Prediabetes and Outcome of Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Meta-analysis

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Background: The association of prediabetes and outcome of patients with ischemic stroke or transient ischemic attack (TIA) remains controversial. We performed a systematic review and meta-analysis to assess the association between prediabetes and outcome of ischemic stroke or TIA.
Methods: We comprehensively searched the PubMed and Excerpt Medica Database (EMBASE) from their inceptions to August 25, 2017. Studies that reported outcomes of patients with ischemic stroke or TIA and with information on prediabetic states at baseline were included. The end points were new stroke, mortality, and poor outcome (modified Rankin Scale score of 3-6 or 2-6).
Results: A total of 8 studies with 10,975 patients with ischemic stroke or TIA were included in this meta-analysis, among which 4 studies reported the endpoint of new stroke, 5 studies reported mortality, and 6 studies reported poor outcome. Prediabetes was at increased risk of stroke compared with normal glucose metabolism (hazard ratio [HR]: 1.42, 95% confidence interval [CI]: 1.13-1.80; P = .003). Poor outcome was also more frequent in patients with prediabetes compared with normal glucose metabolism (odds ratio: 1.33, 95%CI: 1.11-1.59; P = .002), while mortality was not significant (HR: 1.69, 95%CI: 0.84-3.40; P = .14). There was no evidence of statistical heterogeneity among the included studies for stroke and poor outcome, but for mortality.
Conclusions: Prediabetes was associated with an increased risk of new stroke and poor outcome, compared with normal glucose metabolism among patients with ischemic stroke or TIA.
Key Words: Prediabetes—meta-analysis—stroke—transient ischemic attack

Introduction

Prediabetes, including impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and/or impaired hemoglobin A1c (HbA1c), is an intermediate metabolic state between normal glucose metabolism and diabetes.[1,2] The prevalence of prediabetes in nondiabetic patients with ischemic stroke or transient ischemic attack (TIA) ranges from 23%-53%.[2-4] Some previous studies showed that prediabetes was associated with an increased risk of recurrent stroke[5] or mortality[6] in patients with ischemic stroke or TIA. However, other studies did not observe a significant association between prediabetes and recurrent stroke[7] or mortality.[5,8] Therefore, the association of prediabetes

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Received September 24, 2018; revision received October 31, 2018; accepted November 6, 2018.

Financial Disclosure: This study is supported by grants from the Ministry of Science and Technology of the People's Republic of China (2016YFC0901001, 2016YFC0901002, 2017YFC1310901, 2018YFC1311700 and 2018YFC1311706), Beijing Municipal Committee of Science and Technology (D151100002015003), Beijing Municipal Commission of Health and Family Planning (no. 2016-1-2041, SML20150502) and Beijing Municipal Administration of Hospitals (PX2016052) and National Natural Science Foundation of China (81600999).

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.11.008

and outcomes of patients with ischemic stroke or TIA has remained controversial.

With the increased evidences on these issues, we conducted a systematic review and meta-analysis of previous studies to assess the association between prediabetes at baseline and clinical outcomes of patients with ischemic stroke or TIA.

Methods

Search Strategy

We searched the PubMed and Excerpt Medica Database (EMBASE) up to August 25, 2017 with no language restriction to identify prospective studies describing the association between prediabetes and stroke events, mortality and poor outcome of patients with acute ischemic stroke or TIA. The search terms were: "prediabetes" or "pre-diabetes" or "prediabetic state" or "impaired fasting glucose" or "impaired glucose tolerance" and "stroke" or "cerebral infarction" or "transient ischemic attack" or "transient ischaemic attack" or "TIA". We further performed a search of the Cochrane library and manually checked reference lists to identify other potential studies and restricted the search to human studies.

Selection Criteria

Two authors (Y.P. and W.C. both neurologists) performed an initial screen of titles or abstracts to identify studies eligible for further review. Articles were considered for inclusion in this study if they reported original data on the prediabetic states at baseline and clinical outcomes in patients with ischemic stroke or TIA. Reviews, guidelines, editorials, letters, protocols, laboratory studies, and case reports were excluded. The 2 reviewers reached an agreement on the inclusion of articles in the initial screening, and full copies of potentially suitable studies were obtained. Then, we conducted a detailed full-text review to assess the eligibility for inclusion of articles. Studies were included for analysis if they were cohort studies (including both historical cohort and prospective cohort) or posthoc analyses of randomized controlled trials. According to the objective of this analysis, we restricted studies to those including patients with ischemic stroke or TIA, and those including only general population or patients with coronary artery diseases were excluded. Studies were included if they reported on prediabetic states at baseline and clinical outcomes during a follow-up period. Any disagreement was further reviewed by a third reviewer (Y.W.) and resolved by consensus.

DataExtraction and Quality Assessment

We extracted detailed data on publication characteristics, countries of the study, study design, patient characteristics, sample size of patients, definition of baseline prediabetes, proportion of prediabetes, duration and completeness of follow-up, outcomes, covariates adjusted in the multivariate analysis. Two investigators (Y.P. and W. C.) independently extracted data using a standardized form from eligible studies. Discrepancies were resolved by discussion with a third reviewer (Y.W.) after reviewing the article. Uncertainties and detailed data of the studies[7,9,10] were clarified after contact with the investigators.

Prediabetes was defined as IFG according to WHO criteria (fasting plasma glucose: 6.1 mmol/L-6.9 mmol/L)[11] or the ADA criteria (fasting plasma glucose: 5.6 mmol/L-6.9 mmol/L),[12] and/or IGT (2 hours plasma glucose: 7.8 mmol/L-11.0 mmol/L during an oral glucose tolerance test),[12] and/or impaired HbA1c according to ADA criteria (5.7%-6.4%).[12] Prediabetic states used in this meta-analysis were defined in accordance with what were used in the contributing studies. In cases where only 1 or 2 of items of criteria of prediabetes (IFG, IGT, or impaired HbA1c) were performed in the contributing study, the corresponding item of definition was used in this meta-analysis.

The primary outcome was occurrence of new stroke, including ischemic or hemorrhagic stroke. The secondary outcomes included all-cause mortality and poor outcome. Poor outcome was defined as modified Rankin Scale score of 3-6[8,9] or 2-6.[13] Outcomes were assessed at the longest follow-up available. All the 3 outcomes were defined in accordance with what were used in the contributing studies.

We used the Newcastle-Ottawa Scale to assess the quality of the observational studies.[14] The Newcastle-Ottawa scale is a quality score (range 0-9) generated according to a maximum of 1 star for each item on selection (4 items), comparability (2 items), and outcome (3 items). In this meta-analysis, only the studies with Newcastle-Ottawa Scale score greater than equal to 7 were included.

Statistical Analysis

We performed a detailed meta-analysis to evaluate the association of prediabetes at baseline with outcome of patients with ischemic stroke or TIA, compared with normal glucose metabolism. The included studies either performed analysis with diabetic patients as a separate group[5,6,8-10,13,15] or only included nondiabetic patients.[7]

All data were analyzed using Stata version 13.0 (StataCorp LP, College Station, TX). For meta-analysis, we used data of adjusted hazard ratio (HR) and 95% confidence intervals (CIs) for the endpoint of new stroke and mortality, and odds ratio (OR) and 95%CIs for the endpoint of poor outcome. We logarithmically transformed these data and calculated corresponding standard errors. An inverse variance approach was used to combine the log HR/OR and standard errors. We performed a fixed-effect model (Mantel-Haenszel) for the endpoint of new stroke and poor outcome, while random-effect model (DerSimonian-Laird) for the endpoint of mortality according to the significance of the test of heterogeneity. Two-sided P values of less than .05 were set as statistically significant. Heterogeneity among studies was assessed by calculating the I^2 statistic and the Q statistic, with a *P* value greater than equal to .10 considered to indicate no significant heterogeneity among the studies.

We evaluated potential publication bias by inspecting funnel plots for each outcome in which the natural log HR/OR was plotted against the standard error, and further testing with Egger's tests and trim-and-fill analysis. For each outcome, we also performed subgroup analyses according to study design (cohort study versus posthoc analysis of randomized control trial), country of study (Asian country and non-Asian country), population size, study quality (higher than median versus lower than median), and duration of follow-up (<1 year versus ≥ 1 year). This study is registered with International prospective register of systematic reviews (PROSPERO) (CRD42017075045), and followed the Meta-analysis of observational studies in epidemiology (MOOSE) guidelines.

Results

Study Selection and Characteristics

Our initial search identified a total of 409 potentially relevant articles (Fig 1). No previous meta-analysis on this issue was identified. After reviewing title and abstract, 171 articles were excluded and 238 articles were qualified for a full-text review in detail. Among the article reviewed, 230 articles were excluded: not ischemic stroke or TIA patients (n = 183), no prediabetic state was reported (n = 15), without clinical endpoint (n = 29), only included prediabetic patients (n = 2), and included patients with intracranial hemorrhage (n = 1).

A total of 8 studies with 10,975 patients were finally included in the meta-analysis. Table 1 showed the characteristics of the included studies. Of the 8 studies, 4 were posthoc analysis of RCTs[5,6,9,15] and 4 were cohort studies.[7,8,10,13] Three studies enrolled both ischemic stroke and TIA patients,[5,6,10] and 5 enrolled ischemic stroke only.[7-9,13,15] Two of the 8 studies defined prediabetes both by IGT and IFG according to WHO criteria,[7,13] 2 studies only measured IFG according to WHO criteria,[5,9] 1 only measured IFG according to ADA criteria,[15] 1 study only measured IGT,[6] and 2 study only measured impaired HbA1c.[8,10] All the studies adjusted at least 3 covariates and had a Newcastle-Ottawa score greater than equal to 7.

Prediabetes and Risk of New Stroke

Among the 8 studies, 4 studies (n = 9791) reported the association between prediabetic states and endpoint of new stroke.[5-7,9] Overall, prediabetes was at increased risk of stroke compared with normal glucose metabolism (HR: 1.42, 95%CI: 1.13-1.80; *P* = .003) (Fig 2A). The random-effect analysis yielded similar effect size (HR: 1.38, 95%CI: 1.02-1.87; *P* = .04) to that obtained with the fixed-effect analysis. There was no evidence of statistical heterogeneity among the included studies by the I^2 statistic and Q statistic (I^2 = 32%, *P* for heterogeneity = 1.22). No evidence of publication bias was observed based on visual inspection of funnel plots (Fig 3A) or according to Egger's tests (*P* = .26).

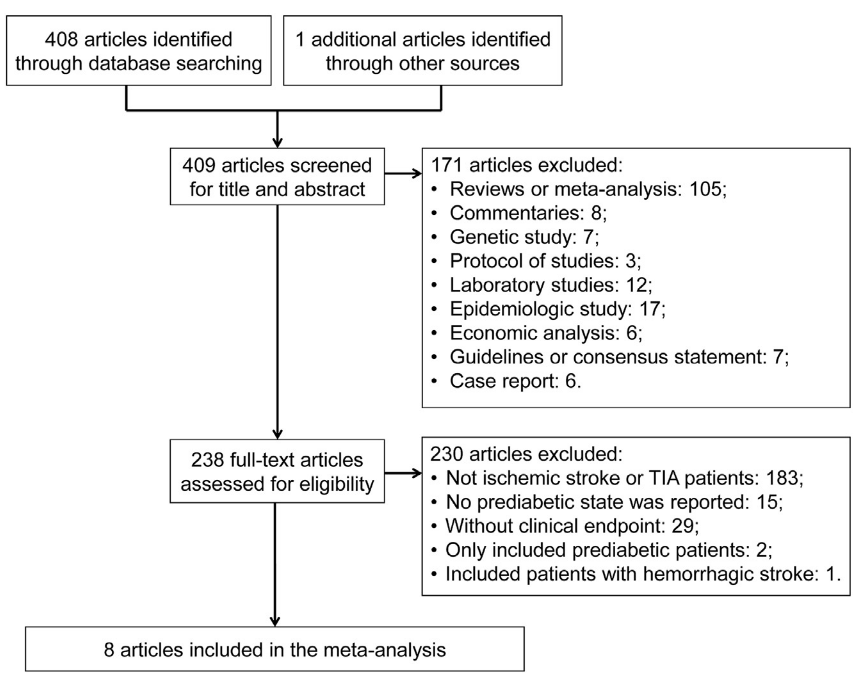

Figure 1. *Flow diagram of the systematic review process.*

Table 1. *Characteristics of the studies included in the systematic review and meta-analysis*

Study and publication year	Study type	Country	Participant	Sample size of cohorts*	Age, mean (SD), y	Women, %	Prediabetes, %	Baseline prediabetes definition	Outcome assessed	Follow-up, mean	Lost to follow-up, %	Adjustment variables	Quality score†
Vermeer (2006)[6]	Post-hoc analysis of RCT	Netherlands	IS or TIA	2843	65.1 (10.0)	35	5.8	IGT	Stroke	2.6 y	0	Age, sex, smoking, hypertension, and minor ischemic stroke in history	9
Tanaka (2013)[13]	Cohort	Japan	IS	116	67.8 (11.7)	28.9	44.8	IFG 6.1, IGT	mRS 2-6	1 m	28	Age, sex, baseline NIHSS, stroke subtype, hypertension, dyslipidemia, atrial fibrillation, body mass index, smoking, thrombolytic therapy, and admission blood glucose levels	7
Roquer (2014)[8]	Cohort	Spain	IS	667	77 (NR)	50.5	40.9	HbA1c 5.7%-6.4%	Death, mRS 3-6	3 m	0	Age, NIHSS and previous mRS	9
Jia (2014)[7]	Cohort	China	IS	926	62.6 (12.5)	36.3	47.4	IFG 6.1, IGT	Stroke, death, mRS 3-6	1 y	17.9	Sex, age, history of atrial fibrillation, pulmonary infection, lipid-lowering drugs during hospitalization, body mass index, NIHSS, and Glasgow coma scale at admission	8
Pan (2016)[5]	Posthoc analysis of RCT	China	Minor IS or TIA	3548	62.6 (10.7)	33.9	11.5	IFG 6.1	Stroke, death, mRS 3-6	3 m	3	Age, sex, history of IS, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, hypertension, hypercholesterolemia, smoking status, index event, NIHSS on admission, time to randomization, and antiplatelet and antihypertensive therapy	9

Table 1. (*Continued*)

Study and publication year	Study type	Country	Participant	Sample size of cohorts*	Age, mean (SD), y	Women, %	Prediabetes, %	Baseline prediabetes definition	Outcome assessed	Follow-up, mean	Lost to follow-up, %	Adjustment variables	Quality score†
Osei (2016)[15]	Posthoc analysis of RCT	Netherlands	IS after IAT	240	61 (15)	48	62	IFG 5.6	mRS 3-6	At discharge	24	Age, sex, NIHSS score on admission, atrial fibrillation, hypertension, history of diabetes and time from stroke onset to IAT.	7
Zhu (2017)[9]	Posthoc analysis of RCT	China	IS	2474	62 (10.9)	35.9	16.7	IFG 6.1	Stroke, death, mRS 3-6	3 m	2.1	Age, sex, time from onset to hospitalization, antihypertensive treatment, current smoking, alcohol consumption, dyslipidemia, baseline systolic blood pressure, ischemic stroke subtypes, and baseline NIHSS score.	9
Lorea (2017)[10]	Cohort	Spain	IS or TIA	161	73.9 (NR)	42	44.1	HbA1c 5.7%-6.4%	Death	30 m	3.9	Age, sex, reason for admission, previous myocardial infarction, glucose, and blood pressure in emergency and NIHSS.	9

Abbreviations: HbA1c, hemoglobin A1c; IAT, intra-arterial treatment; ICH, intracranial hemorrhage; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; IS, ischemic stroke; mRS, modified Rankin Scale; NIHSS, NIH Stroke Scale; NR, not reported; RCT, randomized controlled trial; TIA, transient ischemic attack.

*Only patients with prediabetes and normal glucose metabolism were presented.

†The quality score was determined according to the Newcastle-Ottawa Scale for cohort studies (0-9 points).

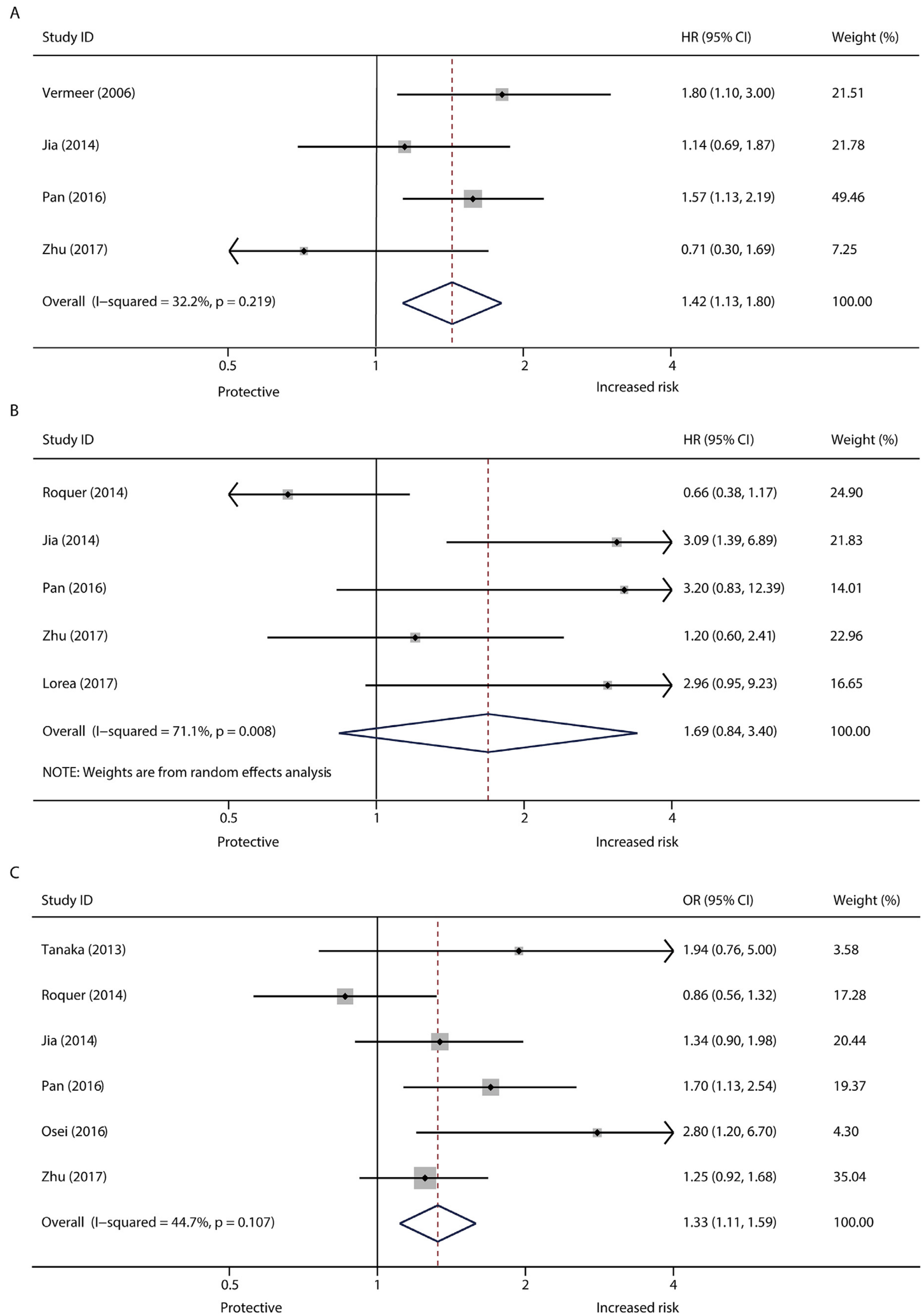

Figure 2. *Risk of (A) stroke (B) mortality (C) poor outcome for ischemic stroke or transient ischemic attack patients with prediabetes to normal glucose metabolism (reference). (Color version of figure is available online.)*

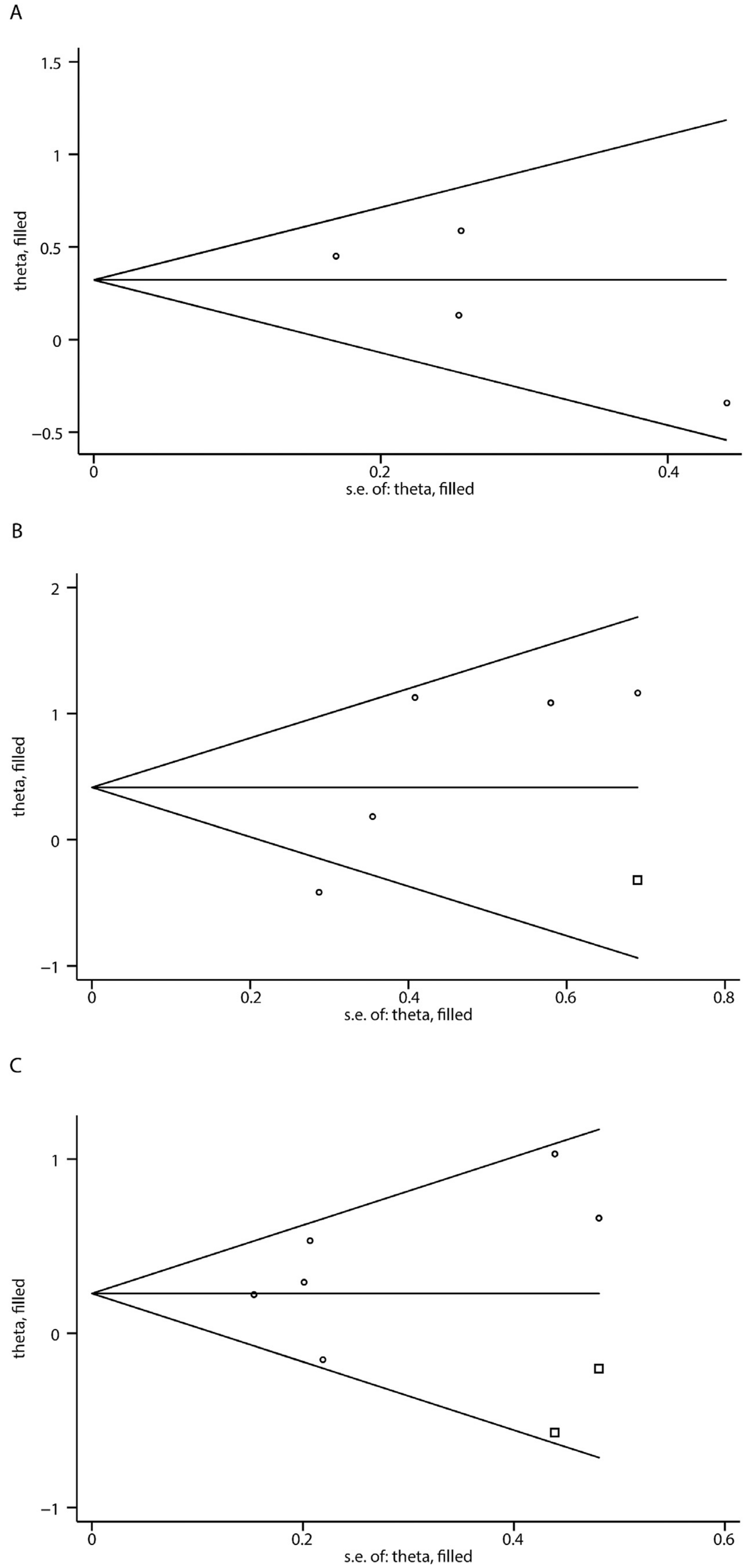

Figure 3. *Filled funnel plot with pseudo 95% confidence limits for (A) stroke (B) mortality (C) poor outcome. Circles are original data, whereas squares are imputed filled values.*

Table 2. *Subgroup analyses for each outcome*

Outcome	Subgroup	No. of studies	Total no. of patients	HR/OR (95% CI)*	*P* value	*P* value for heterogeneity between subgroups
Stroke	Cohort study	1	926	1.14(.69-1.87)	.61	.32
	Posthoc analysis of RCT	3	8865	1.52(1.16-1.97)	.002	
	Asian country	3	6948	1.34(1.03-1.74)	.03	.30
	Non-Asian country	1	2843	1.80(1.10-3.00)	.02	
	Large sample size (n ≥ 2000)	3	8865	1.52(1.16-1.97)	.002	.30
	Small sample size (n < 2000)	1	926	1.14(.69-1.87)	.61	
	High-quality study†	3	8865	1.52(1.16-1.97)	.002	.32
	Low-quality study	1	926	1.14(.69-1.87)	.61	
	Duration of follow-up <1 year	2	6022	1.42(1.04-1.93)	.03	.97
	Duration of follow-up ≥1 year	2	3769	1.43(1.00-2.04)	.047	
Mortality	Cohort study	3	1754	1.72(.55-5.41)	.35	.69
	Posthoc analysis of RCT	2	6022	1.64(.67-4.01)	.28	
	Asian country	3	6948	2.08(1.03-4.18)	.04	.03
	Non-Asian country	2	828	1.28(.30-5.54)	.74	
	Large sample size (n ≥ 2000)	2	6022	1.64(.67-4.01)	.28	.69
	Small sample size (n < 2000)	3	1754	1.72(.55-5.41)	.35	
	High-quality study†	4	6850	1.40(.68-2.91)	.36	.02
	Low-quality study	1	926	3.09(1.39-6.89)	.006	
	Duration of follow-up <1 year	3	6689	1.13(.54-2.36)	.75	.003
	Duration of follow-up ≥1 year	2	1087	3.05(1.58-5.86)	.001	
Poor outcome	Cohort study	3	1709	1.15(.87-1.52)	.33	.19
	Post-hoc analysis of RCT	3	6262	1.47(1.16-1.85)	.001	
	Asian country	4	7064	1.40(1.15-1.71)	.001	.25
	Non-Asian country	2	907	1.09(.74-1.60)	.67	
	Large sample size (n ≥ 2000)	2	6022	1.40(1.10-1.78)	.007	.55
	Small sample size (n < 2000)	4	1949	1.25(.96-1.63)	.10	
	High-quality study†	3	6689	1.24(1.01-1.53)	.04	.24
	Low-quality study	3	1282	1.57(1.12-2.20)	.008	
	Duration of follow-up <1 year	5	7045	1.32(1.08-1.62)	.006	.96
	Duration of follow-up ≥1 year	1	926	1.34(.90-1.99)	.15	

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; HR, hazards ratio; OR, odds ratio.
*HR for the outcome of stroke and mortality, while OR for poor outcome.
†A high-quality study was defined as one having a Newcastle-Ottawa Scale score = 9 (the median value of all studies).

The results of subgroup analyses to estimate the influence of the study design, country the study performed, sample size, study quality, and duration of follow-up on the association of prediabetes with new stroke are shown in Table 2. The increased risk of stroke remained significant in studies performed in Asian country (HR: 1.34, 95%CI: 1.03-1.74) and that performed in non-Asian country (HR: 1.80, 95%CI: 1.10-3.00). After exclusion of studies with small sample size, low-quality score, and duration of follow-up less than 1 year, the magnitude of association between prediabetes and risk of new stroke remained similar.

Prediabetes and Risk of All-cause Mortality

Five studies (n = 7776) reported the association between prediabetic states and all-cause mortality.[5,7-10] Overall, prediabetes was not significantly associated with an increased risk of all-cause mortality compared with normal glucose metabolism based on an random-effect model (HR: 1.69, 95%CI: .84-3.40; P = .14) (Fig. 2B). There was evidence of statistical heterogeneity among the included studies by the I^2 statistic and Q statistic (I^2 = 71%, P for heterogeneity = .008). Potential publication bias was observed based on visual inspection of funnel plots (Fig 3B) or according to Egger's tests (P = .09). When we quantified the potential effect of small-study bias using trim-and-fill analysis, prediabetes was still not associated with all-cause mortality after addition of 1 hypothetical missing study (HR: 1.51, 95%CI: .81-2.84, P = .20).

The results of subgroup analyses showed that prediabetes was associated with an increased risk of death in studies performed in Asian country (HR: 2.08, 95%CI: 1.03-4.18) and those with duration of follow-up greater than equal to 1 year (HR: 3.50, 95%CI: 1.58-5.86) (Table 2).

Prediabetes and Risk of Poor Outcome

Six studies (n = 7971) reported the association between prediabetic states and poor outcome.[5,7-9,13,15] Overall, prediabetes was at increased risk of poor outcome compared with normal glucose metabolism (OR: 1.33, 95%CI: 1.11-1.59; P = .002) (Fig 2C). The random-effect analysis yielded similar effect size (OR: 1.37, 95%CI: 1.06-1.78; P = .02) to that obtained with the fixed-effect analysis. There was no evidence of statistical heterogeneity among the included studies by the I^2 statistic and Q statistic (I^2 = 45%, P for heterogeneity = .11). Potential publication bias was observed based on visual inspection of funnel plots (Fig 3C) but not significant according to Egger's tests (P = .27). When we quantified the potential effect of small-study bias using trim-and-fill analysis, addition of the 2 hypothetical missing studies reduced the summary OR to 1.26 (95%CI, 1.06-1.50; P = .008) for fixed effect model and 1.26 (95%CI, .96-1.64; P = .09) for random-effects model.

The results of sensitivity analyses showed that after exclusion of studies with small sample size and low-quality score, the magnitude of association between prediabetes and risk of poor outcome remained similar (Table 2).

Discussion

In this meta-analysis, including 8 studies with 10,975 patients, we found that prediabetes was at increased risk of new stroke and poor outcome, but not all-cause mortality, compared with normal glucose metabolism among patients with ischemic stroke or TIA. The effect estimate remained significant after using trim-and-fill analysis and other sensitivity analyses.

Prediabetes, an intermediate metabolic state between normal glucose metabolism and diabetes, representing a high risk of developing type 2 diabetes as well as cardiovascular diseases in the future.[2] Several previous original studies or meta-analyses including prospective cohort studies from general populations have showed that prediabetes was associated with an increased risk of stroke,[16,17] cardiovascular diseases,[18,19] all-cause and cardiovascular mortality.[18,20] However, findings from a general population should not be directly applied to patients with stroke. To our knowledge, our study is the first meta-analysis of the association of prediabetes with the outcomes of patients with ischemic stroke or TIA. In this meta-analysis, we included 8 studies, 4 of which came from East Asia, and found that prediabetes was both significantly associated with an increased risk of stroke in studies performed in Asian country and those performed in non-Asian country (Netherlands and Spain).

Our study has implications on clinical care. The estimated overall prevalence of prediabetes was 35%-38% in general population,[21,22] and 23%-53% in nondiabetic patients with ischemic stroke or TIA.[2] People with prediabetes, including IFG, IGT, and/or impaired HbA1c, can be as insulin resistant as people with diabetes.[16] IFG reflects hepatic insulin resistance and a decrease in early-phase insulin response to oral glucose, whereas IGT reflects whole body and muscle insulin resistance.[1,2] Insulin resistance could cause metabolic and cellular changes that may promote atherosclerosis, which is a risk factor for stroke.[23,24] Therefore, abnormal glucose metabolism in patients with prediabetes may result in a high risk of subsequent stroke in the future.[1,3] Our meta-analysis found that prediabetes was associated with an increased risk of stroke and poor outcome, compared with normal glucose metabolism among patients with ischemic stroke or TIA. This may be of significance to help evaluate the outcome of nondiabetic patients with ischemic stroke or TIA in clinical practice. As the prevalence of prediabetes is growing rapidly, there is a growing recognition that patients with prediabetes, especially in patients with basic diseases like stroke, should be treated more aggressively.[2] However, large-scale trials of intervention to control hyperglycemia in ischemic stroke patients is lacking.[9] Several studies showed potential efficacy of antidiabetic medication such as pioglitazone for secondary prevention among stroke patients with prediabetes or insulin resistance.[25,26] Our meta-analysis might also implicate that prediabetes maybe another potential target of treatment for nondiabetic patients with ischemic stroke or TIA in the future studies.

Our study has several limitations. First, included studies varied in many aspects, including the study population, time between event and glucose measurement, definition of prediabetes, and follow-up duration. All these factors could be effect modifiers. Second, the associations of IFG, IGT, impaired HbA1c, and outcomes of ischemic stroke or TIA were not evaluated respectively due to lack of articles for each definition of prediabetes. It has been reported that the potential pathological mechanisms and cardiovascular risks are different in those with IFG, IGT, and impaired HbA1c.[27-29] Third, misclassification of prediabetes or normal glucose metabolism may exist since 3 of 8 included studies only measured IFG, 1 study only measured IGT, and 2 studies only measured impaired HbA1c. Previous studies showed that IFG, IGT, and impaired HbA1c were partly overlapped.[4,30] Finally, there appeared to be potential publication bias for the endpoint of mortality and poor outcome. However, sensitivity analysis using trim-and-fill analysis yielded a similar effect size. Nevertheless, more prospective cohort studies are needed to validate the findings of our study.

In summary, in this meta-analysis including large scale of population, prediabetes was associated with an increased risk of new stroke and poor outcome, compared with normal glucose metabolism among patients with ischemic stroke or TIA. This may help evaluate the outcome and implicate future researches on potential treatment for prediabetes in nondiabetic patients with ischemic stroke or TIA.

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