Methodological Factors in Determining Rates of Dementia in Transient Ischemic Attack and Stroke

(1) Impact of Baseline Selection Bias

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Background and Purpose—Many previous studies on dementia in stroke have restrictive inclusion criteria, which may result in underestimation of dementia rates. We undertook a large prospective population-based study of all transient ischemic attack and stroke to determine the impact of study entry criteria on measured rates of pre- and postevent dementia.

Methods—All patients with acute transient ischemic attack or stroke from a defined population of 92728 are referred from primary care or at hospital admission to the Oxford Vascular Study (2002–2007) and have baseline clinical and cognitive assessment and follow-up. We examined the impact of early death, other nonavailability, and commonly used selection criteria, on measured rates of dementia.

Results—Among 1236 patients (mean age/SD 75.2/12.1 years, 582 men, 403 transient ischemic attack), 139 died or were otherwise unavailable for baseline assessment, 319 had prior dependency, 425 had comorbidity, 512 were aged ≥80 years, 85 were dysphasic, and 502 were hospitalized. Pre-event dementia was 3-fold higher in patients dying preascertainment (10/47, 21%) and twice as high in other nonassessed (14/92, 15%) versus assessed patients (69/1097, 6%; P=0.0006 and P=0.0002) and was several-fold higher in those with prior functional impairment (24% versus 3%; P<0.0001), age >80 years (13% versus 3%; P<0.0001), dysphasia (11% versus 7%; P<0.0001), and comorbidity (10% versus 6%; P=0.04). Findings for postevent dementia were similar: prior functional impairment (40% versus 13%; P<0.0001), age >80 years (28% versus 10%; P<0.0001), dysphasia (39% versus 15%; P<0.0001), and comorbidity (20% versus 15%; P=0.04).

Conclusions—Exclusion of patients unavailable for assessment, and other widely used selection criteria, results in underestimation of the measured rate of dementia associated with transient ischemic attack and stroke.

Key Words: dementia ■ ischemic attack, transient ■ selection bias ■ stroke

Stroke and dementia share similar risk factors and frequently coexist.1 We have previously shown that rates of dementia in the first year after stroke are dependent on case-mix with lowest rates after first ever stroke in population-based studies and highest rates in hospital-based studies on major and recurrent stroke, but there are few data on other sources of inclusion bias.2,3 A better understanding of the effects of selection on the measured cognitive impairment rate is required for understanding the biological mechanisms underpinning the relationship between stroke and dementia, for planning clinical trials and other large pragmatic studies, and for calculating the overall cognitive burden attributable to symptomatic cerebrovascular disease. This article is the first of 3 to examine methodological issues in measuring rates of transient ischemic attack (TIA) and stroke-associated dementia; subsequent studies will examine attrition and applicability of short cognitive tests.

We undertook a large prospective population-based study of dementia associated with all TIA and stroke. Study interview was used in all available patients together with hand-searching of primary care and hospital and mortality records to identify dementia in nonavailable patients. We then determined the impact of various indirect and specific selection criteria applied at study entry on measured rates of pre- and postevent dementia.

Methods

Patients with TIA or stroke were prospectively recruited from April 1, 2002, to March 31, 2007, into the Oxford Vascular (OXVASC) Study, a prospective population-based cohort study of all acute vascular events occurring within a defined population of 92728 covered by 100 general practitioners (GPs; primary care) in 9 GP practices in Oxfordshire, United Kingdom.4,5 The study was approved by the local research ethics committee. Informed written consent (or assent from relatives) was obtained for study interview and follow-up either

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in person or, where not possible, by telephone and also consent/assent for indirect follow-up using primary care physician records, hospital records, and death certificate data. Where patients died before first assessment or where assent from a family member could not be obtained in patients lacking capacity (eg, owing to dysphasia or dementia), the ethics committee approved review of the patient’s medical records.

Patients were ascertained as soon as possible after the initial TIA or stroke by study clinicians through a combination of multiple methods of hot and cold pursuit, which has been shown to achieve near-complete ascertainment of TIA and stroke presenting to medical attention in this population. TIA and stroke were defined clinically by World Health Organization criteria. Major stroke was defined as National Institute of Stroke Scale (NIHSS) >3. Baseline brain and vascular imaging was performed, and all cases were reviewed by a senior vascular neurologist (P.M.R.). Stroke subtype was determined according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Lenient criteria, including the patient had moved away from the area, a qualitative scale based on the severity score (absent, mild, moderate, or severe) of the Blennow scale for CT scans and a modified version of the Fazekas scale for MRI scans as described previously.

Patient data were collected by interview using a standardized form and GP records and entered onto a custom-built database. Risk factors were recorded at study entry. Hypertension, diabetes mellitus, and hypercholesterolemia were defined on the basis of history and use of relevant medication and smoking as current smoking at the time of study entry. Premorbid functional status was assessed using modified Rankin and Barthel scores. The Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) was administered to an informant from 2002 to 2003 in a pilot study. However, owing to the absence of a reliable informant in many patients and redundancy, in that data on premorbid function were available from primary care, it was discontinued thereafter and data were only available for 101 subjects.

Follow-up interviews were done by trained research nurses at 1, 3, 6 months, and 1, 5, and 10 years either in the outpatient clinic or by home visit where hospital clinic visit was not possible. Telephone follow-up was performed where face-to-face follow-up was not possible (eg, because the patient had moved away from the area). Functional status, assessed using modified Rankin and Barthel scores and Nottingham Extended Activities of Daily Living index, was done at 1 month and 1, 5, and 10 years.

Cognitive testing was done at all follow-ups using the Mini-Mental State Examination (MMSE), Telephone Interview for Cognitive Status-modified (TICSm), and Montreal Cognitive Assessment (MoCA). All of which have been validated against the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery. The MMSE was done at all time points until April 1, 2005, when the baseline MMSE was replaced by the 10 point Abbreviated Mental Test Score (AMTS). From April 2007, the MoCA was introduced for the 6-month, 1-, 5-, and 10-year follow-ups as recommended by the NINDS-CSN Vascular Cognitive Impairment Harmonization Standards Working Group. The TICSm or telephone MoCA (out of 12) was done by telephone where possible when face-to-face follow-up was not feasible. Reasons for lack of study interview and lack of cognitive test and problems with cognitive testing, including visual impairment, hemiparesis, and dysphasia, were recorded, as described previously.

Dementia was defined as pre- or postevent according to whether the diagnosis was made before or after the index event. Pre-event dementia was recorded if dementia was a listed diagnosis in the primary care record at the time of the index event. Where there was no listed dementia diagnosis and baseline cognitive testing was above the cutoff for dementia (see below), pre-event dementia was excluded. For remaining cases, pre-event dementia diagnosis was made by S.T.P. (a senior physician/geriatrician with expertise in dementia) after review of all study assessment data that were available and hand-searching of the entire primary care record, including individual consultation records, all hospital outpatient clinic letters, and hospitalization documentation to establish pre-event dementia diagnosis on the basis of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria and by IQCODE score ≥3.6.

Of the 95 patients with pre-event dementia, dementia was present in the primary care problem list for 41 (43%). A further 22 had a nonspecific cognitive problem listed, including memory loss symptom, mental disorder, cognitive decline, confusional state, chronic confusion, memory disturbance, and memory loss of elderly, and the remaining 32 had no record of cognitive impairment in the primary care problem list, but evidence of dementia was obtained from individual primary care consultations, hospital records, and clinic letters.

Postevent dementia diagnosis was made after exclusion of patients with pre-event dementia. Postevent dementia diagnosis required MMSE<24 and remaining <24 for all subsequent follow-ups or MoCA<20 or TICSm<22 or T-MoCA<9. For subjects with an incomplete test (ie, testing was done but there was a problem, such as dysphasia, visual impairment, inability to use the dominant arm, English as a second language), individual patient study records including that from primary care and information from informant were used to determine whether the DSM-IV criteria were met, thus avoiding patients being spuriously classed as impaired on the basis of a low cognitive score. For patients without a direct study assessment, postevent dementia was diagnosed if there was a recorded diagnosis of dementia in the primary care record or if the DSM-IV criteria were met after from hand-searching of the entire primary care record for pre-event dementia as described by Kokmen et al and dementia was listed on the death certificate.

Among the 61 patients diagnosed with postevent dementia after being lost to study follow-up or who never had a study assessment, 30 had dementia diagnosis recorded in the primary care summary or from other physicians and 31 were made by S.T.P. after review of all available information from the primary care record.

To establish that there was no underdiagnosis of dementia in the study, death certificate data were examined for patients dying by April 1, 2013. In 36 patients with death certification of dementia, 3 had not been picked up by either study assessment or S.T.P. primary care search. One died 6 years after completing study follow-up and was diagnosed with dementia in the poststudy period. I moved away and was lost to follow-up and I had a diagnosis of cognitive impairment at 1 year but moved away without forwarding contact and died before 5-year follow-up.

Statistical Analysis

Patients with index stroke who had a recurrent stroke did not re-enter the study and were only included once for the purposes of data analysis. Patients with index TIA who had a subsequent stroke (n=32) entered the study with the time of stroke defined as the new baseline. Demographic and clinical differences between dead and surviving, assessed and nonassessed patients were compared using ANOVA or χ² test as appropriate. Postevent dementia rate was calculated as an actuarial rate (the proportion of dementia cases in the number at risk during the first year [the denominator]). The actuarial method is a way of allowing for withdrawals (deaths) that would only be at risk for part of the year; half the number censored is subtracted from the denominator at the start of the interval in the actuarial risk estimate. The effects of application of various commonly used baseline selection factors on the number of included patients, case-mix, and measured pre- and postevent dementia rate were examined. Indirect selection factors included early death before ascertainment and declining study interview at baseline. Direct inclusion/exclusion criteria were chosen on the basis of their use in previous studies of pre- and poststroke dementia: age ≥80 years, premorbid functional dependency (mRS>3), comorbidity (any significant comorbidity recorded at study entry), dysphasia (NIHSS language score ≥0), and hospitalization.

Results

One thousand two hundred thirty-six patients (mean age/SD 75.2/12.1 years, 582 [47%] male and 403 [33%] TIA, 463...
[37%] minor stroke, 370 [30%] major stroke, 65 [5%] primary intracerebral hemorrhage) were ascertained (Table 1), of which 992 (80.1%) were first ever events. Only 23 of 1236 (<2%) patients had no study assessment or GP records review which 992 (80.1%) were first ever events. Only 23 of 1236 (<2%) patients had no study assessment or GP records review (Table 2). Exclusion of older (>80 years), previously dependent, dysphasic, and comorbid patients resulted in cohorts that were unrepresentative both of the total population and within the hospitalized group.

Nonhospitalized and hospitalized patients had different demographic makeup, functional dependency, and cerebrovascular disease burden: age (mean age/SD 73.9/12.4 versus 77.2/11.3 years), premorbid dependency (Rankin ≥3* 221 [19] versus 110 [25%]), all patients ascertained (173/1143) and among survivors, those with versus without pre-event dementia† (173/1106) (Table 1). These indirect selection effects had a major impact on the measured rate of dementia. Prestroke dementia in those ascertained at baseline was 6% (69/1097) but was >3 times higher in patients who died in the hyperacute phase before ascertainment (104/47 [21%]; P<0.001) and over twice as high in those who survived to baseline ascertainment and among survivors, those with versus without pre-event dementia† (108/894) versus 120 (13%) or within 1 year of death (n=5), resulting in direct or indirect follow-up for >98% of patients.

As a result of death and nonavailability for interview, indirect selection at study entry occurred. Of the 1189 patients alive at ascertainment, 1097 (92%) had a study interview at baseline, with lack of consent or assent preventing assessment in most of the remainder (Figure 1). Patients dying before ascertainment or who were unavailable for baseline study assessment were older (mean/SD age 81.8/10.3 years and 77.5/12.5 years) and had more major stroke (96% and 38%) and less TIA (0% and 37%) than assessed patients (mean/SD age 74.8/12.1 years, 26% major stroke, 34% TIA; all P<0.01; Figure 1; Table 1). These indirect selection effects had a major impact on the measured rate of dementia. Prestroke dementia in those ascertained at baseline was 6% (69/1097) but was >3 times higher in patients who died in the hyperacute phase before ascertainment (104/47 [21%]; P<0.001) and over twice as high in those who survived to baseline but did not have a study assessment (14/92 [15%]; P=0.002; Figure 1). The true population-based pre-event dementia rate was therefore about a third higher at 93 of 1236 (8%) than when measured in the 1097 patients surviving and assessed at baseline (6%, n=69; Table 1). In contrast, the postevent dementia rate in those nonassessed versus assessed at baseline was therefore about a third higher at 93 of 1236 (8%) than when measured in the 1097 patients surviving and assessed at baseline (6%, n=69; Table 1). In contrast, the postevent dementia rate in those nonassessed versus assessed at baseline was therefore about a third higher at 93 of 1236 (8%) than when measured in the 1097 patients surviving and assessed at baseline (6%, n=69; Table 1). In contrast, the postevent dementia rate in those nonassessed versus assessed at baseline was therefore about a third higher at 93 of 1236 (8%) than when measured in the 1097 patients surviving and assessed at baseline (6%, n=69; Table 1). In contrast, the postevent dementia rate in those nonassessed versus assessed at baseline was therefore about a third higher at 93 of 1236 (8%) than when measured in the 1097 patients surviving and assessed at baseline (6%, n=69; Table 1). In contrast, the postevent dementia rate in those nonassessed versus assessed at baseline was therefore about a third higher at 93 of 1236 (8%) than when measured in the 1097 patients surviving and assessed at baseline (6%, n=69; Table 1). In contrast, the postevent dementia rate in those nonassessed versus assessed at baseline was therefore about a third higher at 93 of 1236 (8%) than when measured in the 1097 patients surviving and assessed at baseline (6%, n=69; Table 1).

Specific inclusion criteria also had a major impact on sample size and case-mix (Tables 1 and 2). Exclusion of older (>80 years), previously dependent, dysphasic, and comorbid patients resulted in cohorts that were unrepresentative both of the total population and within the hospitalized group.

### Table 1. Impact of Different Baseline Selection Criteria on Cohort Numbers, Demographics, Case-Mix, and Rates of Pre- and Postevent Dementia

<table>
<thead>
<tr>
<th>Number in study</th>
<th>Population-Based, All</th>
<th>Alive at Ascertainment</th>
<th>Alive and Study Assessment</th>
<th>No Comorbidity</th>
<th>No Premorbid Dependency</th>
<th>Age ≤30 y</th>
<th>Nondysphasic</th>
<th>Nonhospitalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>1236</td>
<td>1189</td>
<td>1097</td>
<td>811</td>
<td>917</td>
<td>724</td>
<td>1151</td>
<td>734</td>
<td></td>
</tr>
<tr>
<td>Mean/SD age</td>
<td>75.2/12.1</td>
<td>75.0/12.1</td>
<td>74.8/12.1</td>
<td>74.1/12.4</td>
<td>72.9/12.1</td>
<td>67.7/10.1</td>
<td>75.0/12.2</td>
<td>73.9/12.4</td>
</tr>
<tr>
<td>Male sex</td>
<td>582 (47)</td>
<td>558 (47)</td>
<td>520 (47)</td>
<td>405 (50)</td>
<td>468 (51)</td>
<td>386 (53)</td>
<td>546 (47)</td>
<td>339 (46)</td>
</tr>
<tr>
<td>Education &lt;12 y</td>
<td>668 (54)</td>
<td>667 (56)</td>
<td>659 (60)</td>
<td>425 (52)</td>
<td>535 (58)</td>
<td>406 (56)</td>
<td>614 (53)</td>
<td>424 (58)</td>
</tr>
<tr>
<td>TIA</td>
<td>403 (33)</td>
<td>403 (34)</td>
<td>378 (34)</td>
<td>285 (35)</td>
<td>338 (37)</td>
<td>257 (35)</td>
<td>402 (35)</td>
<td>343 (47)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>768 (62)</td>
<td>736 (62)</td>
<td>679 (62)</td>
<td>467 (58)</td>
<td>544 (59)</td>
<td>424 (59)</td>
<td>689 (60)</td>
<td>378 (51)</td>
</tr>
<tr>
<td>PICH</td>
<td>65 (5)</td>
<td>50 (4)</td>
<td>40 (4)</td>
<td>59 (7)</td>
<td>35 (4)</td>
<td>43 (6)</td>
<td>60 (5)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>463 (37)</td>
<td>461 (39)</td>
<td>429 (39)</td>
<td>297 (37)</td>
<td>360 (39)</td>
<td>287 (40)</td>
<td>450 (39)</td>
<td>303 (41)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>370 (30)</td>
<td>325 (27)</td>
<td>290 (26)</td>
<td>229 (28)</td>
<td>219 (24)</td>
<td>180 (25)</td>
<td>299 (26)</td>
<td>88 (12)</td>
</tr>
<tr>
<td>Rankin ≥3*</td>
<td>221 (19)</td>
<td>212 (19)</td>
<td>192 (18)</td>
<td>116 (16)</td>
<td>...</td>
<td>72 (10)</td>
<td>201 (19)</td>
<td>109 (16)</td>
</tr>
<tr>
<td>Barthel &lt;20*</td>
<td>292 (26)</td>
<td>283 (26)</td>
<td>273 (26)</td>
<td>154 (21)</td>
<td>120 (13)</td>
<td>108 (16)</td>
<td>265 (26)</td>
<td>158 (23)</td>
</tr>
<tr>
<td>Pre-event dementia</td>
<td>93 (8)</td>
<td>83 (7)</td>
<td>69 (6)</td>
<td>52 (6)</td>
<td>23 (3)</td>
<td>24 (3)</td>
<td>84 (7)</td>
<td>44 (6)</td>
</tr>
<tr>
<td>1-year postevent dementia†</td>
<td>(173/1143)</td>
<td>16.4/1.1</td>
<td>16.7/1.2</td>
<td>17.0/1.2</td>
<td>14.5/1.3</td>
<td>12.7/1.1</td>
<td>9.5/1.1</td>
<td>14.9/1.1</td>
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<td></td>
<td>(173/1106)</td>
<td>(165/1028)</td>
<td>(103/739)</td>
<td>(108/894)</td>
<td>(63/700)</td>
<td>(147/1067)</td>
<td>(74/690)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers are n (%). PICH indicates primary intracerebral hemorrhage; and TIA, transient ischemic attack.

*Premorbid values.
†Actuarial risk/standard error (n/total), excluding pre-event dementia.

Figure 1. Flow chart showing the numbers and characteristics of all patients in the population, of those dying versus surviving to ascertainment and among survivors, those with versus without baseline assessment. TIA indicates transient ischemic attack.

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Penultimate sentence of the abstract: Pendlebury et al (2017) studied the impact of different baseline selection criteria on cohort numbers, demographics, case-mix, and rates of pre- and postevent dementia.
Table 2. Impact of Different Baseline Selection Criteria on Cohort Numbers, Demographics, Case-Mix, and Rates of Pre- and Postevent Dementia for Hospitalized Patients Only

<table>
<thead>
<tr>
<th>Number in study</th>
<th>Hospitalized, All</th>
<th>No Comorbidity</th>
<th>No Premorbid Dependency</th>
<th>Age ≥80 y</th>
<th>Nondysphasic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age/SD</td>
<td>502</td>
<td>313</td>
<td>330</td>
<td>259</td>
<td>437</td>
</tr>
<tr>
<td>Education (&lt;12 y)</td>
<td>243 (48)</td>
<td>167 (53)</td>
<td>175 (53)</td>
<td>154 (59)</td>
<td>218 (50)</td>
</tr>
<tr>
<td>TIA</td>
<td>60 (12)</td>
<td>37 (12)</td>
<td>44 (13)</td>
<td>32 (12)</td>
<td>60 (14)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>390 (78)</td>
<td>227 (73)</td>
<td>259 (78)</td>
<td>194 (75)</td>
<td>330 (76)</td>
</tr>
<tr>
<td>PICH</td>
<td>52 (10)</td>
<td>49 (16)</td>
<td>27 (8)</td>
<td>33 (13)</td>
<td>47 (11)</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>160 (32)</td>
<td>94 (30)</td>
<td>114 (35)</td>
<td>92 (36)</td>
<td>153 (35)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>282 (56)</td>
<td>182 (58)</td>
<td>172 (52)</td>
<td>135 (52)</td>
<td>224 (51)</td>
</tr>
<tr>
<td>Rankin ≥3*</td>
<td>112 (25)</td>
<td>59 (22)</td>
<td>...</td>
<td>35 (15)</td>
<td>96 (25)</td>
</tr>
<tr>
<td>Barthel &lt;20*</td>
<td>134 (31)</td>
<td>67 (25)</td>
<td>49/32 (15)</td>
<td>44 (19)</td>
<td>110 (30)</td>
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<tr>
<td>Pre-event dementia†</td>
<td>49 (10)</td>
<td>30 (10)</td>
<td>12 (4)</td>
<td>13 (5)</td>
<td>42 (10)</td>
</tr>
<tr>
<td>1-year postevent dementia†</td>
<td>25.4/2.2</td>
<td>24.0/2.7</td>
<td>22.6/2.5</td>
<td>16.8/2.5</td>
<td>22.5/2.3</td>
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<tr>
<td>(99/453)</td>
<td>(59/283)</td>
<td>(65/318)</td>
<td>(37/246)</td>
<td>(76/395)</td>
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</tr>
</tbody>
</table>

Numbers are n (%). PICH indicates primary intracerebral hemorrhage; and TIA, transient ischemic attack.

*Premorbid values.
†Actuarial risk/standard error (n/total), excluding pre-event dementia.

The variations in case-mix resulting from the application of different selection criteria resulted in a wide range of measured dementia rates (Tables 1 and 2). Exclusion of older or functionally impaired patients from the population resulted in a halving (P<0.001) of pre-event dementia from 93 of 1236 (8%) to 23 of 917 (3%), whereas exclusion of comorbid and dysphasic patients produced reductions in around a quarter (Table 1), with qualitatively similar although smaller effects in the group of hospitalized patients (Table 2). Exclusion criteria also had significant impact on postevent dementia rates with the greatest effects for age. Rates of pre- and postevent dementia were around twice as high in hospitalized versus nonhospitalized patients: pre-event dementia (49/502 [10%] versus 44/734 [6%]; P=0.01) and postevent dementia (99/453 [25%] versus 74/690 [11%]; P<0.0001).

The impact of selection is unsurprising, given the markedly higher dementia rates in those with specific exclusion criteria (Figure 2). Pre-event dementia was 7 times more prevalent in those with versus without prior functional impairment (70/319 [22%] versus 23/917 [3%]; P=0.0001) and 4 times as common in those aged ≥80 versus ≤80 years (69/512 [13%] versus 24/724 [3%]; P<0.0001). In patients surviving to ascertainment, new postevent dementia (excluding pre-event dementia) was 3 times as common in those with functional impairment (83/212 [39%] versus 90/894 [13%]; P<0.0001) or age ≥80 years (110/406 [27%] versus 63/700 [9%]; P<0.0001). Overall, any dementia (pre- or postevent) was most common in those with premorbid functional impairment followed by those ≥80 years, with dysphasia or who were hospitalized for their event (Figure 2).

Discussion

In our study on >1200 patients with TIA and stroke from a defined population, sample size, case-mix, and measured rates of pre- and postevent dementia were substantially impacted by the application of different baseline selection criteria. Rates of dementia were several-fold higher in groups excluded in previous studies, including in those nonavailable for direct study assessment (for pre-event dementia) and with older age, dysphasia, and prior functional impairment. Dementia rates were twice as high in hospitalized patients, consistent with fact that they were older and had more major stroke than that in nonhospitalized patients.

Even in the absence of restrictive criteria, older, more impaired patients were more likely to die before ascertainment and less likely to undergo formal study interview, in keeping with epidemiological observations from nonstroke populations. Previous inclusive studies on prestroke dementia note difficulties in applying informant-based assessments of premorbid cognitive function in patients with early death in hospital-based studies and before assessment/ascertainment in population-based studies. Our findings show that indirect exclusion of such patients results in underestimation by one-third of pre-event dementia because rates were >3-fold higher in those dying before versus surviving to assessment and >2-fold higher in those not assessed. Postevent dementia rates are less impacted by indirect selective baseline assessment because such patients often die early on follow-up.

Besides being subject to unavoidable indirect baseline selection, many previous studies on stroke-associated dementia also used specific exclusion criteria, commonly including dysphasia, but also older age and comorbidity, dependency or a combination of these. Exclusion of dysphasic patients is often undertaken as there are difficult methodological issues in assessing cognition in such patients. If dysphasic patients are not excluded, it is important to ensure that low cognitive scores are evaluated in the light of other available clinical information. In our large pragmatic study, all cognitive tests from testable dysphasic patients were coded. Where the cognitive scores fell below the dementia threshold, the patient’s study assessment (where available) and all available clinical records were reviewed to establish whether the DSM criteria were satisfied.
For untestable dysphasic patients, diagnosis of dementia was made if the criteria were satisfied after review of all available data, including information from carers and primary care.

Our findings show the extent to which such selection criteria impact on case-mix and thus on measured rates of both pre- and postevent dementia. All selection criteria resulted in unrepresentative cohorts of younger, fitter patients with less severe stroke and dementia rates that were up to 7-fold lower than in the corresponding excluded group. The effect of selection can also be seen when comparing the relatively young mean age (=69–70 years) of subjects included in previously reported hospitalized cohorts with that seen in our study (>77 years).

Both pre- and postevent dementia were more common in hospitalized patients versus that in the total population with symptomatic cerebrovascular disease, and hospitalization was associated with a greater prevalence of major stroke as seen in previous studies. However, the current study demonstrates that hospitalized patients also have a greater prevalence of non-stroke factors associated with dementia, including older age, premorbid functional dependency, and severe leukoaraiosis.

There are some limitations to our study. We relied on the primary care record to inform pre- and postevent dementia status for those without direct study data. Only 41% of patients with pre-event dementia had a formal diagnosis of the condition listed in the primary care record, in keeping with reported under-recording of dementia diagnosis in primary care. However, we tried to correct for this by hand-searching of the entire GP consultation record, including individual consultation records and all hospital clinic and discharge letters to look for evidence of cognitive impairment satisfying the DSM-IV criteria for dementia. Moreover, any underestimation of dementia by this method in nonassessed cases will have resulted in conservative estimates of the impact of bias. Primary care records are of particular value in the United Kingdom where patients have a single primary care provider holding a continuous life-long record for that individual, but this may not be available in other healthcare systems. Next, we used MMSE <24 to diagnose dementia in those with study assessment rather than clinical diagnosis using established dementia criteria, which may have underestimated mild dementia in this cohort with cerebrovascular disease or overestimated it in subjects with low education although recent studies suggest that the MMSE is reliable for detecting multidomain cognitive impairment and dementia in this population.

In conclusion, different baseline selection criteria had a major impact on case-mix and measured pre- and postevent dementia rates in patients with TIA and stroke. The majority of previous studies were subject to these selection biases, likely accounting for heterogeneity in reported dementia rates, which may have been underestimated. Future studies on pre- and post-TIA/stroke cognitive impairment should be as inclusive as possible: interventions to prevent dementia are likely to be ineffective at the population level if developed in response to results from highly selected groups. In particular, older or functionally impaired patients should not be excluded and data should be reported on unavailable patients in whom the use of indirect assessment should be considered.

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**Disclosures**

S.T. Pendlebury planned analyses, performed clinical assessments, collected and assessed data from medical records to make the dementia diagnoses in patients without direct study assessment, and wrote the manuscript. P.-J. Chen, L. Bull, and L. Silver collected data. Z. Mehta performed analyses and provided statistical expertise, and P.M. Rothwell planned and directed the Oxford Vascular (OXVASC) study, cowrote the manuscript, and advised on analyses.

**References**


Methodological Factors in Determining Rates of Dementia in Transient Ischemic Attack and Stroke: (I) Impact of Baseline Selection Bias
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