Association between diabetes mellitus and the occurrence and outcome of intracerebral hemorrhage

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ABSTRACT

Objective: Whether diabetes mellitus (DM) is a risk factor for spontaneous intracerebral hemorrhage (ICH) and influences outcome after ICH remains unclear.

Methods: One reviewer searched Ovid MEDLINE and Embase 1980–2014 inclusive for studies investigating the associations between DM and ICH occurrence or DM and ICH case fatality. Two reviewers independently confirmed each study's eligibility, assessed risk of bias, and extracted data. One reviewer combined studies using random effects meta-analysis.

Results: Nineteen case-control studies involving 3,397 people with ICH and 5,747 people without ICH found an association between DM and ICH occurrence (unadjusted odds ratio [OR] 1.23, 95% confidence interval [CI] 1.04–1.45; $I^2 = 22\%$), which did not differ between 17 hospital-based and 2 population-based studies ($p_{\text{diff}} = 0.70$), and was similar in the 16 studies that controlled for age and sex (unadjusted OR 1.15, 95% CI 0.95–1.40; $I^2 = 14\%$). This association was not identified in 3 population-based cohort studies in which ICH occurred in 38 (0.66%) of 5,724 people with DM and 448 (0.57%) of 78,702 people without DM (unadjusted risk ratio [RR] 1.27, 95% CI 0.68–2.36; $I^2 = 69\%$). DM was associated with a higher case fatality by 30 days or hospital discharge in 18 cohort studies involving 813 people with DM and 3,714 people without DM (unadjusted RR 1.52, 95% CI 1.28–1.81; $I^2 = 49\%$).

Conclusions: The findings suggest that there may be modest associations between DM and ICH occurrence and outcome, but further information from large, population-based studies that account for confounding is required before the association can be confirmed. *Neurology*® 2016;87:870–878

GLOSSARY

CI = confidence interval; DM = diabetes mellitus; ICD-10 = *International Classification of Diseases–10*; ICH = intracerebral hemorrhage; OR = odds ratio; RR = risk ratio.

Spontaneous (nontraumatic) primary intracerebral hemorrhage (ICH) affects at least 2 million people worldwide each year.¹ Two-thirds of these people are dead or disabled within 1 year and survivors have a high risk of recurrent stroke.^{2,3}

Case-control and cohort studies have described the association between diabetes mellitus (DM) and ICH and its outcome, but the findings of individual studies and systematic reviews have left uncertainty about these associations.^{4–6} There was no evidence of an association between DM and ICH in a meta-analysis of 8 case-control studies (unadjusted odds ratio [OR] 1.27, 95% confidence interval [CI] 0.98–1.65)⁶ and the recent INTERSTROKE case-control study,⁴ but an association was found in an individual patient data meta-analysis of prospective cohort studies (adjusted hazard ratio 1.56, 95% CI 1.19–2.05).⁵ A recent systematic review did not find consistent statistically significant associations between DM and long-term case fatality after ICH in 9 small cohort studies, although a meta-analysis was not performed.³

Therefore, in view of the inconsistencies among small individual studies, the different findings of meta-analyses of case-control and cohort studies of the association between DM and ICH occurrence,^{5,6} the publication of many new case-control studies since the most recent study-level

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meta-analysis,⁶ and the lack of a meta-analysis of the association between DM and outcomes of ICH,³ we undertook a systematic review and meta-analysis to further investigate these associations.

METHODS Protocol registration and reporting. We registered our protocol with PROSPERO (CRD42014015039) and report changes to the protocol in this article. We report our study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.⁷

Standard protocol approvals, registrations, and patient consents were not required for this systematic review and meta-analysis of summary-level data.

Eligibility criteria. To investigate the association between DM and the occurrence of ICH, we sought case-control and cohort studies reporting people of any age with and without ICH and quantifying the number in each group with DM. In the protocol, we intended to restrict inclusion to studies of first-ever ICH, but because many studies were unclear about this, or included a small number of patients with recurrent ICH, we broadened this criterion and explored it in sensitivity analyses. Because studies varied in their inclusion of incident first-ever ICH, recurrent ICH, or prevalent ICH, we simply refer to the occurrence of ICH. We included only studies that compared the occurrence of ICH to control groups free of stroke. To investigate the association between DM and outcome after ICH, we sought cohort studies of people with ICH of any age, describing the numbers of people with and without DM, and reporting in each group case fatality in a defined time period, disability or dependence, or stroke recurrence. Studies were eligible if they reported confirmation of ICH diagnosis by brain imaging, surgery, or pathologic examination. If studies reported people with extracerebral intracranial hemorrhage, ICH secondary to an underlying cause (such as trauma, intracranial tumor, or vascular malformation), or hemorrhagic transformation of cerebral infarction, we only included them if we could extract data on the group with primary ICH alone. We relied on studies' own definitions of DM, diagnosed before or at the time of ICH. If there were multiple publications from one study cohort, we included only the publication with the largest amount of data relevant to this review. We did not restrict inclusion by language of publication or sample size.

Information sources. One reviewer (M.B.) searched Ovid MEDLINE and Embase and the bibliographies of relevant studies.

Search. We used electronic strategies to search databases (appendix e-1 at [Neurology.org](#)) and restricted results to studies of humans indexed between 1980 and November 5, 2014.

Study selection and data collection. After automated deduplication in EndNote X7, one reviewer (M.B.) screened all titles and available abstracts for potentially eligible studies, and 2 reviewers (M.B. and M.T.C.P.) independently screened the full text of these studies, using a data extraction form to assess eligibility and extract data for meta-analysis. We obtained a translation of any publication in languages other than English, French, Spanish, and Chinese. One of 2 other reviewers (R.A.-S.S. or S.H.W.) resolved any uncertainties or disagreements between reviewers.

Data items. We extracted data on the following: aspects of study design that affected inclusion; the risk of bias in individual studies (see below); known potential confounders (e.g., age, sex, pre-ICH

hypertension, pre-ICH antithrombotic drug use, Glasgow Coma Scale score, ICH location, ICH volume, and intraventricular extension); DM definition and characteristics (e.g., type, duration, glycemic control, and use of insulin or oral hypoglycemic drugs); and follow-up in cohort studies (e.g., duration and number of events).

Risk of bias in individual studies. Two reviewers (M.B. and M.T.C.P.) independently classified eligible studies' methods, and assessed risk of bias at the study level, guided by the REMARK guidelines,⁸ based on whether the design was population-based or hospital-based and prospective or retrospective. In case-control studies, we also assessed the method of selecting controls and whether cases and controls appeared to be comparable in age, sex, and pre-ICH hypertension. In cohort studies reporting the outcome of ICH, we also considered whether there was selection bias in the assembly of the cohort, differences between people with and without DM that might confound associations, information bias from differential surveillance of people with and without DM, blinding of outcome assessment, complete follow-up, and whether missing data affected studies' results. Risk of bias across studies was not assessed.

Summary measures. We described associations using the OR for case-control studies and risk ratio (RR) for cohort studies.

Synthesis of results. We used meta-analysis to pool studies' unadjusted summary measures of association using the Mantel-Haenszel random-effects method. We quantified statistical heterogeneity between studies with the χ^2 test and inconsistency across studies using the I^2 statistic that describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error.⁹ We performed statistical analyses in Review Manager version 5.3.

RESULTS Study selection. After identifying 4,331 titles from searching databases and 20 titles from hand searching, duplicate removal, screening, and eligibility assessment led to the inclusion of 49 studies,^{10–32,e1–e26} 40 of which had data suitable for meta-analysis (figure e-1).^{10–30,32,e1–e18}

Association between DM and the occurrence of ICH.

Study characteristics. We identified 23 eligible studies,^{10–32} of which one study did not report data to enable its inclusion in quantitative meta-analysis,³¹ leaving 19 case-control studies and 3 cohort studies including 84,426 people for analysis (table 1).^{10–30,32}

Risk of bias within studies. Of the 22 studies included in the quantitative analysis, only 26% were population-based and 83% were restricted to first-ever ICH (table 1). In 19 case-control studies, 11 (58%) studies selected controls from people admitted to the same hospitals as cases for conditions other than stroke, 2 (11%) randomly selected controls, 1 (5%) selected controls from participants in another study, 1 (5%) selected controls from relatives of the cases, and 4 (21%) studies did not specify. Of the 13 (68%) case-control studies that compared the frequency of men and average age between cases and controls, the frequencies were comparable in 11 (85%) studies. Of the 18 (95%) studies

Table 1 Characteristics of the 22 studies included in the meta-analysis of the association between diabetes mellitus and the occurrence of intracerebral hemorrhage (ICH)

Reference	Study location	Study period	Study design	Choice of controls	Control matching or cohort design	ICH type	ICH diagnosis	Diabetes definition	Mean age of cases, ^a y	Men in cases, ^a %	Hypertension in cases, ^a %
Case-control studies											
26	Turkey	2010-2011	H	NS	NS	First-ever	I	C	58.5	66.6	37
10	Poland	2002-2010	H	Patients	Not matched	First-ever	I	C	66.1	50.6	78.9
29	Sweden	2000-2003	H	NS	NS	First-ever/recurrent	I	C	66	55.5	NS
25	Turkey	NS	H	NS	G	First-ever	I	N	53.8	60	71.5
27	Taiwan	NS	H	Patients	NS	First-ever	I	N	61.3	69.1	57.6
24	USA	1994-1999	H	Random selection	I	First-ever	I	C	NS	56.2	56.2
23	Italy	1998-2000	H	Patients	I	First-ever	I	C	64	52.3	52.3
30	France	1985-1992	P	Patients	NS	NS	I	C	64	54.6	41.1
22	Japan	1991-1998	H	Patients	I	First-ever	I/pathologic	C	67.1	56.6	77.2
21	Italy	1985-1986	H	Patients	Not matched	First-ever	I	C	62.6	52.6	50.8
20	Finland	NS	H	Patients	G	First-ever	Pathologic	C	46.6	61.5	54.5
19	Japan	1992-1994	H	Patients	I	First-ever	I	C	54.3	63.9	NS
18	Korea	2002-2007	H	Patients	I	First-ever	I	C	65	37.5	54.2
17	Taiwan	1989	H	NS	NS	First-ever	I/pathologic	C	61.5	86.1	NS
16	Italy	2002-2011	H	Participants	Not matched	NS	I	C	75	57.5	63.7
15	Greece	NS	H	Patients	I	First-ever	I	C	63.4	54.3	77.1
14	Finland	1993-1995	P	Random selection	NS	Mixed	I	C	65	58.2	41.4
12	Australia	1990-1992	H	Relatives	I	First-ever	I/pathologic	C	63.4	89.7	16.6
11	China	2000-2001	H	Patients	NS	First-ever	I	C	58.1	64.3	64.2
Cohort studies											
28	Japan	1990-1998	P	NA	NS	First-ever	I	N	NS	NS	NS
13	USA	1989-1993	P	NA	NS	First-ever	I	C	NS	44 ^b	43.7 ^b
32	Sweden	1989-2011	P	NA	Prospective	First-ever	I/pathologic	C	60 ^b	39.3 ^b	17.7 ^b

Abbreviations: C = pre-ICH diabetes; G = group matching; H = hospital-based; I = brain imaging; N = newly diagnosed diabetes at the time of the ICH; NA = not applicable; NS = not specified; P = population-based.

^a Patients with ICH in case-control studies and patients with diabetes in cohort studies.

^b Characteristic of the entire cohort.

that compared the frequency of hypertension between cases and controls, the frequencies were similar in 4 (22%) studies, but they were statistically significantly higher in cases than in controls in 14 (78%) studies. Only 2 case-control studies adjusted measures of association for one of these potential confounders.^{19,22} In 3 cohort studies, one was prospective,³² but none described the prevalence of known risk factors for ICH (e.g., age, history of hypertension, and antithrombotic drug use) in people with and without DM. Among all 22 studies, assessing the association between DM and ICH was the primary aim of just 1 study.²⁸ None of the studies reported information about DM type, duration, glycemic control, and hypoglycemic treatment.

Results of individual studies and synthesis of results. In 19 case-control studies involving 3,397 people with ICH and 5,747 without ICH, DM was associated with ICH occurrence (unadjusted OR 1.23, 95% CI 1.04–1.45; $I^2 = 22\%$; figure 1). However, in 3 population-based cohort studies involving 5,724

patients with DM (38 [0.66%] of whom developed first-ever ICH) and 78,702 patients without DM (448 [0.57%] of whom developed first-ever ICH), there was no evidence of an association between DM and ICH incidence (unadjusted RR 1.27, 95% CI 0.68–2.36; $I^2 = 69\%$; figure 2). We were unable to adjust our analyses for other risk factors because data were not presented by DM status.

Additional analyses. There was no difference in the association between DM and ICH occurrence in hospital-based case-control studies (OR 1.21, 95% CI 1.01–1.45) vs population-based studies (OR 1.36, 95% CI 0.78–2.37; $p_{\text{diff}} = 0.70$; figure 1). A borderline association between DM and ICH occurrence was found in the 16 studies in which cases and controls were comparable for age and sex (OR 1.15, 95% CI 0.95–1.40; $I^2 = 14\%$; figure e-2). We performed a post hoc subgroup analysis and did not find a significant difference between studies that were restricted to first-ever ICH and those that were not ($p_{\text{diff}} = 0.05$; figure e-3).

Figure 1 Association between diabetes mellitus (DM) and the occurrence of intracerebral hemorrhage (ICH) in 19 case-control studies, stratified by study design and ordered by mid-year of each study sample (if known)

CI = confidence interval; events = number of people with DM; M-H = Mantel-Haenszel; year = study mid-year, where known.

Figure 2 Association between diabetes mellitus and the incidence of intracerebral hemorrhage (ICH) in 3 cohort studies, ordered by study mid-year

CI = confidence interval; events = number of people with ICH; ICH = intracerebral hemorrhage; M-H = Mantel-Haenszel; year = study mid-year.

Association between DM and outcome after ICH. Study characteristics. We identified 26 eligible cohort studies,^{e1–e26} in which case fatality was reported at hospital discharge (8 studies), 7 days (one study), 30 days (9 studies), 3 months (5 studies), 1 year (3 studies), and 3 years (one study). Some studies reported case fatality at more than 1 timepoint. In the quantitative meta-analysis, we combined the 18 studies that reported case fatality in 4,527 people by 30 days or hospital discharge (table 2).^{e1–e18}

Risk of bias within studies. Of the 18 studies included in the quantitative meta-analysis of case fatality by 30 days or hospital discharge, 1 (6%) was population-based, 12 (67%) were prospective, and 3 (17%) specified restriction to first-ever ICH. Six (33%) studies specified a minimum age of 18 years and 3 (16%) specified further selection criteria, but none quantified the proportion of all eligible patients constituted by the cohort. Although many studies provided summary measures of known risk factors for poor outcome after ICH, these were not described separately for people with and without DM, and only 6 (33%) adjusted measures of association for at least one of these potential confounders.^{e4,e5,e9–e11,e16} Missing data and completeness of follow-up were quantified by 2 studies, though never separately for people with and without DM, so differential loss to follow-up could not be assessed; outcomes were assessed blind to DM diagnosis in just one study.^{e11} Assessing the association between DM and ICH outcome was the primary aim of only one study.^{e2} Studies did not report information on DM type, duration, glycemic control, or hypoglycemic treatment.

Results of individual studies and synthesis of results. In 18 cohort studies involving 813 people with DM and 3,714 patients without DM, DM was associated with a higher risk of death by 30 days or hospital discharge (unadjusted RR 1.52, 95% CI 1.28–1.81; $I^2 = 49\%$; figure 3). We were unable to adjust our analyses for other risk factors for poor outcome because of the lack of data on these potential confounders in people by DM status.

Additional analyses. There was no difference in the association between DM and ICH outcome in 3 studies

restricted to first-ever ICH (RR 1.31, 95% CI 0.89–1.92) vs 15 studies that did not specify first-ever ICH or included recurrent ICH (RR 1.57, 95% CI 1.29–1.91; $p_{\text{diff}} = 0.40$; figure 3).

DM was associated with a higher 3-month case fatality rate in 5 hospital-based studies (unadjusted RR 1.64, 95% CI 1.27–2.12; $I^2 = 62\%$)^{e1,e11,e19–e21} and a higher 1-year case fatality rate in 3 studies (unadjusted RR 1.21, 95% CI 1.03–1.42; $I^2 = 21\%$).^{e3,e21,e22} The prospective population-based study restricted to first-ever ICH did not find an association between DM and death within 3 years (unadjusted RR 0.96, 95% CI 0.54–1.69).^{e18}

DISCUSSION In our meta-analysis of unadjusted study-level data from case-control studies, there was a relative increase of about 23% in the frequency of DM in people with ICH, although the estimate of this risk was imprecise and we found no association between DM and ICH in our meta-analysis of cohort studies. In our meta-analysis of unadjusted study-level data of case fatality reported in cohort studies, which were at moderate risk of bias and did not allow us to account for confounders, DM was associated with a relative increase of about 52% in the risk of dying by 30 days or hospital discharge after ICH.

Our finding that people with DM seem to have an increased risk of ICH updates a previous meta-analysis of study-level data that did not find this association.⁶ However, the previous meta-analysis included fewer studies and some did not meet our more demanding eligibility criteria. Although this association between DM and ICH was not confirmed by our meta-analysis of summary level data from 3 cohort studies (figure 2), an association was found in a recent individual patient data meta-analysis of prospective cohort studies.⁵ Our results were consistent with the study that specifically assessed the association between DM and the incidence of ICH²⁸ and the study that specifically assessed the association between DM and outcome after ICH.^{e2} If these modest associations between DM and ICH occurrence and outcome are real, they might be mediated by mechanisms such as the

Table 2 Characteristics of the 18 studies included in the meta-analysis of the association between diabetes mellitus and death by 30 days or hospital discharge

Study reference	Study location	Study period	Study design	Cohort design	ICH type	ICH diagnosis	Diabetes definition	Mean age of patients with diabetes, y	Median Glasgow Coma Scale score at admission	Average ICH volume, cm ³	Intraventricular hemorrhage, %	Infratentorial origin of ICH, %
e1	USA	2009-2010	H	Prospective	NS	I	C	61.6	NS	23.1	17.9	NS
e2	Spain	1986-1995	H	Prospective	NS	I	C	67.1	NS	NS	69.4	NS
e3	Turkey	2004-2005	H	Retrospective	NS	I	C	70	NS	NS	33	NS
e4	Taiwan	2003-2006	H	Retrospective	NS	I	C	73	NS	NS	56.8	15.1
e5	Taiwan	2007-2010	H	Prospective	First-ever/ recurrent	I	C	73	NS	NS	29.4	NS
e6	USA	1996-1997	H	Prospective	NS	I	C	58.3	NS	NS	NS	NS
e7	Finland	1985-1991	H	Retrospective	First-ever/ recurrent	I/pathologic	C	74.4	NS	NS	1.2	12.2
e8	Argentina	2002-2003	H	Prospective	NS	I	C	60.3	NS	NS	0.3	10.2
e9	Korea	2010	H	Retrospective	NS	I	C	62.1	NS	NS	NS	NS
e10	Korea	2000-2009	H	Prospective	First-ever	I	C	61.8	10.44	NS	29.9	13.8
e11	Iran	2012	H	Prospective	NS	I	C	62.1	11.95	NS	NS	NS
e12	Spain	1995-2003	H	Prospective	NS	I	C	65.9	13.4	21.9	28.9	NS
e13	Malaysia	2002-2003	H	Prospective	NS	I	C	68.2	9.9	NS	42.4	27.3
e14	USA	2006-2008	H	Prospective	First-ever	I	C	69	NS	DM: 34.7/non-DM: 41.9	47.7	NS
e15	Germany	2008-2009	H	Retrospective	First-ever/ recurrent	I	C	NS	NS	DM: 70.3/non-DM: 40.4	0.8	20.7
e16	Iran	1999-2002	H	NS	NS	I	C	70.5	NS	NS	42.6	NS
e17	Malaysia	2007-2009	H	Prospective	NS	I	C	73.6	NS	NS	12.5	15
e18	Sweden	1993-2000	P	Prospective	First-ever	I	C	71.6	NS	26.6	42.8	12.7

Abbreviations: C = pre-ICH diabetes; DM = diabetes mellitus; H = hospital-based; I = brain imaging; ICH = intracerebral hemorrhage; NS = not specified; P = population-based.

Figure 3 Association between diabetes mellitus and case fatality after intracerebral hemorrhage (ICH) by 30 days or hospital discharge in 18 cohort studies, stratified by ICH type and ordered by mid-year of each study sample

CI = confidence interval; events = number of deaths; M-H = Mantel-Haenszel; year = study mid-year.

association between DM and the occurrence of cerebral small vessel disease³³ and the association between hyperglycemia and ICH volume expansion.³⁴

The strengths of our study include its exhaustive literature search, lack of restriction by language of publication, its requirements for internal validity of included studies, independent review of eligibility by at least 2 reviewers, and exploration of any heterogeneity in the association by key risk of bias attributes. We took the opportunity to quantify the associations between DM and ICH occurrence and outcome in many studies that provided the data to do so, but had not set out to specifically examine these associations.

This study has some limitations. It was unavoidably influenced by the sampling frame, selection biases, and other aspects of the design of included studies, which covered a long time during which definitions of DM and hypertension have changed,^{35–37} leaving the possibility of misclassification bias. The risk of bias of the included studies was moderate. Case-control studies far exceeded the number of cohort studies investigating the association between DM and ICH and there is considerable potential for selection bias as many case-control studies did not describe how they identified cases or controls. We were unable to control for major

confounders such as systemic arterial hypertension and age (although we performed a post hoc sensitivity analysis, excluding one study restricted to adults aged 18–49 years,²⁴ which did not change the overall association in figure 1). The differences in characteristics of participants in the studies (for example, type or duration of DM, degree of glycemic control, and use of different treatments) may have influenced the moderate inconsistency between studies, but we used conservative random-effects meta-analysis models to take this into account. Most of the studies were hospital-based, which are much more vulnerable to selection bias than population-based studies, as is evident in the outcomes that they report.³ We were also unable to control for all known confounders of the association between DM and ICH occurrence and outcome, because these data were scarce and not reported by DM status. No data were available in individual studies on DM characteristics (type of DM, duration of DM, and glycemic control), even among studies whose primary aim was to assess the association between ICH outcome and DM; therefore we were not able to examine whether occurrence of ICH or subsequent case fatality differed among subgroups of patients with DM. No studies reported stroke recurrence risks, precluding explorations

of the association of DM with these outcomes. Our inclusion criteria resulted in the exclusion of 18 studies that had specifically examined the association between DM and ICH incidence or outcome because they had identified ICH using ICD-10 coding (n = 3)^{e27–e29} or other criteria that did not meet our eligibility criteria (n = 2),^{e30–e31} had reported data on hemorrhagic stroke but not on ICH alone (n = 3),^{e32–e34} compared ICH to another subtype of stroke (n = 5),^{e35–e39} or used a study design that did not meet our eligibility criteria (n = 5).^{e40–e44}

Differences in the methods of individual studies assessing the association between DM and ICH occurrence may partly explain the variations in the estimates and the weak association we found. Further research is needed to confirm and investigate explanations for any associations and to identify whether subgroups of people with DM are at higher risk of ICH and ICH case fatality and whether improved glycemic control reduces risk of ICH and ICH case fatality. Large, prospective observational cohort studies, adjusting for all known risk factors for ICH and its outcome and stratified by type of DM, are required to further investigate the association between DM and case fatality and also to investigate whether DM influences stroke recurrence and functional outcome.

AUTHOR CONTRIBUTIONS

Collected data: M.B., M.T.C.P. Participated in study design: M.B., M.T.C.P., S.H.W., and R.A.-S.S. Performed statistical analysis: M.B. Interpreted the results: M.B., M.T.C.P., S.H.W., and R.A.-S.S. Drafted the manuscript: M.B. and R.A.-S.S. Edited/reviewed the manuscript: M.T.C.P., S.H.W., and R.A.-S.S.

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DISCLOSURE

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