Meta-analyses

Risk factors for malnutrition in stroke patients: A meta-analysis

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S U M M A R Y

Background & aims: Stroke is a common cause of death and disability worldwide. Among stroke patients, malnutrition is a significant problem that contributes to poor outcome. Clinical evidence is required to identify risk factors for malnutrition and to adopt appropriate management strategies during early stroke intervention. Thus, we performed a meta-analysis of potential risk factors related to malnutrition in stroke patients.
Methods: We systemically searched relevant observational studies in MEDLINE, EMBASE, Chinese Biomedical Literature Database (CBLD), China National Knowledge Infrastructure (CNKI), and VIP Database of Chinese periodicals from January 1990 to September 2017 in any language. Patients included in this study were adults who suffered from stroke. Stata 12.0 and Review Manager 5.1 software were used to pool useful data and calculate odds ratios (ORs) and their 95% confidence intervals (CIs). We also performed heterogeneity and sensitivity analyses, and evaluated publication bias.
Results: Twenty-nine observational studies involving 8838 participants who met our inclusion criteria were incorporated into the meta-analysis, and thirteen risk factors related to malnutrition were studied. The following variables probably correlated with an increased risk of malnutrition in stroke patients: malnutrition on admission (OR = 8.34, 95% CI = 4.60—15.10, P < 0.00001), dysphagia (OR = 2.60, 95% CI = 2.24—3.03, P < 0.00001), previous stroke (OR = 3.04, 95% CI = 2.35—3.95, P < 0.00001), diabetes mellitus (OR = 1.79, 95% CI = 1.35—2.38, P < 0.0001), tube feeding (OR = 5.43, 95% CI = 3.99—7.37, P < 0.00001) and reduced level of consciousness (OR = 2.82, 95% CI = 2.12—3.75, P < 0.00001). The factors alcohol consumption, hypertension, male sex, depressed mood, pneumonia and infection need to be re-evaluated. Conversely, smoking was most likely not associated with post-stroke malnutrition.
Conclusions: Our meta-analysis has revealed a variety of risk factors for malnutrition during hospital stay among stroke patients. Early identification of these factors is warranted for improving patient outcomes.
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1. Introduction

Stroke is the second most common cause of death worldwide [1], and the leading cause of death in China [2]. The Lancet shows that by 2030 an estimated 12 million stroke deaths will occur each year, up from about six million deaths in 2010 [3]. Malnutrition has been identified as a common problem associated with poor outcomes in stroke patients [4—7]. Malnutrition, synonymous with undernutrition, can be defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" [8]. In clinical practice, stroke patients can develop malnutrition due to neurological and cognitive deficits. Up to 62% of stroke patients suffer from post-stroke malnutrition [9], which can be caused by malnutrition on admission [5,10—13], dysphagia [5,12,14—23], stroke subtype (ischemic or hemorrhagic) [12,24], history of stroke [6,10,23], history of smoking [12,16] etc. These factors especially affect convalescent stroke patients aged 65 years or older [25].

An undernourished status in stroke patients could increase the rate of serious complications such as pneumonia and gastrointestinal bleeding, prolong the length of hospitalization, reduce functional improvement during rehabilitation, and ultimately, exacerbate mortality among stroke patients [11]. Apart from those mentioned above, malnutrition-related risk factors such as: tube feeding [13,22,26], polypharmacy [27], diabetes mellitus [21,28],

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hypertension [5], cardiac disease [6,10], lesion location of stroke (left hemisphere, right hemisphere or brain stem) [10], upper extremity paresis [29], history of severe alcoholism [12], reduced level of consciousness [12,18,21], depressed mood [17,30], impaired cognitive function [17,23], visual neglect [29], age [5,6,10–13, 17,23,26,31,32], sex [5,12,17], poor nursing care [29,33], infection [17,26], pneumonia [7], pressure sores [7], have been previously reported among stroke patients. However, some reports are controversial, and lack convincing and rigorous designs.

To improve strategic intervention and prognosis, systematic analysis of factors contributing to malnutrition and clear identification of post-stroke patients who are likely to have malnutrition are indispensable. Thus, this meta-analysis was conducted to estimate risk factors and provide more reliable evidence for the clinical setting.

2. Methods

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [34] guidelines throughout the design, implementation, analysis and reporting of this study.

2.1. Search strategy and information sources

Searches of studies from MEDLINE, EMBASE, Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI) and VIP database of Chinese periodicals from January 1990 to September 2017 were performed to identify potentially relevant observational studies, including cohort, case–control and cross-sectional studies. Search terms were set with the subject headings and key words "Stroke or Intracranial Embolism or Thrombosis or Cerebrovascular Disorders" and "Malnutrition or Nutrition Disorders or Nutritional Deficiency or Subnutrition or Undernutrition".

2.2. Study selection

Two qualified investigators (Ning Chen and Yanbo Li) independently assessed the eligibility of the literature; discrepancies were resolved by discussion. We used broad inclusion criteria for the studies with no limitations on language, stroke type or stroke phase. An initial screening of titles or abstracts that addressed the research question of interest was performed to check for potential relevance. Afterwards, relevant full-texts were obtained and re-evaluated for eligibility, which decided the final inclusion of the study in the meta-analysis (Fig. 1). Studies were included if they: (1) were published between January 1990 and September 2017; (2) reported data from an original, peer-reviewed observational study or from an observational source in the study; (3) focused on any possible risk factor of malnutrition among post-stroke adults aged 18 years and over; and (4) used definite parameters to assess stroke patients' nutritional statuses which could be variant but acceptable. We excluded studies that: (1) had an ambiguous definition of malnutrition; (2) enrolled patients diagnosed as transient ischemic attack, non-stroke, or with comorbid diseases such as cancer and severe liver or renal disease; (3) were unpublished or published as reviews, editorials, duplicate citations, non-human studies or abstracts with unavailable data. In the case of missing data, corresponding authors of the included studies were contacted electronically with requests for the missing data.

2.3. Data extraction and quality assessment

Extraction of data for each included study was also performed by two investigators with a standardized data extraction form that included the authors, publication year, study country, study design, number of participants, study setting, participants' age and sex, exposure factors for malnutrition, study quality, nutritional assessment parameters and analysis strategy.

The selected studies included cohort, case–control and cross-sectional studies, which were incompatible with the New-castle–Ottawa Quality Assessment Scale. Thus, quality assessment was performed using a validated five-point scale [35] that included the following variables: appropriateness and reporting of inclusion and exclusion criteria, exposure assessment, outcome assessment, control of confounding variables, and evidence of bias. A value of 0 or 1 was assigned to each variable, with 1 being a better score than 0. Quality scores from 0 to 3 were considered low quality, while scores of 4–5 were considered high.

2.4. Statistical analysis

Analyses were performed with Review Manager Software version 5.1 and Stata version 12.0. Odds ratios (ORs) were used for quantitative analyses. Forest plots were produced to visually assess the ORs and corresponding 95% confidence intervals (CIs) for each risk factor, and chi-square tests were used for hypothesis testing (Z distribution, P < 0.05, considered statistically significant). The ORs were first pooled using fixed-effect models first, and random-effect model were incorporated when the sensitivity analysis predicted instability. Sensitivity analyses were performed by Stata version 12.0 to assess the influences of individual studies on the pooled estimates of each risk factor. Heterogeneity among studies was assessed using chi-square test-based I^2 statistics (values of 0%–40%: might not be important, 30%–60%: may represent moderate heterogeneity, 50%–90%: may represent substantial heterogeneity). Once heterogeneity was assessed, analyses predefined by stratifying original estimates such as study design (cohort; non-cohort) and timing of nutritional assessment (acute assessment: nutritional assessment at admission for acute patients; non-acute assessment: nutritional assessment at admission for non-acute patients or after at least one week of the hospital stay for acute patients), or regression analysis according to characteristics of the studies, were used to further investigate the sources of heterogeneity between studies.

Publication bias assessments were performed by qualitative analyses using visual funnel plots or quantitative analyses based on Begg's and Egger's tests on risk factors with ten or more pooled studies [36,37] (P < 0.05 was considered indicative of statistically significant publication bias).

Meta-analysis was conducted if sources were available from a minimum of three studies.

3. Results

3.1. Literature search and quality assessment

We identified 29 observational studies with a total of 8838 participants who met the inclusion criteria (Table 1) from 70 full-text articles out of 12,014 screened abstracts, after removal of duplicates and ineligible studies (Supplementary 1). Our e-mail requests for original data from six authors were met with no reply. Among the included studies, twenty were written in Chinese and nine were written in English. Nineteen of these observational studies were cohort studies, eight were cross-sectional studies and one was a case–control study. In addition, one multicentre randomized trial from which observational data was accessible was also included. Quality assessments were conducted, resulting in nine of the included studies being categorized as low quality, and the others being classified as high quality (Table 1). In all the
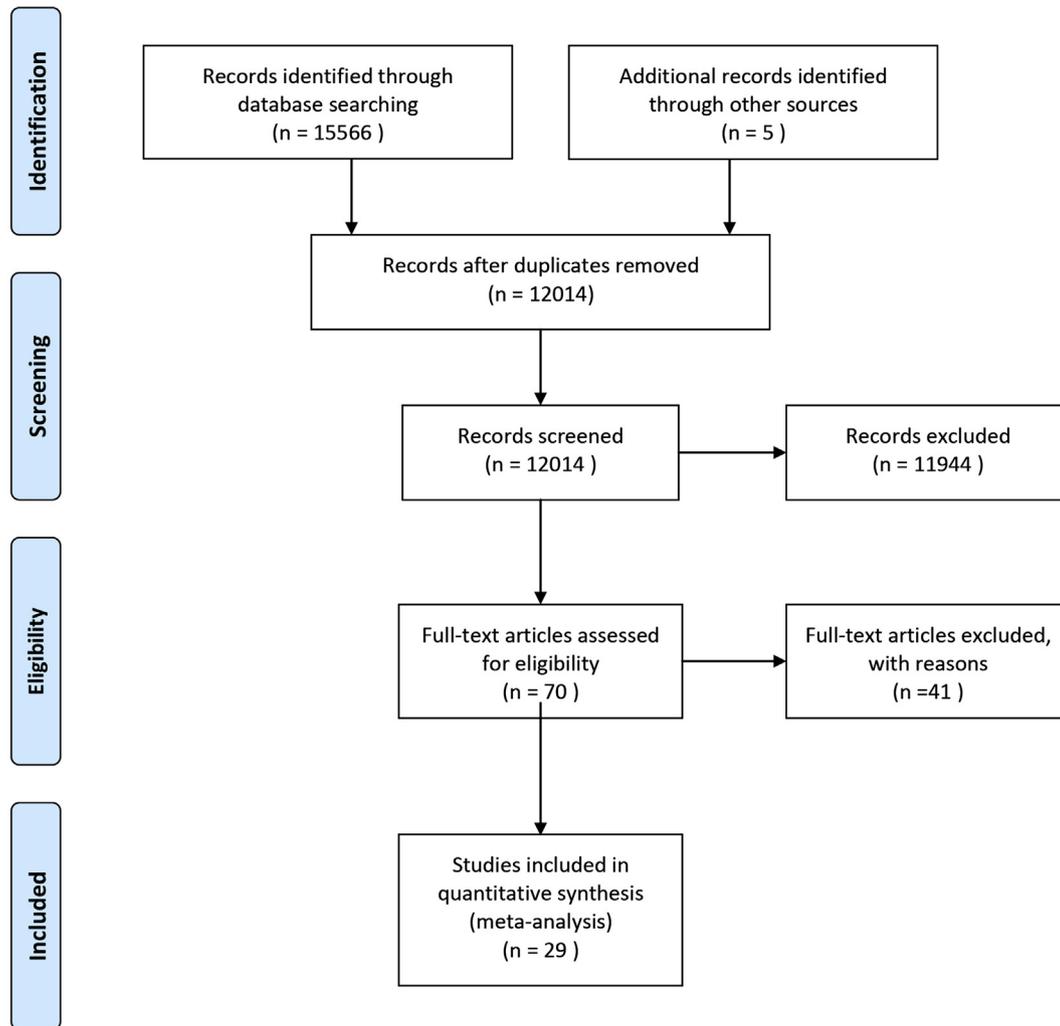
Fig. 1. PRISMA flow chart of study selection process.

included studies, 402 participants underwent hemorrhagic stroke and 989 underwent ischemic stroke. The pooled analyses showed that compared with ischemic stroke patients, hemorrhagic stroke patients were more prone to develop malnutrition.

3.2. Risk factors

Thirteen possible risk factors related to malnutrition were analyzed, including malnutrition on admission, dysphagia, previous stroke, smoking status, alcohol consumption, diabetes mellitus, hypertension, male sex, tube feeding, depressed mood, reduced level of consciousness, pneumonia and infection.

3.3. Malnutrition on admission

Four included studies with high-quality and non-acute assessments reported the impact of malnutrition at admission on the nutritional status of stroke patients. The heterogeneity of these studies was detected, showing $I^2 = 69\%$ (P = 0.02), under fixed-effect model. The synthesized OR was 8.34 (95% CI = 4.60–15.10, P < 0.00001), as shown in Fig. 2. Sensitivity analysis revealed that two studies were possible outliers [12,13]. Random-effect model was then added, showing an OR of 10.59 (95% CI = 3.17–35.36, P = 0.0001). Restricting the analysis to cohort studies by depleting

one of the two aberrant studies [12] ($I^2 = 52\%$, P = 0.13) resulted in an OR of 5.49 (P < 0.00001). Omitting the other aberrant research [13], according to the sensitivity analysis, sharply reduced the obvious heterogeneity ($I^2 = 0\%$, P = 0.43) and increased the OR to 19.54 (P < 0.00001).

3.4. Dysphagia

Nineteen studies that explored the relationship between dysphagia and post-stroke malnutrition were included in the meta-analysis, as shown in Fig. 3. The pooled data under fixed-effect model showed an OR of 2.60 (95% CI = 2.24–3.03, P < 0.00001), with substantial heterogeneity ($I^2 = 84\%$, P < 0.00001). The sensitivity analysis results were similar to the overall results. Restricting the analysis to cohort studies [5,7,19,21,26,38–41,43,44] resulted in similar findings, with $I^2 = 85\%$ (P < 0.00001; OR = 1.71, P < 0.00001). Restricting the analysis to studies not assessed in an acute period [5,12,16–18,20–22,26,39,40,42–45] also resulted in similar findings, with $I^2 = 81\%$ (P < 0.00001; OR = 3.66, P < 0.00001). Results from restricting the analysis to high-quality studies [5,7,12,16–18,22,26,38–40,42] also resembled those from former analyses, with $I^2 = 86\%$ (P < 0.00001; OR = 2.89, P < 0.00001). An appropriate interpretation of heterogeneity did not result from univariate meta-regression analysis by year

Table 1
Characteristics of included studies.

Study	Publication on year	Study country	Study design	Number of participants	Study setting	Sex (M/F)	Age (year)	Exposure factors[a]	Quality
Chai et al. [16]	2008	Singapore	Cross-sectional	61	Hospital	33/28	76.0 ± 12.8	2,4,5,6,9,10	4
Chen et al. [39]	2006	China	Cohort	121	Hospital	–	65.49 ± 12.55	1,2,6,7,14	4
Chen et al. [17]	2010	China	Cross-sectional	203	Hospital	132/71	59 ± 13	2,8,9,10,13,14	4
Chen et al. [59]	2014	China	Cohort	208	Hospital	100/108	75.9 ± 7.4	14	3
Davalos et al. [5]	1996	Spain	Cohort	104	Hospital	67/37	66 ± 10	1,2,3,4,5,6,7,8,14	4
Davis et al. [6]	2004	Australia	Cohort	185	Hospital	98/87	–	3,6,7,8,14	5
Deng et al. [13]	2013	China	Cohort	122	Hospital	70/52	67 ± 10.2	1,4,5,6,7,8,9,14	5
Finestone et al. [10]	1995	Canada	Cohort	49	Rehabilitation center	32/17	60(M) (20–77) 62(F) (20–78)	1,2,3,6,7,9,14	4
FOOD Trial Collaboration [7]	2003	UK	Randomized trial	3012	Hospital	1520/1492	73.3 ± 12.0	2,8,12,13,14	5
Han et al. [31]	2015	China	Cohort	110	Hospital	56/54	55.3 ± 5.4	14	2
Liao et al. [43]	2015	China	Cohort	80	Rehabilitated depart.	52/28	70.1 ± 2.2	2,9	2
Liu et al. [41]	2009	China	Cohort	95	Hospital	60/35	63.5	2,5,6,10,11,13,14	3
Lu et al. [32]	2014	China	Cohort	217	Rehabilitation center	112/105	73.4 ± 11.7(M) 78.2 ± 8.0(F)	2,3,8,9,14	4
Martineau et al. [38]	2005	Australia	Cohort	73	Hospital	44/29	72 ± 12.9	2,14	4
Niu et al. [42]	2013	China	Cross-sectional	260	Hospital	173/97	64.52 ± 7.33	2,8,14	4
Poels et al. [40]	2006	Netherlands	Cohort	69	Rehabilitation center	47/21	56.7 ± 11.0	2,8,10,14	4
Ruan et al. [18]	2011	China	Cross-sectional	572	Hospital	332/240	65 ± 7	2,11,12	4
Wang et al. [21]	2014	China	Cohort	106	Hospital	64/42	–	2,6,7,8,11,12	2
Wang et al. [20]	2015	China	Cross-sectional	98	Hospital	62/36	62.95 ± 9.08	10,11,13,14	3
Wu et al. [22]	2016	China	Cross-sectional	332	Hospital	238/94	70.9 ± 13.9	2,3,9,14	5
Xu et al. [44]	2016	China	Cohort	104	Hospital	62/42	68.54 ± 7.28	2,9,11	2
Yang et al. [30]	2009	China	Cross-sectional	438	Hospital	226/212	73.4 ± 11.7(M) 78.2 ± 8.0(F)	2,3,5,8,10,14	4
Yang et al. [19]	2014	China	Cohort	100	Hospital	63/37	66.05 ± 13.84	2	2
Yoo et al. [11]	2008	Korea	Cohort	131	Hospital	85/46	64.8 ± 10.3	1	5
Yu et al. [12]	2009	China	Case-control	286	Hospital	167/119	67 ± 11	2,4,5,6,8,11,14	4
Zhang et al. [26]	2015	China	Cohort	760	Hospital	494/266	–	8,9,13,14	5
Zhao et al. [23]	2015	China	Cohort	421	Hospital	204/217	68.2 ± 8.5 (malnourished); 60.8 ± 11.4 (well-nourished)	2,3,4,5,6,7,8,14	4
Zhao et al. [33]	2016	China	Cohort	416	Rehabilitation center	213/203	76.3 ± 5.9	8,14	4
Zou et al. [45]	2013	China	Cross-sectional	105	Rehabilitated depart.	65/40	68.80 ± 10.10	2,9	2

–: not provided.

[a] Exposure factors: 1. malnutrition on admission; 2. dysphagia; 3. previous stroke; 4. smoking; 5. alcohol consumption; 6. diabetes mellitus; 7. hypertension; 8. male sex; 9. tube feeding; 10. depressed mood; 11. reduced level of consciousness; 12. pneumonia; 13. infection; 14. age; 15. stroke subtype.
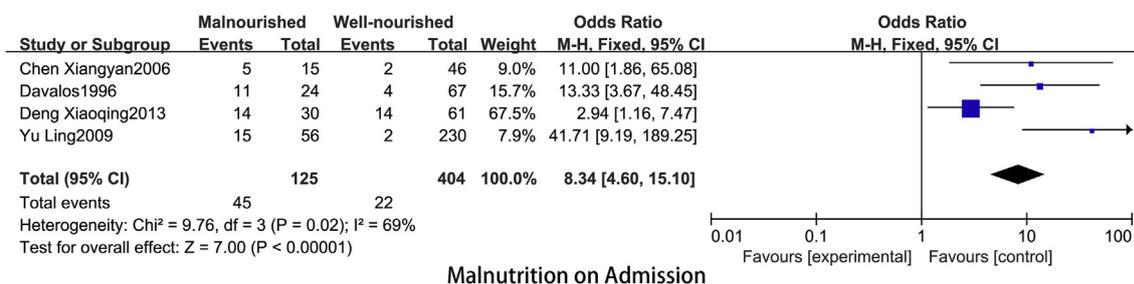

Fig. 2. Forest plot of malnutrition on admission and post-stroke malnutrition risk.

($I^2 = 99.83\%$, adjusted $R^2 = -4.04\%$, $P = 0.588$). Overall, dysphagia was associated with a higher risk of malnutrition, and there was no evidence for between-study heterogeneity.

3.5. Previous stroke

Investigators in six studies reported on relationships between previous stroke and malnutrition among stroke patients (Fig. 4). All the included studies were determined to be high-quality. With an OR of 3.04 (95% CI = 2.35–3.95, $P < 0.00001$), the previous stroke factor showed a significant trend towards higher malnutrition risk, under fixed-effect model ($I^2 = 63\%$, $P = 0.02$). Sensitivity analysis showed no unstable data. Stratified analyses restricted to cohort studies [5,6,23,32,40] ($I^2 = 70\%$, $P = 0.009$) or studies with non-acute assessment [5,30,32,40] ($I^2 = 64\%$, $P = 0.04$) and univariate meta-regression analyses by year ($I^2 = 87.31\%$, adjusted $R^2 = 68.74\%$, $P = 0.059$) were conducted for heterogeneity analyses, yielding similar findings. With the exclusion of one small study [40], between-study heterogeneity was reduced to $I^2 = 48\%$ ($P = 0.10$) with an OR of 3.30 ($P < 0.00001$).
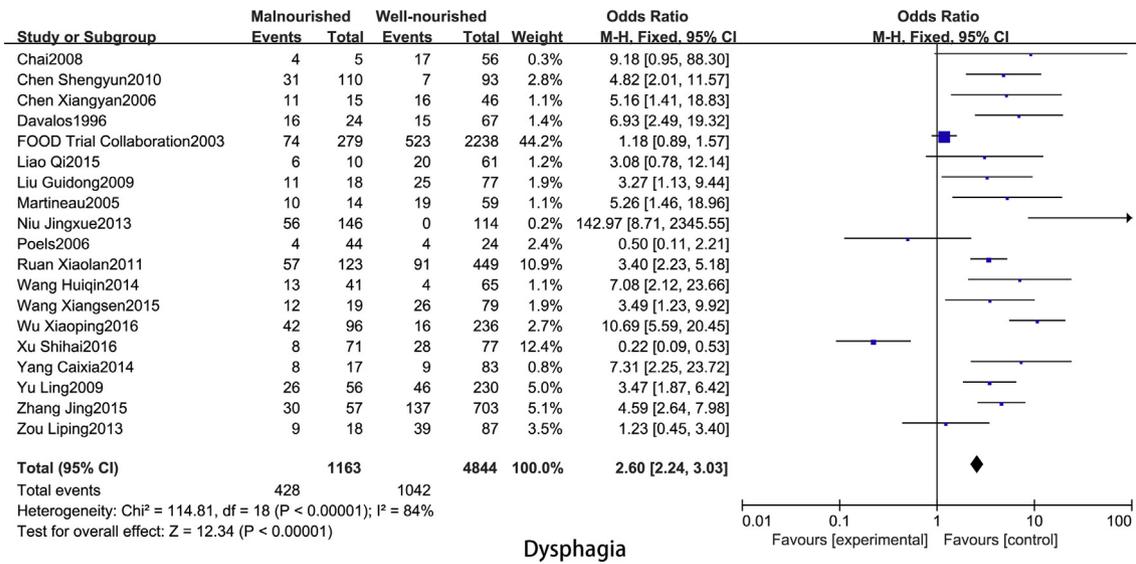
Study or Subgroup	Malnourished Events	Total	Well-nourished Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chai2008	4	5	17	56	0.3%	9.18 [0.95, 88.30]
Chen Shengyun2010	31	110	7	93	2.8%	4.82 [2.01, 11.57]
Chen Xiangyan2006	11	15	16	46	1.1%	5.16 [1.41, 18.83]
Davalos1996	16	24	15	67	1.4%	6.93 [2.49, 19.32]
FOOD Trial Collaboration2003	74	279	523	2238	44.2%	1.18 [0.89, 1.57]
Liao Qi2015	6	10	20	61	1.2%	3.08 [0.78, 12.14]
Liu Guidong2009	11	18	25	77	1.9%	3.27 [1.13, 9.44]
Martineau2005	10	14	19	59	1.1%	5.26 [1.46, 18.96]
Niu Jingxue2013	56	146	0	114	0.2%	142.97 [8.71, 2345.55]
Poels2006	4	44	4	24	2.4%	0.50 [0.11, 2.21]
Ruan Xiaolan2011	57	123	91	449	10.9%	3.40 [2.23, 5.18]
Wang Huiqin2014	13	41	4	65	1.1%	7.08 [2.12, 23.66]
Wang Xiangsen2015	12	19	26	79	1.9%	3.49 [1.23, 9.92]
Wu Xiaoping2016	42	96	16	236	2.7%	10.69 [5.59, 20.45]
Xu Shihai2016	8	71	28	77	12.4%	0.22 [0.09, 0.53]
Yang Caixia2014	8	17	9	83	0.8%	7.31 [2.25, 23.72]
Yu Ling2009	26	56	46	230	5.0%	3.47 [1.87, 6.42]
Zhang Jing2015	30	57	137	703	5.1%	4.59 [2.64, 7.98]
Zou Liping2013	9	18	39	87	3.5%	1.23 [0.45, 3.40]
Total (95% CI)		1163		4844	100.0%	2.60 [2.24, 3.03]
Total events	428		1042			

Heterogeneity: Chi² = 114.81, df = 18 (P < 0.00001); I² = 84%
Test for overall effect: Z = 12.34 (P < 0.00001)

Dysphagia

Fig. 3. Forest plot of dysphagia and post-stroke malnutrition risk.

Study or Subgroup	Malnourished Events	Total	Well-nourished Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Davalos1996	5	24	14	67	9.0%	1.00 [0.32, 3.14]
Davis2004	11	30	27	155	8.6%	2.74 [1.17, 6.43]
Lu Bin2014	67	231	24	207	27.7%	3.12 [1.87, 5.20]
Poels2006	0	24	7	45	8.0%	0.10 [0.01, 1.92]
Yang Jiangsheng2009	67	231	24	207	27.7%	3.12 [1.87, 5.20]
Zhao Gaofeng2015	50	93	60	328	18.9%	5.19 [3.17, 8.52]
Total (95% CI)		633		1009	100.0%	3.04 [2.35, 3.95]
Total events	200		156			

Heterogeneity: Chi² = 13.35, df = 5 (P = 0.02); I² = 63%
Test for overall effect: Z = 8.37 (P < 0.00001)
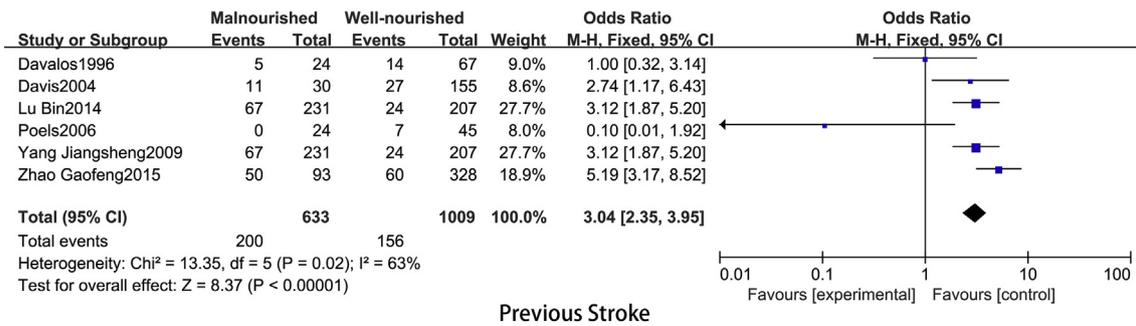
Previous Stroke

Fig. 4. Forest plot of previous stroke and post-stroke malnutrition risk.

3.6. Smoking

Five studies of high quality were pooled to investigate the effect of smoking on the nutritional conditions of stroke patients (Supplementary 2), revealing no statistical significance (OR = 1.01, 95% CI = 0.73–1.40, P = 0.96; fixed-effect model). Substantial heterogeneity was found, with I² = 73% (P = 0.005). Results of the sensitivity analysis were stable. Restriction to cohort studies [5,13,23] (I² = 46%, P = 0.16) or studies with a non-acute assessment [5,12,13,16] (I² = 79%, P = 0.002) did not fully reduce the heterogeneity, and had similar results.

3.7. Alcohol consumption

Alcohol consumption (I² = 53%, P = 0.04) was regarded as a risk factor associated with post-stroke malnutrition, based on eight included studies (Supplementary 3). Analysis was conducted by fixed-effect model, with an OR of 1.31 (95% CI = 0.97–1.77, P = 0.08), presenting no statistical significance. Sensitivity analysis showed that there was an outlier. Random-effect model was then added, also predicting an OR of 1.15 (95% CI = 0.68–1.96, P = 0.61). A subgroup analysis by study design [5,13,23,41] (cohort studies only: I² = 0%, P = 0.39) reduced the between-study heterogeneity, while that by timing of nutritional assessment [5,12,13,16,20,30] (non-acute assessment only: I² = 59%, P = 0.03) did not reduce the between-

study heterogeneity. Conversely, removal of the study [12] that had a possibly aberrant influence on the pooling estimate resulted in a significantly increased risk of malnutrition (OR = 1.62, P = 0.003) among stroke patients who were alcohol consumers, with no heterogeneity (I² = 0, P = 0.42). Restricting the analysis to high-quality studies [5,12,13,16,23,30] likely presented a similar result (OR = 1.39, P = 0.04), with obvious heterogeneity (I² = 63%, P = 0.02).

3.8. Diabetes mellitus

Data on stroke patients with diabetes mellitus were available from 9 studies with a pooled OR of 1.79 (95% CI = 1.35–2.38, P < 0.0001) from the fixed-effect model with I² = 47% (P = 0.06) (Supplementary 4). Sensitivity analysis showed a possibly aberrant study. The analysis under random-effect model showed an OR of 1.72 (95% CI = 1.09–2.71, P = 0.02). Stratified analyses by study design (cohort studies only: I² = 49%, P = 0.08) and timing of nutritional assessment (non-acute assessment only: I² = 63%, P = 0.02) did not reduce the between-study heterogeneity, despite that the results were the same. With the exclusion of one study [21] focusing on aged people (OR = 1.53, P = 0.006), according to the sensitivity analysis, statistical heterogeneity was not evident (I² = 5%, P = 0.39). Restriction to high-quality studies [5,6,12,13,16,23] showed a decreased heterogeneity, with I² = 7% and P = 0.37 (OR = 1.42, P = 0.04).

3.9. Hypertension

Hypertension was not significantly associated with post-stroke malnutrition (pooled OR = 0.75, 95% CI = 0.56−1.01, P = 0.06, under fixed-effect model), based on six studies (Supplementary 5). Sensitivity analysis indicated that the pooled studies were stable and reliable, and statistical heterogeneity between the studies was not evident (I^2 = 17%, P = 0.30). Restriction to high-quality studies [5,6,12,13,23] (I^2 = 23%, P = 0.27) and cohort studies [5,6,13,21,23] (I^2 = 33%, P = 0.20) showed similar results and heterogeneity. However, when studies were restricted to those with a non-acute assessment [5,12,13,21] (I^2 = 0%, P = 0.43; OR = 0.60, P = 0.01), hypertension was not shown to increase malnutrition among stroke patients with statistical significance, and these data showed no heterogeneity.

3.10. Male sex

Thirteen studies evaluated malnutrition in male stroke patients (Supplementary 6). In the overall pooled estimate with fixed-effect model, the male factor played a statistically significant negative role (OR = 0.68, 95% CI = 0.59−0.78, P < 0.00001) with severe between-study heterogeneity (I^2 = 87%, P < 0.00001). Sensitivity analysis also revealed an unstable pooling of the studies. Random-effect model was added, showing an OR of 0.64 (95% CI = 0.42−0.98; P < 0.00001). Restriction to high-quality studies [5−7,12,13, 17,23,26,30,32,40,42] led to similar findings with a heterogeneity of I^2 = 88% (P < 0.00001). Restriction to cohort studies [5−7,13,21, 23,26,32,40] showed similar results, with I^2 = 90% (P < 0.00001). Univariate meta-regression analysis by publication year could not account for the severe heterogeneity (I^2 = 49.35%, adjusted R^2 = −8.86%, P = 0.473). However, when restricting to studies with a non-acute assessment [5,12,13,17,21,26,30,32,40,42] (I^2 = 77%, P < 0.0001; OR = 0.84, P = 0.07), the pooled studies showed a contradictory result, as no significant correlation between male sex and post-stroke malnutrition was observed.

3.11. Tube feeding

Ten studies provided estimates for the relationship of between tube feeding and the incidence of undernourished post-stroke patients, showing obvious statistical significance, with a high OR of 5.43 (95% CI = 3.99−7.37, P < 0.00001) under fixed-effect model and an OR of 5.37 (95% CI = 3.52−8.19, P < 0.00001) under random-effect model. Between-study heterogeneity was not apparent (I^2 = 33%, P = 0.15) (Supplementary 7). All data were extracted from studies with non-acute assessments. A possible interference of study design [10,13,26,32,43,44] was assessed, showing I^2 = 4% (cohort studies only: P = 0.39; OR = 3.68, P < 0.00001). Sensitivity analysis revealed two aberrant studies [22,26], and removal of these studies resulted in a homogeneous pool (I^2 = 0%, P = 0.43) with results similar to those of the overall analysis.

3.12. Depressed mood

Presence of a depressed mood significantly correlated with subnutrition after stroke (OR = 1.82, 95% CI = 1.30−2.53, P = 0.0004) under fixed-effect model in all five selected studies, with a significant heterogeneity of I^2 = 61% (P = 0.04) (Supplementary 8). Because sensitivity analysis implied an unstable pooling of studies, analysis under random-effect model was also conducted, showing an OR of 1.32 (95% CI = 0.61−2.86, P = 0.48). When a relatively low-quality study [41], which was

also the only study with acute assessment, was depleted, severe heterogeneity was still present with an I^2 = 67% (P = 0.03; OR = 1.88, 95% CI = 1.34−2.63, P = 0.0002, fixed effect model). If the model was changed to random-effect model, the analysis resulted in an OR = 1.44 (95% CI = 0.65−3.17, P = 0.37). However, restricting the analysis to three cross-sectional studies [16,17,30] resulted in depressed mood having a significantly higher association with post-stroke undernutrition under both models (OR = 2.21, P < 0.0001, fixed-effect model; OR = 2.22, P < 0.001, random-effect model), without evident heterogeneity (I^2 = 0%, P = 0.50).

3.13. Reduced level of consciousness

Patients with a reduced level of consciousness presented an intimate association with malnourishment after stroke, based on pooled data from six studies. The OR was 2.82 (95% CI = 2.12−3.75, P < 0.00001, fixed-effect model), with no between-study heterogeneity (I^2 = 0%, P = 0.78) (Supplementary 9). When analyses were stratified by study quality [12,18,26] (I^2 = 0%, P = 0.55), study design [21,26,41] (cohort studies only: I^2 = 0%, P = 0.38) or timing of nutritional assessment [12,18,20,21] (non-acute assessment only: I^2 = 0%, P = 0.96), the studies presented homogeneity similar to that overall one, with similar results. The sensitivity analysis results resembled the overall results.

3.14. Pneumonia

Only three of the selected studies evaluated the impact of pneumonia on nutritional status, showing a high incidence (OR = 2.18, 95% CI 1.70−2.79, P < 0.00001, fixed-effect model), with mild between-study heterogeneity (I^2 = 16%, P = 0.30) (Supplementary 10). Though the sensitivity analysis showed an unstable result, there were not enough data to perform stratified analyses. The analysis under random-effect model showed a similar result: OR = 2.20 (P < 0.00001).

3.15. Infection

Infection during hospitalization was estimated as a risk factor for malnutrition based on four studies, yielding an OR of 2.75 (95% CI = 2.18−3.48, P < 0.00001, fixed-effect model) (Supplementary 11). The sensitivity analysis results were variable when each study was omitted. Thus, random-effect model was added with an OR of 6.46 (95% CI = 2.14−19.50, P = 0.0009). While severe heterogeneity was noted (I^2 = 91%, P < 0.00001), data were not interpretable by meta-regression analysis or stratified analyses with study quality [7,17,26] (I^2 = 88%, P = 0.0002; OR = 2.47, P < 0.00001) and timing restriction (17, 20, 26) (non-acute assessment: I^2 = 85%, P = 0.001; OR = 6.68, P < 0.00001). There were too few studies to be stratified by study design for further analysis.

3.16. Publication bias

Publication bias assessments were carried out on studies that examined dysphagia. First, a funnel plot suggested possible publication bias in studies reporting dysphagia and risk of malnutrition, as asymmetric graph was observed (Supplementary 12). Begg's and Egger's tests were then performed for further verification, indicating no quantitative evidence of publication bias. The same results were concluded from the similar estimations carried out on the included studies regarding the male sex and tube feeding factors with a relatively large sample (>10).

4. Discussion

To better identify stroke patients at risk of malnutrition, we conducted a comprehensive, systematic review of studies from the past twenty-six years. The included studies were observational studies comprised of cohort, case—control and cross-sectional studies or non-observational studies with observational data. Thirteen risk factors related to malnutrition among stroke patients were included and analyzed, of which malnutrition on admission, dysphagia, previous stroke, diabetes mellitus, tube feeding, and reduced level of consciousness were most likely associated with malnutrition in stroke patients, with statistical significance. The odds were increased for presentation of the aforementioned risk factors among the malnourished patients.

Malnutrition on admission is the basis for developing malnutrition and increasing susceptibility to pneumonia, infection and gastrointestinal hemorrhage, all of which increase the nutritional demand of the patient [7]. Dysphagia affects the normal dietary and fluid intake, leading to nutritional and water inefficiency, inappropriate social manners and reduced quality of life [46]. Regarding the previous stroke factor, higher numbers of stroke episodes are correlated with more neurological defects, especially for self-feeding impairment, which can result in malnutrition [30,47]. Diabetes mellitus, though controversial in different studies, has been associated with dysphagia, which also contributes to malnutrition. In addition, diabetes can also compromise the patient's nutritional intake directly [16]. Tube feeding is unable to both complement the substantial total protein loss in a hyper-catabolic state and prevent the high incidence of diarrhea in comatose acute stroke patients. In addition, compared to a simple glucose solution, active tube feeding may also upset the nitrogen balance during the acute stage from days 4—14 [48]. A reduced level of consciousness can decrease a patient's food intake and result in malnutrition [12].

In contrast, smoking was demonstrated to possibly not be a significant risk factor of post-stroke malnutrition according to our analysis.

However, the other six factors, alcohol consumption, hypertension, male sex, depressed mood, pneumonia and infection, did not present enough evidence to correlate with malnutrition among stroke patients due to unstable data. These factors were probably affected by the location, race and small number of included studies. Cessation of alcohol consumption upon admission to the infirmary likely ameliorated the effects of previous alcohol consumption on nutritional status [16,49], as alcohol is known to affect the quality of a patient's diet. Depression is a major determinant of malnutrition, as shown by several studies [50,51] due to low food consumption as well as poor appetite and chewing problems. In addition, comorbidity with infection [52] and pneumonia [53] increases the nutritional demand of a patient's body, resulting in an overall loss of nutrition. Mechanisms underlying the effects of hypertension and male sex on malnutrition have not been previously elucidated.

There was moderate to severe heterogeneity among studies of nine risk factors. Analyses of heterogeneity on each risk factor were performed as shown in Table 2. Hypertension and depressed mood were shown to have contradictory results, when we standardized the study design (only cross-sectional studies) and the timing of nutritional assessment (only studies with non-acute assessment). The confounding study designs had a strong impact on our conclusions, possibly resulting in reduced reliability and recommendation intensity. Therefore, more homogeneous studies are needed for compensation. Regarding the timing of nutritional assessment, a recent study demonstrated that: 'Nutritional improvement at discharge and energy intake at admission are associated with recovery of patients following a cerebrovascular disorder' [54]. Hence, multiple nutritional assessments should be executed, not only at admission but also at least once to twice per week and at discharge for nutritional management according to the published consensus [55—57], to ensure more reliable and clinically meaningful data can be extracted for further analysis.

In addition, several studies [5,6,10—13,17,26,31,32,39] found that malnutrition was possibly correlated with advanced age; nevertheless, the data from these studies could not be pooled due to their diverse study designs. If possible, the potential age risk factor should be re-evaluated in the future, and the potential risk factor of impaired cognitive function [16,17,23,30] also requires further investigation.

For quality assessment, twenty-nine percent of our studies were considered low-quality, and, more high quality studies are thus

Table 2
Contribution to the heterogeneity.

Exposure factors	Contribution to the heterogeneity between the studies reporting the risk factor						
	Possible discrepancy by aberrant studies	Study design	Timing of nutritional assessment	Small sample effect	Study quality	Age	Publication year of the study
Malnutrition on admission	Probable illustration	/	/	/	/	/	/
Dysphagia	—	—	—	—	—	—	—
Previous stroke	/	/	/	√	/	/	/
Smoking	—	—	—	—	—	—	—
Alcohol consumption	Probable illustration	Probable illustration	/	/	/	/	/
Diabetes mellitus	/	/	/	/	√	√	/
Hypertension	/	/	Probable illustration	/	/	/	/
Male sex	—	—	—	—	—	—	—
Tube feeding	Probable illustration	√	/	/	/	/	/
Depressed mood	/	Probable illustration	/	/	/	/	/
Reduced level of consciousness	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pneumonia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Infection	—	—	—	—	—	—	—

Probable illustration: The reason may account for the obvious heterogeneity to a great extent.
√: The illustration for the heterogeneity partially.
/: The heterogeneity could not be omitted by the above-mentioned reasons.
—: The heterogeneity could not be omitted by the above-mentioned reasons, however, possibly due to racial diversity, non-uniform judgments, discrepant stroke lesions or some other unnoticed reasons.
N/A: Not available. There was no obvious heterogeneity between studies reporting reduced level of unconsciousness and pneumonia.

needed. No publication bias was discovered among the selected studies, and there was thus no threat to the meta-analysis validity.

No other meta-analysis has been performed to assess such a variety of risk factors for malnutrition thus far. This analysis will provide a rationale to allow risk testing at an early stage, and possibly form a basis for the development of clinical scoring to stratify nutritional management according to the risk of malnutrition in stroke patients.

4.1. Limitations

Our study still has some potential limitations to consider. The standard for estimating risk factors differed with the study design in variable literature, which could have led to discrepant results. To date, no diagnostic golden standard of post-stroke malnutrition has been established, which is an inevitable bias in our study. A widely accepted criterion should be negotiated, and authorized consensus must be promoted and executed in the clinical setting and among researchers worldwide. Furthermore, recent criteria for malnutrition, provided by guidelines from the European Society of Clinical Nutrition and Metabolism (ESPEN), highlight criteria for being "at nutritional risk" according to any validated nutritional risk screening tool [8]. Similarly, the American Society for Parenteral and Enteral Nutrition (ASPEN) proposed the risk of developing malnutrition and its related complications "on admission" even though the recommended characteristics for consensus-derived malnutrition diagnoses are difficult to discern during early stroke stage [58]. Since more attention is given to the risk of nutritional status before malnutrition [4,25], corresponding studies should be performed. In addition, our study incorporated twenty studies published in Chinese periodicals, which may affect the overall conclusions. These studies focused more on risk factors such as depression, consciousness change, pneumonia and infection, which did not demonstrate an association with post-stroke malnutrition because of the short of evidence. A sub-analysis restricted to studies published in English was performed (Supplementary 13) to compare with the overall data, revealing the necessity of more studies on doubtful risk factors for post-stroke malnutrition.

5. Conclusions

According to our study, malnutrition on admission, dysphagia, previous stroke, diabetes mellitus, tube feeding and a reduced level of consciousness among stroke patients probably increased the risk of malnutrition during the hospital stay. Furthermore, smoking is most likely not a risk factor according to our analysis. The ambiguous impacts of alcohol consumption, hypertension, male sex and depressed mood on post-stroke malnutrition need to be re-evaluated. The roles of pneumonia and infection on post-stroke subnutrition also require additional evidence to support and improve the reliability of our analyses. Patients with the aforementioned risk factors should routinely undergo nutritional screening and assessment for the early identification and treatment of malnutrition, to reduce the morbidity and mortality correlated with post-stroke recovery.

Authors' contributions

Ning Chen and Yanbo Li made substantial contributions to the study conception, acquisition of data, methodological assessment and main drafting of the manuscript. Jinghuan Fang and Qian Lu performed data analysis and interpretation and drafted the study search and inclusion criteria. Li He designed and revised the manuscript. All the authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2017.12.014.

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