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# The epidemiology of functional stroke mimic (FSM) patients: a systematic review and meta-analysis.

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## Conflicts of interest

None

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**Running title:** Functional stroke mimic (FSM) patients: a systematic review and meta-analysis.

**Key words:** systematic review, meta-analysis, stroke, functional disorder, prevalence


## Abstract

### Background

Stroke mimics form a significant proportion of cases in acute stroke services and some present with functional neurological disorder. Little is known about the prevalence or clinical characteristics of functional stroke mimics (FSMs).

### Methods

A systematic literature search and meta-analysis was carried out on published studies reporting suspected stroke and stroke mimic rates; 114 papers met inclusion criteria of which 70 provided a FSM rate. Random-effects models estimated prevalence rates across settings and moderators of FSM rate.

### Findings

Pooled proportions indicate 25% of suspected stroke cases were stroke mimics (95% CI, 22%-27%). Within the 67 studies providing positive FSM rates, FSMs represented 15% (95% CIs, 13%-18%) of stroke mimics and 2% of suspected strokes (95% CIs, 2%-3%). FSMs were younger and more likely to be female, presented more with weakness/numbness but less with reduced consciousness or language problems. Stratified analyses suggest higher stroke mimic rates in primary care vs acute settings (38% v 12%) but higher FSM rates in stroke

units compared to primary care (24% v 12%). Functional rates were higher in studies that were descriptive, retrospective and in patients receiving thrombolysis.

**Discussion**

Several studies report the proportion of functional stroke patients presenting to stroke services. FSMs have discernible demographic and clinical characteristics, but there is a conspicuous lack of evidence on their presentation or guidance for treatment. The social and psychological mechanisms underlying FSM presentations need more accurate quantification to help inform stroke pathways and improve care for these patients.



## Introduction

Stroke is a leading cause of death worldwide. As aging populations grow, swift and accurate stroke diagnosis is increasingly important.[1] Clinicians across settings diagnose stroke using a combination of physical examination, history taking and brain imaging (plain CT being the front-line imaging tool).[2]

A proportion of suspected strokes are 'stroke mimics' with symptoms attributable to other medical conditions (namely '*medical mimics*'), or no organic cause ('*functional mimics*'). A previous systematic review reported stroke mimic rates between 20-25%.[3] Functional stroke mimic (FSM) patients accounted for 7.4% of mimics, while 5% were 'non-specified'. Other studies have estimated a functional presentation rate of between 38 - 41% of stroke mimics.[4-6]

Only one retrospective review at a London acute stroke unit has investigated FSM clinical features, finding that FSMs were more likely to present with isolated weakness or slurred speech compared to medical mimics or patients with vascular stroke (ischemic, intracerebral

haemorrhage or subarachnoid haemorrhage). FSM were reported to be younger and be more likely to have depression, back pain, migraine and asthma.[4, 6, 7] Finally, FSM more often received an MRI scan and had shorter lengths of stay. A systematic review of functional motor symptoms reported prognosis to be variable, with 39% seeing no improvementworsening symptoms at an average follow-up of 7.4 years.[8]

In 2010, Hyper Acute Stroke Units (HASUs) were established in London, UK, leading to improvements in stroke patient outcomes and service delivery targets.[9, 10] Improved service design, along with public health campaigns may have inadvertently led to increased numbers of stroke mimics entering specialised stroke pathways. [11] In the US, the excess direct hospital cost of stroke mimics is $15 million per year and there may be costs for patients with potential iatrogenic harm. [12]. There are no specific guidelines or gold standard treatments for FSMs. Understanding the presentation of FSMs to stroke services is the first step to improving their treatment and care pathways.

This systematic review and meta-analysis aims to:

1. Review published literature on the prevalence of stroke mimic and FSM patients;
2. Review research describing the demographic and/or symptom profiles of stroke vs stroke mimics and FSMs; and
3. Investigate moderators of FSM rates.

## Methods

This review was registered with the National Institute for Health Research's International Prospective Register of Systematic Reviews on the 31st October 2014*. A literature search was performed in three stages. Meta-analyses were reported with reference to PRISMA

* Code: PROSPERO 2014:CRD42014014632. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014632

guidelines.[13] The study did not require ethics committee approval as all data was fully anonymised and there was no primary data collection.

**Inclusion criteria**

Criteria included papers that: i) reported the proportion of patients with a final stroke mimic diagnosis from a sample of suspected stroke patients; ii) reported a series of consecutively eligible patients; and iii) were available in English. Papers were excluded if: i) they included only transient ischemic attack (TIA) patients; and ii) they were 'grey' literature' (published in non-commercial form e.g. conference abstract).

**Literature search**

A preliminary search was conducted in October and November 2014 for papers published from 1980 in databases CINAHL, PubMed, OvidSP and Google Scholar, using the search term "stroke mimic*". Thirty-four met inclusion criteria. The first search was insufficient in its search criteria so a second in June 2015 utilised OvidSP, searching databases PsychINFO, Embase and Ovid Medline (search terms available online only). These searches formed part of author NOC's PhD thesis, archived in the British Library and KCL website. Of 11,915 papers reviewed, 53 met criteria. Using the same search strategy, limited to publication years 2015-2018, author AJ implemented an update of Google and Ovid searches in September and October 2018 to ensure the inclusion of the most up-to-date literature. This third search returned 1127 papers, of which 27 met criteria. Final paper inclusions were determined by two raters (authors NOC and AJ). For simplicity, Figure 1 shows the combined selection strategy for all searches.

***Figure 1*. PRISMA flowchart.**

Six studies provided two independent stroke mimic rates [14-19] and one study [20] provided three stroke mimic rates. Overall, 114 papers met inclusion criteria (online only materials), providing 122 rates across service settings.

**Data extracted**

Data were extracted on: sample size, age and sex of patients; stroke, stroke mimic and FSM prevalence; diagnostic method; setting; symptom presentation of FSMs; most common stroke mimic diagnosis and thrombolysis administration.

To address potential bias, quality scores were calculated from criteria outlined by Kmet [21]. Papers were rated on 14 criteria (the rating scale was "yes" = 2, "partial" = 1, "no" = 0 or N/A). Final scores reflected the sum of criteria divided by the highest possible total from items, excluding items marked "NA".

**Statistical analysis**

Systematic review analysis was performed using Excel Version 14 and SPSS Version 22. Independent sample *t*-tests conducted on raw data compared ages between groups and chi-square tests compared sex and symptom proportions; *t*-test confidence intervals (CIs) represent the difference between group means and chi-square CIs represent the difference between population proportions.[22] Meta-analyses were conducted in Stata version 15.1.[23] Random-effects models were executed using the *metaprop* command to calculate prevalence and summary statistics with score CIs.[24] These models assume variance in effect sizes between studies and make inferences about population parameters likely larger than the set of

observed studies.[25] The $I^2$ statistic assessed heterogeneity for analyses containing ≥2 rates. $I^2$ represents the percentage of between-study variation attributable to heterogeneity rather than chance, values over 75% are considered high.[26]

## Results

### Systematic review

Of the total 114 papers, 92 (75%) were published in or after 2008. Articles contained data originating from 25 countries; most commonly from the US (*n*=50), the UK (*n*=15), Germany (*n*=9) and Canada (*n*=7).

#### Study design and quality

Approximately half the studies were prospective/retrospective (Table 1). Most studies were descriptive in their aims. Thirty-eight papers were screening tool validation studies, including five assessing biomarkers. Three had mixed aims (e.g. both diagnostic validation and epidemiological aims). Quality scores ranged from 16.60% – 94.40% (Table 1).

#### Study samples and settings

Average sample size was 742 (SD=1236.78, range: 20[27] – 8187[28]). The most frequent study setting was emergency departments (*n*=40). Study settings included from acute units (i.e. HASUs), more generic stroke units or multiple settings i.e. Emergency services and ED(Table 1). Eleven papers did not report selection criteria for their study samples and 27 reported none. In the remaining papers, the most common exclusion criterion was 'incomplete data' (18 papers), 'non-receipt of thrombolysis' (17 papers) and 'patients aged under-18' (20 papers). Two papers [29, 30] excluded patients aged under-16. Three used paediatric samples [27, 31, 32], one investigated patients aged over-65[33], and one excluded patients whose initial clinical examination showed no sign of stroke.[34]

### Stroke and stroke mimic definitions and diagnoses

Studies varied in definitions of stroke and stroke mimics. Thirty papers compared stroke mimics to stroke and TIA patients. Seventeen papers used the term 'stroke' with no further detail, 16 examined ischemic stroke only and 11 examined ischemic stroke, TIA and intracranial haemorrhage. The rest used a variety of definitions and combinations of stroke types. TIA and subarachnoid haemorrhage patients categorised as stroke mimics were reclassified as stroke in our analysis, increasing the proportion of cases considered vascular stroke.

There were 84,574 suspected stroke patients; 18,496 were later diagnosed as stroke mimics. Eighty-nine papers listed stroke mimic diagnoses though 17 gave only a partial account; seizure was the most frequent mimic-diagnosis in 26 papers, functional disorder in 17 papers, and migraine in 15 papers.

Functional symptoms were most commonly described as "conversion disorder" (24 studies), followed by "functional" (*n*=13) and "psychiatric" (*n*=7). One paper grouped two patients diagnosed with "anxiety", one diagnosed with "depression", and two classified "conversion disorder" under the definition, 'psychiatric'. All were regarded FSMs for this review.[16]

From 70 papers listing functional disorder there were a total of 1022 FSMs. Three papers listed functional disorder but reported no FSM cases (signifying a true 'zero' rate), leaving 67 papers reporting positive FSM rates.

### Accounting for 'other' categories

Of the 89 papers giving stoke mimic diagnoses, 43 listed a miscellaneous 'other' category (Figure 2). We hypothesized that FSMs might be hidden within the 'other' category when functional disorder was not listed. Subsequently, the 'other' rate was compared between papers listing 'other' but not functional disorder and papers listing both categories.

*Figure 2.* **Flow diagram of papers with 'other' and 'functional' categories.**

The 24 papers listing functional disorder and 'other' had an average 'other' rate of 18.04% as a proportion of stroke mimics, and an average FSM rate of 13.83%. The mean 'other' rate across 19 papers listing 'other' but no functional disorder was approximately double at 36.94% ($\chi^2$ (1) = 1265.94, 95% CIs, 17.86-19.94, $p < 0.001$). This suggests FSMs may be hidden within miscellaneous categories when not explicitly listed.

### Demographics

Sixty-seven papers provided total samples' age, giving a weighted mean of 66.90 years (pooled SD from 28 studies= 17.16). Seventy-one papers gave sex data. The overall rate of female patients was 49%. Weighted mean age with SD and sex proportions for stroke patients, medical mimics and functional mimics are shown in Table 2. Medical stroke mimics were younger than true stroke patients and functional mimics were significantly younger than medical mimics.

Twelve papers provided information allowing comparisons between FSMs and medical mimics. FSMs were younger and more often female than medical mimics (Table 2).

### FSM clinical symptoms

Ten papers gave information on functional patients' symptoms ($n$=321). Patients commonly presented with multiple symptoms. In both FSMs and medical mimics, the most common symptoms were weakness and numbness, followed by language impairments. There were no reports of functional mimic patients presenting with seizures or convulsions. As a proportion of total symptoms reported, FSMs were more likely than medical mimics to present with weakness or numbness, and less likely to present with reduced consciousness or language impairments (Table 2).

**Meta-analysis**

A meta-analysis examined the pooled prevalence of stroke mimics and FSMs. The first analysis included all studies (*n*=114), second included only studies listing functional disorder (*n*=70).

There was a total of 84,574 suspected stroke patients of whom 18,496 were eventually diagnosed as stroke mimics. The pooled proportion of stroke mimics was 25% (95% CI, 22%-27%), with high between-study heterogeneity ($I^2$=99.41%).

Of the 70 studies providing FSM rates, 67 reported rates greater than zero. The pooled prevalence of FSMs was 15% (95% CIs, 13%-18%, $I^2$=91.56%) as a proportion of stroke mimic patients, and 2% (95% CIs, 2%-3%, $I^2$=90.50%) as a proportion of total suspected strokes.

Potential moderators of FSM rate were examined in stratified analyses. Analysis by service setting suggested higher stroke mimic rates in primary care or outpatient settings (38% of suspected stroke patients, 95% CI, 24%-51%, $I^2$=95.95%), and emergency medical services (37%; 95% CI, 25%-49%, $I^2$=98.55%). The lowest rate of stroke mimic patients was in studies from mixed settings (12%; 95% CI, 6%-18%, $I^2$=91.99%) (Figure 3).

However, when the proportion of FSMs was derived from stroke mimics, the highest proportion was from mixed settings (65%; 95% CI, 53%-77%), followed by stroke units (24%; 95% CI, 16%-32%, $I^2$=86.71%) (Figure 3). See online only materials for FSM rates from individual studies.

***Figure 3.*** **Forest plot displaying the proportion of stroke mimic patients in suspected stroke patients, and derived proportion of functional mimic patients across diagnosis setting.**

†Stroke mimic rate as percentage of total sample of suspected stroke patients. Functional mimic rate as a percentage of stroke mimic patients.

FSM rates were highest in descriptive studies (aiming to describe a population or service), followed by service audits and observational studies (aiming to observe the effects of exposure to a particular factor/phenomenon) (Table 3). Overlapping CIs suggest these are not statistically significant differences. Retrospective and prospective study designs provided rates of 19% and 11% respectively. In study cohorts receiving thrombolysis, the pooled proportion of stroke mimics within total samples was 9% (95% CIs, 7%-11%, $I^2$=97.71%) within which the FSM rate was 32% (95% CIs, 24%-39%, $I^2$=91.08%). In comparison the FSM rate was 5% in studies where participants did not receive thrombolysis (95% CIs, 4%-7%, $I^2$=0%). Please see discussion section for reflection on this finding.

## Discussion

This paper explored the epidemiology of stroke mimic and FSM presentations. Stroke mimics account for 25% of suspected strokes (95% CI, 22-27). In papers providing FSM rates, 15% of stroke mimics had functional diagnoses (95% CIs, 13-18), representing 2% (95% CI, 2-3) of all suspected strokes.

Our stroke mimic rate is comparable to the 26% reported by Gibson and Whiteley [3] although we included retrospective studies. Our FSM rate is higher than their 7.4% as we extended the definition of functional disorders to include depression and anxiety diagnoses.

FSMs were more commonly female than medical mimics (50.3 v 45.2%), corresponding with epidemiological research on functional disorders.[15, 35-38]. FSMs are also younger than medical mimics, similar to other neurological conditions, where functional patients are younger on average than patients with typical disorders.[35]

Functional patients are more likely to present with weakness/numbness and less likely to have reduced consciousness, language impairments or vertigo. This may result from functional symptoms being defined as a loss of function alongside unclear imaging evidence, despite calls to employ positive signs.[39] Reduced consciousness may deter a functional diagnosis if a clinical history is difficult to obtain. The symptom of vertigo may be considered a stand-alone diagnosis or may denote abnormalities linked to the posterior cerebral circulation, which are less commonly classed as functional symptoms.

**Study Setting**

Stroke mimic rates were highest in ambulatory, emergency and primary care settings suggesting more mimic patients are identified earlier in stroke care pathways. In contrast, functional rates were higher in mixed and acute settings and lower in emergency settings. Functional disorders may be a challenging differential for non-specialist clinicians, particularly considering the risks in giving a false negative stroke diagnosis. Clinicians in secondary and tertiary settings, with access to specialised diagnostics, may be more confident or willing to make functional diagnoses.

**Study aims and design**

FSM rates were highest in service audits and studies with descriptive and observational designs; fewer exclusion criteria may be applied in these studies and they were also commonly in acute settings, where functional rates are higher. FSM rates were higher in retrospective versus prospective studies. Functional diagnoses may serve as an umbrella term

when authors cannot retrospectively give a positive differential diagnosis. To improve validity, future research should aim to use neuropsychiatric expertise when categorising stroke mimic patients.[4]

**Thrombolysis treatment**

Perhaps surprisingly, FSM rates were higher in patients receiving thrombolysis which may again be explained by higher FSM rates in acute settings, and the number of studies using samples who all received thrombolysis. Furthermore, thrombolysis can be administered even when a patient's diagnosis is uncertain as it is relatively safe, especially compared to the risk of not treating true stroke.[40]

**Limitations**

The scope of this study was limited by the lack of descriptive data on available FSM presentations and in many reports, different symptoms were clustered together. A relatively high proportion of studies lacked detail on differential diagnoses. Only 12 studies gave FSMs' age and sex and there was no consistent reporting of symptomatology or clinical outcomes.

The FSM rate we report is likely an underestimate. Neurologists use terms like migraine and 'functional overlay' when writing referral letters to GPs to avoid labelling patients and potentially causing distress.[41] It is possible therefore that such terms were avoided or overlooked by authors of our included studies. Addressing this potential bias, we demonstrated that papers not listing functional disorders have inflated observations in miscellaneous categories compared to studies who report positive functional rates, strongly suggesting a proportion of functional cases are hidden within the 'other' category.

Studies had wide-ranging definitions of stroke mimic patients: some definitions included patients referred for medical follow-up, others necessitated the presence of an alternative non-stroke diagnosis while in others the lack of positive imaging findings was sufficient for a stroke mimic diagnosis. Many studies did not describe their definition of functional disorder or who made the diagnosis, and none used structured interviews. Without explanation, some papers used multiple terms to describe patients that were grouped as one disorder in other studies. This inconsistency likely contributes to the high heterogeneity observed. A further issue relates to the classification of functional stroke symptoms. Due to the pooled nature of our data, we can provide only broad symptom descriptions. Our symptom categorisations were guided by the Gargalas et al. paper (2016) as it provided by far the most detailed description of FSM symptomatology, data derived from a national stroke database. Future research would benefit from a detailed categorisation of FSM symptom presentation and chronicity.

Due to the heterogeneity in stroke mimic definitions we were unable to count all stroke mimic diagnoses, instead counting only the most frequent mimic diagnosis in each study. Stratified analyses explored heterogeneity, though such analyses are necessarily limited. Heterogeneity can arise from a range of unreported factors such as: clinician expertise, varying referral pathways and broader macro-level differences like health insurance systems. Such factors likely affect both stroke mimic and FSM rates.

**Conclusions**

This review is the first to explore functional disorder rates across stroke settings, demographic and symptom patient profiles and moderators of prevalence rates. As the burden of stroke increases and public awareness of stroke symptoms grow, we can expect more functional stroke mimic presentations.

Despite ongoing presence of functional stroke patients across medical settings, management of these patients is not explicitly addressed in stroke protocols. Expertise in the diagnosis and management of functional disorders at each stage of the stroke care pathway is important to help avoid unnecessary admission and the possibility of iatrogenic harm.

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*Table 1.* Table of review paper information from systematic review.

| | Mean (SD) |
|---|---|
| **Study quality** | 69.15% (15.75%) |
| | **Frequency (%)** |
| **Study Design** | |
| Prospective | 58 (50.90) |
| Retrospective | 56 (49.10) |
| **Study aims** | |
| Descriptive | 42 (36.84) |
| Screening tool validation | 33 (28.95) |
| Service audit/evaluation | 22 (19.30) |
| Diagnostic validity | 6 (5.26) |
| Biomarker validation | 5 (4.39) |
| Mixed aims | 3 (2.63) |
| Observational | 3 (2.63) |
| **Study setting** | |
| Emergency department | 40 (71.43) |
| Stroke unit | 24 (42.86) |
| Ambulance | 14 (25.00) |
| Acute unit | 12 (21.43) |
| Hospital | 11 (19.43) |
| Telestroke | 5 (8.92) |
| Mixed | 5 (8.92) |
| Primary care/ Outpatient | 3 (5.36) |

*Table 2.* Weighted demographics of true stroke, medical stroke mimic and functional stroke mimics and clinical symptoms of medical and functional mimics with means and proportion

| | True stroke | Medical mimics | Functional mimics | *t* (df) | 95% CIs | *p*-value |
|---|---|---|---|---|---|---|
| **Age** | | | | | | |
| Studies (n) | 67 | 12 | 12 | | | |
| Weighted age (mean) | 68.1 | 60.21 | 48.20 | -3.51 (22)[a] | -19.83, -5.13 | 0.002 |
| Studies (n) | 33 | | | | | |
| SD | 14.06 | 16.62 | 15.51 | | | |
| | | | | **$X^2$ (df)** | **95% CIs** | ***p*-value** |
| **Sex** | | | | | | |
| Studies (n) | 46 | 10 | 9 | | | |
| Pooled proportion females | 44.60 | 45.17 | 50.29 | 5.60 (1)[a] | 1.29, 13.80 | 0.018 |
| **Clinical symptoms** | | | | | | |
| Studies (n) | | 10 | 10 | | | |
| Symptoms reported (n) | | 866 | 429 | | | |
| Weakness or numbness (n, %) | | 460 (53.1) | 304 (70.9) | 37.34 | 12.2, 23.0 | 1 |
| Reduced consciousness (n, %) | | 68 (7.9) | 7 (1.6) | 20.77 | 3.9, 8.5 | 0.001 |
| Posterior circulation (n, %) | | 34 (3.9) | 15 (3.5) | 0.15 | -2.0, 2.5 | 0.703 |
| Visual symptoms (n, %) | | 57 (6.6) | 12 (2.8) | 8.14 | 1.3, 5.9 | 0.04 |
| Dysarthria, dysphasia, aphasia or anomia (n, %) | | 175 (53.1) | 71 (16.6) | 158.40 | 31.5, 41.2 | 0.01 |
| Seizures or convulsions (n, %) | | 2 (0.2) | 0 (0) | | - | - |
| Cognitive impairment, confusion or memory loss (n, %) | | 26 (3.0) | 12 (2.8) | .04 | -2.0, 2.0 | 0.08 |
| Vertigo (n, %) | | 44 (5.1) | 8 (1.9) | 7.72 | 1.0, 5.1 | 0.04 |

tests comparing two mimic groups.

**[a]Means and proportion tests based on raw, not weighted data.**

*Table 3.* Table showing pooled proportions of FSM by study type, design and economic setting with 95% confidence intervals and heterogeneity statistic.

| | Pooled proportion (%) | 95% CIs | $I^2$ |
|---|---|---|---|
| **Study type** | | | |
| Descriptive & validation | 6 | 4-8 | - |
| Descriptive | 19 | 15-23 | 93.63 |
| Diagnostic tool validation | 7 | 1-12 | - |
| Observational | 17 | 0-34 | - |
| Screening tool validation | 9 | 6-11 | 71.81 |
| Service evaluation/audit | 17 | 11-23 | 90.98 |
| | | | |
| **Design** | | | |
| Retrospective | 19 | 15-23 | 94.24 |
| Prospective | 11 | 9-14 | 82.41 |