

# BMJ Open Quantifying the risk of heart disease following acute ischaemic stroke: a meta-analysis of over 50 000 participants

Trishna Gunnoo,<sup>1</sup> Nazeeha Hasan,<sup>1</sup> Muhammad Saleem Khan,<sup>1</sup> Julia Slark,<sup>2</sup> Paul Bentley,<sup>1</sup> Pankaj Sharma<sup>3,4</sup>

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<sup>1</sup>Department of Medicine, Imperial College London, London, UK

<sup>2</sup>Faculty of Medical & Health Sciences, University of Auckland, Auckland, New Zealand

<sup>3</sup>Ashford & St Peters Hospital, Surrey, UK

<sup>4</sup>Institute of Cardiovascular Research Royal Holloway University of London (ICR2UL), London, UK

**Correspondence to** Professor Pankaj Sharma; [pankaj.sharma@rhul.ac.uk](mailto:pankaj.sharma@rhul.ac.uk)

## ABSTRACT

**Objective:** Following an acute stroke, there is a high risk of recurrence. However, the leading cause of mortality following a stroke is due to coronary artery disease (CAD) and myocardial infarction (MI) but that risk has not been robustly quantified. We sought to reliably quantify the risk of ischaemic heart disease (IHD) in patients presenting with acute ischaemic stroke (AIS) in the absence of a known cardiac history.

**Setting:** A meta-analysis study. PubMed, MEDLINE, EMBASE and Google Scholar were searched for potential studies up to October 2015. Included studies reported an acute cerebral ischaemic event and followed for CAD or MI within 1 year in patients without known IHD. Using arcsine transformed proportions for meta-analysis, studies were combined using a generic inverse variance random-effects model to calculate the pooled standardised mean difference and 95% CIs. These were interpreted as the percentage prevalence of CAD or incidence of MI following AIS.

**Results:** 17 studies with 4869 patients with AIS demonstrated a mean average of asymptomatic CAD in 52%. Anatomical methods of CAD detection revealed a prevalence of asymptomatic  $\geq 50\%$  coronary stenosis in 32% (95% CI 19% to 47%;  $p < 0.00001$ ). 8 studies with 47229 patients with ischaemic stroke revealed an overall risk of MI in the year following stroke of 3% (95% CI 1% to 5%;  $p < 0.00001$ ) despite the absence of any cardiac history.

**Conclusions:** One-third of patients with ischaemic stroke with no cardiac history have more than 50% coronary stenosis and 3% are at risk of developing MI within a year. Our findings provide a reliable quantitative measure of the risk of IHD following AIS in patients with no cardiac history.

## INTRODUCTION

Cardiovascular disease is the single leading cause of mortality worldwide,<sup>1</sup> costing the UK economy £19 billion every year, with the National Health Service in England spending around £6.8 billion on cardiovascular disease in 2012/2013.<sup>2</sup> Given our ageing population and global increase in non-communicable diseases, the burden of heart

## Strengths and limitations of this study

We study the risk of heart disease following a stroke in those patients with no cardiac history. This study is the largest of its kind and, by bringing together multiple data sets, robustly quantifies the risk of heart disease following stroke. As with all meta-analyses, the main limitation of this work relates to publication bias.

- Most patients with stroke die of heart disease.
- One in three patients with ischaemic stroke with no cardiac history have more than 50% coronary stenosis.
- 3% are at risk of developing myocardial infarction within a year of their stroke.
- Patients with stroke need to be screened for silent heart disease and appropriate and aggressive management of total cardiovascular risk factors is required.

disease and stroke is becoming an ever increasing public health issue.<sup>3</sup>

Atherosclerosis as a systemic process; common risk factors and pathophysiology exists between ischaemic stroke, coronary artery disease (CAD) and myocardial infarction (MI).<sup>4</sup> Any acute atherosclerotic event increases the risk for another in the same or different vascular bed.<sup>5</sup> Following an acute ischaemic stroke (AIS), there is a high short-term risk of recurrence; however, the leading cause of mortality in these patients is MI.<sup>4 6 7</sup>

A number of studies have evaluated the relationship between stroke and MI yet show varying results on the rate of subsequent cardiovascular events<sup>6 8 9</sup> with wide discrepancy in the observed prevalence of asymptomatic CAD ranging from 15% to 80% following AIS.<sup>10 11</sup> While it is probable that those with an established history of ischaemic heart disease (IHD) will account for the majority of subsequent coronary events following AIS, the true risk of CAD and MI in patients with stroke in the absence of a cardiac history is unclear.

In an attempt to provide clarity and quantification on this issue, we conducted a systematic review and meta-analysis to determine the prevalence of asymptomatic CAD and incidence of MI in patients with AIS in the absence of previous cardiac disease. To the best of our knowledge, this is the largest such study conducted to date.

## METHODS

### Data sources

A search was performed using electronic databases PubMed, MEDLINE, EMBASE and Google Scholar to identify all relevant published studies up to October 2015. The search strategy included keywords with synonyms and MeSH terms: [stroke] OR [cerebrovascular accident] OR [CVA brain] OR [cerebral infarction] OR [transient ischaemic attack] OR [transient ischemic attack] OR [TIA] OR [Cerebral Infarction] OR [Stroke] OR [Brain Ischemia] OR [Ischemic Attack] OR [Transient], along with [asymptomatic coronary artery disease] OR [asymptomatic CAD]; [asymptomatic coronary heart disease] OR [asymptomatic CHD], along with [subclinical ischaemic heart disease] OR [silent myocardial infarction] OR [silent MI] OR [silent myocardial ischaemia]. Search criteria were limited to humans. All terms were then subjected to interaction with each other with Boolean operators *AND* or *OR*. Foreign language literature was included and papers translated where necessary. Manual searches identified additional studies from the references of electronically identified studies.

### Study selection

Studies were selected by TG, NH and JS if they fulfilled the following inclusion criteria: (1) acute onset of stroke or transient ischaemic attack (TIA); (2) lesion confirmed by brain imaging (CT/MRI) or at autopsy; (3) investigations for CAD with acceptable levels of sensitivity and specificity<sup>12</sup>; (4) diagnosis of MI according to criteria of the third universal definition proposed by international expert consensus,<sup>13</sup> and (5) follow-up data for CAD or MI up to 1 year from stroke onset.

Studies were excluded if: (1) age < 18 years; (2) haemorrhagic stroke and (3) history of IHD (CAD or MI), unless subgroup data were presented for extraction. Owing to the low specificity of ECG to detect ischaemia, investigations using ECG or exercise ECG alone were excluded, except when in conjunction with another modality of testing such as troponin.<sup>14</sup> Where duplicate studies were identified, data from the latest data set were used. In an attempt to enhance the quality of our analyses, only studies that recruited a minimum of 50 participants were included for final analysis. Studies with a higher minimum number of participants were more likely to be conducted in a systematic manner with a probably more reliable result.<sup>15</sup> We used the STROBE<sup>16</sup> checklist as an initial screen of cohort studies and to extract data, MOOSE<sup>17</sup> criteria for the reporting of

observational studies and the PRISMA statement to guide our reporting of the meta-analyses.<sup>18</sup>

### Data extraction

Data extraction was undertaken independently by two investigators (TG and JS) and any disagreements were resolved by consensus or by the opinion of a third reviewer. For each selected study, the total population of patients with ischaemic stroke without a history of IHD and the proportion with asymptomatic CAD or MI were extracted. Additional information on study design, method of CAD/MI diagnosis, as well as baseline characteristics such as mean age, sex, ethnicity and the presence of risk factors for cardiovascular disease, was documented.

### Statistical analysis

Since this was a one-sided investigation without a comparison group, a double arcsine transformation was used for proportion meta-analysis.<sup>19 20</sup> For each study, the proportion of patients with stroke who were positive for asymptomatic CAD or silent MI from the total population of patients was recorded. The proportions *P* within the populations were calculated by dividing the number of positive events by the number of patients with stroke without known heart disease.

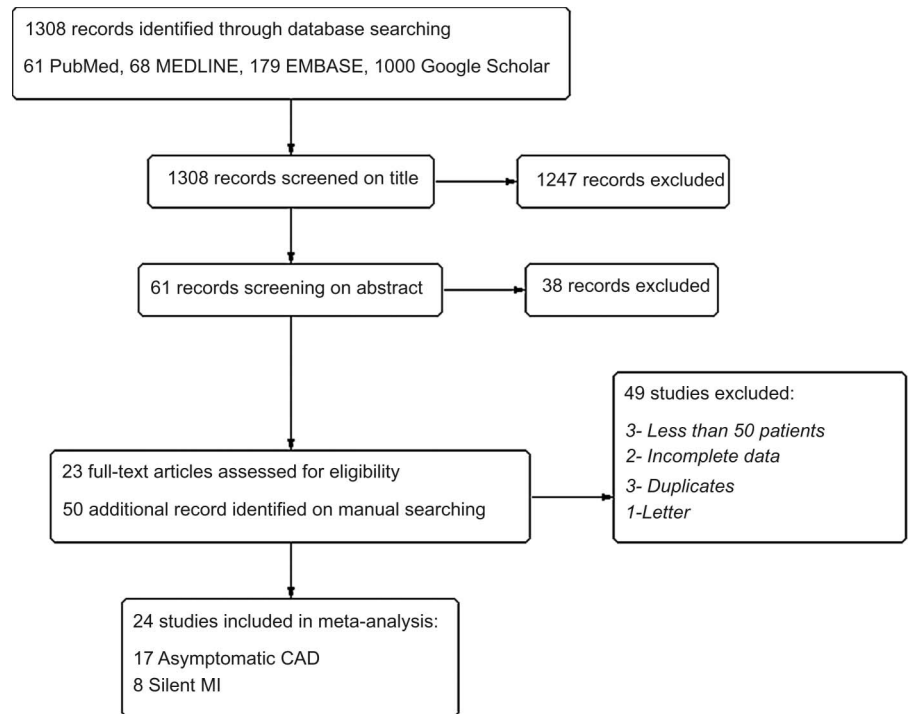
The standardised mean difference (SMD) and SE for each proportion were then calculated: Standardised mean difference (SMD) =  $2 \times \arcsin(\sqrt{P})$  and SE was generated by  $1/\sqrt{n}$ . The results were combined using a generic inverse variance random-effects model (DerSimonian and Laird) to calculate weighted pooled SMD and 95% CIs using review manager SMD = (A).<sup>21</sup> The concluding result was interpreted as the percentage prevalence of CAD or incidence of MI by transforming data back to the original scale to give pooled percentage prevalence: % prevalence =  $(\sin \times (A/2))^2 \times 100$ .<sup>22</sup>

To accurately determine the prevalence of asymptomatic CAD, meta-analysis was restricted to studies reporting more sensitive methods of CAD investigation and significant coronary artery occlusion ( $\geq 50\%$  stenosis). Tests for heterogeneity and sensitivity analysis were performed by systematically and iteratively removing one study at a time and re-running the model to determine the overall effect size. On the basis of the statistical method used, it was not possible or appropriate to assess for publication bias in this study.<sup>20</sup>

## RESULTS

In total, 1308 records were identified and, following screening for exclusions, a total of 24 studies met our inclusion criteria (figure 1). Seventeen studies with 4869 patients with AIS/TIA investigated for asymptomatic CAD and eight studies with 47 229 patients demonstrated risk of MI following ischaemic stroke in those without a cardiac history (table 1). Twenty-three studies recruited patients prospectively.

**Figure 1** Flow diagram of search strategy (CAD, coronary artery disease; MI, myocardial infarction).



### Prevalence of asymptomatic CAD

There was a similar proportion of males to females in each of the included studies, with an average of 55% males and a mean age of 66 years. With the exception of a single autopsy study<sup>23</sup> where the median time between stroke and death was 12 days (IQR 5–32 days), all studies recruited patients with stroke within 10 days. While most studies included ischaemic stroke of atherosclerotic aetiology, three studies excluded cardioembolic stroke<sup>5 10 32</sup> and only one study included those with suspected cardioembolism.<sup>29</sup> Three studies looked exclusively at first ischaemic stroke.<sup>28 32 27</sup> There were limited data available for the risk factors present in patients found to have asymptomatic CAD; where evaluated, there were varying levels of all risk factors, except hypertension which coexisted in 42–67% of patients with stroke and was as high as 96% in one study.<sup>24</sup> Owing to the variety of methods of investigation with varying levels of sensitivity, and wide range of results, it was not appropriate to perform a meta-analysis on all 17 studies, but the mean average of asymptomatic CAD was 52%.

Meta-analysis was performed on 11 studies using coronary angiography, CT coronary angiography (CTCA), coronary calcium score (CCS) and autopsy as more sensitive investigations for asymptomatic CAD in patients with AIS. This revealed for any degree of coronary plaque a pooled SMD of 1.41 (95% CI 1.16 to 1.66;  $T^2=0.27$ ;  $I^2=99\%$ ;  $p<0.00001$ ) equivalent to a prevalence of 53% (95% CI 43% to 63%) (figure 2). A pooled SMD of 1.20 (95% CI 0.89 to 1.51;  $T^2=0.27$ ;  $I^2=99\%$ ;  $p<0.00001$ ) was observed (figure 3), equivalent to a prevalence of  $\geq 50\%$  asymptomatic coronary stenosis of 32% (95% CI 19% to 47%). Significant heterogeneity

was observed, which was unchanged following iterative analysis, removal of patients with TIA<sup>5 31</sup> and a unique autopsy study conducted prior to the year 2000.<sup>23</sup> Prevalence of any degree of coronary artery stenosis was not statistically significant, most likely due to the high variance in the studies analysed. However, removal of non-Caucasian populations<sup>11 25–31</sup> yielded a statistically significant pooled SMD of 1.03 (95% CI 0.88 to 1.17;  $p=0.01$ ), equivalent to an asymptomatic CAD prevalence of 24% (95% CI 18% to 30%).

### Incidence of myocardial infarction

With the exception of one study,<sup>39</sup> all eight studies prospectively recruited patients with stroke. The majority of studies were based in predominately Caucasian populations from across Europe, Canada and the USA. The largest observational study included a total of 37 214 participants from multiple stroke centres across Austria.<sup>37</sup> For each study, there were similar demographics including a balanced proportion of males to females, with an average of 53% males and a mean age of 70 years. There were limited data evaluating risk factors in those patients with MI which was diagnosed within 3 months of the AIS and, in most studies in-hospital. A pooled SMD of 0.35 (95% CI 0.24 to 0.46;  $T^2=0.02$ ;  $I^2=98\%$ ;  $p<0.00001$ ) equivalent to a total MI incidence of 3% (95% CI 1% to 5%) in patients with stroke with no cardiac history (figure 4).

### DISCUSSION

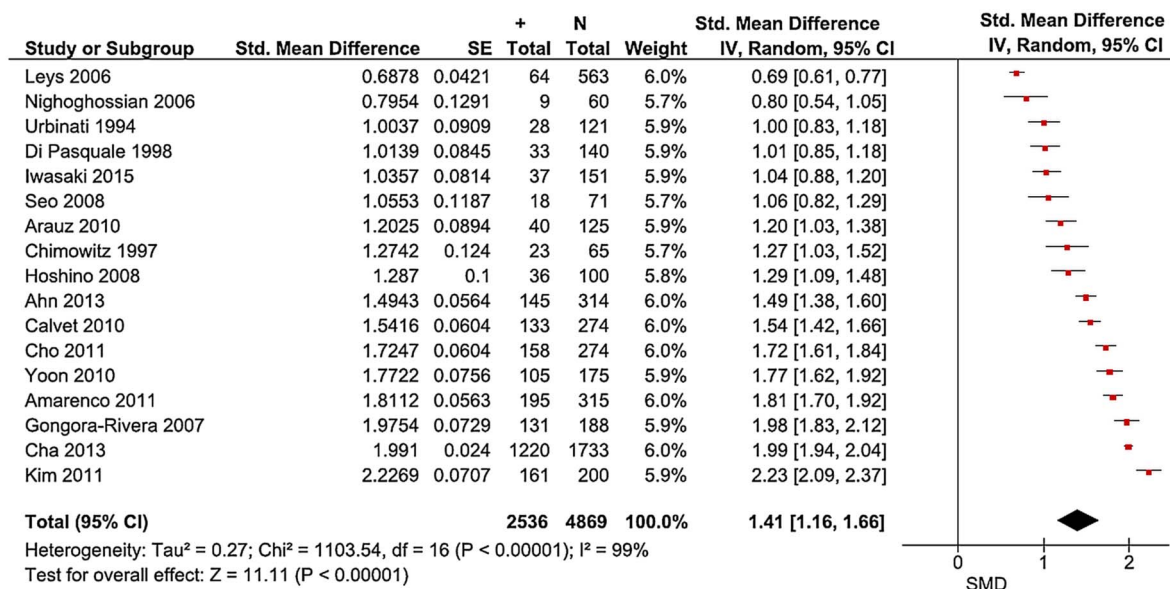
This study, which quantifies the risk of IHD following ischaemic stroke, revealed that over half of such patients with stroke have evidence of asymptomatic coronary

**Table 1** Studies and their characteristics

Study	Location	Male (%)	Mean age	Ischaemic event	Method of investigation	N	Asymptomatic CAD			MI	
							n	Per cent	>50% stenosis	n	Per cent
Gongora-Rivera <i>et al</i> , <sup>23</sup> MASS	France	55	60	Fatal stroke	Autopsy: plaque, ischaemia, MI necrosis/fibrosis >1 cm	188	131	70	29	59	31
Amarenco <i>et al</i> , <sup>24</sup> AMISTAD	France	72	62	Stroke	Coronary angiography	315	195	62	26	–	–
Ahn <i>et al</i> <sup>25</sup>	Korea	65	66	Stroke/TIA	CTCA	314	145	46	46	–	–
Calvet <i>et al</i> , <sup>5</sup> PRECORIS	France	70	63	Stroke/TIA	CTCA	274	133	49	18	–	–
Cha <i>et al</i> <sup>26</sup>	Korea	64	63	Stroke/TIA	CTCA	1733	1220	70	33	–	–
Cho <i>et al</i> <sup>27</sup>	Korea	60	68	1st stroke	CTCA	274	158	58	22	–	–
Hoshino <i>et al</i> <sup>28</sup>	Japan	72	66	1st stroke	CTCA	100	36	36	36	–	–
Iwasaki <i>et al</i> <sup>11</sup>	Japan	67	63	Stroke	CCS (calcium score)	151	37	25	25	–	–
Kim <i>et al</i> <sup>29</sup>	Korea	70	67	Stroke	CTCA	200	161	81	36	–	–
Seo <i>et al</i> <sup>30</sup>	Korea	63	68	Stroke	CTCA	71	18	25	25	–	–
Yoon <i>et al</i> <sup>31</sup>	Korea	50	71	Stroke/TIA	CTCA	175	105	60	21	–	–
Arauz <i>et al</i> <sup>32</sup>	Mexico	69	62	1st stroke	Stress SPECT	125	40	32	–	–	–
Chimowitz <i>et al</i> <sup>33</sup>	USA	64	61	Stroke/TIA	Stress thallium myocardial scintigraphy	65	23	35	–	–	–
Di Pasquale <i>et al</i> <sup>34</sup>	Italy	73	56	Stroke/TIA of the carotid system	Exercise thallium myocardial imaging	140	33	24	–	–	–
Urbinati <i>et al</i> <sup>35</sup>	Italy	71	64	Stroke/TIA of the carotid system	Exercise thallium myocardial scintigraphy	121	28	23	–	–	–
Nighoghossian <i>et al</i> <sup>10</sup>	France	80	59	Stroke	Stress echo	60	9	15	–	–	–
Leys <i>et al</i> , <sup>36</sup> DETECT	France	74	69	Stroke	ECG+echo	563	64	11	–	–	–
Gattringer <i>et al</i> <sup>37</sup>	Austria	53	74	Stroke/TIA	Troponin+ECG	37 214	–	–	–	181	0.5
Jensen <i>et al</i> <sup>38</sup>	Denmark	52	75	Stroke	Troponin+ECG	244	–	–	–	7	3
Lee <i>et al</i> <sup>39</sup>	Korea	56	67	Stroke	Troponin+ECG	1247	–	–	–	8	1
Liao <i>et al</i> <sup>40</sup>	Canada	52	72	Stroke	Troponin+ECG	7199	–	–	–	129	2
Mathias <i>et al</i> <sup>41</sup>	USA	52	64	Stroke	Troponin+ECG+echo	323	–	–	–	7	2
Prosser <i>et al</i> , <sup>42</sup> VISTA	Canada, Germany, Sweden, UK, USA	49	73	Stroke	Cardiac mortality & serious cardiac adverse events	458	–	–	–	33	7
Song <i>et al</i> <sup>43</sup>	Korea	56	72	Stroke	Troponin+ECG	356	–	–	–	0	0

AMISTAD, Asymptomatic Myocardial Ischemia in Stroke and Atherosclerotic Disease; CAD, coronary artery disease; CCS, coronary calcium score; CTCA, CT coronary angiography; MASS, Multiple Atherosclerosis Site in Stroke; MI, myocardial infarction; TIA, transient ischaemic attack.





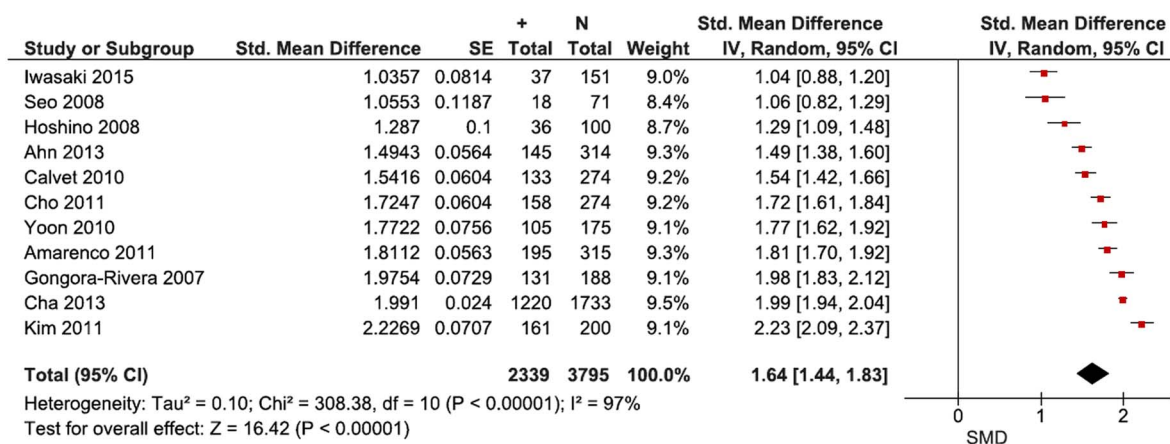
**Figure 2** Forest plot: prevalence of asymptomatic coronary artery disease after stroke.

plaque and one in three patients have an occlusion of clinical significance (>50% stenosis). Given the strong evidence linking coronary artery stenosis >50% to the high risk of acute MI,<sup>44 45</sup> and our findings that 3% of patients with ischaemic stroke suffer from MI within 1 year, it is clear that many more individuals with no history of IHD may be at risk of MI than previously appreciated.

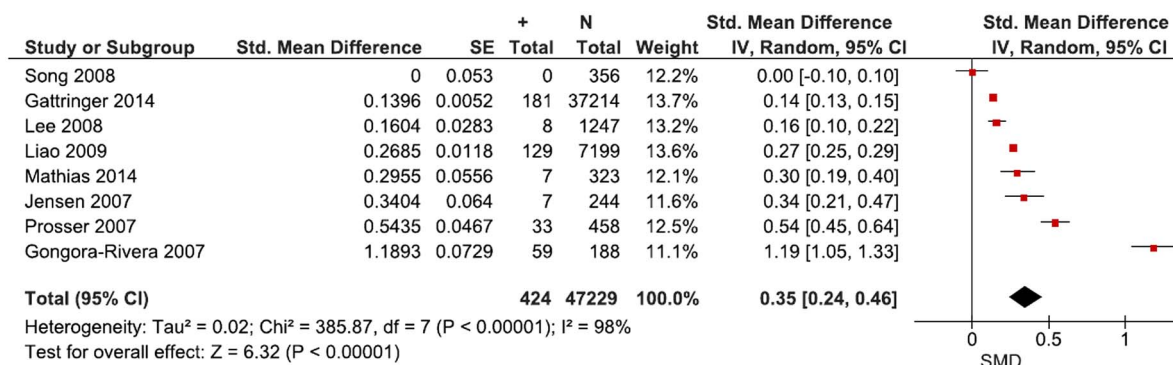
Our results are supported by previously published data that demonstrate a high burden of coronary plaque even when there is no previous evidence of systemic disease. The Asymptomatic Myocardial Ischemia in Stroke and Atherosclerotic Disease (AMISTAD) study set out to determine whether asymptomatic coronary atherosclerosis predicts a higher risk of major vascular event in patients with stroke and found that, from a baseline diagnosis of asymptomatic CAD, the 2-year HR of patients with stroke developing  $\geq 1$  vessel disease (coronary stenosis >50%) was 3.43 (95% CI 1.48 to 7.93).<sup>24</sup> In the Multiple Atherosclerosis Site in Stroke (MASS)

study, patients with stroke with no atherosclerotic plaque in the cerebral arteries demonstrated prevalence of coronary plaque as high as 51%.<sup>23</sup> Thus, despite the limitations in predicting the presence of asymptomatic CAD, based on the detection of extra-cardiac atherosclerosis, an association exists and there is a significant global vascular burden in patients with stroke.

There are limited data to compare our results with the prevalence of subclinical atherosclerosis in an asymptomatic population of similar age. A Norwegian study in 1852 asymptomatic male office workers found that 2.7% had at least one coronary stenosed artery  $\geq 50%$  by coronary angiography.<sup>46</sup> A recent European study with 244 asymptomatic patients undergoing CTCA found a 5% prevalence of obstructive CAD requiring further investigation.<sup>47</sup> One larger Korean study with 6311 asymptomatic patients found a prevalence of coronary atherosclerosis >50% stenosis in 9% by CTCA.<sup>48</sup> Thus, there is considerable difference in cardiac risk between



**Figure 3** Forest plot: prevalence of asymptomatic coronary artery disease >50% stenosis after stroke.



**Figure 4** Forest plot: incidence of myocardial infarction after stroke.

the asymptomatic population and patients with stroke, with a prevalence gap from these few studies ranging between 23% and 29%.

Following a cerebrovascular ischaemic event, patients with no known IHD history the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial demonstrated not only the high risk of cardiac events but also supports the benefits of statin therapy in the treatment of stroke when considering this ischaemic event as a coronary risk equivalent.<sup>49</sup> In determining the beneficial effects of blood pressure reduction, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) found that 1.2% of patients with ischaemic stroke went on to have non-fatal MI or death accountable to coronary heart disease (CHD), concluding that secondary prevention should target the cause of the original event as well as mixed vascular risk factors.<sup>50</sup> The results from an older meta-analysis<sup>6</sup> calculated a 2.2% annual risk of MI after ischaemic stroke/TIA, although it failed to estimate the risk of MI according to the cardiac history. Our results support proposals of the American Heart Association and American Stroke Association recommending that patients with stroke be considered for further cardiac evaluation on the basis of their individual cardiovascular risk factor profile.<sup>50 51</sup>

Despite our efforts, no meta-analysis is free from publication bias. A considerable level of heterogeneity in our analyses reflects clinical differences between the studies with inclusion of different subtypes of ischaemic events partly accounting for some of the observed variation. In particular, the different investigations to determine the extent and severity of coronary stenosis (eg, formal coronary angiography, CT angiogram, CCS) may not be equally comparable in terms of their assessment of stenosis. Although we categorise the data by cardiac investigation in [table 1](#), the overall pooled result is subject to this limitation. To limit the effect of major differences occurring in clinical cardiovascular care, studies prior to the year 2000 were removed. We attempted to improve quality control by incorporating studies with at least 50 participants. These larger studies tend to be better conducted. Study populations located worldwide demonstrated the global burden of asymptomatic disease;

however, our results should be extrapolated to other ancestral populations with caution.

We demonstrate that up to a third of patients with ischaemic stroke with no cardiac history have more than 50% coronary stenosis and 3% are at risk of developing MI within 1 year following their stroke even in the absence of any previous cardiac symptoms. The cardiac risk posed to patients with ischaemic stroke is substantial even in the absence of an IHD history.

**Contributors** PS conceived the idea and designed the overall strategy. He critically revised the first and all subsequent drafts and gave final approval to submit. He agrees to be accountable for all aspects of this work. TG, NH and JS undertook the preliminary searches and designed the search criteria. TG wrote the first draft and gave final approval to submit. They both agree to be accountable for all aspects of this work. NH, PB and MS undertook independent statistical analysis of the data with each providing their expert statistical advice. They critically reviewed and revised all manuscript drafts, particularly in relation to the statistical aspects, and all agree to be accountable for all aspects of this work.

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**Competing interests** None declared.

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**Data sharing statement** No additional data are available.

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