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Prevalence, knowledge, and treatment of transient ischemic attacks in China

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Supplemental data at Neurology.org

ABSTRACT

Objectives: To investigate the prevalence, knowledge, and treatment of TIA in a Chinese adult population.

Methods: We conducted a complex, multistage, probability sampling–designed, cross-sectional, nationwide survey of 98,658 Chinese adults in 2010. Possible TIA cases were first identified by symptoms recall or self-reported history of TIA through face-to-face interviews, and the final diagnosis was then made by expert neurologists through phone interviews or record review.

Results: The age-standardized prevalence of TIA was 2.27%. Clinically, only 16.0% of the participants were diagnosed before the study. The prevalence of TIA was higher in women and in patients who were older, had less education, were current smokers, lived in rural or undeveloped areas, and had a history of stroke, hypertension, myocardial infarction, dyslipidemia, or diabetes. Based on the survey responses, approximately 3.08% of Chinese adults had knowledge of TIA. Among patients with TIA, only 5.02% received treatment and 4.07% received guideline-recommended therapy.

Conclusions: TIA is prevalent and an estimated 23.9 million people in China may have experienced a TIA. Public knowledge on TIA is very limited. TIA appears to be largely undiagnosed and untreated in China. There is an urgent need to develop strategies to improve the identification and appropriate management of TIA. *Neurology®* **2015;84:2354–2361**

GLOSSARY

BMI = body mass index; **CCDRFS** = China Chronic Disease and Risk Factor Surveillance; **CI** = confidence interval; **HbA_{1c}** = glycated hemoglobin A_{1c}.

Stroke is the leading cause of mortality and adult disability in China [1,2] and the second leading cause of death worldwide.[3] TIA is a major risk factor for stroke. Many recent studies have shown a risk of 10% to 15% stroke occurrence within 90 days after a TIA, half of which occur in the first 2 days.[4–13] Reducing risk of stroke after TIA could have substantial impact on public health. Recent studies have demonstrated that providing early treatments or urgent clinic care to patients with TIA or minor stroke could reduce the occurrence of stroke.[14–17] The combination of clopidogrel and aspirin therapy also reduces stroke risk compared with aspirin alone in the first 90 days.[17] Understanding the prevalence and treatment pattern of TIA is essential for developing an effective public health strategy to prevent stroke. However, the population prevalence and treatment pattern of TIA have not yet been evaluated in China.

To estimate the prevalence of prior TIA, evaluate knowledge about its symptoms and definition, and characterize treatment patterns for TIA in the general Chinese population, we conducted a population-based national survey with a representative sample of 98,658 adults in 2010.

METHODS

Study participants. The study design was based on the China Chronic Disease and Risk Factor Surveillance (CCDRFS) 2010. CCDRFS is an ongoing national representative surveillance conducted in 162 districts/counties and all 31 provinces,

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autonomous regions, and municipalities in mainland China. The TIA survey questionnaire (TIA Questionnaire 1 in appendix e-1 on the *Neurology*® Web site at Neurology.org), developed by a neurologist expert panel at Tiantan Hospital, was integrated into the CCDRFS in 2010. The population of the national Disease Surveillance Points system (DSPs) accounts for approximately 7% of the total Chinese population. The field work started in August and ended by the end of November 2010. A multistage, stratified, cluster random sampling survey was used to select noninstitutionalized Chinese civilian adults who were older than 18 years. Detailed subdistrict sampling, household selection, and replacement principles were described previously.[18] A total of 109,023 people were selected and 98,658 participated in the survey with a response rate of 90.5%.

Data collection and risk factor definition. All staffs enrolled from local health facilities were certified after 1 week of training and passing their examinations. Certificated staff performed face-to-face questionnaire interviews, physical measurements, and blood sample collections. The content of the questionnaire included questions on household socioeconomic status, medical history, behavioral risk factors, and TIA etiology. We applied parallel double entry to ensure the data quality.

Current smoking was self-reported. Current drinking was defined as having at least 1 drink in the past 12 months. The dietary information was collected by using a food-frequency questionnaire asking about dietary behavior in the past 12 months. Lack of vegetable and fruit intake was defined as intake less than 400 g of vegetables or fruits per day. Regular exercise was defined as participating in more than 2 physical exercise periods per week with at least 10 minutes each time. Body weight was measured using a unified portable weighting scale with accuracy of 0.1 kg. Body height was measured by stadiometer with accuracy of 0.1 cm. Waist circumference was measured at the midpoint between the lower edge of the costal arch and the upper edge of the iliac crest. Overweight was defined as a body mass index (BMI) of 25.0 to 29.9, and obesity was defined as a BMI of 30.0 or higher. Central obesity was defined as waist circumference ≥90 cm in men and ≥80 cm in women. Blood pressure was measured in a seated position after 5 minutes of rest using an OMRON HEM-7071 device (OMRON, Beijing, China). The nondominant arm was measured 3 times consecutively with a 1-minute interval between the measurements. The final blood pressure was calculated as the mean of the second and third measurements. Hypertension was defined as the average systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or a documented history of hypertension. Blood samples were collected and sent to a central laboratory to test for blood lipid and glycated hemoglobin A_{1c} (HbA_{1c}). Fasting and 2-hour oral glucose tolerance test blood sugar were tested at local qualified laboratories; laboratory quality-control measures were described previously.[19] Dyslipidemia was defined as serum total cholesterol level of ≥5.18 mmol/L and/or low-density lipoprotein cholesterol ≥3.37 mmol/L and/or triglycerides ≥1.7 mmol/L. Diabetes was defined as a self-reported diagnosis by health care professionals, or fasting plasma glucose level of ≥7.0 mmol/L (126 mg/dL), and/or 2-hour glucose ≥11.1 mmol/L (200 mg/dL), and/or HbA_{1c} ≥6.5%. We categorized the 162 study sites into underdeveloped, intermediately developed, or developed region according to their local gross domestic product per capita in 2009.

TIA ascertainment and public knowledge. Ascertainment of TIA was conducted through a 2-stage method: identification of possible TIA, and case adjudication by the neurologist expert panel, which consisted of 4 experienced neurologists from Tiantan Hospital (Yilong Wang, J. Jing, X. Meng, and J. Xu). Possible TIA cases were identified by self-reported history and symptoms recalled through face-to-face questionnaire interview by trained interviewers (neurologists or medical professionals). Individuals with any of the following symptoms previously were identified: sudden numbness, weakness on one side of the body or face; sudden monocular or binocular blackening, blurred vision; sudden blackening or absence of visual field on the same side, sudden dysphasia or dysaudia, and sudden imbalance.[20,21] A documented TIA was identified if a physician-diagnosed TIA was shown in their diagnosis records (held by the individuals) and confirmed by the neurologist expert panel based on the chief complaints in the records. An individual who reported a physician-diagnosed TIA but failed to provide his or her medical record was considered as a possible TIA case. Each possible TIA case was then randomly assigned to 1 of the 4 members of the neurologist expert panel, and a phone interview was conducted within 1 month after the initial contact. A TIA was confirmed by case review if the recalled symptoms were consistent with TIA as judged by the interviewing neurologist. The total TIA cases were the sum of documented TIA and TIA confirmed by the neurologist expert panel (TIA by review). To ensure quality, we developed standard operation manuals and trained all reviewers of the neurologist expert panel. The interrater variability among 4 members of the neurologist expert panel was assessed by 50 "mock" questionnaires (TIA Questionnaire 2 in appendix e-2). The interrater agreement for case adjudication was evaluated by using the overall percentage of agreement and Fleiss κ statistics.[22] The overall agreement was 92% with the κ value of 0.84 (95% confidence interval [CI] 0.81–0.87).

A participant was considered to have knowledge of TIA if he or she reported having heard of the term "transient ischemic attack (TIA)," recognized TIA as involving symptoms related to stroke that were potentially harmful, and was able to name at least 1 of the 5 typical symptoms of TIA described above.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the ethical review committees of the Chinese Center for Disease Control and Prevention and all other participating institutes. Written informed consent was obtained from all participants by interviewers before data collection.

Missing values. There were 85 missing values for BMI and 75 missing values for waist circumference (central obesity). All estimates related to BMI and central obesity were calculated in participants with a completed dataset.

Statistical analysis. Basic characteristics of study participants were described in means with 95% CIs for continuous variables and frequency (%) for categorical variables in the overall population, in the subpopulation with TIA identified through phone interview by neurologists, and in the subpopulation with documented TIA. Prevalence and 95% CIs of total TIA, documented TIA, and knowledge about TIA were estimated by subgroups and overall. Age-standardized prevalence of Chinese adults with total TIA, documented TIA, and knowledge about TIA was also estimated by subgroups and overall.

Estimations of the population prevalence of TIA, documented TIA, and proportion having knowledge of TIA were weighted to represent the overall Chinese adult population aged 18 years and older. Weight coefficients were calculated by considering sampling weights, nonresponse weights, and poststratification weights to obtain the national estimates. Population information from China census data 2010 was used to calculate poststratification weights. The estimates of proportion of documented TIA from total TIA and proportions of treated TIA were without weighting. Multivariable logistic regression analyses were used to examine the association of risk factors with the odds of total TIA, documented TIA, documented TIA vs TIA by review (in the total TIA population), and knowledge about TIA. All p values were 2-tailed, and $p < 0.05$ was considered statistically significant. All analyses were performed by using SAS software version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS Of 98,658 participants, 8,560 possible TIA cases were identified, and 2,780 individuals (2.82%) were considered as having a TIA. Among the 2,780 TIA cases, 407 had documented diagnosis and confirmed by the neurologist expert panel (documented TIA); 2,373 had experienced TIA (TIA by review) symptoms confirmed by the expert neurologists through phone interviews. Figure 1 is a detailed flowchart of case ascertainment. The demographic, socioeconomic characteristics, and risk factors for non-TIA, TIA by review, and documented TIA subpopulations are listed in table 1.

Prevalence of total TIA and documented TIA. The crude prevalence of TIA was 2.82%, with 2.41% identified by review and 0.41% documented. The age-standardized prevalence of total TIA was 2.27%, and only 16% of total TIA had documented diagnosis. The age-specific prevalence of total TIA and documented TIA increased with age for both men and women ($p < 0.001$ for all comparisons) (figure 2, table e-1). The age-standardized prevalence of TIA was higher in women and those in rural and undeveloped areas ($p < 0.001$). The age-standardized prevalence of documented TIA was lower in rural areas ($p = 0.002$) (figure 2, table e-1).

In the multivariable logistic models, female sex, older age, overweight or obesity, less education, residence in rural or undeveloped areas, current smoking, history of stroke, history of hypertension, history of myocardial infarction, lower level of high-density lipoprotein, dyslipidemia, and diabetes were associated with increased risk of TIA (table 2). In addition, older age, history of stroke, history of hypertension, history of myocardial infarction, and lower level of high-density lipoprotein were also significantly associated with increased risk of a documented diagnosis of TIA. Unlike for total TIAs, documented TIA was more prevalent in the population living in an urban area with higher education. Among individuals with a TIA, the proportion having a documented diagnosis was significantly higher in those with a history of stroke and those with higher education, but significantly lower in rural residents, smokers, and patients with dyslipidemia (table 2).

Knowledge and treatment of TIA. Only 3.08% of the Chinese adults had any knowledge about TIA (table e-2). In the multivariable, multinomial, and logit models analysis, women, current drinkers, individuals living in more developed areas, and those with higher

Figure 1 Flowchart for TIA case ascertainment

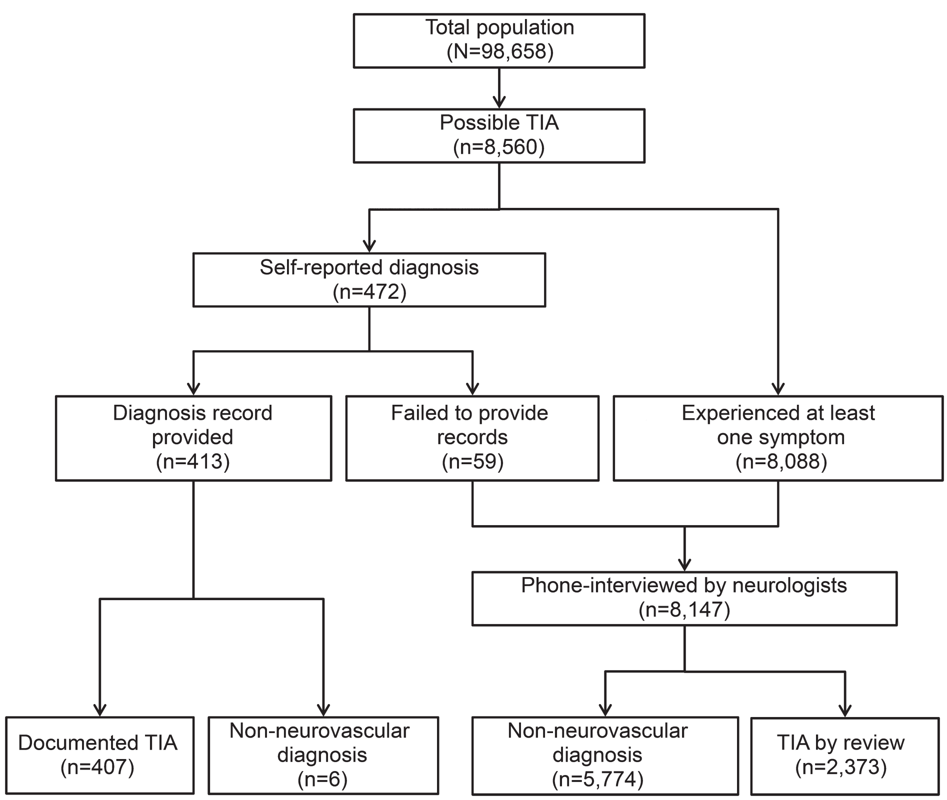


Table 1 Characteristics of the TIA, TIA by review, and documented TIA population in Chinese adults

Variable	Non-TIA	TIA by review	Documented TIA
Overall	95,878 (97.18)	2,373 (2.41)	407 (0.41)
Female	51,941 (54.2)	1,347 (56.8)	227 (55.8)
Age, mean (95% CI), y	46.2 (38.6–53.8)	57.9 (51.3–64.4)	57.9 (51.1–64.7)
BMI, mean (95% CI),[a] kg/m^2	23.9 (20.2–27.6)	24.8 (20.9–28.6)	24.9 (21.3–28.5)
Central obesity	35,028 (36.6)	1,153 (48.6)	213 (52.3)
Rural residency	57,904 (60.4)	1,642 (69.2)	184 (45.2)
Development			
Undeveloped	28,112 (29.3)	865 (36.5)	105 (25.8)
Intermediately developed	33,820 (35.3)	806 (34.0)	116 (28.5)
Developed	33,946 (35.4)	702 (29.6)	186 (45.7)
Junior high school education or higher	54,584 (56.9)	762 (32.1)	239 (58.7)
Regular exercise	12,083 (12.6)	310 (13.1)	80 (19.7)
Current smoker	25,306 (26.4)	690 (29.1)	84 (20.6)
Current alcohol drinker	33,686 (35.1)	718 (30.3)	107 (26.3)
Lack of vegetable and fruit intake	51,747 (54.0)	1,365 (57.5)	197 (48.4)
Systolic blood pressure, mean (95% CI), mm Hg	132.3 (123.2–141.4)	146.7 (137.0–156.4)	145.2 (135.5–154.9)
Diastolic blood pressure, mean (95% CI), mm Hg	81.2 (74.5–88.0)	86.0 (79.0–93.1)	86.7 (79.5–93.8)
Fasting plasma glucose, mean (95% CI), mg/dL	100.4 (90.3–110.5)	108.2 (96.5–119.9)	107.1 (95.9–118.3)
2-h plasma glucose, mean (95% CI), mg/dL	113.1 (99.8–126.4)	126.5 (112.0–141.1)	123.7 (110.5–136.9)
Total cholesterol, mean (95% CI), mg/dL	158.1 (145.2–170.9)	170.6 (157.6–183.6)	166.8 (153.7–179.9)
High-density lipoprotein, mean (95% CI), mg/dL	42.9 (36.0–49.8)	43.0 (36.1–49.9)	41.3 (34.7–47.9)
Low-density lipoprotein, mean (95% CI), mg/dL	88.9 (78.0–99.8)	97.0 (85.9–108.2)	95.6 (84.3–106.9)
Triglycerides, mean (95% CI), mg/dL	123.8 (102.6–145.0)	149.7 (126.5–172.9)	138.4 (117.1–159.8)
Hemoglobin A_{1c}, mean (95% CI), %	5.8 (4.0–7.6)	6.1 (4.0–8.2)	6.1 (4.0–8.1)
History of stroke	407 (0.4)	153 (6.4)	83 (20.4)
Hypertension	35,567 (37.1)	1,634 (68.9)	285 (70.0)
History of myocardial infarction	509 (0.5)	84 (3.5)	15 (3.7)
Dyslipidemia	28,521 (29.7)	1,072 (45.2)	158 (38.8)
Prediabetes	47,842 (50.6)	1,254 (53.5)	204 (50.9)
Diabetes	11,939 (12.6)	574 (24.5)	94 (23.4)

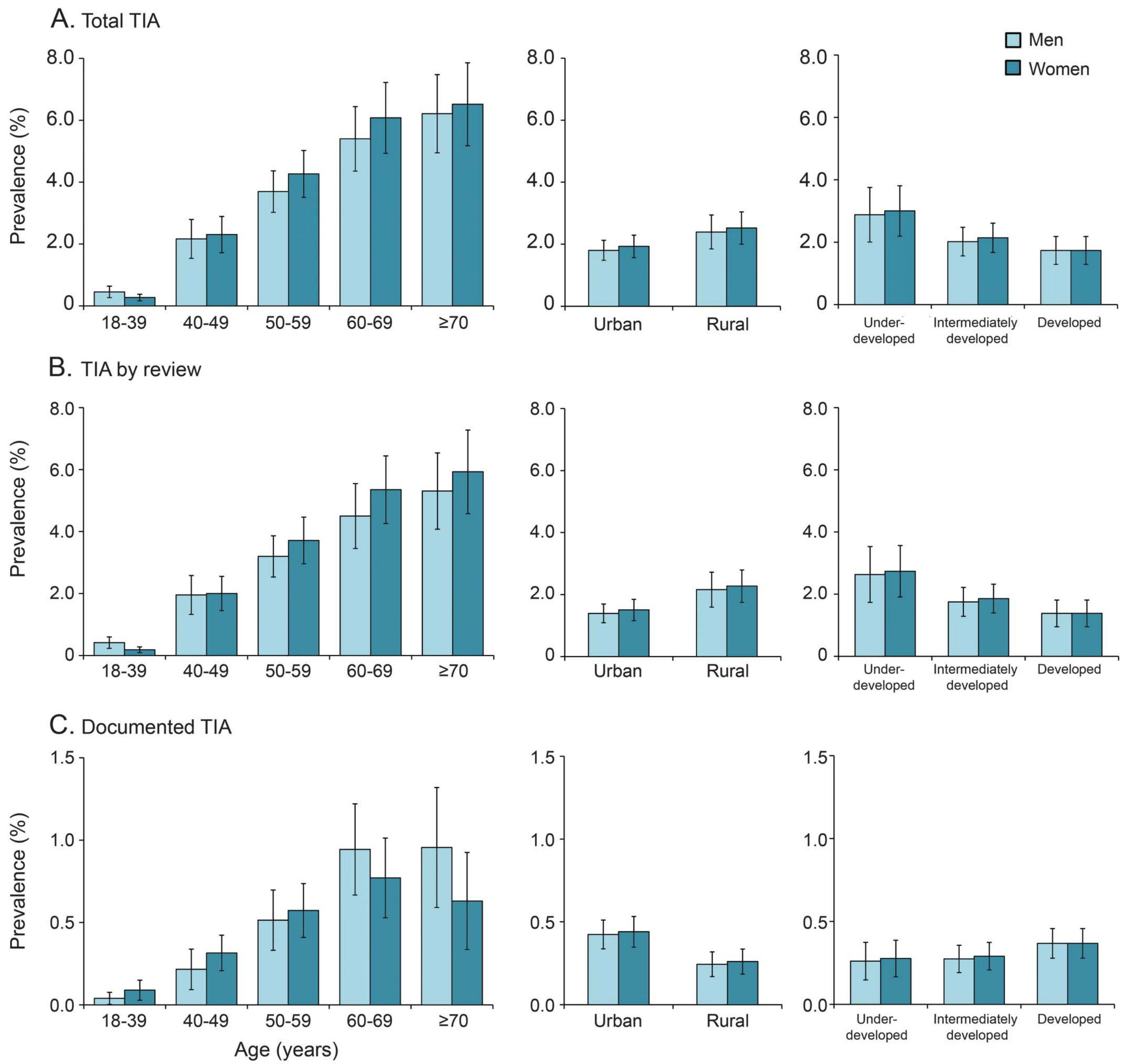
Abbreviations: BMI = body mass index; CI = confidence interval.
Data are n (%) unless otherwise indicated.
[a] There were 85 missing values for BMI and 75 missing values for waist circumference (central obesity).

education, exercising regularly, or with dyslipidemia had significantly more knowledge of TIA (table 3). Older age, central obesity, living in rural areas, current smoking, and lacking vegetable and fruit intake in the diet were significantly associated with unawareness of TIA.

Among the documented TIA population, only 44.0% (179) saw a physician within 24 hours of the event, 26.3% received guideline-recommended therapy, and 6.1% were treated with traditional Chinese medicines only. Traditional Chinese medicines were also used in 35.5% of the individuals who received proven treatments. Among the total TIA population, only 4.07% received guideline-recommended therapy and 0.95% used traditional Chinese medicines only (table e-2). In the multivariable logistic model, history of hypertension predicted a lower likelihood of using traditional Chinese medicines as the only treatment of TIA.

DISCUSSION Our nationwide survey in a random sample representative of a Chinese adult population suggests that TIA is prevalent in China, with an estimated 23.9 million adults (11.8 million men and 12.2 million women) having had a TIA in the past 12 months. The vast majority (86%) of them did not seek medical attention and therefore did not receive appropriate care. Given the high risk of stroke

Figure 2 Age-specific prevalence of TIA (A), TIA by review (B), and documented TIA (C) in Chinese adults in 2010



Number of participants

	18-39	40-49	50-59	60-69	≥70	Urban	Rural	Under-developed	Intermediately developed	Developed
Men	15,296	10,985	9,340	6,088	3,434	17,281	27,862	13,373	16,078	15,692
Women	17,422	14,005	11,625	6,721	3,741	21,647	31,868	15,709	18,664	19,142

Error bars indicate 95% confidence intervals.

after TIA, such substantial underdiagnosis and undertreatment of TIA may be a significant contributor to the heavy stroke burden in China.

The prevalence of TIA has been estimated in a number of populations across various countries and the estimates in adults have varied widely,[13,20,21,23–29] ranging from 0.2% among adults aged 40 years and older in a western Japanese town[24] to 9.7% among those aged 35 years and older in a Pakistan community.[28] Differences in population selection, risk factor prevalence, and criteria used to define TIA may contribute to the heterogeneity of these estimates.[21] Most of the studies were conducted in community-based and older populations,[20,24–29] as compared to our study. Our estimated population prevalence of TIA is 2.27%, almost identical to the prevalence of physician-diagnosed TIA (2.3%) in the United States based on a nationwide survey of US

Table 2 Multivariable-adjusted odds ratios for total TIA and clinically documented TIA in Chinese adults

Effect	Total TIA	*p* Value	Documented TIA	*p* Value	Documented TIA vs TIA by review[a]	*p* Value
Female	1.24 (1.12-1.38)	<0.001	1.06 (0.83-1.36)	0.62	0.84 (0.64-1.10)	0.21
Age per 10 y	1.46 (1.42-1.51)	<0.001	1.52 (1.40-1.65)	<0.001	1.03 (0.92-1.15)	0.66
BMI[b]		<0.001		0.13		0.07
Overweight	1.15 (1.05-1.25)		1.24 (0.99-1.54)		1.10 (0.86-1.41)	
Obesity	1.41 (1.22-1.63)		0.98 (0.65-1.48)		0.65 (0.41-1.02)	
Junior high school education or higher	0.77 (0.70-0.84)	<0.001	1.96 (1.56-2.47)	<0.001	2.78 (2.17-3.57)	<0.001
Rural	1.19 (1.08-1.31)	<0.001	0.68 (0.54-0.87)	0.002	0.49 (0.37-0.66)	<0.001
Development		<0.001		0.23		0.78
Intermediately developed	0.74 (0.68-0.82)		0.79 (0.60-1.04)		0.96 (0.71-1.30)	
Developed	0.69 (0.62-0.77)		0.85 (0.64-1.12)		1.07 (0.76-1.51)	
Current smoker	1.39 (1.25-1.56)	<0.001	0.86 (0.65-1.15)	0.31	0.58 (0.42-0.79)	<0.001
Current alcohol drinker	0.95 (0.86-1.05)	0.30	0.77 (0.60-1.00)	0.048	0.72 (0.54-0.95)	0.02
History of stroke	11.02 (9.22-13.17)	<0.001	22.81 (17.23-30.20)	<0.001	3.62 (2.61-5.01)	<0.001
Hypertension	1.99 (1.82-2.18)	<0.001	1.95 (1.53-2.48)	<0.001	0.96 (0.73-1.24)	0.74
History of myocardial infarction	2.62 (2.04-3.37)	<0.001	1.25 (0.70-2.23)	0.45	0.70 (0.38-1.30)	0.26
Dyslipidemia	1.45 (1.33-1.57)	<0.001	1.06 (0.86-1.31)	0.60	0.71 (0.56-0.90)	0.004
Diabetes	1.30 (1.18-1.43)	<0.001	1.03 (0.81-1.33)	0.79	0.79 (0.60-1.04)	0.09

Abbreviation: BMI = body mass index.
Data represent odds ratio (95% confidence interval).
[a] Documented TIA vs TIA by review: the association between baseline covariates with being documented TIA vs TIA by review in the total TIA population.
[b] There were 85 missing values for BMI; estimates were calculated in individuals with complete data.

adults.[21] Among the same age group, our estimated prevalence of TIA in China is also comparable to that of 3.7% in the Atherosclerosis Risk in Communities Study (age 45–64 years)[20] and 4.4% in a Japanese study that included those aged 40 and older,[24] but generally higher than that reported in other studies.[25–29]

Table 3 Multivariable-adjusted odds ratios for knowledge of TIA in Chinese adults

Variable	OR (95% CI)	*p* Value
Female	1.21 (1.10-1.33)	<0.001
Age per 10 y	0.96 (0.93-0.98)	0.003
Central obesity[a]	0.89 (0.82-0.96)	0.004
Rural	0.62 (0.56-0.68)	<0.001
Development		<0.001
Intermediately developed	1.32 (1.18-1.48)	
Developed	1.49 (1.32-1.68)	
Junior high school education or higher	5.55 (4.89-6.30)	<0.001
Regular exercise	1.92 (1.76-2.09)	<0.001
Current smoker	0.69 (0.62-0.77)	<0.001
Current alcohol drinker	1.41 (1.29-1.53)	<0.001
Lack of vegetable and fruit intake	0.77 (0.71-0.83)	<0.001
History of stroke	2.19 (1.53-3.13)	<0.001
Dyslipidemia	1.11 (1.03-1.21)	0.01

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] There were 75 missing values for waist circumference; estimates were calculated in individuals with complete data.

Our study showed that patients with TIA in the general population were poorly diagnosed. Underdiagnosis was more prevalent in individuals living in rural areas and those with less education. Lack of knowledge about TIA symptoms may be a key reason why people do not seek medical attention rapidly after TIA. Only 3.08% of Chinese adults in this study reported having heard of the term "transient ischemic attack (TIA)," recognized TIA as producing stroke-like symptoms that are potentially harmful, and were able to name at least 1 of the 5 typical symptoms of TIA. Again, individuals living in rural areas and less developed regions and those with less education were less likely to have knowledge of TIA, which explains the underdiagnosis of TIA among these individuals. Because of lack of knowledge and underdiagnosis of TIA, the majority of patients with TIA failed to seek medical attention after the event. This might explain why the hospitalization rate of patients with TIA in China was low.[30] Rural areas, less developed regions, and less education may be related to higher utilization of health care resources, but poor adherence to treatments for risk factors.[21,31] Deficient TIA knowledge may be an important target for educational campaigns in China.

Our study has several strengths. First, it was the first national population-based representative survey of knowledge and prevalence of TIA in China. Second, ascertainment of TIA was conducted through a 2-stage method: with a face-to-face questionnaire survey by trained interviewers to screen possible TIA cases first, and then case confirmation by neurologist experts either through review of medical records or phone interview at the second stage. This method should greatly improve the precision of the estimation of TIA prevalence compared to estimation based on medical records or self-reported history alone.

Our study also has a number of limitations. The hospitalized patients with TIA during the investigational period were not included in the analysis, which would lead to underestimation of the TIA prevalence. Since the rate of hospitalization for TIA is very low in China,[30] its impact would be minimal. It is unclear whether the first-stage screening process had any effect on an individual's response to the second-stage interview and therefore the case ascertainment. Phone interview may also lead to uncertain error in case ascertainment compared with face-to-face interview by neurologists. However, it is possible that the rate of false-positives was balanced out by the false-negatives so that the observed prevalence would be likely true. Conversely, since both phone and face-to-face interviews solely depend on patients' recall of symptoms, the accuracy of diagnosis in such retrospective studies may not be as reliable. In addition, we cannot rule out the possibility of an error in recall, especially in individuals who had an event long before the investigation or living in rural areas or less developed regions with less education, resulting in an underestimated prevalence of TIA.

In summary, TIAs are largely underdiagnosed and untreated in China, and there is an urgent need to develop strategies to improve TIA identification and provide the appropriate treatment.

AUTHOR CONTRIBUTIONS

Yilong Wang: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript. Xingquan Zhao: study supervision or coordination. Yong Jiang: acquisition of data, analysis and interpretation of data. Hao Li: analysis and interpretation of data. Limin Wang: acquisition of data. S. Claiborne Johnston: study concept and design, revising the manuscript for content. Liping Liu: study supervision or coordination. Ka Sing Lawrence Wong: revising the manuscript for content. Chunxue Wang: drafting of the manuscript. Yuesong Pan: analysis and interpretation of data. Jing Jing: acquisition of data. Jie Xu: acquisition of data. Xia Meng: acquisition of data. Mei Zhang: acquisition of data. Yichong Li: acquisition of data. Yong Zhou: acquisition of data. Wenhua Zhao: study concept and design, study supervision or coordination. Yongjun Wang: study concept and design, obtaining funding, study supervision or coordination, revising the manuscript for content.

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DISCLOSURE

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