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ORIGINAL RESEARCH

Education Level and Long-Term Mortality, Recurrent Stroke, and Cardiovascular Events in Patients With Ischemic Stroke

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BACKGROUND: Epidemiological studies have reported discrepant findings on the relationship between education level and outcomes after stroke. We aimed to prospectively investigate the relationship between education level and mortality, recurrent stroke, and cardiovascular events in Chinese patients with ischemic stroke.

METHODS AND RESULTS: We included 3861 participants from the China Antihypertensive Trial in Acute Ischemic Stroke. Education level was categorized as illiteracy, primary school, middle school, and college. Study outcomes were all-cause mortality, stroke-specific mortality, recurrent stroke, and cardiovascular events within 2 years after ischemic stroke. A meta-analysis was conducted to incorporate the results of the current study and previous other studies on the association of education level with outcomes after stroke. Within 2 years after ischemic stroke, there were 327 (8.5%) all-cause deaths, 264 (6.8%) stroke-specific deaths, 303 (7.9%) recurrent strokes, and 364 (9.4%) cardiovascular events, respectively. The Kaplan–Meier curves showed that patients with the lowest education level had the highest cumulative incidence rates of all-cause mortality, stroke-specific mortality, and cardiovascular events (log-rank $P \leq 0.01$). After adjusted for covariates, hazard ratios and 95% CIs of illiteracy versus college education were 2.79 (1.32–5.87) for all-cause mortality, 3.68 (1.51–8.98) for stroke-specific mortality, 2.82 (1.20–6.60) for recurrent stroke, and 3.46 (1.50–7.95) for cardiovascular events. The meta-analysis confirmed the significant association between education status and mortality after stroke (pooled relative risk for lowest versus highest education level, 1.24 [95% CI, 1.05–1.46]).

CONCLUSIONS: Low education level was significantly associated with increased risk of mortality, recurrent stroke, and cardiovascular events after ischemic stroke, independently of established risk factors.

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Key Words: cardiovascular events ■ education ■ ischemic stroke ■ mortality

Stroke is the second most common cause of death and a leading cause of serious, long-term disability worldwide, which produce an enormous burden on society.[1] In China, stroke has been the top leading cause of death and disability-adjusted life-years, exceeding ischemic heart disease and lung cancer.[2] Understanding socioeconomic factors influencing outcomes of stroke has considerable clinical and public health significance for improving stroke prognosis and promoting the rehabilitation of patients with stroke.

Low socioeconomic status has been known to be associated with receiving poor quality of stroke care, increased risk of stroke recurrence, and lower survival rate.[3] Education status, a commonly used indicator of

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CLINICAL PERSPECTIVE

What Is New?

- Our prospective study demonstrated that low education level was associated with increased risk of mortality, recurrent stroke, and cardiovascular events in Chinese patients with acute ischemic stroke, independently of several established risk factors.
- The meta-analysis based on 10 previously published studies and the current study further confirmed the association between low education level and mortality after stroke.

What Are the Clinical Implications?

- Our findings have important public health and clinical implications for reducing education-related health inequality and promoting health care and rehabilitation practice for patients with low education level.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CATIS	China Antihypertensive Trial in Acute Ischemic Stroke
HRs	hazard ratios

socioeconomic status, has also been considered to be an important determinant of health outcomes including mortality, coronary heart disease, and stroke.[4] Low education attainment is usually accompanied by higher prevalence of cardiovascular risk factors, and is regarded as a proxy for limited access to medical care and increased psychological stress, which may contribute to excess risk of development and progression of stroke.[5,6] However, findings on the association between education level and outcomes after stroke are not consistent. Some[7–9] but not all studies[10,11] have demonstrated a significant association between education level and stroke prognosis.

Most of the existing studies were based on Western populations and investigated single outcome of stroke.[8,12,13] Data on the association of education level with stroke-related comprehensive outcomes are scarce in China, where disparities in stroke prevalence and mortality influenced by socioeconomic status are of particular concern.[14] Therefore, we prospectively investigated the association between education level and all-cause mortality, stroke-specific mortality, recurrent stroke, and cardiovascular events after stroke onset in a Chinese population with ischemic stroke. Furthermore, we conducted a meta-analysis that combined our data with previous other studies published to assess overall evidence of predictive effect of education level on stroke prognosis.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study was conducted among patients from the CATIS (China Antihypertensive Trial in Acute Ischemic Stroke), a multicenter, single-blind randomized controlled clinical trial performed among 4071 patients with acute ischemic stroke. We have described the detailed methods and main results of CATIS previously.[15] In brief, eligible participants were ≥22 years old, had ischemic stroke confirmed by computed tomography or magnetic resonance imaging within 48 hours of symptom onset, and had an elevated systolic blood pressure (BP) between 140 and <220 mm Hg. The CATIS trial excluded patients with a BP ≥220/120 mm Hg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, serious cerebrovascular stenosis (≥70%), or resistant hypertension and those in a deep coma. In the present analysis, we further excluded patients with ischemic stroke without educational data (n=14) or without available follow-up data (n=196); a total of 3861 participants were included.

This study was approved by the ethical committee at Soochow University in China and the institutional review boards at Tulane University in the United States, as well as ethical committees at the 26 participating hospitals. Written informed consent was obtained from all study participants or their immediate family members. The CATIS is registered with clinicaltrials.gov (NCT01840072).

Education Status and Potential Covariates

Information about educational level and exact years of education for all participants was collected using a validated questionnaire at baseline, and educational level was categorized as illiteracy (without any formal education), primary school education, middle school education, and college education. Data on demographic characteristics, other socioeconomic indicators, lifestyle risk factors, medical history, and medication history were collected at the time of enrollment. Annual per capita family income was classified into 4 groups: <¥5000 (RMB), ¥5000 to 9999, ¥10 000 to 19 999, and ≥¥20 000, which was calculated based on family size and annual family income during the past year. Stroke severity was assessed using the National Institutes of Health Stroke Scale score by trained neurologists at admission.[16] Three BP measurements were obtained at baseline interview by trained nurses according to a common protocol adapted from procedures recommended by the American Heart Association.[17]

Outcome Determination

Study participants were followed up at 3, 12, and 24 months after ischemic stroke onset to collect the study outcomes within 2 years. In this analysis, study outcomes were defined as death from any cause (all-cause death), stroke-specific mortality, recurrent stroke, and cardiovascular events, respectively, within 2 years after stroke. The causes and date of death were verified by examining hospital medical records. Stroke-specific mortality was defined as code numbers I60 to I69 of the *International Classification of Diseases, Tenth Revision* (*ICD-10*).[18,19] Recurrent stroke was defined as a new neurological deficit or a deterioration of the previous deficit that lasted longer than 24 hours and fitted the definitions for ischemic or hemorrhagic stroke.[20] Cardiovascular events included vascular deaths, nonfatal stroke, nonfatal myocardial infarction, and hospitalization and treatment for angina, congestive heart failure, or peripheral arterial disease. A trial-wide outcomes assessment committee, blinded to treatment assignment, reviewed and adjudicated outcome events based on the criteria established.

Statistical Analysis

Baseline characteristics of study participants were compared across 4 education categories ranging from illiteracy to college education. The cumulative incidence rates of 2-year outcomes (including all-cause mortality, stroke-specific mortality, recurrent stroke, and cardiovascular events) across 4 education categories were estimated using Kaplan–Meier cumulative incidence curves and compared using log-rank tests. Cox proportional hazards models were performed to estimate associations between education levels and outcomes within 2 years after ischemic stroke, and hazard ratios (HRs) with corresponding 95% CIs were calculated for each stratum of education level with "college education" group as reference. The proportional hazards assumption of the Cox models was tested using Schoenfeld residuals, which showed no significant departure from proportionality (P>0.05).[21] We performed 3 multivariate proportional hazards models. We first adjusted for age, sex, current smoking, alcohol consumption, occupation, and income in model 1, and in model 2, we adjusted for clinical characteristics of stroke including baseline National Institutes of Health Stroke Scale score, systolic BP, ischemic stroke subtype, treatment assignment, and time from onset to randomization in addition to model 1. In model 3, we further adjusted for history of cardiovascular diseases (hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease, family history of stroke) and medications (use of antihypertensive and lipid-lowering medications) in addition to model 2. Tests for linear trend in HRs across 4 groups were conducted by modeling education level as an ordinal variable. To further test robustness of association between education level and outcomes after ischemic stroke, a sensitivity analysis was conducted by reclassifying participants according to tertiles of education years: <6 years of school, 6 to 9 years of school, >9 years of school, and HRs (95% CIs) of each group were calculated using >9 years as reference.

Multiple imputations for missing values of covariates were performed using the Markov chain Monte Carlo method. We generated 5 imputed data sets, and the HRs were then averaged across the 5 imputations. Two-tailed P<0.05 were considered statistically significant. For multiple outcomes, the threshold for statistical significance after Bonferroni correction for multiple comparisons was set at P<0.0125 (correcting for 4 outcomes: 0.05/4=0.0125). Statistical analysis was conducted using SAS statistical software (version 9.4, Cary, NC).

Meta-Analysis

Based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses,[22] we conducted a meta-analysis that incorporated the results of the current study and previous studies on education levels and outcomes after stroke. Literature search and data extraction were independently performed by 2 investigators. The following data elements were extracted from each included study: first author, year and place of study, participants' characteristics (ie, age, stroke types), outcomes of stroke, education categories, number of events/participants, effect size (HRs or relative risks), and adjusted covariates. Heterogeneity was assessed using Cochrane's Q test and I^2 statistic. Potential publication bias was examined using funnel plot, Begg test, and Egger's asymmetry test.[23,24] All analyses were performed using STATA11.0 (StataCorp LP, College Station, TX). Detailed methods of this meta-analysis are described in Data S1.

RESULTS

Baseline Characteristics of Study Participants

Among the included 3861 participants with mean age of 62.0±10.9 years, 2492 (64.5%) were men. The median (interquartile range) of education years

Table 1. Characteristics of Participants According to Education Level

Characteristics*	Total (n=3861)	Illiteracy (n=496)	Primary (n=1463)	Middle (n=1701)	College (n=201)	*P* Value for Trend
Demographic						
Age, y	62.0±10.9	69.5±9.9	63.5±9.8	58.9±10.6	58.0±11.6	<0.001
Male sex	2492 (64.5)	165 (33.3)	863 (59.0)	1293 (76.0)	171 (85.1)	<0.001
Current cigarette smoking	1416 (36.7)	105 (21.2)	493 (33.7)	726 (42.7)	92 (45.8)	<0.001
Current alcohol drinking	1196 (31.0)	75 (15.1)	420 (28.7)	599 (35.2)	102 (50.8)	<0.001
Socioeconomic status						
Occupation						<0.001
Nonmanual workers	718 (18.6)	29 (5.9)	99 (6.8)	423 (24.9)	167 (83.1)	
Manual workers	1705 (44.2)	157 (31.6)	597 (40.8)	926 (54.4)	25 (12.4)	
No job	1438 (37.2)	310 (62.5)	767 (52.4)	352 (20.7)	9 (4.5)	
Annual per capita income, Yuan (RMB)						<0.001
<5000	1874 (48.5)	286 (57.7)	826 (56.4)	728 (42.8)	34 (16.9)	
5000–9999	839 (21.7)	112 (22.6)	339 (23.2)	350 (20.6)	38 (18.9)	
10 000–19 999	763 (19.8)	84 (16.9)	237 (16.2)	389 (22.9)	53 (26.4)	
≥20 000	385 (10.0)	14 (2.8)	61 (4.2)	234 (13.7)	76 (37.8)	
Clinical features						
Baseline systolic BP, mm Hg	166.1±16.9	167.2±17.9	166.3±16.7	165.7±16.8	164.8±16.0	0.11
Baseline diastolic BP, mm Hg	96.7±11.1	94.6±10.6	96.3±11.2	97.6±11.1	97.6±11.4	0.003
Admission NIHSS score	4.0 (2.0–7.0)	5.0 (3.0–9.0)	5.0 (3.0–8.0)	4.0 (2.0–7.0)	4.0 (2.0–6.0)	<0.001
Time from stroke onset to randomization, h	10.0 (4.5–24.0)	10.0 (4.0–24.0)	11.5 (4.0–24)	10.0 (5.0–24.0)	10.0 (5.0–24.0)	0.83
Disease history						
Hypertension	3039 (78.7)	376 (75.8)	1108 (75.7)	1379 (81.1)	176 (87.6)	<0.001
Hyperlipidemia	263 (6.8)	18 (3.6)	73 (5.0)	140 (8.2)	32 (15.9)	<0.001
Diabetes mellitus	678 (17.6)	72 (14.5)	213 (14.6)	349 (20.5)	44 (21.9)	<0.001
Coronary heart disease	416 (10.8)	72 (14.5)	129 (8.8)	185 (10.9)	30 (14.9)	0.99
Family history of stroke	722 (18.7)	65 (13.1)	241 (16.5)	362 (21.3)	54 (26.9)	<0.001
Medication history						
Use of antihypertensive medications	1881 (51.3)	235 (47.4)	715 (48.9)	826 (48.6)	105 (52.2)	0.45
Use of lipid-lowering medications	123 (3.2)	11 (2.2)	38 (2.6)	61 (3.6)	13 (6.5)	0.003
Treatment during hospitalization						
Receiving immediate BP reduction	1941 (50.3)	252 (50.8)	712 (48.7)	876 (51.5)	101 (50.3)	0.45
Glucose-lowering agents	701 (18.2)	94 (19.0)	243 (16.6)	325 (19.1)	39 (19.4)	0.35
Anticoagulants	1308 (33.9)	210 (42.3)	450 (30.8)	562 (33.0)	86 (42.8)	0.37
Antiplatelet agents	3758 (97.3)	487 (98.2)	1419 (97.0)	1656 (97.4)	196 (97.5)	0.69
Ischemic stroke subtype						
Thrombotic	2994 (77.5)	371 (74.8)	1107 (75.7)	1367 (80.4)	149 (74.1)	0.04
Embolic	176 (4.6)	24 (4.8)	99 (6.8)	49 (2.9)	4 (2.0)	<0.001
Lacunar	691 (17.9)	101 (20.4)	257 (17.6)	285 (16.7)	48 (23.9)	0.59

BP indicates blood pressure; and NIHSS, National Institute of Health Stroke Scale.
*Continuous variables are expressed as mean±SD or as median (interquartile range). Categorical variables are expressed as frequency (percentage).

was 6 (5–9). Baseline characteristics of participants according to education level are shown in Table 1. Participants with higher education level were more inclined to be younger, male, cigarette smokers, alcohol drinkers, and nonmanual workers; have higher income, baseline diastolic BP and higher proportions of hypertension, hyperlipidemia, diabetes mellitus, family history of stroke, use of lipid-lowering medications, thrombotic and embolic infarcts; and have lower baseline National Institutes of Health Stroke Scale score, compared with those with lower education level.

Education Level, Mortality, and Cardiovascular Events

During 2 years of follow-up, there were 327 (8.5%) all-cause deaths, 264 (6.8%) stroke-specific deaths, 303 (7.9%) recurrent stroke, and 364 (9.4%) cardiovascular events. From illiteracy to college education level, the cumulative incidences of all-cause mortality were 16.7%, 10.1%, 5.2%, and 4.5%, respectively; the cumulative incidences of stroke-specific mortality were 15.3%, 8.0%, 3.8%, and 3.0%, respectively; the cumulative incidences of recurrent stroke were 8.9%, 8.3%, 7.7%, and 3.5%, respectively; and the cumulative incidences of cardiovascular events were 10.9%, 10.0%, 9.2%, and 3.5%, respectively. Overall, Kaplan–Meier plots illustrated that patients with the lowest education had the highest cumulative incidence rates of all-cause mortality, stroke-specific mortality, and cardiovascular events (log-rank $P \leq 0.01$, Figure 1).

After adjustment for age, sex, current smoking, alcohol consumption, occupation, and income, individuals with illiteracy were at increased risks for all-cause mortality, stroke-specific mortality, recurrent stroke, and cardiovascular events compared with those with college education. These associations remained significant when additional adjustment was made for several clinical characteristics of stroke. In fully adjusted models that further adjusted for history of cardiovascular diseases and medications, HRs (95% CIs) of illiteracy versus college education were 2.79 (1.32–5.87) for all-cause mortality, and 3.68 (1.51–8.98) for stroke-specific mortality, respectively. In addition, multivariate adjusted HRs (95% CIs) of middle, primary, and illiteracy versus college were 2.25 (1.04–4.89),

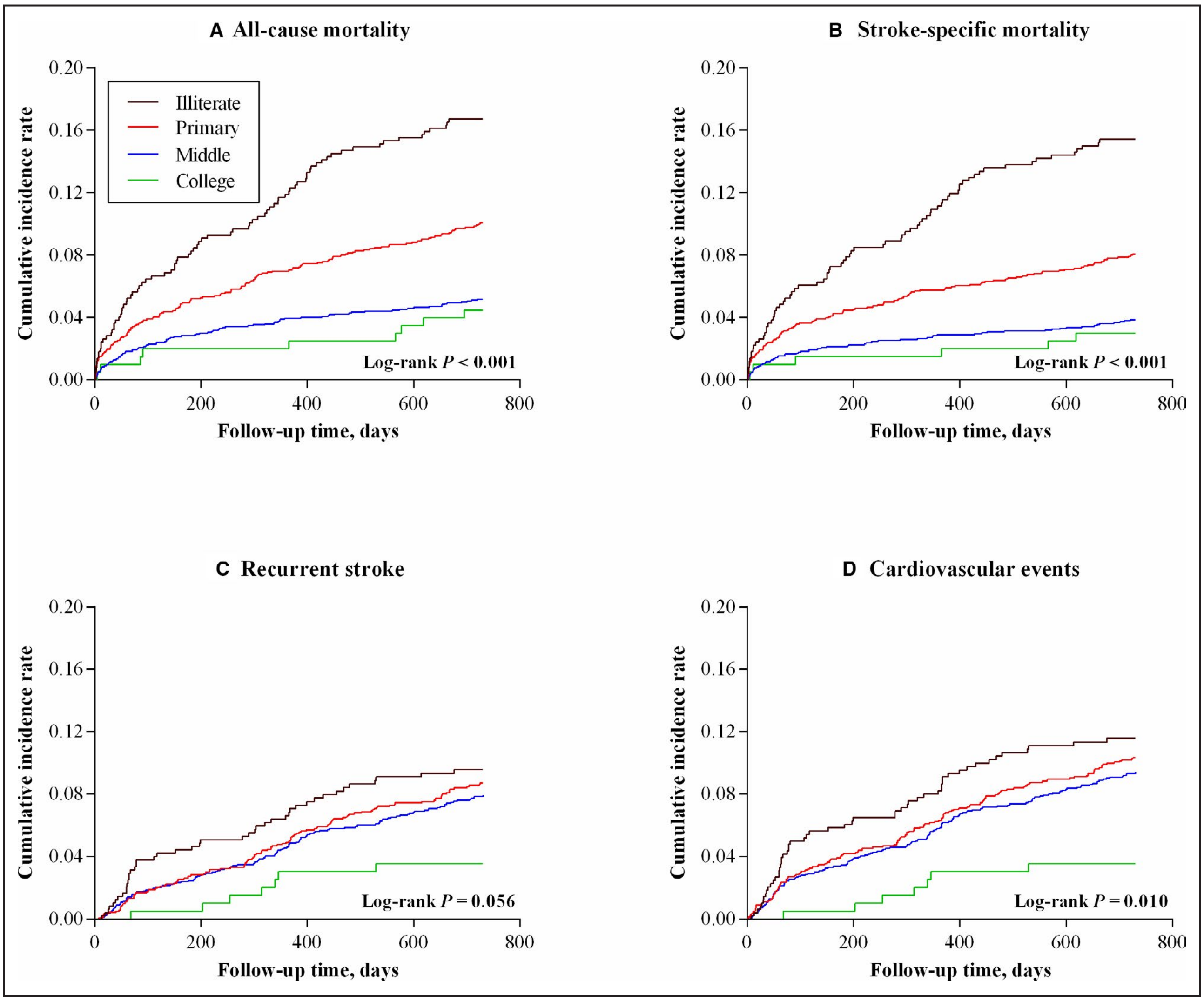

Figure 1. Kaplan–Meier survival curves of all-cause mortality (A), stroke-specific mortality (B), recurrent stroke (C), and cardiovascular events (D) according to educational level.

2.48 (1.11–5.53), and 2.82 (1.20–6.60) for recurrent stroke, 2.78 (1.29–5.99), 3.05 (1.38–6.73), and 3.46 (1.50–7.95) for cardiovascular events, respectively (P<0.05 for all, Table 2). After Bonferroni correction for multiple outcomes, the associations among education level and all-cause mortality, stroke-specific mortality, and cardiovascular events after ischemic stroke were still significant (P for trend<0.0125 for all). Similarly, sensitivity analysis also showed statistically significant associations between years of education and outcomes after ischemic stroke. The fully adjusted HRs (95% CIs) of <6 years versus >9 years were 2.05 (1.40–3.01) for all-cause mortality, 2.41 (1.55–3.73) for stroke-specific mortality, 1.73 (1.19–2.50) for recurrent stroke, and 1.74 (1.23–2.46) for cardiovascular events, respectively (P for trend <0.0125 for all, Table 3).

Meta-Analysis

Ten published prospective studies and the current study were included in this meta-analysis (Figure S1). General characteristics of eligible studies are shown in Data S1 and Table S1. Consistent with our findings, this meta-analysis indicated that lower education level was significantly associated with increased risk of mortality after stroke (the pooled relative risk of 1.24 [95% CI, 1.05–1.46], Figure 2).[10–13,25–30] Substantial heterogeneity was observed across studies (I^2=78.5%, P<0.001), which was probably caused by sample size and differences in classifications of education. Review of the funnel plot could not eliminate potential publication bias (Figure S2). Begg and Egger tests further suggested no evidence of potential publication bias (P>0.05 for both). Several sensitivity analyses according to different education classifications further confirmed the significant association between lower education and mortality after stroke (Table S2).

DISCUSSION

In this large-scale prospective study among the CATIS patients, we observed that low education level was significantly associated with increased risk of

Table 2. HRs and 95% CIs of Study Outcomes According to Education Level Among Patients With Acute Ischemic Stroke

	College (Reference)	Middle		Primary		Illiteracy		*P* Value for Trend
		HRs (95% CIs)	*P* Value	HRs (95% CIs)	*P* Value	HRs (95% CIs)	*P* Value	
All-cause mortality								
Events, n (%)	9 (4.5)	88 (5.2)		147 (10.1)		83 (16.7)		<0.001
Unadjusted	1.00	1.17 (0.59–2.31)	0.66	2.32 (1.18–4.55)	0.01	4.01 (2.01–7.97)	<0.001	<0.001
Model 1	1.00	1.14 (0.57–2.29)	0.72	1.93 (0.95–3.95)	0.07	2.77 (1.32–5.82)	0.007	<0.001
Model 2	1.00	1.13 (0.56–2.27)	0.74	1.83 (0.90–3.74)	0.10	2.64 (1.25–5.55)	0.01	<0.001
Model 3	1.00	1.18 (0.58–2.37)	0.65	1.90 (0.93–3.90)	0.08	2.79 (1.32–5.87)	0.007	<0.001
Stroke-specific mortality								
Events, n (%)	6 (3.0)	65 (3.8)		117 (8.0)		76 (15.3)		<0.001
Unadjusted	1.00	1.29 (0.56–2.98)	0.55	2.77 (1.22–6.28)	0.02	5.49 (2.39–12.60)	<0.001	<0.001
Model 1	1.00	1.25 (0.54–2.93)	0.60	2.27 (0.96–5.37)	0.06	3.74 (1.54–9.10)	0.004	<0.001
Model 2	1.00	1.23 (0.53–2.88)	0.63	2.12 (0.89–5.02)	0.09	3.51 (1.44–8.56)	0.006	<0.001
Model 3	1.00	1.29 (0.55–3.01)	0.56	2.18 (0.92–5.18)	0.08	3.68 (1.51–8.98)	0.004	<0.001
Recurrent stroke								
Events, n (%)	7 (3.5)	131 (7.7)		121 (8.3)		44 (8.9)		0.05
Unadjusted	1.00	2.28 (1.06–4.87)	0.03	2.50 (1.17–5.36)	0.02	2.83 (1.28–6.28)	0.01	0.02
Model 1	1.00	2.34 (1.08–5.08)	0.03	2.59 (1.17–5.77)	0.02	2.90 (1.24–6.79)	0.01	0.05
Model 2	1.00	2.31 (1.06–5.00)	0.03	2.55 (1.14–5.67)	0.02	2.87 (1.23–6.71)	0.02	0.05
Model 3	1.00	2.25 (1.04–4.89)	0.04	2.48 (1.11–5.53)	0.03	2.82 (1.20–6.60)	0.02	0.06
Cardiovascular events								
Events, n (%)	7 (3.5)	157 (9.2)		146 (10.0)		54 (10.9)		0.01
Unadjusted	1.00	2.72 (1.28–5.80)	0.01	3.01 (1.41–6.42)	0.004	3.46 (1.57–7.59)	0.002	0.005
Model 1	1.00	2.85 (1.32–6.15)	0.008	3.16 (1.43–6.95)	0.004	3.51 (1.53–8.04)	0.003	0.02
Model 2	1.00	2.81 (1.30–6.05)	0.008	3.08 (1.40–6.79)	0.005	3.44 (1.50–7.89)	0.004	0.03
Model 3	1.00	2.78 (1.29–5.99)	0.009	3.05 (1.38–6.73)	0.006	3.46 (1.50–7.95)	0.004	0.03

Model 1: adjusted for age, sex, current smoking, alcohol intake, occupation, and income; Model 2: adjusted for model 1 and further adjusted for baseline National Institutes of Health Stroke Scale scores, systolic blood pressure, ischemic stroke subtype, treatment assignment, and time from onset to randomization; Model 3: adjusted for model 2 and further adjusted for medical history (hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease), family history of stroke, and use of antihypertensive and lipid-lowering medications. HRs indicates hazard ratios.

Table 3. HRs and 95% CIs of Study Outcomes According to Education Years Among Patients With Acute Ischemic Stroke: Sensitivity Analysis

	Education Level, y			*P* Value for Trend
	>9	6–9	<6	
All-cause mortality				
Events, n (%)	42 (4.8)	100 (6.3)	185 (13.1)	<0.001
HRs (95% CIs)				
Unadjusted	1.00	1.33 (0.93–1.91)	2.87 (2.05–4.01)	<0.001
Model 1	1.00	1.22 (0.84–1.77)	2.18 (1.49–3.18)	<0.001
Model 2	1.00	1.16 (0.80–1.68)	1.99 (1.36–2.91)	<0.001
Model 3	1.00	1.18 (0.81–1.72)	2.05 (1.40–3.01)	<0.001
Stroke-specific mortality				
Events, n (%)	30 (3.4)	73 (4.6)	161 (11.4)	<0.001
HRs (95% CIs)				
Unadjusted	1.00	1.36 (0.89–2.08)	3.49 (2.36–5.15)	<0.001
Model 1	1.00	1.24 (0.80–1.92)	2.62 (1.69–4.06)	<0.001
Model 2	1.00	1.16 (0.75–1.80)	2.35 (1.51–3.64)	<0.001
Model 3	1.00	1.19 (0.76–1.84)	2.41 (1.55–3.73)	<0.001
Recurrent stroke				
Events, n (%)	51 (5.8)	124 (7.9)	128 (9.1)	0.005
HRs (95% CIs)				
Unadjusted	1.00	1.38 (1.00–1.91)	1.67 (1.21–2.31)	0.002
Model 1	1.00	1.43 (1.02–2.00)	1.75 (1.21–2.53)	0.003
Model 2	1.00	1.39 (0.99–1.95)	1.72 (1.19–2.49)	0.004
Model 3	1.00	1.40 (1.00–1.97)	1.73 (1.19–2.50)	0.004
Cardiovascular events				
Events, n (%)	59 (6.7)	153 (9.7)	152 (10.8)	0.002
HRs (95% CIs)				
Unadjusted	1.00	1.47 (1.09–1.98)	1.71 (1.27–2.31)	<0.001
Model 1	1.00	1.51 (1.11–2.07)	1.75 (1.24–2.46)	0.002
Model 2	1.00	1.47 (1.08–2.01)	1.71 (1.21–2.40)	0.003
Model 3	1.00	1.49 (1.09–2.04)	1.74 (1.23–2.46)	0.002

Model 1: adjusted for age, sex, current smoking, alcohol intake, occupation, and income; Model 2: adjusted for model 1 and further adjusted for baseline National Institutes of Health Stroke Scale scores, systolic blood pressure, ischemic stroke subtype, treatment assignment, and time from onset to randomization; Model 3: adjusted for model 2 and further adjusted for medical history (hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease), family history of stroke, and use of antihypertensive and lipid-lowering medications. HRs indicates hazard ratios.

all-cause mortality, stroke-specific mortality, recurrent stroke, and cardiovascular events within 2 years after stroke onset, independently of established risk factors. In the meta-analysis based on available data from 10 previously published studies and this study, we also found a significant increase in long-term mortality after stroke among patients with lower education level.

Overall, previous evidences on the relationship between education status and outcomes of stroke were inconsistent.[3] For example, in a population-based study from Denmark, there was no significantly increased mortality within 1 year for patients with lower education level.[10] However, a Brazilian community-based study including 430 consecutive first-ever stroke patients revealed that low education level was associated with poor 1-year stroke survival.[12] A cohort study in the United States showed that long-term mortality was higher among participants with low education level (age-adjusted mortality rate ratio for less than high school versus college graduate, 1.5; 95% CI, 1.1–1.9).[25] These studies had either relatively small sample sizes, short follow-up period, or insufficient adjustment for possible confounders, especially for stroke severity. In addition, effect of education level on stroke prognosis may be divergent in countries with different races, or different socioeconomic development and health-care levels. Therefore, it was necessary to evaluate this association in Chinese patients with ischemic stroke.

To our knowledge, very limited prior studies on association between education level and prognosis of stroke have been conducted in China, especially for

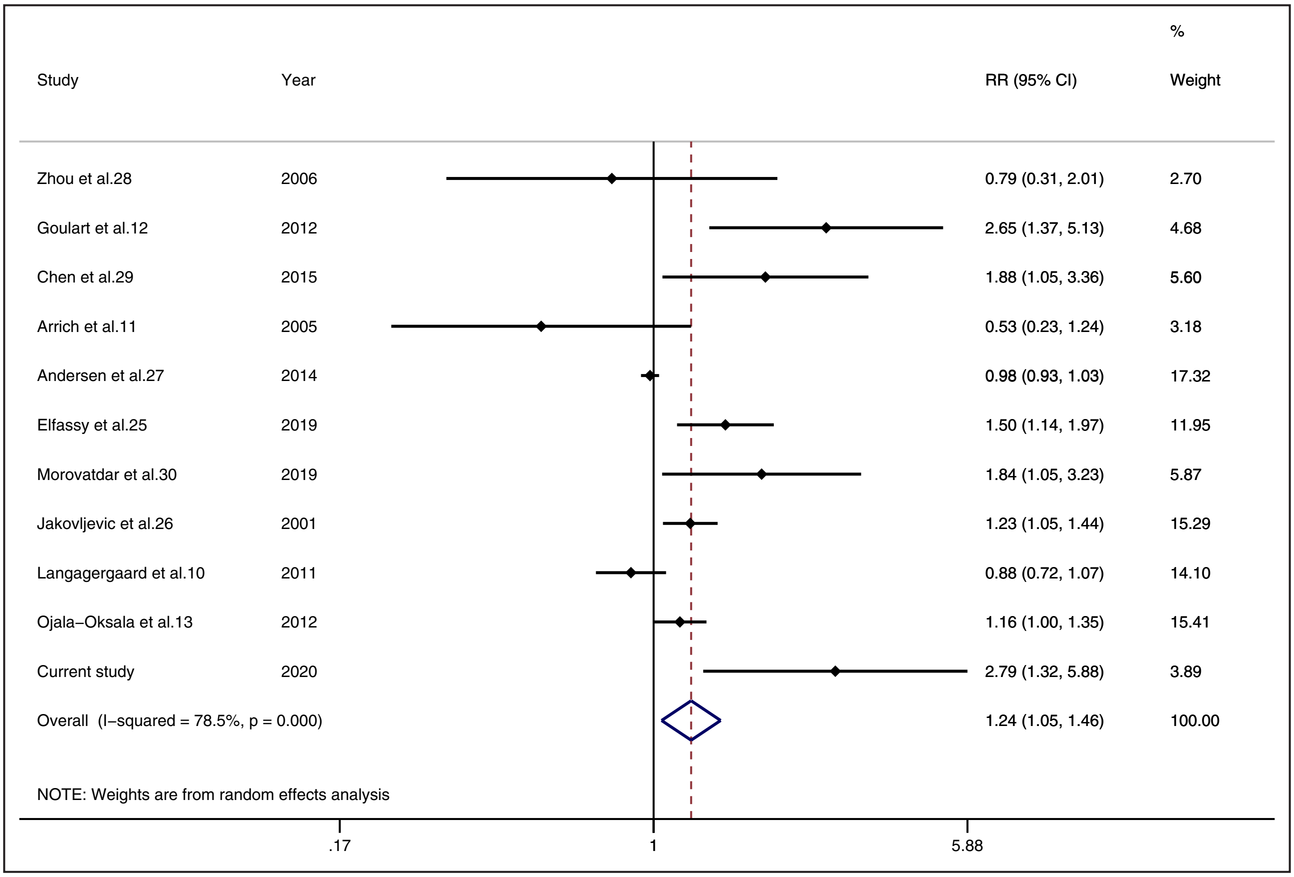

Figure 2. Meta-analysis of relative risks (RRs) and 95% CIs for the lowest vs highest education categories and mortality after stroke.

stroke-specific mortality and recurrent stroke. Using data from the CNSR (China National Stroke Registry), Pan et al[7] reported a significant association between education levels and prognosis of ischemic stroke, but they only evaluated association of education level with all-cause mortality after ischemic stroke. In comparison with their study,[7] we evaluated the associations of education level with comprehensive outcomes including all-cause mortality, stroke-specific mortality, recurrent stroke, and cardiovascular events within 2 years after ischemic stroke. Similarly, our study found that low education level was associated with increased risk of all-cause mortality, stroke-specific mortality, recurrent stroke, and cardiovascular events. Compared with the patients with college education level, those with illiteracy had >2.5-fold risk of all study outcomes, even after adjusted for important confounders including occupation, income, severity of stroke, as well as medical history. Furthermore, the meta-analysis pooling of published conflicting results also supported our findings. Taken together, these findings suggested that education level should be a valuable predictor of long-term prognosis of stroke.

The association between education level and prognosis of stroke is often considered to be because of different prevalence of conventional risk factors among populations with different education levels, such as unhealthy lifestyles and cardiovascular disease history,[6] which may be partly attributed to an insufficient understanding of the importance of proper management of cardiovascular risk factors in the population with low education level.[31] Also, education level is closely related to income and occupation, 2 other indictors of socioeconomic status. Our findings showed that the association between education level and outcomes of stroke was attenuated but remained significant after adjusting for income and occupation, suggesting the association basically was independently of income and occupation. The patients with lower education level might have poor adherence to stroke medication, ignore regular re-examination and rehabilitation practice, and have high prevalence of poststroke depression in response to cumulative stress.[32,33] The CNSR suggested that low education level was significantly associated with receiving poor quality of care in patients with ischemic stroke, which might also lead to increased incidences of cardiovascular events or mortality.[34] A recent genome-wide associations study identified some education-related genetic variants, indicating that genetic factors may play a role in the association of education level with health outcomes in humans.[35,36]

China bears the biggest stroke burden in the world, because of a huge population and high prevalence. The National Epidemiological Survey of Stroke in China showed that stroke burden was particularly high in residents of rural areas with lower socioeconomic status and low education level.[14] We also noted that >50% included participants in this study only have primary or lower education. Therefore, our findings have important public health and clinical implications for reducing education-related health inequality and promoting health care and rehabilitation practice for patients with low education.

The present study was a large sample study based on the CATIS trial, which was conducted according to standardized protocols, and strict quality control procedures were adopted for data collection and outcome assessment. In the analysis, we adjusted for some main confounding factors including income, occupation, and severity of stroke. In addition, we conducted a sensitivity analysis and meta-analysis to test the robustness of our findings. Regarding methodology, our study was rigorous and appropriate, which was helpful to clarify the relationship between education and outcomes of ischemic stroke. Several limitations of this study should be taken into consideration. First, the current study was an observational study from the CATIS, excluding patients with ischemic stroke with BP ≥220/120 mm Hg or treated with intravenous thrombolytic therapy at admission. A selection bias was inevitable. However, the proportion of patients with BP ≥220/120 mm Hg or treated with intravenous thrombolytic therapy is low in China, and baseline characteristics of participants in this study were similar to those from the CNSR.[15,37] In addition, most baseline characteristics of enrolled and excluded patients in this analysis were well balanced. Second, despite adjustment for some main potential confounders in analysis, we cannot exclude the possibility of residual confounding. For instance, we did not collect the data on access to stroke education, which may play an important role in improving poststroke outcomes, especially among those patients with lower educational level.[32] Third, in the meta-analysis, we included published studies with multiple classifications of education status. Differences in categorizing the level of education may be a possible explanation for inconsistencies of associations between education and outcomes after stroke. However, sensitivity analyses restricted to studies with similar classification confirmed the significant association of education level with mortality. Although many efforts have been attempted to reduce this possible bias, caution is needed in interpreting the results of the present study.

CONCLUSIONS

Our prospective study demonstrated that low education level was associated with increased risk of mortality, recurrent stroke, and cardiovascular events in patients with acute ischemic stroke, independently of several established risk factors.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Meta-analysis

Based on the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[22], we conducted a meta-analysis that incorporated the results of current study and previous studies on education levels and outcomes after stroke. A systematic literature search was conducted on PubMed from inception to July 2019, using the search terms ‘stroke’ (or ‘cerebrovascular disease’, ‘cerebral hemorrhage’, ‘subarachnoid hemorrhage’, ‘intracranial hemorrhage’) and ‘outcome’ (or ‘prognosis’, ‘mortality’, ‘survival’, ‘recurrence’, ‘cardiovascular events’) in combined with ‘education attainment’ (or ‘education level/status’, ‘socioeconomic status/factors/disparities’). The literature search was limited to English publications. Besides, the search was supplemented with reference lists of selected articles for further relevant studies. Studies were selected if they met following criteria: (1) included an investigation of the association between education levels and stroke outcomes; (2) study design was a prospective study; (3) had at least one stroke outcome of interest (all-cause mortality, stroke-specific mortality, recurrent stroke and cardiovascular events); (4) reported covariate adjusted hazard ratios (HRs), relative risks (RRs) with 95% confidence intervals (CIs).

Literature search and data extraction were independently performed by two investigators. The following data elements were extracted from each included study: first author, year and place of study, participants’ characteristics (i.e. age, stroke types), outcomes of stroke. Additionally, we also extracted education categories, number of events/participants, effect size (HRs or RRs), and adjusted covariates. RR was used as the effect size of the association between education levels and stroke outcomes across studies, and the HRs reported in the original studies were considered equivalent to RR[38]. Because education categories were reported differently across studies, we consistently adopted RRs (95% CIs) for the lowest versus highest education categories to pool effect size of the current study and other studies identified. To account for potential bias due to different measures of association and categories of education, sensitivity analyses were performed according to various inclusion criteria. Heterogeneity was assessed using Cochrane's Q test and I^2 statistic. Heterogeneity was present if the *P* value of the Q test was <0.1 or I^2 >25%.

Potential publication bias was examined using funnel plot, Begg test and Egger's asymmetry test[23, 24]. All *P* values were two-sided, and the level of significance was at <0.05. All analyses were performed using STATA 11.0 (StataCorp LP, College Station, Texas, USA).

Supplemental Results

Meta-analysis

Ten published prospective studies and current study were included in this meta-analysis (Figure S1). General characteristics of eligible studies were shown in Table S1. All studies were published between 2001 and 2019. Five studies were conducted in Europe[10, 11, 13, 26, 27], three in Asia[28-30], one in South America[12], and one in the United States[25]. Duration of follow-up ranged from 29 days to 12 years.

Consistent with our findings, this meta-analysis indicated that lower education level was significantly associated with increased risk of mortality after stroke (the pooled RR of 1.24 [95% CI: 1.05-1.46], Figure 2). Several sensitivity analyses further confirmed the robustness of the above association (Table S2). Substantial heterogeneity was observed across studies (I^2=78.5%, *P*<0.001), which was probably caused by sample size and differences in classifications of education. Review of funnel plot could not eliminate potential publication bias (Figure S2). Begg and Egger tests further suggested no evidence of potential publication bias (*P*>0.05 for both).

Table S1. Summary of characteristics in eligible studies on education level and mortality after stroke.

First author, year, country	Type of stroke	Age	Stroke outcomes	Education categories	No. of events /participants	Adjusted RRs/HRs (95% CIs)	Adjusted covariates
Zhou, 2006, China[28]	Ischemic stroke	71.0±11.2 y	3-year all-cause mortality	Illiterate	166/806	0.79 (0.31–2.01)	age, sex, smoking, hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, myocardial infarction, prior TIA, and NIHSS
				Primary school		0.97 (0.39–2.40)	
				Junior high school		0.70 (0.28–1.77)	
				Senior high school		0.96 (0.33–2.78)	
				Technical training		1.81 (0.62–5.28)	
				University degree[a]		1.00	
Goulart, 2012, Brazil[12]	Stroke	*	1-year stroke survival	Illiterate	322/430	2.65 (1.37–5.13)	sociodemographic and cardiovascular factors
				1-7 y		*	
				≥ 8 y[a]		1.00	
Chen, 2015, China[29]	Stroke	73.4±7.0 y	1-year all-cause mortality	≤ Primary	18/64	1.88 (1.05-3.36)	age, sex, body mass index, smoking status, alcohol drinking, marital status, living alone, hypertension, hypercholesterolemia, diabetes, angina, depression, dementia, occupational class, family income, and rural/urban living
				> Primary[a]	46/103	1.00	
Arrich, 2005, Austria[11]	Stroke	67±14 y	2.5-year overall mortality	No basic education	13/110	0.53 (0.23–1.25)	age, sex, stroke severity, history of stroke, ischemic heart disease, hypertension, elevated plasma lipids, diabetes, peripheral vascular disease, and smoking status
				Secondary school graduation	91/488	1.02 (0.62–1.67)	
				Technical training/apprenticed	196/1155	0.99 (0.64–1.53)	
				Higher secondary school	33/265	0.65 (0.37–1.14)	
				University graduate[a]	36/215	1.00	
Andersen, 2014, Denmark[27]	Stroke	71.9 y	3.1-year mortality	Basic[a]	9435/22435	1.00	age, sex, stroke severity score, hypertension, diabetes mellitus, atrial fibrillation, previous myocardial infarction, intermittent claudication, smoking, alcohol consumption, and stroke type
				Vocational	7304/26085	0.99 (0.96–1.03)	
				Higher	2077/8061	1.02 (0.97–1.07)	
Elfassy, 2019, USA[25]	Stroke	69 y	5-year mortality	College graduate+[a]	134/386	1.00	age
				Some college	136/342	1.2 (0.9-1.5)	
				High-school graduate	167/386	1.3 (1.0-1.6)	
				Less than high school	111/214	1.5 (1.1-1.9)	
Morovatdar, 2019, Iran[30]	Stroke	65.4±14.7 y	5-year mortality	< 12 years	330/624	1.84 (1.05–3.23)	sex, vascular risk factors, employment, smoking status, age, severity of stroke
				≥ 12 years[a]		1.00	

Jakovljevic, 2001, Finland[26]	Ischemic stroke	25-74 y	1-year mortality	Basic Secondary or higher[a]	1551/6903	M 25-59 y: 1.27 (0.89–1.80) M 60-74 y: 1.16 (0.91–1.46) W 25-59 y: 2.70 (1.18-6.17) M 60-74 y: 1.19 (0.93–1.54)	age, urban/rural residence, study area, and living alone or with a family member
Langagergaard, 2011, Denmark[10]	Stroke	18-65 y	1-year mortality	Long[a] Medium Short	1202/14545	1.00 0.94 (0.78–1.12) 0.88 (0.72–1.07)	patient characteristics, hospital department, proportion of relevant processes of care received, income, and employment status
Ojala-Oksala 2012, Finland[13]	Ischemic stroke	72.0 y	12-year survival	Tertile	*	0.86 (0.74-1.00)	age, sex, marital status, NIHSS, WML
Current study, 2020, China	Ischemic stroke	62.0±10.9 y	2-year all-cause mortality	Illiterate Primary school Middle school College[a]	83/496 147/1463 88/1701 9/201	2.79 (1.32-5.87) 1.90 (0.93-3.90) 1.18 (0.58-2.37) 1.00	age, sex, current smoking, alcohol intake, occupation, income level, baseline National Institutes of Health Stroke Scale scores, systolic blood pressure, ischemic stroke subtype, treatment assignment, time from onset to randomization, medical history (hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease), family history of stroke, use of antihypertensive and lipid lowering medications

RRs, relative risks; HRs, hazard ratios; CIs, confidence intervals; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; M, men; W, women; WML, white matter lesions.

[a] Reference group.

Table S2. Meta-analyses of education level and mortality after stroke: Sensitivity analyses.

	N	RRs (95% CIs)	*P* value
All studies	11	1.24 (1.05-1.46)	0.01
Sensitivity analysis 1[a]	10	1.20 (1.01-1.42)	0.04
Sensitivity analysis 2[b]	2	1.25 (1.09-1.44)	0.002
Sensitivity analysis 3[c]	5	1.23 (1.02-1.48)	0.03

RRs, relative risks; CIs, confidence intervals.

[a] Restricted to studies reported hazard ratio as effect size.

[b] Restricted to studies reported the relative risks of “<6 years” versus “>9 years” of education.

[c] Restricted to studies reported the relative risks of “primary/basic” versus “secondary/higher” education level.

Figure S1. Flow chart of study selection.

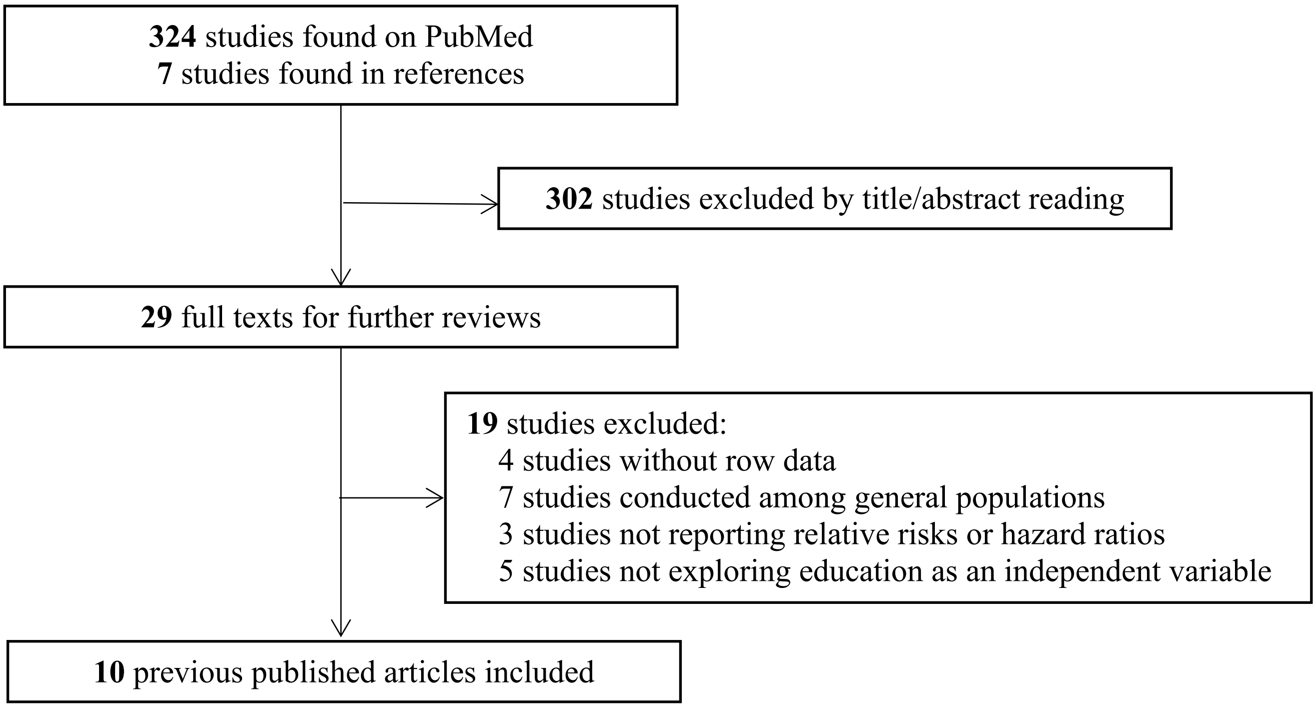

Figure S2. Funnel plot of education level and mortality after stroke.