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Citation for published version:
Feigin, V, Norrving, B, Sudlow, C & Sacco, RL 2018, 'Updated criteria for population-based stroke and transient ischemic attack incidence studies for the 21st century' Stroke. DOI: 10.1161/STROKEAHA.118.022161

Digital Object Identifier (DOI):
10.1161/STROKEAHA.118.022161

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Stroke

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Download date: 05. Apr. 2019

Updated criteria for population-based stroke and transient ischemic attack incidence studies for the 21st century

Cover title: criteria for population-based stroke incidence studies

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Key words: stroke, transient ischemic attack, epidemiology, community

Word count: 5814 words

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Introduction

Stroke is the second leading cause of death and disability worldwide and the burden of stroke over the last three decades has increased significantly.[1] There have also been noticeable changes in stroke epidemiology, including diverging trends in stroke incidence and mortality rates in high-income and low to middle-income countries,[2] disproportionally increasing burden of stroke in developing countries,[3] and increased proportion of disability and deaths due to stroke compared to all diseases.[4] Moreover, while most countries have no accurate data on stroke incidence and outcomes,[5] in countries where such studies have been conducted we know that there are large within and between country geographical differences in stroke burden,[1,3] large ethnic/racial disparities in stroke,[6-11] and noticeable secular changes in the natural history of stroke and risk factors.[12,13]

All these changes, differences, trends and gaps in knowledge necessitate further, more advanced epidemiological studies of stroke in various populations. Accurate and comparable population-based data on stroke incidence and outcomes and their trends can provide reliable data for evidence-based stroke care planning, health care resource allocation and priority setting. Current criteria for population-based stroke incidence studies include a standard clinical WHO definition of stroke and transient ischemic attack (TIA)[14] and maximally complete case ascertainment of both fatal and non-fatal, hospitalised and non-hospitalised new stroke events using multiple overlapping sources of information.[15-20]

More recently, the definitions of TIA and stroke have been updated to incorporate both clinical and tissue criteria by the American Heart Association and American Stroke Association,[21] and a similar definition also appears in the upcoming International Classification of Diseases 11th revision (ICD-11).[22] The new definitions of stroke and TIA require a reconsideration of the criteria for an 'ideal' stroke incidence study. Moreover, there are more countries using/adapting alternative methods for population-based stroke incidence and outcome estimates, including national health record-linkage systems and various stroke registries. The issue becomes even more imperative given ongoing advances in acute stroke management and rehabilitation that require additional accurate epidemiological and health care information from stroke incidence studies. The aims of this article are to extend and refine the latest criteria for an 'ideal' stroke incidence study[17,18,23] taking into consideration the new stroke and TIA definitions and latest developments in

stroke care and systems with the goal of suggesting updated criteria for standard definitions, methods and data presentation (Table 1).

Updated standard definitions of TIA and Stroke

The addition of the WHO clinical definition of TIA (any acute focal cerebrovascular event with symptoms lasting <24 hours)[14] to the core criteria would allow evaluation of the burden of two major acute cerebrovascular disorders - stroke and TIA - separately and combined. A wide use of thrombolytic therapy within the first hours after acute ischemic cerebrovascular event occurrence when the time-based *clinical* differentiation of stroke and TIA is not possible, means that new TIA events could and should be registered along with new stroke events. From a public health perspective, it is important to know the incidence of all acute cerebrovascular events, including TIA, as they all require urgent diagnosis and management with associated health care resource utilisation. This means that a search for new TIA events must be as complete and thorough as it is for new stroke events, although it will require additional resources and may be a challenging task in resource-poor countries. Additionally, adjudication of potential TIA events in a community setting is particularly challenging because of TIA mimics and hospitalisation bias.[24,25] However, there are already a few population-based studies in which both stroke and TIA were ascertained and registered at the same time in the same study population,[26-31] thus providing support for the feasibility of such joint stroke and TIA incidence studies in different populations.

While it is crucial to keep using the previous WHO clinical definition of stroke ("rapidly developing clinical signs of focal [or global] disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin")[14] and TIA (a sudden onset of a focal neurologic symptom and/or sign lasting less than 24 hours and caused by reversible cerebral ischemia)[14] in all epidemiological studies of stroke incidence to allow comparisons between different locations and over time (geographical and trends analysis), it is also important to include/add the new tissue-based definition of stroke and TIA in the latest epidemiological studies. Routine use of modern neuroimaging, vascular/cardiac and other laboratory investigations has become generally available in many hospitals/centres, thus allowing more precise etiologic and anatomical

classifications of TIA, ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage.

In the new AHA/ASA definition, ischemic stroke is defined on the basis of clinical *and* tissue criteria "as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury".[32] Effectively, it includes formerly defined TIAs with neuroimaging evidence of ischemic brain lesion in the clinically relevant area of the brain and does not depend on the duration of neurological symptoms associated with the cerebrovascular ischemic event. TIA is now defined as "transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction",[21] thereby eliminating the time-based components noted in the classical WHO definition.[14] Moreover, the new AHA/ASA definition for stroke included "silent" or "subclinical" tissue-based strokes that can only be detected with more sensitive brain imaging. Most population-based incidence studies would not be able to adequately enumerate silent strokes because of the need for advanced imaging and the inability to accurately determine the date of onset of such events.

In the upcoming ICD 11 at WHO [https://icd.who.int/dev11/l-m/en], TIA is defined as "Transient episode of focal neurological dysfunction caused by focal brain ischemia without acute infarction in the clinically relevant area of the brain. Symptoms should resolve completely within 24 hours". Cerebral ischemic stroke is defined as "Acute focal neurological dysfunction caused by focal infarction at single or multiple sites of the brain. Evidence of acute infarction may come either from a) symptom duration lasting more than 24 hours, or b) neuroimaging or other technique in the clinically relevant area of the brain. The term does not include infarction of the retina". Although the ICD 11 definitions of stroke and TIA do not include monocular blindness with transient ischemia of the retina or retinal infarct, to be consistent with previous epidemiological studies of stroke we recommend to register these retinal ischemic events. The WHO ICD 11 definition of stroke requires the presence of acute neurological dysfunction and encompasses the entities cerebral ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and stroke not known to be ischemic or hemorrhagic. In the WHO ICD 11 definition, silent cerebral infarcts and microinfarcts are not included in the definition of stroke.

Both new definitions require more advanced neuroimaging or neuropathological confirmation of infarction. Computerized tomography is less sensitive to detection of small ischemic lesions than MRI with diffusion-weighted sequences (DW-MRI), which is more likely to detect an acute lesion in the clinically relevant area. Increasing use of DW-MRI will lead to transient cerebral events labelled as TIAs under the classical WHO definition being called cerebral ischemic strokes under the WHO ICD-11 definition.

According to the AHA/ASA stroke definitions, intracerebral hemorrhage is defined as "rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma"; and subarachnoid hemorrhage as "rapid signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and pia mater of the brain or spinal cord), which is not caused by trauma". These definitions of intracerebral hemorrhage and subarachnoid hemorrhage are similar to the ICD-11 definitions.[22]

To allow meaningful comparison of epidemiological studies by stroke etiological and anatomical subtypes and over time it is important to use standard and validated classification systems. Ischemic stroke can be further classified into five etiological groups (large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined aetiology, and stroke of undetermined etiology) according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[33] If possible, stroke of undetermined etiology can be further classified based on the extent of the diagnostic investigations into three groups: (1) Two or more causes identified, (2) Negative evaluation despite a complete investigation, and (3) Incomplete diagnostic evaluation.[33] The ICD 11 classification of cerebral ischemic stroke builds on the TOAST classification. Some studies have also proposed classifying a proportion of the infarcts of undetermined etiology (cryptogenic strokes) with adequate diagnostic investigations as embolic stroke of undetermined source (ESUS) among those with non-lacunar syndromes without significant proximal arterial atherosclerosis or a definite cardioembolic source.[34 35] More recent etiological classification schemes, such as the Clinical Classification System, have been developed with the aim of providing improvements in inter-observer reliability and reducing the proportion of ischemic strokes attributed to undetermined etiology.[36,37] Clinical

anatomic subgroups have also been used to classify ischemic strokes into five anatomical groups (total anterior circulation syndrome [TACS], partial anterior circulation syndrome [PACS], lacunar syndrome [LACS], posterior circulation syndrome [POCS], and uncertain circulation syndrome) according to the Oxfordshire Community Stroke Project [OCSP] clinical classification.[38] This classification system provides less information on presumed etiology, but is less dependent on the availability of data from brain and vascular imaging, giving it the advantage that almost all strokes can be assigned to a subtype. Better comparability of studies by stroke severity are achieved through use of a well validated and widely used scales, such as the National Institutes of Health Stroke Scale (NIHSS).[39] NIHSS score can be obtained either prospectively (if clearly present in medical files) or retrospectively based on clinical data obtained from medical files.[40] Such subtype classification and severity scoring systems are recommended to be used as supplementary criteria for an 'ideal' stroke incidence and outcomes study.

Although categorisation of different pathological types of stroke into various etiological and anatomical groups might be very challenging in population-based epidemiological studies, especially in resource-poor countries, there have been several such studies accomplished in the past.[41-50] For example, if possible, intracerebral hemorrhages should be classified into lobar, deep, and infratentorial hemorrhages; while subarachnoid hemorrhages should be classified into aneurysmal and non-aneurysmal hemorrhages. These classifications help in the management, and predicting prognosis and planning secondary preventive measures, justifying their use in population-based stroke incidence studies. Such classification systems may also require the use of an adjudication committee to reduce bias and help minimize misclassification.[24]

Suggested supplementary data collection

Suggested additional supplementary data collection also includes registration of recurrent TIA (because recurrent TIA has different management and prognostic significance); capture-recapture estimates to ascertain the completeness of stroke and TIA case ascertainment,[51,52] follow-up of stroke and TIA patients' functional status for at least 3 months (there is evidence that 3-month disability, as measured by the modified Rankin

Scale pre- and post-stroke, is a strong independent predictor of long-term disability and mortality);[53,54] and collecting data on risk factors among stroke and TIA patients to allow firmer conclusions to be drawn about the factors impacting the trends in incidence and outcomes as well as to reflect on the effect of trends in health policy on stroke and TIA outcomes.[41,55] Complete, population-based case ascertainment, based on multiple overlapping sources of information (hospitals, outpatient clinics, general practitioners, death certificates) and high level of acute brain neuroimaging coverage, with an expert adjudication of the events is very important for the capture and diagnosis/classification of all new stroke and TIA cases[24] based on both old (clinical) and new stroke and TIA definitions. The new definitions of stroke and TIA require the use of DW-MRI for the precise distinction between TIA and ischemic stroke if the events are shorter than 24 hours, whereas for events lasting 24+ hours brain CT scanning is sufficient. Consistent with previous criteria for a population-based stroke incidence study,[16-18] we recommend that when DW-MRI is done for cerebrovascular events lasting less that 24 hours it must be done in less than a week at least 80% of the time. Reporting of proportions examined and timing of the examination with each technique is important for comparative purposes.

Given the prognostic importance of stroke for the subsequent development of cognitive decline and dementia, as well as its effect on quality of life and other health outcomes, it is also recommended to include additional validated measurements (e.g. cognitive impairment, daily activities, quality of life, mood, socio-economic status, direct and indirect costs). Preferences should be given to the validated assessment tools that are easier (e.g. over the phone) and faster to administer in stroke/TIA patients and their family caregivers. As quality and timing of acute stroke/TIA care are important determinants of their outcomes, it is also desirable to include some quality indicators of stroke care.[56] The choice and number of assessment tools to be used in a population-based stroke incidence study should be determined by the purpose of the study, expertise of study researchers and available resources.

Updated Standard Methods of Case Ascertainment

The standard methods for conducting population-based stroke incidence studies are also applicable for determining stroke incidence using either the WHO STEPS approach to

stroke surveillance,[19] national registries (e.g. record-linkage systems) or a special door-to-door survey[20] (Figure). These survey methods require use of instruments that allow clinical ascertainment of non-hospitalized and non-fatal stroke and TIA events among study participants and include a validated verbal-autopsy technique for fatal events (interviewing family members and/or relevant health professionals about the circumstances of a death of after the event over the last couple of years). Such door-to-door surveys for studying stroke incidence have been successfully accomplished in Italy and China.[57-59] Advantages of this approach include relatively low cost and simplicity (door-to-door survey is the most commonly used design of stroke epidemiological studies in resource-poor settings). Disadvantages include the potential for under-estimating incidence rates by missing very mild stroke cases, recall bias (although this can be minimized by restricting the period of recall to 3 years), and the need to study a large sample size.[20] It should be emphasised that the WHO STEPS stroke surveillance can only be called a population-based study if it includes all three steps of the surveillance (hospital register, death certificates and non-hospitalised case ascertainment in the catchment area). The updated classifications of TIA and stroke may also require greater access to advanced brain imaging to use classification systems that rely on tissue-based criteria for infarction and hemorrhage.

Updated standard data presentation

To allow comparisons between different stroke incidence studies and analysis of temporal trends, it is important to conduct a study in a way that (a) allows accommodation of both core and supplementary criteria, and (b) follows standard guidelines for reporting study results, such as the Standards of Reporting of Neurological Disorders Checklist (STROND)(Table 2).[60,61] We suggest calling a study that meets both core and supplementary criteria and standard data presentation (Tables 1 and 2) an 'advanced' population-based stroke incidence study. However, such stroke incidence studies are expensive and require special expertise for their design and execution, which is particularly challenging in resource-poor countries. Therefore, studies that meet just basic criteria for a stroke incidence study set up by Malmgren et al.[15] and then updated by Sudlow and Warlow[16] (including studies that accommodate all three WHO STEPS surveys and studies based on a special door-to-door survey, as explained above) remain acceptable as basic population-

based stroke and/or TIA incidence studies. There is an obvious lack of even these studies in most parts of the world,[5,27] and even fewer population-based stroke incidence studies exist on trends in stroke incidence and outcomes.

For stroke incidence studies that use the new definitions of stroke, data on TIA with or without neuroimaging evidence of brain infarct, data on stroke and TIA by age, sex and/or ethnic/racial groups should be presented separately and combined. A checklist for standard data reporting is presented in Table 2.

Impact and implication of new criteria

As suggested by Sacco et al.[62] changing the definition of stroke and TIA will have significant effects on stroke/TIA surveillance, burden estimates and prognosis. As the new clinical and tissue-based stroke definition will include formerly diagnosed TIAs with evidence of brain lesion, the number of strokes will be increased, and overall stroke severity reduced. Preliminary estimates suggest that adopting this definition of stroke, for example, in the USA would lower annual incidence rates of TIA by 33%, but increase the rate of ischemic stroke by 33%.[11,63] It is likely that overall stroke severity will also be reduced by approximately the same amount. However, population-based studies in various populations adopting the new definitions of stroke and TIA are required to estimate the effect of changing stroke and TIA definitions on stroke and TIA incidence and outcomes and to provide new comparable estimates. It is our hope that the wider use of the updated alongside the classical criteria for population-based stroke incidence studies will advance our knowledge on changing stroke epidemiology in the world and further facilitate evidence-based health care planning, priority setting, and resource allocation for people with acute cerebrovascular events, and, as consequence, save millions of lives.

Disclaimer

None.

Acknowledgement

None.

Disclosures

None of the authors has competing financial interests.

Authors' contributions

VF prepared the first draft. BN, CS and RS reviewed and edited the draft and approved the final version of the manuscript.

Table 1. Criteria for basic and advanced population-based stroke and TIA incidence studies (Adapted from Feigin et al.,[17,18] with permission)

Domains	Core criteria for Basic Studies	Supplementary criteria for Advanced Studies
Standard definitions	WHO clinical definition of stroke WHO clinical definition of TIA* At least 80% CT/MRI verification of the diagnosis of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage within first week of stroke onset First ever-in-a-lifetime stroke or TIA	AHA/ASA/ICD-11 clinical and tissue definition of stroke* TIA without evidence of brain infarct* At least 80% DW-MRI for tissue-based distinction of TIA and stroke for events resolving within first 24 hours of the onset* Classification of ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage into etiological and anatomical groups* Stroke severity by NIHSS or similar* Recurrent stroke and TIA*
Standard methods	Complete, population-based case ascertainment, based on multiple overlapping sources of information (hospitals, outpatient clinics, general practitioners, death certificates) Prospective study design Large, well-defined, and stable population, allowing at least 100,000 person-years of observation Reliable method for estimating denominator (census data ≤5 years old) Follow-up of patients' vital status for at least 1 month	Ascertainment of patients with TIA, recurrent strokes and those referred for brain, carotid, or cerebral vascular imaging "Hot pursuit' of cases Direct assessment of under-ascertainment by regular checking of general practitioners' databases and hospital admissions for acute vascular problems and cerebrovascular imaging studies and/or interventions Capture-recapture estimates of the completeness of case ascertainment* Follow-up of stroke and TIA patients' functional status for at least 3 months* Collecting data on stroke risk factors and quality of acute care*
Standard data presentation	Complete calendar years of data; ≤5 years of data averaged together Men and women presented separately Mid-decade 10 or 5-year age bands (e.g. 55 to 64 years) used in publications, including oldest age group (≥85 years)	Data on old (WHO) and new (AHA/ASA/ICD-11) stroke and TIA estimates presented separately* Data also presented by major ethnic/racial groups*

	95% confidence interval around rates STROND guidelines for reporting*	

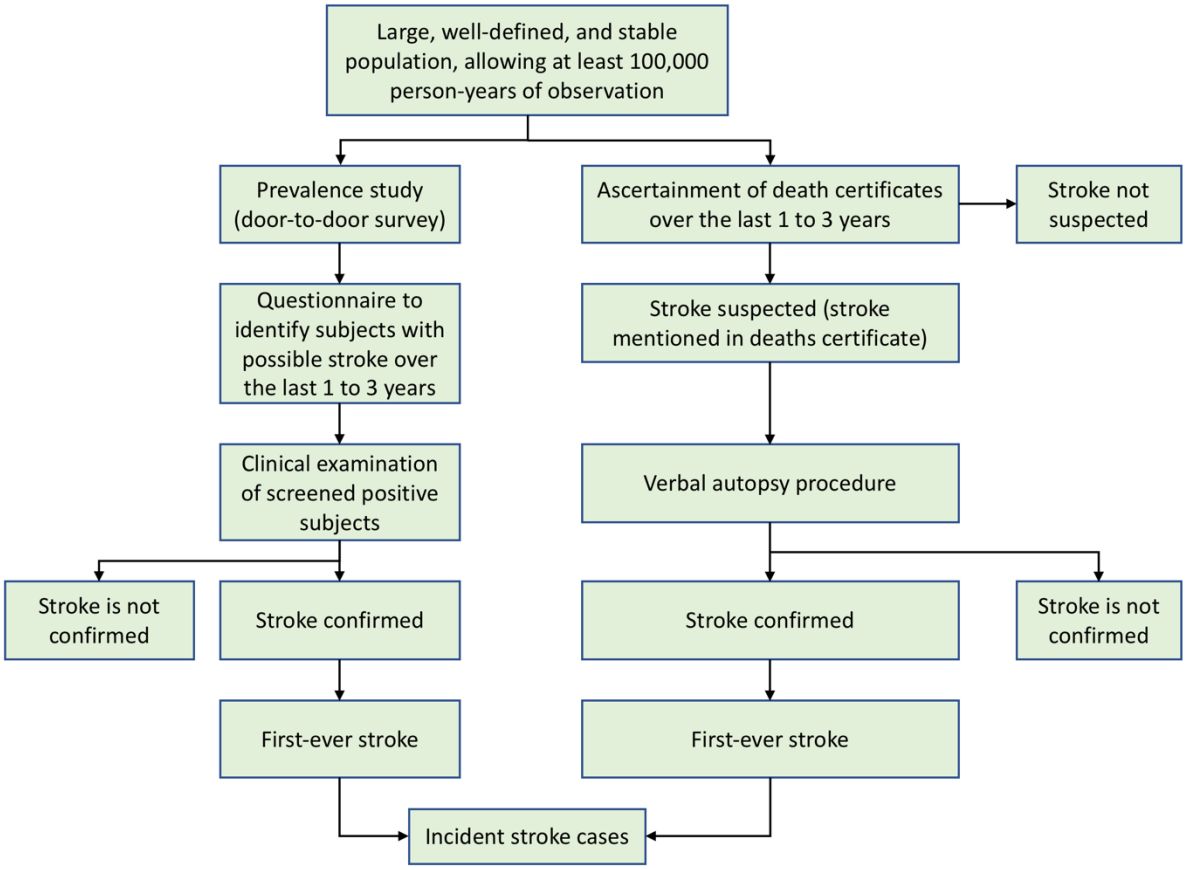
*New criteria.

Table 2. Standards for reporting population-based stroke and TIA incidence studies (Adapted from Bennett et al.,[60] with permission)

SECTION/TOPIC	RECOMMENDATION
Title	Give the type of study design employed using a widely recognised term
Abstract	The abstract should give an accurate summary of how the study was conducted and the main findings
Introduction	
Background	Details of the scientific rationale for the study should be reported
Aims/objectives	State the specific aims and objectives of the study
Methods	
Study design	Give a full description of the study design, and what criteria it meets to be called a population-based study
Setting	Clearly defined (usually, but not always, on a geographic basis), and stable, with reliable information on in- and out-migration
Source population	Description of how all eligible members of the population were identified and through what data sources (e.g. hospitals, outpatient clinics, death certificates). Source of data used for the study (e.g. administrative database, medical records). If administrative database used algorithms for data extraction should be described. Description of the rate of hospital admission. Details of health care system in the country (study region) where the study was conducted (e.g. public versus private health care system). Description of how a person with stroke or TIA is referred in the country (study region) where the study was conducted. Description and characteristics of response rate/drop outs and exclusion rate if applicable.
Study participants	Definition of stroke and/or TIA is clearly identified and presented in sufficient detail. Details of the sampling method are described (are participants representative of the source population). Fully validated source of diagnosis or ''reference-standard'' criteria applied. Definition and justification of disease severity (preferably using a standardised scale). Description of how types/subtypes of stroke/TIA are distinguished (if relevant). Description of how completeness of case-ascertainment was assessed. Description of whether completeness of case ascertainment was adequate.
Ethical approval	Details of ethics approval/informed consent/data governance should be reported.
Measurement	Give details of how incidence was determined (based on timing of data collection either prospectively or retrospectively). Definition and justification of timing of measurements. The data presented to some specified time period (usually whole years or person-time). Raw numbers are reported in sufficient detail to calculate the appropriate rates (e.g. by age or gender).
Statistical methods	If rates have been standardised (e.g. by age or gender), then the details of the standard population used should be given. If possible two standard populations should be used one with local relevance and the other to facilitate international comparisons. Description of any assumptions made in the calculations should be reported. An explanation of how missing data was addressed in the analyses.
Results	
Main findings	Consider a flow diagram that describes how participants were included in the study (useful in order to assess how a person with stroke/TIA is referred). Give appropriate

	rates with their associated 95% confidence intervals. Report results of any sensitivity analyses.
Discussion	
Key findings	Summarise the key findings in relation to the study aims and objectives.
Interpretation	Interpret the results in the context of the evidence from other well performed studies with similar designs and objectives. Reliability of the estimates (i.e. based on the reporting of the statistical methodology, and study design, measurement of key information)
Limitations	Discuss potential limitations of the study. Include details of risk of bias (e.g. selection bias), completeness of case ascertainment, and data quality (assessment of its probability, size and potential importance)
Generalisability	Discuss the external validity of the study findings. Are the results consistent with reviews of descriptive epidemiological studies on the same topic that cover different settings.
Implications	Discuss implications of the research findings for practice and future research

Figure. A basic population-based stroke and TIA incidence study utilising door-to-door survey (Adapted from Feigin,[20] with permission)



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