European Journal of Neurology 2014, **21:** 1258–1267 doi:10.1111/ene.12469

REVIEW ARTICLE

Fatigue, psychological and cognitive impairment following transient ischaemic attack and minor stroke: a systematic review

G. M. Moran[a], B. Fletcher[a,b], M. G. Feltham[a], M. Calvert[a], C. Sackley[c] and T. Marshall[a]

[a]*Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham;* [b]*Primary Care Health Sciences, Radcliffe Observatory Quarter, University of Oxford, Oxford; and* [c]*Faculty of Medicine and Health, University of East Anglia, Norwich Research Park, Norwich, UK*

Keywords:
anxiety, cognitive impairment, depression, fatigue, minor stroke, post-traumatic stress disorder, quality of life, transient ischaemic attack

Received 13 January 2014
Accepted 7 April 2014

Transient ischaemic attack (TIA) and minor stroke are characterized by short-lasting symptoms; however, anecdotal and empirical evidence suggests that these patients experience ongoing cognitive/psychological impairment for which they are not routinely treated. The aims were (i) to investigate the prevalence and time course of fatigue, anxiety, depression, post-traumatic stress disorder(PTSD) and cognitive impairment following TIA/minor stroke; (ii) to explore the impact on quality of life (QoL), change in emotions and return to work; and (iii) to identify where further research is required and potentially inform an intervention study. A systematic review of MEDLINE, EMBASE, PSYCINFO, CINAHL, the Cochrane libraries and the grey literature between January 1993 and April 2013 was undertaken. Literature was screened and data were extracted by two independent reviewers. Studies were included of adult TIA/minor stroke participants with any of the outcomes of interest: fatigue, anxiety, depression, PTSD, cognitive impairment, QoL, change in emotions and return to work. Random-effects meta-analysis pooled outcomes by measurement tool. Searches identified 5976 records, 289 were assessed for eligibility and 31 studies were included. Results suggest high levels of cognitive impairment and depression post-TIA/minor stroke which decreased over time. However, frequencies varied between studies. Limited information was available on anxiety, PTSD and fatigue. Meta-analysis revealed that the measurement tool administered influenced the prevalence of cognitive impairment: Mini-Mental State Examination 17% [95% confidence interval (CI) 7, 26]; neuropsychological test battery 39% (95% CI 28, 50); Montreal Cognitive Assessment 54% (95% CI 43, 66). There is evidence to suggest that TIA/minor stroke patients may experience residual impairments; however, results should be interpreted with caution because of the few high quality studies. Notwithstanding, it is important to raise awareness of potential subtle but meaningful residual impairments.

Introduction

Transient ischaemic attack (TIA) and minor stroke are characterized by short-lasting symptoms [1,2]. These patients are discharged rapidly from hospital and treatment guidelines focus on secondary prevention of stroke [3]. However, there is evidence to suggest that TIA and minor stroke patients may experience residual impairments for which they are not routinely offered treatment. Coutts *et al.* [4] reported 15% of a sample of TIA and minor stroke participants ($n = 499$) were disabled at 90 days as defined by a modified Rankin Scale score ≥2. In addition, Fens *et al.* [5] found that approximately half of a sample of TIA and minor stroke participants ($n = 55$) self-reported cognitive and communication difficulties, which was significantly higher ($P \leq 0.001$) than angina controls ($n = 72$). Anecdotal evidence from patient interviews revealed that TIA and minor stroke patients experienced a variety of ongoing residual symptoms including memory and speech difficulties; feeling confused and more emotional; mild limb weakness and numbness [6]. Subtle but meaningful impairment post-TIA and minor stroke may go undetected. If untreated, these impairments may result in a reduced quality of life (QoL), affect people's ability to return to work and social activities and

Correspondence: G. M. Moran, Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK (tel.: +44 (121) 414 5463; fax: +44 (121) 414 3759; e-mail: gxt513@bham.ac.uk).

EUROPEAN JOURNAL OF NEUROLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

may affect behaviour related to future stroke prevention. Fatigue, psychological and cognitive impairments occur post-stroke and are potential sequelae of TIA and minor stroke; therefore, there is a need for a comprehensive systematic review of the literature to investigate these impairments post-TIA/minor stroke.

The aims of this systematic review were (i) to establish the prevalence of fatigue, anxiety, depression, post-traumatic stress disorder (PTSD) and cognitive impairment following TIA and minor stroke and to investigate the temporal course of these impairments; (ii) to explore the impact on QoL, change in emotions and return to work; (iii) to identify where further research is required and to potentially inform an intervention study, e.g. a cognitive rehabilitation intervention study, if impaired cognition was observed.

Methods

The full protocol for this systematic review was published as 'A systematic review investigating fatigue, psychological and cognitive impairment following TIA and minor stroke: protocol paper' [7]. The methods are summarized in brief below.

Eligibility criteria

Studies that reported the frequency of fatigue, anxiety, depression, PTSD or cognitive impairment, measured by validated tests, after TIA or minor stroke were identified. Studies reporting QoL, change in emotions and return to or performance at work were also included. Studies of mixed populations whereby it was possible to extract TIA or minor stroke data were included. Studies were excluded if they reported participants who had a history of stroke or a stroke during follow-up. All study designs were eligible with the exception of single case series and reviews. If possible, data were extracted from a control group if participants were free of stroke, TIA and minor stroke. There was no limit to the duration of follow-up. Full journal articles, conference abstracts and theses were included. Non-English papers were eligible and were screened for inclusion by research-active translators; however, none met the inclusion criteria.

Search strategy and data extraction

The following electronic databases were searched: MEDLINE, EMBASE, PSYCINFO, CINAHL, DARE, CENTRAL and CDSR. For pragmatic and quality of reporting reasons the search was limited to 20 years; therefore, databases were searched from January 1993 to April 2013. Grey literature was searched including Google Scholar, ProQuest Dissertation Theses Database, thesis.com and Conference Proceedings Citation Index. References from included studies were also checked. A comprehensive search strategy was developed through scoping searches and comprised the following elements: TIA, minor stroke, fatigue, anxiety, depression, PTSD and cognitive impairment (Appendix S1).

Two authors (GM and BF) independently screened titles and abstracts of search results; assessed the full text of relevant studies for eligibility; and completed data extraction and risk of bias assessments for included studies. Information was extracted on study characteristics, participants, controls and outcomes. The risk of bias assessment focused on sampling, measurement of outcomes, attrition and analysis. This assessment did not generate an overall risk of bias score but a judgement of 'yes', 'no' or 'unclear', as recommended by Cochrane (Fig. S1).

Analysis

To explore the time course of outcomes, studies were grouped into short term (<3 months after TIA/minor stroke), medium term (3–12 months) and long term (over 12 months). Due to the heterogeneity of the measurement tools, it was not appropriate to pool frequencies at these time points as pre-specified. It was deemed appropriate to pool outcomes by measurement tool; therefore, a random-effects meta-analysis pooled studies which used the same measurement tool. For studies measuring outcomes at more than one time point, the protocol planned exploratory analysis of new cases compared with persistent cases to investigate the natural history of the outcomes. However, this information was only reported by one study. Anecdotal evidence suggests that TIA and minor stroke patients experience residual memory and attention impairments; therefore, an analysis to investigate these specific domains was planned in the protocol. However, not enough studies were included that reported these data to conduct this sub-analysis. Chi-squared and Fisher's exact tests were used to detect a statistically significant difference in a sub-analysis of studies with a suitable control group and to compare TIA and minor stroke frequencies. All statistical analysis was performed using STATA v12 (College Station, TX, USA). A narrative synthesis of results was also conducted.

Results

Electronic database searches identified 5976 records; 4237 remained after duplicate removal; 3954 were excluded on the basis of their titles leaving 289 to be

assessed for eligibility and 31 met the inclusion criteria and were subsequently included (Fig. 1).

Study characteristics

The 31 studies included 4109 participants and comprised 26 full text publications, three conference abstracts and two unpublished theses. Study designs were either case series ($n = 25$) or cohort studies ($n = 6$). Studies were located in Europe, North America and Asia. The majority ($n = 22$) recruited from a secondary care setting and 11 out of 15 studies that reported recruitment methods used consecutive recruitment.

Risk of bias

Assessment of the risk of bias revealed that the sampling domain was the weakest; only 10% of studies reported how the sample size was determined and consequently it was unclear if sample sizes were adequate. Furthermore, the presence of any of the outcomes before TIA or minor stroke was measured in under half the studies. The measurement, attrition and analysis domains were generally reported well (Fig. S1).

Prevalence of cognitive impairment

Cognitive impairment was measured in 15 studies [8–22]; 13 reported overall cognitive impairment (Table 1) and five impairment of specific cognitive domains (Table S1). A wide variation in prevalence of cognitive impairment was observed between studies and there was marked variation in frequencies assessed by different measurement tools. The meta-analysis pooled studies by measurement tool: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and neuropsychological test battery when overall cognitive impairment was reported rather than individual tests. The pooled point estimate of the prevalence of cognitive impairment was lowest as estimated by the MMSE at 17% [95% confidence interval (CI) 7, 26] followed by the neuropsychological test battery at 39% (95% CI 28, 50) and MoCA at 54% (95% CI 43, 66) (Fig. 2a). The higher prevalence of cognitive impairment when assessed by MoCA compared with MMSE was confirmed in the two studies that directly compared these tools and observed a significant difference ($P \leq 0.001$) [9,17].

An overall decrease in frequency of cognitive impairment with time was observed across studies; however, at individual time points there was variation in frequencies between studies (Fig. 3). In contrast to the overall trend, the two studies that measured cognitive impairment at two time points found no significant difference in prevalence [18,20]. MoCA produced a greater difference in prevalence of cognitive impairment than MMSE when comparing TIA and minor stroke participants to controls, which was significant in two studies ($P \leq 0.01$) [12,22]. Significantly higher frequencies of cognitive impairment ($P \leq 0.05$) were observed in minor stroke participants compared with TIA participants [8,9,18].

Prevalence of depression

Depression was reported in 10 studies (Table 2) [8,10,23–30]. Prevalence of depression was high within 1 month of TIA or minor stroke and decreased between 6 weeks and 3 months. With the exception of

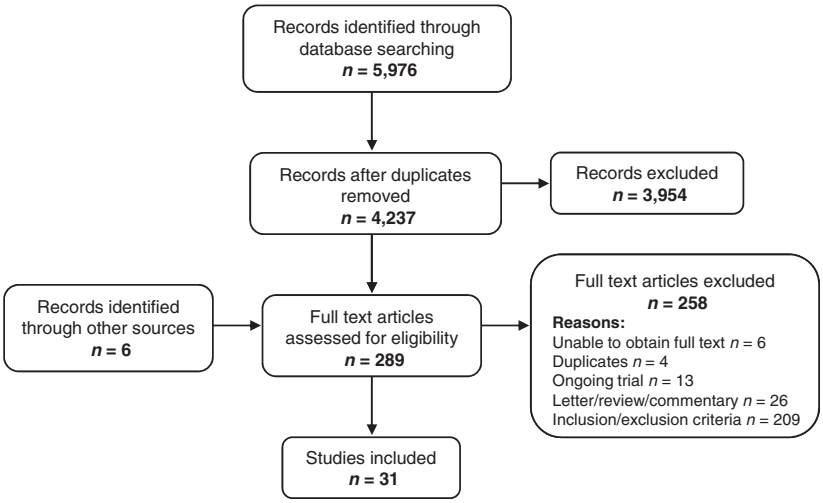

Figure 1 Summary of study selection.

Table 1 Studies measuring cognitive impairment: summary of measurement tool, participants' diagnosis, time point of assessment, sample size and frequencies

Study (year)	Measure (cut-off score)	Diagnosis	Time point (weeks)	Sample size	Frequency (%)
Bakker *et al.* (2004) [8]	Neuropsychological test battery (≥2 SD worse than norm score in ≥2 tasks)	TIA	<26	26	39
		Minor stroke		47	70
Blackburn *et al.* (2013) [9]	MMSE (<27)	TIA	<2	13	23
		Minor stroke		37	32
	MoCA (<26)	TIA		13	46
		Minor stroke		37	78
Carlsson *et al.* (2003) [10]	MMSE (NR)	Minor stroke	52	75	8
Dong *et al.* (2012) [11]	Neuropsychological test battery (impaired on ≥1 domain but no dementia)	TIA	13–26	46	22
Guyomard *et al.* (2011) [12]	MoCA (<26)	TIA	1–3	68	57
		Controls		68	0
Harnadek *et al.* (2010) [13]	MMSE (<24–29)	Both	1	140	5
Luck *et al.* (2010) [14]	DSM-III-R, DSM-IV, ICD-10	TIA	78/156	157	21
Narasimhalu *et al.* (2011) [15]	Neuropsychological test battery (impaired on ≥1 domain but no dementia)	Both	13–17	345	47
Pendlebury *et al.* (2012) [17]	MMSE (<27)	TIA	>26	142	13
		Controls		107	12
	MoCA (<26)	TIA		142	52
		Controls		107	40
Pendlebury *et al.* (2011) [18]	MMSE (baseline score ≥2 points lower than the 1 month follow-up score)	TIA	<1	84	32
			>1–4	38	16
			<4	122	27
		Minor stroke	<4	158	39
Radman *et al.* (2012) [20]	Neuropsychological test battery (below 2 SD on ≥1 domain)	Minor stroke	26	109	30
			52	99	34
Samuelsson *et al.* (1998) [21]	MMSE (≤23)	Minor stroke	1–4	19	5
		Controls		34	0
Wilson *et al.* (2010) [22]	MoCA (<26)	TIA	NR	29	34
		Controls		30	7

DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders III-R; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; ICD-10, International Classification of Diseases 10; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NR, not reported; TIA, transient ischaemic attack.

one study [10], the prevalence of depression remained relatively low between 3 and 12 months (Fig. 2b). No significant difference in the prevalence of depression was observed between TIA or minor stroke participants and controls in the two studies that measured this [8,24]. Likewise, one study reported prevalence of depression separately for TIA and minor stroke participants and found no significant difference between these participants [24].

Prevalence of fatigue

Three studies measured fatigue, all between 6 and 12 months following TIA or minor stroke; however, each study administered a different fatigue questionnaire (Table 3) [20,31,32]. Prevalence estimates were similar for all studies (Fig. 2c). One study found no significant difference in prevalence of fatigue ($P = 0.741$) measured at 6 and 12 months [20]. This was the only study to investigate the natural history of fatigue and found that two-thirds of the participants who reported fatigue at 6 months remained fatigued at 12 months. One study found that minor stroke participants reported a significantly higher prevalence of fatigue compared with TIA participants ($P = 0.008$) [32].

Prevalence of anxiety

Two studies measured anxiety. One observed anxiety frequencies of 52% and 65% for TIA and minor stroke participants respectively at 14 days; these frequencies were significantly different ($P \leq 0.005$) compared with controls (23%) [24]. The other study found a prevalence of anxiety in 24% of minor stroke participants at 12 months [25]. Both these studies administered the anxiety questions of the Hospital Anxiety and Depression Scale (HADS-A); however, two different cut-off scores of >4 [24] and >8 [25] were used to define anxiety.

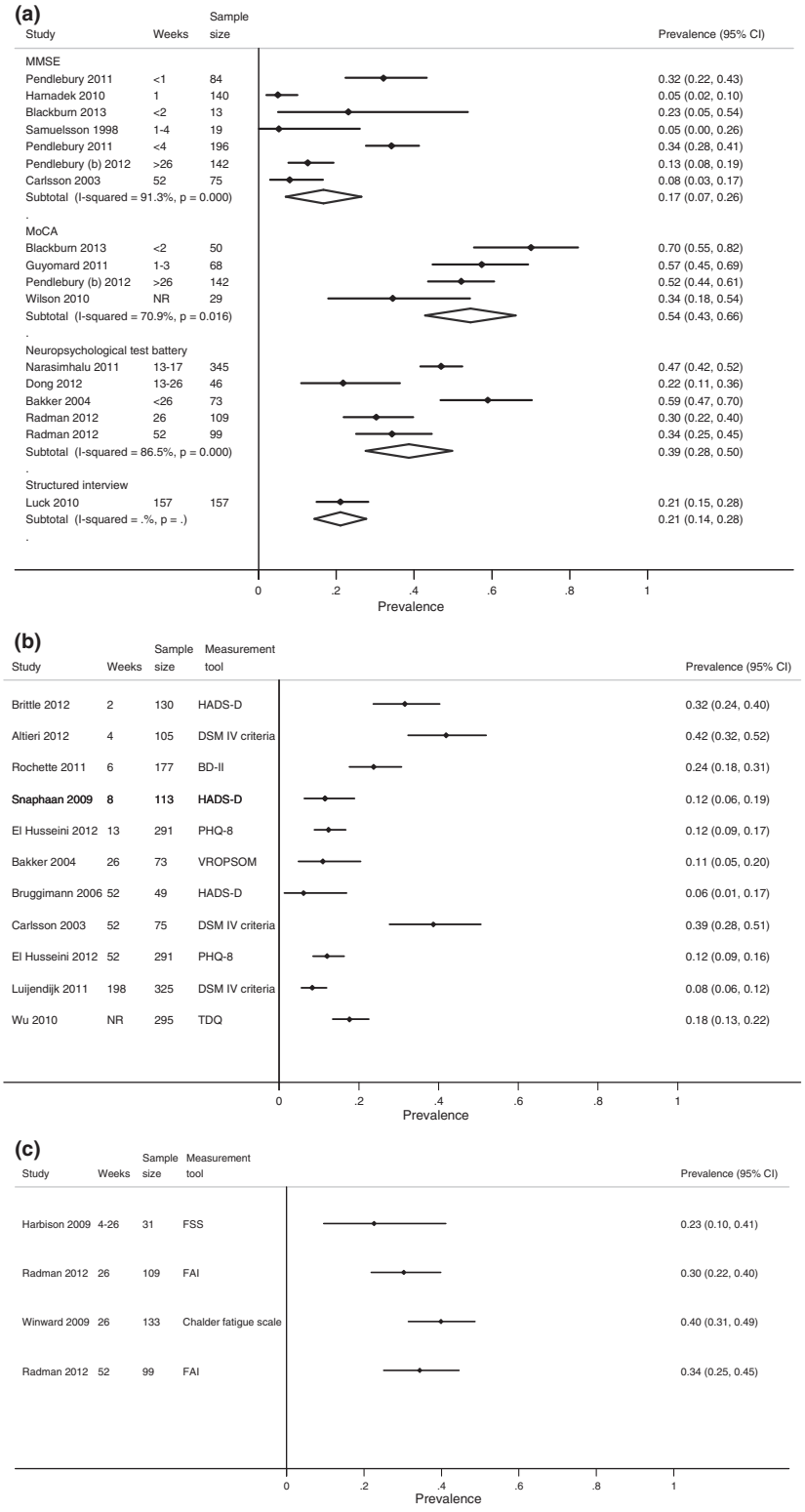

Figure 2 Prevalence of cognitive impairment, depression and fatigue after transient ischaemic attack (TIA) and minor stroke: (a) random-effects meta-analysis pooled estimates for the proportion of cognitive impairment as assessed by Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and neuropsychological test battery; (b) proportion of depression; (c) proportion of fatigue.

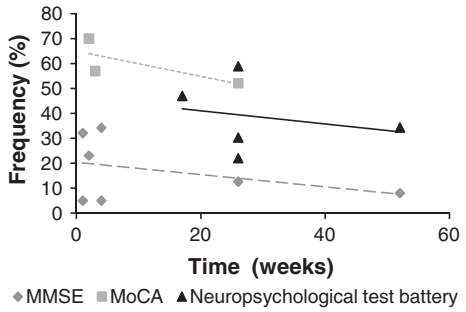

Figure 3 Time course of cognitive impairment after transient ischaemic attack (TIA) or minor stroke as measured by the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and neuropsychological test battery.

Prevalence of PTSD

Only one study reported PTSD, finding a prevalence of 31% at 12 months after minor stroke [25]. This study used the Impact of Events Scale with a cut-off score of 30 and had a small sample size (n = 49).

Secondary outcomes

Quality of life (QoL) was measured by six studies and there was considerable variation in the measurement tools administered and how the results were reported (Table S2) [33–38]. Muss *et al.* [38] reported that 43% of TIA and minor stroke participants had a worse QoL at 12 months compared with pre-stroke QoL. Return to work was reported in three studies between 6 and 12 months post-minor stroke. The definition of return to work varied between the studies but high frequencies of non-return, between 55% and 66%, were observed [10,20,33]. Two studies reported change in emotions following minor stroke; emotional lability was found in 38% of participants at 12 months [10] and irritable mood in 22% of participants at 6 months [33].

Discussion

This comprehensive systematic review explored the prevalence of fatigue, psychological and cognitive impairment after TIA and minor stroke. The findings provided evidence of residual impairments in this patient group which supports other studies that reported ongoing impairment post-TIA/minor stroke [4,5]. Both cognitive impairment and depression have relatively high prevalence following TIA and minor stroke which decreases over time. However, the findings are limited as few high quality studies are currently available, the reported prevalence was variable and the studies varied in methodology and case mix.

Frequency of cognitive impairment following TIA and minor stroke was influenced by the measurement tool used. This could be expected as a neuropsychological test battery is considered the gold standard but MMSE and MoCA were developed as cognitive screening tools for dementia [39] and mild cognitive impairment [40] respectively. Low levels of cognitive

Table 2 Studies measuring depression: summary of measurement tool, participants' diagnosis, time point of assessment, sample size and frequencies

Study (year)	Measure (cut-off score)	Diagnosis	Time point (weeks)	Sample size	Frequency (%)
Altieri *et al.* (2012) [23]	DSM-IV	Minor stroke	4	105	42
Bakker *et al.* (2004) [8]	VROPSOM (NR)	Both	<26	73	11
		Controls		73	7
Brittle (2012) [24]	HADS-D (>4)	TIA	<2	111	30
		Minor stroke		19	41
		Controls		30	20
Bruggimann *et al.* (2006) [25]	HADS-D (>8)	Minor stroke	52	49	6
	HDRS (>12)			49	10
Carlsson *et al.* (2003) [10]	DSM-IV	Minor stroke	52	75	39
El Husseini *et al.* (2012) [26]	PHQ-8 (≥10)	TIA	52	291	12
			13	291	12
Luijendijk *et al.* (2011) [27]	DSM-IV	TIA	198 (mean)	325	8
		TIA[a]		169	7
Rochette *et al.* (2011) [28]	BDI-II (NR)	Minor stroke	6	177	24
Snaphaan *et al.* (2009) [29]	HADS-D (>8)	TIA	6–8	113	12
Wu *et al.* (2010) [30]	TDQ (>9)	TIA	NR	295	18

BDI-II, Beck Depression Inventory II; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; HADS-D, Hospital Anxiety and Depression Scale – Depression; HDRS, Hamilton Rating Scale for Depression; NR, not reported; PHQ-8, Patient Health Questionnaire; TDQ, Taiwanese Depression Questionnaire; TIA, transient ischaemic attack; VROPSOM, Dutch version of the Depression Adjective Check Lists. [a]TIA participants with no history of depression.

Table 3 Studies measuring fatigue: summary of measurement tool, participants' diagnosis, time point of assessment, sample size and frequencies

Study (year)	Measure (cut-off score)	Diagnosis	Time point (weeks)	Sample size	Frequency (%)
Harbison *et al.* (2009) [31]	FSS (>4)	TIA	4–26	31	23
Radman *et al.* (2012) [20]	FAI (>4)	Minor stroke	52	99	34
			26	109	31
Winward *et al.* (2009) [32]	Chalder fatigue scale (>3)	TIA	26	74	30
		Minor stroke		59	53

FAI, Fatigue Assessment Instrument; FSS, Fatigue Severity Scale; TIA, transient ischaemic attack.

impairment were observed when assessed with MMSE and high levels with MoCA. This suggests that TIA and minor stroke patients may experience mild cognitive impairment, rather than dementia, which was not detected by MMSE. Indeed, MMSE has been shown to be insensitive to mild cognitive impairment in stroke patients [41], no better than chance in detecting cognitive impairment [42] and has an apparent ceiling effect [43]. Therefore, MMSE may not be a suitable screening tool for TIA and minor stroke patients. In addition, the cognitive profile of vascular cognitive impairment, which would be expected following stroke, shows prominent attentional and executive deficits [44]. MoCA detects more deficits in these domains compared with MMSE [45]. Therefore, frequency estimates of cognitive impairment as assessed by MMSE may be unreliable.

Across all studies, a relatively high level of cognitive impairment post-TIA and minor stroke was observed which decreased over time. However, cohort studies with two time points did not support this trend. A non-significant decrease in frequency of cognitive impairment was observed by Pendlebury *et al.*[18] and Radman *et al.*[20] between <1 and 1–4 weeks and 6 and 12 months respectively. Likewise, stroke studies have reported cognitive impairment to remain constant over 3 [46] and 14 years [47]. Our systematic review found frequencies of cognitive impairment were variable at the same time point even for studies using the same measurement tool. This is probably caused by the heterogeneity between studies. A systematic review of post-stroke dementia found 93% of the variance in dementia rates to be explained by study design and inclusion criteria [48].

It is important to determine if cognitive impairment observed in TIA and minor stroke patients is greater than age-related cognitive decline. The three MoCA studies with a control group showed a significant or near significant difference in cognitive impairment between TIA or minor stroke participants and controls [12,17,22]. However, when MMSE was used a non-significant difference was observed [17,21]. Given the previous discussion, it could be speculated that TIA and minor stroke patients experience mild cognitive impairment which is not detected by MMSE. However, these results should be interpreted with caution: only two control groups were age and sex matched and one used a memory clinic cohort as a control group which was obtained from a different study to the TIA participants. Also, none of the studies detailed if assessors were blinded to the participants' diagnosis which may introduce bias.

Depression appeared to be relatively high in the acute stage after TIA and minor stroke followed by an overall decrease in frequency over time across all studies. This trend is supported by Verbraak *et al.* [49] who reported that frequency of depression in TIA and minor stroke participants at 1 month had halved by 6 months; however, a fifth of this sample had a history of stroke. In contrast, the one study in our review to measure depression at two time points found no difference in prevalence [26]. A non-significant difference was also observed between prevalence of depression in TIA or minor stroke participants and controls in two studies [8,24]. Again, our findings should be interpreted with caution. The influence of confounding variables must be considered. For instance, only two studies excluded people with a history of depression. Furthermore, the average age across studies varied between 51 and 72 years, half of the studies had over 60% male participants and there were seven different measurement tools administered across the studies. Limited information was available for anxiety and PTSD and further research is required to provide reliable estimates of the prevalence of these outcomes after TIA and minor stroke.

Prevalence of fatigue post-TIA and minor stroke was measured by three studies between 6 and 12 months. Fatigue prevalence appears to be consistent within this time period following TIA and minor stroke. One study measured fatigue at an individual level and found two-thirds of participants with fatigue at 6 months remained fatigued at 12 months. Constant fatigue status over time (either fatigued or not fatigued) was observed in 72% [50] and 83% [51] of stroke participants in longitudinal stroke studies. This

supports the trend that fatigue is stable at an individual level. None of the fatigue studies included in our review had a comparator group. Fatigue has been found in the elderly in the absence of physical or psychological explanation and is more prominent in females [52]. Therefore, age and sex matched controls are required to differentiate TIA or minor stroke induced fatigue.

Despite being important patient-centred outcomes, there were few studies available that measured return to work and emotionalism post-minor stroke and none post-TIA. In addition, the information on QoL for this patient group could not be meaningfully interpreted without a comparator group.

The main strength of this review is that it was designed and conducted according to Cochrane [53] and the Centre for Reviews and Dissemination (CDR) guidelines [54]. Furthermore, it is free of language bias and, to reduce publication bias, conference abstracts and theses of unpublished studies were included and grey literature was searched. Two reviewers worked independently to reduce human error and increase reliability. A limitation of the review is that authors of included studies were not contacted to obtain missing information. At an individual study level there were many limitations which impacted on the reliability and generalizability of the results. Studies were heterogeneous in methodology and case mix and there were a small number of studies for some of the outcomes. An important consideration is the lack of comparator group for most studies. Consequently, it was not possible to determine if prevalence of the outcomes in TIA or minor stroke patients is higher than prevalence for age and sex stratified subjects in the general population. In addition, the prevalence of the outcomes pre-TIA or minor stroke was unknown for most of the included studies.

Conclusion

The findings of this systematic review are relevant to primary healthcare professionals as TIA and minor stroke patients are discharged rapidly from hospital. Although the results are inconclusive, it is important to raise awareness of the potential subtle but meaningful residual impairments following TIA and minor stroke. These can be missed in patients who appear to have functionally recovered but may struggle with more complex activities affecting daily activities and social, work and family responsibilities.

Our results are most relevant to inform future research. Future research should comprise a cohort study with age and sex matched controls. Studies must adjust for confounding variables and measure or estimate the presence of the outcome(s) pre-TIA or minor stroke to produce reliable results. In addition, choice of measurement tool should be carefully considered in the context of the population. It is reasonable to advise that a neuropsychological test battery should be used to measure cognitive impairment in TIA and minor stroke patients and, when this is not feasible, MoCA is preferred over MMSE. Future studies should investigate the natural history of outcomes as well as the time course.

Overall, the results of this systematic review are limited as the evidence in the literature is weak. There is some evidence to suggest that TIA and minor stroke patients may experience residual impairments which appear to reduce in prevalence over time, but these findings should be interpreted with caution. Notwithstanding, this review is valuable to provide a platform to generate hypotheses and inform future trial design in the context of the limitations in the available literature.

Acknowledgements

This work forms part of Ms Moran's PhD which is funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR). Dr Feltham is funded by the NIHR's Primary Care Research Network. Prof. Calvert is an investigator in the MRC Midland Hub for Trials Methodology Research, University of Birmingham, UK (MRC Grant ID G0800808). Prof. Sackley is in receipt of an NIHR Senior Investigator award. Dr Marshall is partly funded by the NIHR through the Collaborations for Leadership in Applied Health Research and Care for Birmingham and the Black Country (CLAHRC-BBC) programme. The views expressed in this publication are not necessarily those of the NIHR, the Department of Health, NHS Partner Trusts, MRC, the University of Birmingham or the CLAHRC-BBC Management Group. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure of conflicts of interest

Dr Calvert reports grants from the National Institute for Health Research School for Primary Care Research and grants from the Medical Research Council during the conduct of the study. Dr Feltham reports personal fees from NIHR's Primary Care Research Network during the conduct of the study. Dr Marshall, Dr Sackley, Mr Fletcher and Ms Moran have nothing to disclose.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Risk of bias graph for sampling, measurement, attrition and analysis.
Table S1. Studies measuring individual cognitive domains: summary of measurement tool, participants' diagnosis, time point of assessment, sample size and frequencies.
Table S2. Studies measuring QoL: summary of measurement tool, participants' diagnosis, time point of assessment, sample size and results reported.
Appendix S1. Search strategy for MEDLINE (via Ovid) 1993 to April 2013.

References

1. Albers G, Caplan L, Easton J, *et al*. Transient ischemic attack – proposal for a new definition. *N Engl J Med* 2002; **347:** 1713–1716.
2. Fischer U, Baumgartner A, Arnold M, *et al*. What is a minor stroke? *Stroke* 2010; **41:** 661–666.
3. National Institute for Health and Clinical Excellence. Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) 2008. Available at: http://www.nice.org.uk/nicemedia/pdf/cg68niceguideline.pdf (accessed 16/05/2014).
4. Coutts SB, Modi J, Patel SK, *et al*. What causes disability after transient ischemic attack and minor stroke? Results from the CT and MRI in the triage of TIA and minor cerebrovascular events to identify high risk patients (CATCH) study. *Stroke* 2012; **43:** 3018–3022.
5. Fens M, Van Heugten CM, Beusmans GH, *et al*. Not as transient: patients with transient ischaemic attack or minor stroke experience cognitive and communication problems; an exploratory study. *Eur J Gen Pract* 2013; **19:** 11–16.
6. Healthtalkonline. Residual symptoms after transient ischaemic attack (TIA) 2011. Available at: http://www.healthtalkonline.org/nerves_and_brain/transient_ischaemic_attack/Topic/4076/ (accessed 06/01/2013).
7. Moran GM, Fletcher B, Calvert M, Feltham MG, Sackley C, Marshall T. A systematic review investigating fatigue, psychological and cognitive impairment following TIA and minor stroke: protocol paper. *Syst Rev* 2013; **2:** 72.
8. Bakker FC, Klijn CJM, van der Grond J, Kappelle LJ, Jennekens-Schinkel A. Cognition and quality of life in patients with carotid artery occlusion: a follow-up study. *Neurology* 2004; **62:** 2230–2235.
9. Blackburn DJ, Bafadhel L, Randall M, Harkness KA. Cognitive screening in the acute stroke setting. *Age Ageing* 2013; **42:** 113–116.
10. Carlsson GE, Moller A, Blomstrand C. Consequences of mild stroke in persons <75 years – a 1-year follow-up. *Cerebrovasc Dis* 2003; **16:** 383–388.
11. Dong Y, Venketasubramanian N, Chan BP, *et al*. Brief screening tests during acute admission in patients with mild stroke are predictive of vascular cognitive impairment 3–6 months after stroke. *J Neurol Neurosurg Psychiatry* 2012; **83:** 580–585.
12. Guyomard V, Metcalf AK, Naguib MF, Fulcher RA, Potter JF, Myint PK. Transient ischaemic attack, vascular risk factors and cognitive impairment: a case-controlled study. *Age Ageing* 2011; **40:** 641–644.
13. Harnadek M, Chan R, Mayer C, Hachinski V. Mini-Mental State Exam lacks sensitivity to cognitive impairment associated with TIA and minor ischemic stroke. *Stroke* 2010; **41:** E495.
14. Luck T, Riedel-Heller SG, Luppa M, *et al*. Risk factors for incident mild cognitive impairment – results from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe). *Acta Psychiatr Scand* 2010; **121:** 260–272.
15. Narasimhalu K, Ang S, De Silva DA, *et al*. The prognostic effects of poststroke cognitive impairment on dementia and domain-specific cognitive impairments in nondisabled ischemic stroke patients. *Stroke* 2011; **42:** 883–888.
16. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and stroke. *Stroke* 2012; **43:** 464–469.
17. Pendlebury ST, Markwick A, de Jager CA, Zamboni G, Wilcock GK, Rothwell PM. Differences in cognitive profile between TIA, stroke and elderly memory research subjects: a comparison of the MMSE and MoCA. *Cerebrovasc Dis* 2012; **34:** 48–54.
18. Pendlebury ST, Wadling S, Silver LE, Mehta Z, Rothwell PM. Transient cognitive impairment in TIA and minor stroke. *Stroke* 2011; **42:** 3116–3121.
19. Philipose LE, Alphs H, Prabhakaran V, Hillis AE. Testing conclusions from functional imaging of working memory with data from acute stroke. *Behav Neurol* 2007; **18:** 37–43.
20. Radman N, Staub F, Aboulafia-Brakha T, Berney A, Bogousslavsky J, Annoni JM. Poststroke fatigue following minor infarcts: a prospective study. *Neurology* 2012; **79:** 1422–1427.
21. Samuelsson H, Hjelmquist EKE, Jensen C, Ekholm S, Blomstrand C. Nonlateralized attentional deficits: an important component behind persisting visuospatial neglect? *J Clin Exp Neuropsychol* 1998; **20:** 73–88.
22. Wilson DM, Madden M, Power M, Fullerton K, Wiggam MI, Passmore AP. Cognitive impairment after first ever TIA. *Int J Stroke* 2010; **5:** 49.
23. Altieri M, Maestrini I, Mercurio A, *et al*. Depression after minor stroke: prevalence and predictors. *Eur J Neurol* 2012; **19:** 517–521.
24. Brittle NG. Functional, cognitive and emotional outcomes after transient ischaemic attack: a systematic review and controlled cohort study. M. Phil thesis, University of Birmingham, 2012.
25. Bruggimann L, Annoni JM, Staub F, von Steinbuchel N, Van der Linden M, Bogousslavsky J. Chronic posttraumatic stress symptoms after nonsevere stroke. *Neurology* 2006; **66:** 513–516.
26. El Husseini N, Goldstein LB, Peterson ED, *et al*. Depression and antidepressant use after stroke and transient ischemic attack. *Stroke* 2012; **43:** 1609–1616.

27. Luijendijk HJ, Stricker BH, Wieberdink RG, *et al*. Transient ischemic attack and incident depression. *Stroke* 2011; **42:** 1857–1861.
28. Rochette A, Korner-Bitensky N, Bishop D, *et al*. Individuals experiencing a 'mild' stroke: who are they and what are their major concerns in the first six weeks post-stroke? *Stroke* 2011; **42:** E618.
29. Snaphaan L, van der Werf S, Kanselaar K, de Leeuw FE. Post-stroke depressive symptoms are associated with post-stroke characteristics. *Cerebrovasc Dis* 2009; **28:** 551–557.
30. Wu KY, Liu CY, Chau YL, Chang CM. Transient ischemic attack and incidence of depression in old age: evidence from a population-based analysis in Taiwan. *Am J Geriatr Psychiatry* 2010; **18:** 382–387.
31. Harbison JA, Walsh S, Kenny RA. Hypertension and daytime hypotension found on ambulatory blood pressure is associated with fatigue following stroke and TIA. *QJM* 2009; **102:** 109–115.
32. Winward C, Sackley C, Metha Z, Rothwell PM. A population-based study of the prevalence of fatigue after transient ischemic attack and minor stroke. *Stroke* 2009; **40:** 757–761.
33. Edwards DF, Hahn M, Baum C, Dromerick AW. The impact of mild stroke on meaningful activity and life satisfaction. *J Stroke Cerebrovasc Dis* 2006; **15:** 151–157.
34. Franzen-Dahlin A, Laska AC. Gender differences in quality of life after stroke and TIA: a cross-sectional survey of out-patients. *J Clin Nurs* 2012; **21:** 2386–2391.
35. Haacke C, Althaus A, Spottke A, Siebert U, Back T, Dodel R. Long-term outcome after stroke: evaluating health-related quality of life using utility measurements. *Stroke* 2006; **37:** 193–198.
36. Martinez C. Quality of life after stroke: A comparison of occupational therapy interventions for stroke patients. PhD thesis, Touro University International, USA, 2006.
37. Muren MA, Hutler M, Hooper J. Functional capacity and health-related quality of life in individuals post stroke. *Top Stroke Rehabil* 2008; **15:** 51–58.
38. Muus I, Petzold M, Ringsberg KC. Health-related quality of life among Danish patients 3 and 12 months after TIA or mild stroke. *Scand J Caring Sci* 2010; **24:** 211–218.
39. Tatemichi TK, Desmond DW, Paik M, *et al*. The Mini-Mental State Examination as a screen for dementia following stroke. *J Clin Exp Neuropsychol* 1991; **13:** 419.
40. Nasreddine ZS, Phillips NA, Bedirian V, *et al*. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53:** 695–699.
41. Mitchell AJ. A meta-analysis of the accuracy of the Mini-Mental State Examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res* 2009; **43:** 411–431.
42. Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, Kappelle LJ, de Haan EH. Restrictions of the Mini-Mental State Examination in acute stroke. *Arch Clin Neuropsychol* 2005; **20:** 623–629.
43. Pendlebury ST, Cuthbertson FC, Welch SJ, Mehta Z, Rothwell PM. Underestimation of cognitive impairment by Mini-Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study. *Stroke* 2010; **41:** 1290–1293.
44. Sachdev PS, Brodaty H, Valenzuela MJ, *et al*. The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. *Neurology* 2004; **62:** 912–919.
45. Dong Y, Sharma VK, Chan BP, *et al*. The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. *J Neurol Sci* 2010; **299:** 15–18.
46. Liman TG, Heuschmann PU, Endres M, Flöel A, Schwab S, Kolominsky-Rabas PL. Changes in cognitive function over 3 years after first-ever stroke and predictors of cognitive impairment and long-term cognitive stability: the Erlangen Stroke Project. *Dement Geriatr Cogn Disord* 2011; **31:** 291–299.
47. Douiri A, Rudd AG, Wolfe CD. Prevalence of post-stroke cognitive impairment: South London Stroke Register 1995–2010. *Stroke* 2013; **44:** 138–145.
48. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol* 2009; **8:** 1006–1018.
49. Verbraak ME, Hoeksma AF, Lindeboom R, Kwa VI. Subtle problems in activities of daily living after a transient ischemic attack or an apparently fully recovered non-disabling stroke. *J Stroke Cerebrovasc Dis* 2012; **21:** 124–130.
50. Christensen D, Johnsen SP, Watt T, Harder I, Kirkevold M, Andersen G. Dimensions of post-stroke fatigue: a two-year follow-up study. *Cerebrovasc Dis* 2008; **26:** 134–141.
51. Snaphaan L, van der Werf S, de Leeuw FE. Time course and risk factors of post-stroke fatigue: a prospective cohort study. *Eur J Neurol* 2011; **18:** 611–617.
52. Wijeratne C, Hickie I, Brodaty H. The characteristics of fatigue in an older primary care sample. *J Psychosom Res* 2007; **62:** 153–158.
53. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 The Cochrane Collaboration*. 2011. www.cochrane-handbook.org (accessed 16/05/2014).
54. Centre for Reviews and Dissemination. *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care*. York: CRD, University of York, 2009: 3–109.