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ORIGINAL ARTICLE

Ongoing impairments following transient ischaemic attack: retrospective cohort study

G. M. Turner, M. Calvert, M. G. Feltham, R. Ryan and T. Marshall

Institute of Applied Health Research, University of Birmingham, Birmingham, UK

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Background and purpose: Clinical management after transient ischaemic attack (TIA) is focused on stroke prevention; however, a number of small studies suggest that patients may experience ongoing residual impairments.
Methods: This was a retrospective matched-cohort study using anonymized electronic primary care records from The Health Improvement Network database, which covers approximately 6% of the UK population. Adults (≥ 18 years old) who experienced a first TIA between 2009 and 2013 were matched in a ratio of 1:5 to controls by age, sex and general practice. The time to first consultation for fatigue, psychological impairment or cognitive impairment was estimated by Kaplan–Meier survivor functions and adjusted hazard ratios.
Results: A total of 9419 TIA patients and 46 511 controls were included. The Kaplan–Meier curves showed that TIA patients were more likely than controls to consult for all three impairments ($P < 0.0001$). Within 7.1 months (95% confidence interval (CI), 6.2–8.2), 25% of TIA patients consulted for psychological impairment compared with 23.5 months (95% CI, 22.5–24.6) for controls. Hazard ratios for TIA patients were 1.43 (95% CI, 1.33–1.54) for consulting for fatigue, 1.26 (95% CI, 1.20–1.31) for psychological impairment and 1.45 (95% CI, 1.28–1.65) for cognitive impairment.
Conclusions: Transient ischaemic attack is associated with significantly increased subsequent consultation for fatigue, psychological impairment and cognitive impairment. These findings suggest that impairments exist after initial symptoms of TIA have resolved, which should be considered by clinicians when treating TIA patients.

Introduction

Transient ischaemic attack (TIA) is clinically important because patients have increased risk of having a full stroke [1]. TIAs are common and incidence has increased over the past two decades [2]; approximately 46 000 people experience a first TIA each year and there are 510 000 people living with a history of TIA in the UK [3]. Historically, TIA was differentiated from stroke using a time-based definition (symptoms lasting less than 24 h). However, following advances in imaging, this was reclassified to a tissue-based definition (a brief episode of neurologic dysfunction without evidence of acute infarction) [4]. Despite this, brain imaging is not routinely used to diagnose TIA and diagnosis is based on clinical history [5].

Guidelines relevant to TIA promote rapid evaluation of patients with suspected TIA and focus on diagnosis, determining the affected vascular territory and assessing stroke risk [5,6]. Follow-up for TIA patients is focused on management of stroke risk factors through medical, surgical and lifestyle interventions [5]. Clinical guidelines recognize that stroke patients may experience ongoing impairments that require rehabilitation; however, these guidelines do not extend to TIA [5,7].

Correspondence: G. M. Turner, Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK (tel.: +44 121 414 5463; fax: +44 121 414 3759; e-mail: g.turner.1@bham.ac.uk).

The long-term impact of TIA is unclear and the UK's leading stroke charity, Stroke Association, recommended the investigation of this as a research priority in their TIA campaign report (2014) [8]. Our systematic review, which investigated the prevalence of fatigue, psychological and cognitive impairment after TIA and minor stroke [9], suggests a relatively high prevalence of cognitive impairment and depression post-TIA/minor stroke. However, very few studies had a control group and we were unable to determine whether the prevalence of these impairments was higher than in people of a similar age without TIA/minor stroke. If patients experience ongoing residual impairments after TIA, these impairments could impact on their health, wellbeing and ability to return to work and social activities. Our study aimed to investigate the association between TIA and consultation for fatigue, psychological impairment or cognitive impairment in primary care.

Methods

The full protocol for this study has been published elsewhere [10]; the methods are summarized in brief below.

Study design and data source

This was a retrospective matched-cohort study of first-ever TIA patients using anonymized, routinely collected, primary care data from The Health Improvement Network (THIN) database [11]. This database is broadly representative of the UK population, with approximately 6% coverage [11] and diagnosis of TIA has been validated in THIN [12]. Data are extracted from contributing general practices using Vision patient records software [11]. Analysis of THIN data is ethically approved by the National Health Service South-East Multi-centre Research Ethics Committee subject to independent scientific review [13]. This study received approval by a Scientific Review Committee in February 2014 (reference no. 14-008).

Population

The population consisted of patients aged 18 years and over with a first-ever diagnosis of TIA between January 2009 and December 2013. TIA patients would have been diagnosed according to the UK National Institute for Health and Care Excellence guidelines, which define TIA as 'stroke symptoms and signs that resolve within 24 h' [5]. In accordance with these guidelines, brain imaging is not routine; however, it is recommended when the vascular territory or pathology is uncertain [5]. TIA patients were matched with up to five TIA-free controls [14] on: year of birth ($\pm$ 2 years), sex, general practice and date of TIA (index date). TIA patients and controls were free from stroke at baseline. The index date must have occurred at least 1 year after the general practice began using Vision patient records software and after the date of acceptable mortality recording (markers of data quality) [15]. TIA patients and matched controls had to be registered at their general practice for at least 1 year prior to the index date to allow baseline data to be recorded by their practice and had to have remained alive and registered for at least 1 month after the index date to allow time for the outcomes of interest to be recorded.

Variables

There were three separate substudies for the first consultation after the index date with a record of (i) fatigue, (ii) psychological impairment [comprised of anxiety, depression and post-traumatic stress disorder (PTSD)] or (iii) cognitive impairment. These outcomes were defined by appropriate clinical codes for diagnoses and symptoms. In addition, a first prescription of an antidepressant or antianxiety drug was used to define psychological impairment. Cognitive impairment included memory, attention, spatial awareness, perception, apraxia and executive functioning impairments but not a diagnosis of dementia [16]. Cognitive impairment was defined by Read codes for diagnoses (such as 28E0.00: mild cognitive impairment) and symptoms (such as 1B1A.12: memory loss symptom) related to overall cognitive impairment and impaired individual cognitive domains [9]. Overall cognitive impairment and impaired individual cognitive domains were evaluated as one outcome. For each substudy, follow-up continued until the first consultation for the relevant outcome (e.g. consultation for fatigue in the fatigue substudy). Censoring occurred at the first occurrence of: death, stroke, the patient leaving the practice or the last data collection from the general practice. Diagnosis of TIA in the follow-up was permitted for TIA patients but controls were censored at the date that a TIA diagnosis was recorded and subsequently became eligible for inclusion in the TIA group.

Potential confounding variables were identified using the most recent baseline demographic and clinical characteristics prior to the index date. These included age, sex, body mass index, Townsend deprivation, urban/rural residence, smoking status, alcohol consumption and comorbidities. Comorbidities

comprised the chronic conditions included in the UK chronic disease quality monitoring programme, the Quality and Outcomes Framework (business rules version 27; see Table 1) [17]. Numbers of consultations in the follow-up were included because patients who consult more have more opportunities to report residual impairments. To control for presence of the outcomes at baseline, the most recent consultations prior to the index date for fatigue, psychological impairment or cognitive impairment were extracted.

Quality checks, missing data and extreme values

The absence of a clinical code or relevant drug code for an individual diagnosis prior to the index date was taken to indicate that the diagnosis was not present. For clinical measurements (height, weight and body mass index), implausible values were excluded based on pre-defined cut-off scores (Supporting Information Table S1). As data are unlikely to be missing at random [18], no attempt was made to impute numeric missing data. Instead, variables were categorized and a separate 'missing' category was created. Data were initially extracted between 2000 and 2013; however, there was evidence of under-reporting of TIA before 2008, with the number of incident TIA events before 2008 less than 15% of recorded TIA after 2009 (Supporting Information Fig. S1). After 2009, this was more stable and therefore only patients with a TIA recorded from 1 January 2009 were included.

Analysis

All analysis was conducted using STATA version 12 (StataCorp, College Station, TX, USA). The study was an open cohort and therefore Kaplan–Meier (K-M) survivor functions were used to estimate time to consultation for each outcome and log rank tests compared survivor functions of TIA patients and controls. Cox proportional hazard models adjusted for potential confounding of demographic and clinical characteristics. Inclusion of covariates in the model was selected using backwards elimination with a *P*-to-eliminate value of > 0.05. All variables were categorical with the exception of multimorbidity (number of comorbidities), which was continuous. Age and sex were forced into the model, because these were identified as important confounding variables and general practice was included as a random effect [19–21]. Fatigue, psychological impairments and cognitive impairments were analysed separately in three substudies. Exploratory analysis investigated the impact of excluding patients with presence of the outcome prior to the index date for each substudy.

Results

The total cohort comprised 55 930 individuals (9419 TIA patients and 46 511 controls). The median age was 74 years (interquartile range 63, 82) and 48% were males. Demographic and clinical characteristics of TIA patients and controls are presented in Table 1.

Fatigue

A total of 55 754 individuals were included in the survival analysis for the fatigue substudy (9250 TIA patients matched to 46 504 controls) (169 TIA patients and 7 controls were excluded because fatigue was recorded on the index date). The median follow-up was 17.2 (range 0–60.5) months for TIA patients and 19.1 (range 0–60.5) months for controls. Fatigue was recorded in 3632 individuals (907 TIA patients and 2725 controls). The K-M curves show that TIA patients were more likely to consult for fatigue compared with controls ($P < 0.0001$; Fig. 1a). The 10th percentile for time to fatigue was 20.7 months [95% confidence interval (CI), 18.6–23.5] for TIA patients and 42.4 months (95% CI, 40.6–44.8) for controls (Fig. 1a). TIA patients had a 43% increased risk of consulting for fatigue compared with controls following adjustment for demographic and clinical characteristics [hazard ratio (HR) 1.43; 95% CI, 1.33–1.54; $P < 0.0001$, Table S2].

Psychological impairment

A total of 55 483 individuals were included in the survival analysis for the psychological impairment substudy (9240 TIA patients matched to 46 243 controls) (179 TIA patients and 268 controls were excluded because psychological impairment was recorded on the index date). The median follow-up was 11.2 (range 0–60.5) months for TIA patients and 14.4 (range 0–60.5) months for controls. Psychological impairment was recorded in 14 285 individuals (3159 TIA patients and 11 126 controls). Of these, 11 040 consulted for depression, 2691 for anxiety, 546 for anxiety and depression, and 8 for PTSD. The K-M curves show that TIA patients were more likely to consult for/be prescribed drugs for psychological impairment compared with controls ($P < 0.0001$; Fig. 1b). The 25th percentile for time to psychological impairment was 7.1 months (95% CI, 6.2–8.2) for TIA patients and 23.5 months (95% CI, 22.5–24.6) for controls (Fig. 1b). Following adjustment for demographic and clinical characteristics, TIA patients had a 26% increased risk of consulting for psychological impairment compared with controls (HR 1.26; 95% CI, 1.20–1.31; $P < 0.0001$, Table S3).

Table 1 Demographic and clinical characteristics of transient ischaemic attack (TIA) patients and controls

	Control		TIA	
	Frequency	%	Frequency	%
Total	46 511	100	9419	100
Age (years)				
< 45	1416	3.0	279	3.0
45–49	1576	3.4	293	3.1
50–54	2378	5.1	495	5.3
55–59	3092	6.6	600	6.4
60–64	4338	9.3	879	9.3
65–69	5559	12.0	1120	11.9
70–74	6303	13.6	1247	13.2
75–79	7223	15.5	1502	15.9
80–84	6886	14.8	1378	14.6
85–89	5013	10.8	1009	10.7
≥ 90	2727	5.9	617	6.6
Sex				
Male	22 245	47.8	4504	47.8
Smoking status				
Non-smoker	23 435	50.4	4505	47.8
Ex-smoker	13 970	30.0	2964	31.5
Current	5748	12.4	1555	16.5
Missing	3358	7.2	395	4.2
Alcohol intake[a]				
Never	5954	12.8	1212	12.9
Light	7930	17.0	1671	17.7
Moderate	5617	12.1	1165	12.4
High	12 624	27.1	2630	27.9
Missing	14 386	30.9	2741	29.1
BMI[b]				
Healthy	14 872	32.0	2971	31.5
Underweight	944	2.0	199	2.1
Overweight	16 552	35.6	3469	36.8
Obese	10 220	22.0	2179	23.1
Missing	3923	8.4	601	6.4
Deprivation				
1 (least deprived)	12 353	26.6	2383	25.3
2	11 171	24.0	2241	23.8
3	9399	20.2	1908	20.3
4	7635	16.4	1623	17.2
5 (most deprived)	4771	10.3	1073	11.4
Missing	1182	2.5	191	2.0
Rurality				
Urban	17 642	37.9	3522	37.4
Rural	28 867	62.1	5893	62.6
Missing	2	0.0	4	0.0
Comorbidities				
Atrial fibrillation	3273	7.0	1055	11.2
Asthma	4909	10.6	1176	12.5
Cancer	4387	9.4	1074	11.4
CHD	6631	14.3	1680	17.8
CKD	7553	16.2	1779	18.9
COPD	2700	5.8	689	7.3
Dementia	1579	3.4	375	4.0
Depression	8109	17.4	2103	22.3
Diabetes	5734	12.3	1376	14.6
Epilepsy	618	1.3	199	2.1
Heart failure	1695	3.6	421	4.5
Hypertension	20 112	43.2	4617	49.0
Hypothyroidism	4098	8.8	982	10.4
Learning disability	107	0.2	44	0.5
Osteoporosis	3128	6.7	770	8.2
PAD	1376	3.0	414	4.4
Palliative care	319	0.7	89	0.9
Psychosis	499	1.1	112	1.2
Rheumatoid arthritis	794	1.7	206	2.2
Impairment prior to index date				
Fatigue	10 074	21.7	2910	30.9
Psychological impairment	22 127	47.6	5396	57.3
Cognitive impairment	1983	4.3	664	7.0
Median consultations in year post-index date [IQR]	5 [210]		10 [6, 17]	

CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PAD, peripheral artery disease.

[a]Alcohol intake: never (0 units/day); light (1–2 units/day); moderate (3–6 units/day); high (≥ 7 unit/day); [b]Body mass index (BMI): healthy (18.5–25.9 kg/m^2); underweight (< 18.5 kg/m^2); overweight (26–30 kg/m^2); obese (> 30 kg/m^2).

Cognitive impairment

A total of 55 905 individuals were included in the survival analysis for the cognitive impairment substudy (9397 TIA patients matched to 46 508 controls) (22 TIA patients and 3 controls were excluded because cognitive impairment was recorded on the index date). The median follow-up time was 18.8 (range 0–60.5) months for TIA patients and 20.0 (range 0–60.5) months for controls. Cognitive impairment was recorded in 1425 individuals (363 TIA patients and 1062 controls). The K-M curves show that TIA patients were more likely to consult for cognitive impairment compared with controls ($P < 0.0001$; Fig. 1c). The 5th percentile for time to cognitive impairment was 31.1 months (95% CI, 25.9–35.6) for TIA patients and 52.7 months (95% CI, 48.6–56.4) for controls (Fig. 1c). Following adjustment for demographic and clinical characteristics, TIA patients had a 45% increased risk of consulting for cognitive impairment compared with controls (HR 1.45; 95% CI, 1.28–1.65; $P < 0.0001$, Table S4).

Exploratory analysis

Distinguishing between recurrent impairments after the index date and ongoing impairments is difficult. Therefore, we explored the effect of excluding individuals with a record of the outcome prior to the index

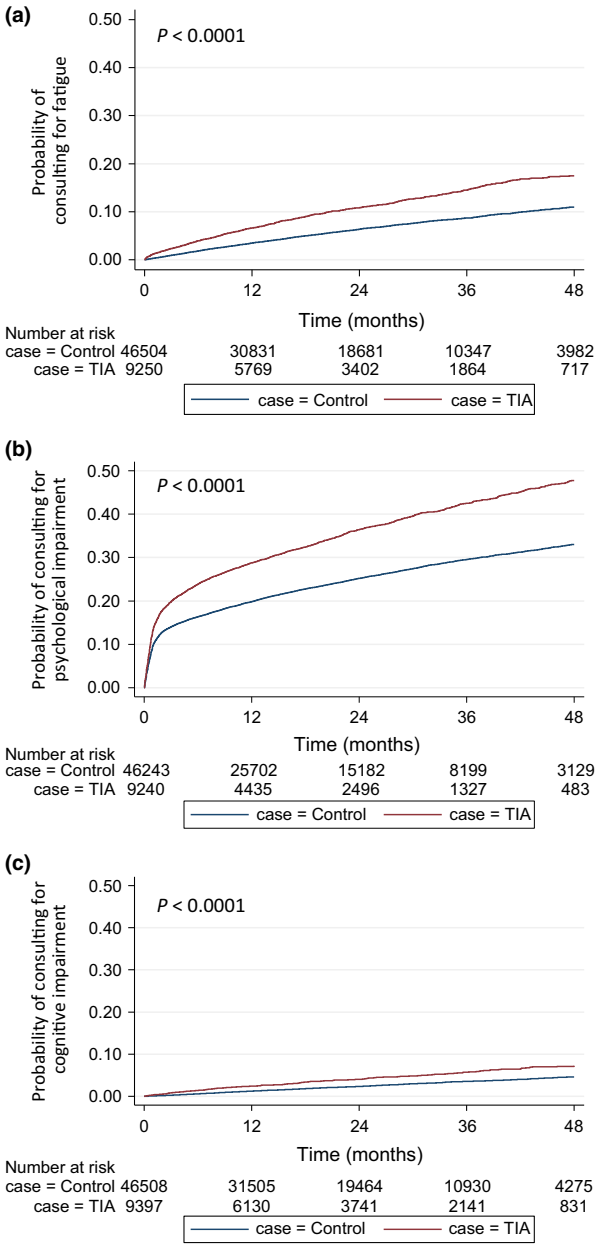

Figure 1 Kaplan–Meier (K-M) failure estimates for transient ischaemic attack (TIA) patients and controls consulting for: (a) fatigue, (b) psychological impairment and (c) cognitive impairment. The maximum follow-up time was 60.5 months for each substudy. However, the K-M graphs are cut-off at 48 months when approximately < 10% of the sample remains.

date. In this exploratory analysis, 42 836 individuals were included in the survival analysis for the fatigue substudy (6400 TIA patients and 36 436 controls), 28 390 in the psychological impairment substudy (4013 TIA patients and 24 377 controls) and 53 265 in the cognitive impairment substudy (8739 TIA patients and 44 526 controls). Results showed that a significant difference between TIA patients and controls remained for all three impairments ($P < 0.0001$; Fig. 2). The 5th percentile for time to consultation for fatigue was 15.9 months for TIA patients and 41.6 months for controls; the 10th percentile for time

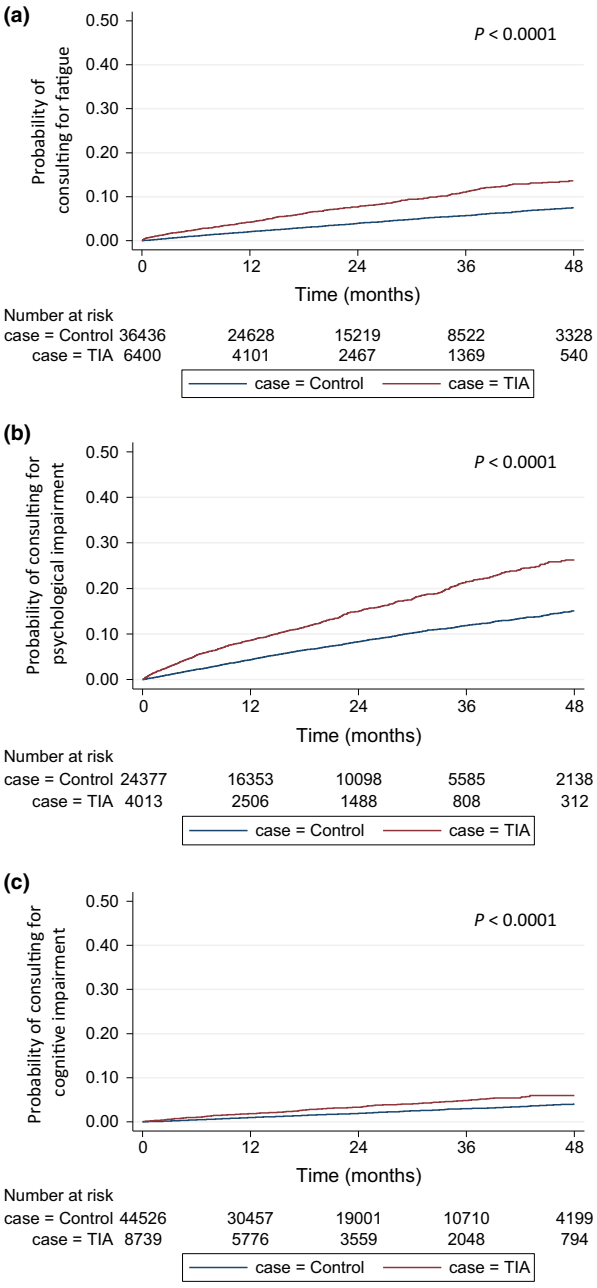

Figure 2 Kaplan–Meier (K-M) failure estimates for transient ischaemic attack (TIA) patients and controls with no record of the impairment prior to the index date and consulting for: (a) fatigue, (b) psychological impairment and (c) cognitive impairment. The maximum follow-up time was 60.5 months for each substudy. However, the K-M graphs are cut-off at 48 months when approximately < 10% of the sample remains.

to consultation/drug prescription for psychological impairment was 12.6 months for TIA patients and 24.2 months for controls; and the 5th percentile for time to consultation for cognitive impairment was 24.9 months for TIA patients and 48.2 months for controls. Adjusted HRs increased to 1.75 (95% CI, 1.57–1.94) for fatigue, 1.66 (95% CI, 1.50–1.84) for psychological impairment and 1.54 (95% CI, 1.35–1.77) for cognitive impairment.

Discussion

Clinically diagnosed TIA patients in a large UK general practice population were more likely than matched controls to consult for fatigue, psychological impairment and cognitive impairment. Compared with controls, TIA patients had an increased risk of 43% for consulting for fatigue, 26% for psychological impairment and 45% for cognitive impairment. These differences remained after adjustment for potential confounders and when patients with previous impairments were excluded from the analysis. Our findings suggest that, for many patients, TIA is not a transient event and patients experience impairments after initial symptoms have resolved.

The main strengths of our study include the very large sample size (> 55 700 patients), data were available from different regions across the UK and are representative of the UK population, and data represent real-life primary care practice. The study design addressed limitations of existing studies in this field by including a control group and controlling for confounding variables, particularly the presence of fatigue, psychological or cognitive impairment prior to the index date and comorbidities. Recording of these impairments is likely to vary between general practices. We therefore matched TIA patients and controls on this variable and included it as a random effect in the regression models.

A limitation of the study concerns the recording of TIA in primary care. Although general practitioners (GPs) are incentivized to keep a register of TIA patients in the UK, TIA may be misdiagnosed [22,23] or under-reported [24]. Misdiagnosis of a TIA 'mimic' (e.g. migraine with TIA-like symptoms) or minor stroke as TIA may dilute or overestimate the association between TIA and residual impairments, respectively. However, diagnosis of TIA has been validated in the THIN database [12]. There are also limitations regarding the recording of our outcomes, which rely on patients consulting with residual impairment and clinicians recording these in patients' electronic medical records. Clinical codes for signs and symptoms were used in addition to clinical codes for diagnoses to define our outcomes. Therefore, our outcomes may not be equivalent to clinical diagnoses of fatigue, psychological impairment or cognitive impairment, e.g. there was no distinction between a clinical diagnosis of anxiety and feeling anxious. Stroke prevention medication was not included as a confounder in the analysis. There is some evidence that beta-blockers may cause fatigue [25]. However, as they are not recommended as a first-line treatment for hypertension in this age group [26], it is unlikely that many patients were prescribed them. Bias may be introduced in our study because: (i) TIA patients consulted more in follow-up and therefore would have more opportunity to report impairment(s) and (ii) patients may be more conscious of their health following a TIA compared with controls, resulting in increased reporting of impairments. It is important to emphasize that not all patients who experienced impairments post-TIA would have consulted their GP about them in primary care. Therefore, our findings do not represent the incidence of residual impairment post-TIA in the community. Finally, time to consultation may not reflect the onset of the impairments as patients may have waited before consulting their GP.

The systematic review conducted prior to our study found a limited number of studies that measured residual impairment after TIA and included a control group [9]. None of the included studies that measured fatigue or PTSD had a control group. Only one study that measured anxiety included a control group and found a statistically significant difference in frequency of anxiety between TIA and control patients [27]. However, two depression studies that included controls reported no difference [27,28]. Three studies that measured cognitive impairment and included a comparison group were included in the systematic review [29–31]. Two of these studies found a statistically significant difference in frequency of cognitive impairment between TIA patients and controls. However, most of the studies included in the systematic review that had a control group did not adjust for confounding variables and the sample sizes were relatively small (< 350 participants). Subsequent to the systematic review, a Dutch study found a reduction in cognitive functioning in TIA patients compared with controls in all cognitive domains except episodic memory. However, the sample size was relatively small (n = 189) and the TIA patients and controls were not matched [32]. Other studies conducted after our systematic review that investigated psychological impairment post-TIA did not include a control group [33,34]. Our study addressed the limitations of

existing studies and found an increased risk of consulting for fatigue, psychological and cognitive impairment in TIA patients compared with controls.

The mechanism of residual impairments post-TIA is unknown. However, there are a number of potential explanations for our findings. Diagnoses of TIA within our study would have been based on clinical diagnosis rather than tissue-based diagnosis because brain imaging is not routinely used to diagnose TIA within the UK [5]. Therefore, patients may have had cerebral infarction, which could be responsible for the residual impairments and, by the tissue-based definition of TIA, should be considered as a minor stroke. A systematic review found evidence of ischaemic lesion in one-third of TIA patients diagnosed according to the time-based definition [35]. Alternatively, contrary to the tissue-based definition, TIA may cause microinfarcts that are not detected by neuroimaging with computed tomographic or magnetic resonance imaging. Microinfarcts have been detected by histological examination, and pooled analysis of autopsy studies from community prospective cohorts found an association between microinfarcts and dementia [36]. Studies have found evidence of abnormal neural activity in TIA patients with no lesions on conventional magnetic resonance imaging compared with controls [37,38]. Furthermore, these studies reported an association between abnormal neural activity and cognitive impairment. Another possible mechanism of residual impairments post-TIA could the psychological impact of the event. The psychological impact of TIA and minor stroke has been described in qualitative research [39]. A psychological mechanism has been proposed for post-stroke depression [40] and depression after minor stroke has been found to be independent of cerebral lesions [41]. Furthermore, an association between depression and cognitive impairment has been reported post-stroke [42].

Future research should establish the severity, onset, duration and natural history of residual impairments post-TIA. Additional research should develop intervention(s) to identify TIA patients with fatigue, psychological impairment or cognitive impairment and improve the healthcare and rehabilitation of these patients in a cost-effective way. It is important for future research to determine the impact that residual impairments post-TIA have on quality of life and ability to return to work and social activities. Furthermore, research that investigates the mechanism underlying the association between TIA and residual impairments may facilitate the development of a rehabilitation intervention and could challenge the current definition of TIA.

Conclusion

Transient ischaemic attack patients are more likely to consult for fatigue, psychological and cognitive impairment in primary care compared with controls. These findings challenge the 'transient' characterization of TIA and suggest that these patients may require therapy beyond stroke prevention. Dissemination of our finding to primary care clinicians and policy makers is important to increase the detection and treatment of residual impairments after TIA.

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Disclosure of conflicts of interest

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Supporting Information

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

Table S1. Values outside clinically plausible ranges which were excluded.
Table S2. Adjusted* hazard ratios for the effects of demographic and clinical characteristics on consultations for fatigue in TIA patients and controls.
Table S3. Adjusted* hazard ratios for the effects of demographic and clinical characteristics on consultations for psychological impairment in TIA patients and controls.
Table S4. Adjusted* hazard ratios for the effects of demographic and clinical characteristics on consultations for cognitive impairment in TIA patients and controls.

Figure S1. Number of incident transient ischaemic attack (TIA) events recorded in The Health Improvement Network (THIN) database between 1 January 2000 and 31 December 2013.

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