceptibility to type 2 diabetes and risk of late-onset AD have shown that genotype risk scores for diabetes were not associated with increased risk of late-onset AD. Therefore, even though we attempted to control for confounding, it is probable that the observed association between diabetes and nonvascular dementia is noncausal and possibly is driven by other disease processes or known (and unknown) risk factors that are common to both diabetes and nonvascular dementia. But, both the size of the association and the fact that diabetes is a known risk factor for microvascular and macrovascular complications, including coronary heart disease and stroke, would suggest that the relationship between diabetes and vascular dementia is robust and not solely driven by confounding.

Studies in support of a biological relationship between diabetes and vascular and nonvascular dementia suggest a multifactorial pathogenesis involving insulin metabolism, hyperglycemic toxicity, chronic inflammatory processes, and vascular changes (27,28). Insulin resistance is thought to promote atherosclerosis, to change cerebral energy metabolism, and to lead to vascular-related cognitive impairment and dementia (27). Oxidative stress due to chronic hyperglycemia can also lead to vascular changes in the nervous system and an accumulation of advanced glycation end products that are found in AD (28). Conversely, severe hypoglycemia, which in most cases is driven by insulin or sulfonylurea treatment of diabetes, is associated with cognitive impairment by precipitating neuronal death and increased production of coagulation factors (27). Type 2 diabetes is also associated with an increased expression of interleukin-6 in the central nervous system, causing inflammation of the brain and, in conjunction with oxidative stress, is implicated in the pathogenesis of AD (27). Two prospective neuropathological cohort studies (28,29) suggested that diabetes may lower the threshold for the amount

of amyloid required for the development of AD by inducing adverse microvascular changes—small-vessel infarcts—in the brain. There is now growing evidence to suggest that dementia subtypes are more heterogeneous pathologically than previously thought and that underlying vascular changes play a role in both vascular and nonvascular dementia (3).

The present analyses provide further support for the hypothesis that the adverse consequences of diabetes on vascular risk are stronger in women than in men (7–9). Although a sex disparity in the management and treatment of diabetes, most often to the detriment of women, may be involved, accruing evidence suggests that real biological differences between women and men underpin the excess risk of diabetes-related vascular risk in women. For example, exposure to endogenous estradiol in women may also play a role; a recent study (30) among postmenopausal women found that higher levels of endogenous estradiol, especially in women with diabetes, conferred a greater risk of dementia. There is also some evidence from autopsy studies to suggest that the greater diabetes-related excess risk of vascular dementia observed in women may be mediated by greater neurological microvascular damage: on the basis of neuropathological assessment, the Adult Changes in Thought (ACT) Study reported two patterns of cerebral injury associated with dementia in individuals with and without diabetes. In those individuals without diabetes, dementia was associated with higher amyloid B peptide, whereas in individuals with diabetes, dementia was characterized by greater microvascular infarcts and neuroinflammation (Supplementary Reference 15). However, whether the latter was more pronounced in women than in men was not examined and requires further investigation by future studies that are adequately powered to detect sex differences.

Limitations of our study include the differences across studies in study design and duration, end point definition, and ascertainment of diabetes (which was either measured or based on self-report depending on the study). We were also unable to include data from 14 eligible cohorts with 2,300 incident cases of dementia. However, given that the current analyses are based on >100,000 incident cases, it is unlikely

that their omission had a profound impact on the results. It should be noted, however, that >96% of the cases were derived from two large studies; reassuringly, however, the exclusion of either study did not materially alter the pattern of the results (although in some instances the associations were not statistically significant). It should be noted, however, that the heterogeneity in the method of diagnosis of dementia and its subtypes is a significant (and unquantifiable) limitation of this analysis. For example, ascertainment of dementia from the two large Asian cohorts was reliant on diagnoses obtained from administrative databases that may be particularly susceptible to detection bias or case reporting (Supplementary Reference 16), whereas in other, much smaller studies, a diagnosis of dementia was based on clinical examination by two or more clinicians (25). We also did not examine the association between duration of diabetes or glycemic control and the risk for dementia, nor did we evaluate the association between diabetes and cognitive functioning. The diagnosis of vascular dementia in epidemiological studies, and its overlap with AD and other forms of dementia, without neuropathological validation is also a significant limitation and may have overestimated the impact of diabetes for dementia subtypes. While we used accepted criteria to distinguish between AD and vascular dementia, there is increasing recognition that dementia has a mixed pathophysiology (Supplementary References 17 and 18). At present, no standardized thresholds by which to categorize mixed dementia exist and were not examined within the individual studies; hence, we were unable to examine sex differences in the diabetes-related risk of mixed dementia. Misclassification of dementia status, which may have occurred differentially in women and men, will have introduced bias, the extent (and direction) of which remains unknown. We also did not have information on the duration of diabetes status and level of glycemic control, either of which may have significantly interacted with risk of dementia (either to a similar or different extent in women and men).

Future prospective studies, with extensive phenotypic and genetic data on risk factors common to both diabetes and subtypes of dementia, are needed to examine whether these relationships are

causal. Moreover, our finding of a greater diabetes-related risk of vascular dementia in women than in men contributes to the growing evidence base that diabetes confers a proportionally greater vascular hazard in women than in men.

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