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REVIEW ARTICLE

Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting

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Brain microbleeds (BMBs) are seen as small, homogeneous, round foci of low signal intensity on magnetic resonance imaging gradient echo (GRE) T_2^* sequences. BMBs might only be a biomarker for microangiopathy, or alternatively BMBs might provide useful diagnostic and prognostic information, potentially with therapeutic implications for the treatment of stroke. Because of the rapid expansion in recent BMB research, we systematically reviewed and critically appraised the published literature according to QUADAS, STARD and Cochrane principles. Our selection criteria were met by 54 studies of 53 case series involving 9073 participants, 4432 of whom were people with cerebrovascular diseases. There were significant biases in many of the studies: variation in MRI magnet strength, flip angle, slice gap and slice thickness; inconsistent definitions of BMB size (23% did not define size at all, and of those that did 44% chose a diameter of $\leqslant$5 mm); only 30% included participants who were representative of the disease under study; and only 53% mentioned that BMB evaluation was blinded to other factors of interest. By pooling data from similar studies, we found that the prevalence of BMBs was 5% [95% confidence interval (CI) 4–6] in healthy adults, 34% (95% CI 31–36) in people with ischaemic stroke, and 60% (95% CI 57–64) in people with non-traumatic intracerebral haemorrhage (ICH). In the studies where a distinction could be made, BMBs were more prevalent among recurrent strokes than first-ever strokes: they affected 23% (95% CI 18–29) with first-ever ischaemic stroke but 44% (95% CI 34–54) with recurrent ischaemic stroke, and 52% (95% CI 47–56) with first-ever ICH but 83% (95% CI 71–90) with recurrent ICH. By pooling data that could be extracted from similar studies, it appears that BMBs are associated with hypertension (OR 3.9, 95% CI 2.4–6.4) and diabetes mellitus (OR 2.2, 95% CI 1.2–4.2) in otherwise healthy adults, and that they are associated with hypertension (OR 2.3, 95% CI 1.7–3.0) in adults with cerebrovascular diseases. The association with hypertension was robust in sensitivity analyses. There is a pressing need for better designed studies to assess the diagnostic utility of BMBs, disentangle the many likely influences on their occurrence, and determine their prognostic utility and whether they should influence treatment. We conclude by proposing criteria for ideal study design and reporting.

Keywords: stroke; intracerebral haemorrhage; magnetic resonance imaging; microbleeds; epidemiology

Abbreviations: BMB = brain microbleeds; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; CI = confidence interval; EPI = echo planar imaging; GRE = gradient echo; ICH = intracerebral haemorrhage; OR = odds ratio; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; STARD = Standards for the Reporting of Diagnostic Accuracy; T = tesla; TIA = transient ischaemic attack; tPA = tissue plasminogen activator; TR = Relaxation Time; TE = Echo Time

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Introduction

The increasing use of haem-sensitive GRE T_2^* sequences in magnetic resonance imaging (MRI) of the brain during the research and clinical investigation of neurological disorders—especially stroke—has led to the frequent detection of apparently spontaneous, small, homogeneous, round foci of low signal intensity. These abnormalities were first described in the mid-1990s using a variety of synonyms (Chan *et al.*, 1996; Greenberg *et al.*, 1996; Offenbacher *et al.*, 1996), but because of the common use of the term 'microbleed' and the need to be organ-specific, we prefer to call them brain microbleeds (BMB). Although BMBs have a characteristic appearance, they can be mimicked by flow voids in pial blood vessels in cortical sulci, type IV cavernous malformations (Zabramski *et al.*, 1994), haemorrhagic transformations of cerebral infarcts, and symmetrical hypointensities in the globi pallidi due to iron deposition or calcification (the latter can be distinguished using computed tomography) (Fig. 1).

So far, published reports of the pathology of BMBs relate to fewer than 20 people. The pathological abnormalities underlying BMBs detected on brain MRI were studied in 11 people who died after non-traumatic intracerebral haemorrhage (ICH) (Fazekas *et al.*, 1999), and in three people who died from a variety of other diseases (Tanaka *et al.*, 1999). BMBs visualized on gradient echo (GRE) MRI bore the pathological hallmarks of old haemorrhages, and the deep perforating arteries feeding the areas of the brain harbouring BMBs showed moderate to severe lipohyalinosis and occasional amyloid deposits in one study (Fazekas *et al.*, 1999), and ruptured arteriosclerotic microvessels in another (Tanaka *et al.*, 1999).

On the other hand, imaging studies of BMBs have accumulated rapidly: three were published in 1996 rising to 32 in 2004. However, it is uncertain whether BMBs are useful diagnostic markers (for example, of cerebral amyloid angiopathy), significant risk factors (for example, for future ICH) and whether BMBs should influence treatment (for example, secondary prevention of future stroke, and even vascular dementia). Some of this uncertainty may have arisen from variation in BMB definitions and the imaging sequences used for diagnosis, as well as the selection of study participants who were not wholly representative of their disease group. So far, there have been three useful narrative reviews about BMBs, but none of them appeared to use systematic literature searches, critical appraisal criteria or subgroup/sensitivity analyses (Fiehler, 2006; Koennecke, 2006; Viswanathan and Chabriat, 2006).

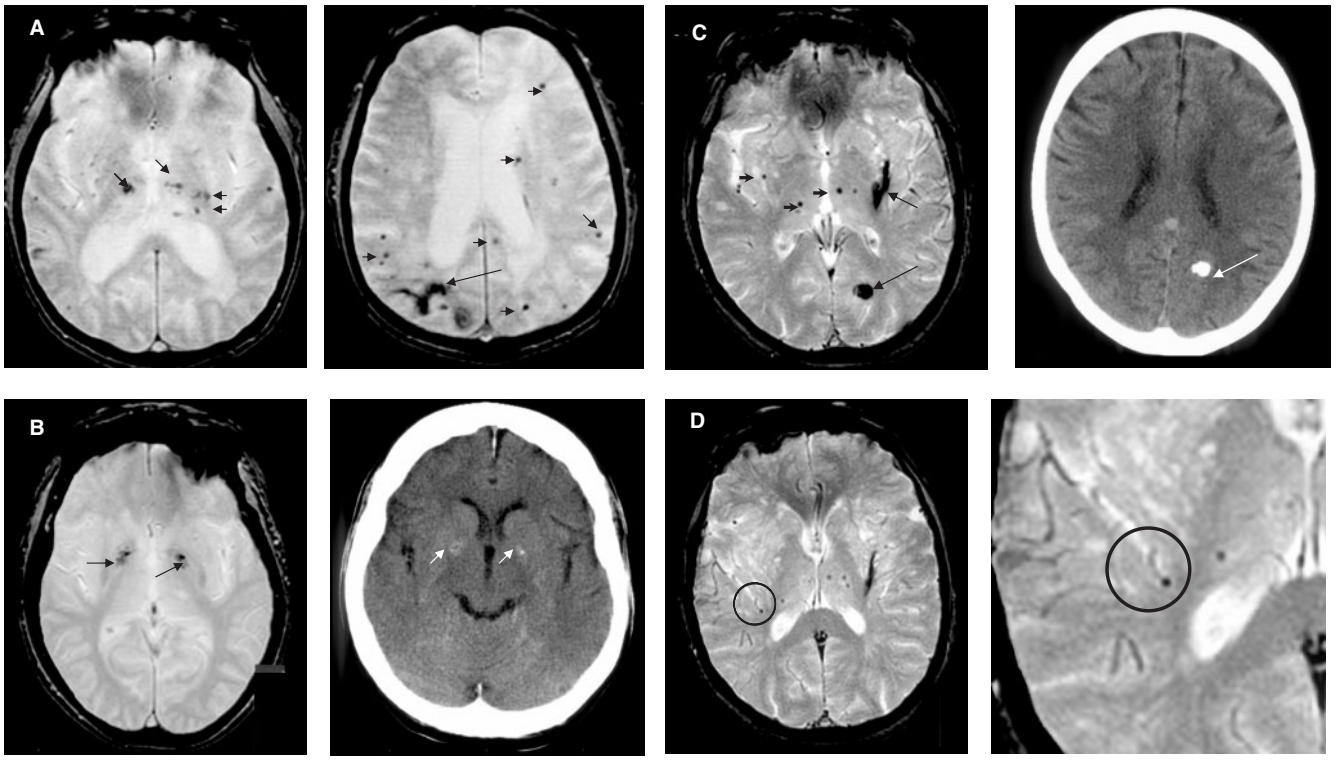

Fig. 1 Illustrative imaging of BMBs and their mimics. MRI parameters: 1.5 teslas, T_2^*-GRE, TE 15 ms, TR 625 ms, two excitations, flip angle 20°, FOV 240 mm, slice thickness 5 mm, slice gap 1 mm, matrix 256 × 192. (**A**) BMBs (short arrows). Note also the old intracerebral haemorrhage in the right occipital region (long arrow). Not all BMBs are marked as they are too numerous. (**B**) Basal ganglia calcification (arrows) on MRI (left) and CT (right). (**C**) Calcification (long arrow) mimicking a BMB on MRI (left), CT (right). Also true BMBs (arrowheads) and old intracerebral haemorrhage (short arrow). (**D**) Flow void mimicking a BMB (left, circled), enlarged on right. Note the vessel in a sulcus leading up to the black dot indicating that it is a vessel flow void in cross section.

Therefore, we set out to systematically review the published studies of BMBs and critically appraise their methodological quality in order to pool comparable studies of BMBs to answer several important questions in clinical practice:

- How frequent are BMBs?
- Do definitions of BMB size and the MR sequence parameters used to image BMBs influence the apparent prevalence of BMBs?
- Are vascular risk factors, gender or age associated with BMBs?
- Is antiplatelet or anticoagulant treatment associated with a higher prevalence of BMBs?
- Are radiological lacunes and leucoaraiosis associated with BMBs?
- Is the distribution of BMBs diagnostically useful?
- Are BMBs associated with an increased risk of future stroke occurrence/recurrence?
- Does treatment with antiplatelet, anticoagulant or thrombolytic agents increase the future risk of intracerebral haemorrhage for people with BMBs?

Table 1 Ideal design of studies of BMBs

Prevalence of BMBs in particular disease groups
• MRI parameters specified and including a suitable GRE sequence
• BMB appearance and size clearly defined
• Participants' diagnosis clearly defined (ideally clinical ± radiological, independent of risk factors, at a uniform inception point in the disease)
• Participants generalizable
Classification of BMB distribution
• Anatomical areas clearly defined
• Inter- and intra-observer agreement quantified
Association of BMBs with clinical/radiological features
• Risk factors clearly defined
• Assessment of BMBs blinded to clinical features of interest
• Comparison group(s) chosen appropriately
Assessment of BMBs as predictors of prognosis
• Prospective study design
• Objective, predefined and validated outcome events/measures
• Outcome assessed blind to prognostic factors of interest
• Stratification of outcome by differences in treatment, where relevant
• Follow-up >90% complete

Each set of criteria adds to those preceding it. BMB = brain microbleed; MRI = magnetic resonance imaging.

Material and methods

Literature search strategy

On 14 February 2006 we searched Ovid Medline from 1966 and Embase from 1980 using a 20 line electronic search strategy (Supplementary Table 1). Because there was no Medical Subject Heading for BMBs, the search strategy used text words reflecting the variety of synonyms used for BMBs (Supplementary Table 1).

The electronic search was supplemented by the authors' personal files, hand searching the bibliographies of articles retrieved by the electronic search and by surveillance of key journals' tables of contents (*Annals of Neurology*, *Brain*, *Lancet*, *Neurology* and *Stroke*). Although we restricted this review to published data, we did not restrict it by language of publication. One reviewer (CC) performed the literature search and screened the titles and abstracts of retrieved citations to identify potentially suitable studies relating to spontaneous (non-traumatic) BMBs, which were read in full by two reviewers (CC and RAS). One reviewer extracted data from included studies (CC). Uncertainties and disagreements were resolved by discussion with co-reviewers.

Critical appraisal

We critically appraised studies against a customized checklist of ideal characteristics for a study of BMBs (Table 1), based on the principles of the Cochrane collaboration, QUality Assessment of Diagnostic Accuracy Studies (QUADAS) (Whiting *et al.*, 2003) and Standards for the Reporting of Diagnostic Accuracy (STARD) (Bossuyt *et al.*, 2003). We did not develop a study quality score, but focused on study characteristics that might affect results due to bias, confounding or chance.

Our only absolute requirement of every study in this review was the use of GRE T_2^*-weighted or T_2^* echo planar imaging (EPI) MR sequences to diagnose BMBs. GRE T_2^*-weighted sequences are more sensitive to haemosiderin than T_2-weighted spin echo sequences (Atlas *et al.*, 1988). GRE T_2^*-weighted imaging may be more sensitive than T_2^*-EPI images (especially those obtained as the base images from dynamic susceptibility weighted perfusion imaging) but direct comparisons are scant. We therefore included both studies using GRE T_2^*-weighted imaging and those using T_2^*-EPI images but performed sensitivity analyses with and without studies using T_2^*-EPI. Other study attributes in Table 1 were simply desirable. Two attributes deserve further explanation. We made qualitative decisions about the generalizability of included studies, sometimes referred to as 'external validity', by which we mean the extent to which each study can be extrapolated to other groups of people with the same disease, or how representative of the disease group the study is. Selection bias is the main determinant of the extent of bias impairing generalizability of studies' findings (Grimes and Schulz, 2002). Secondly, in comparative studies, the ideal choice of an appropriate comparison group should involve clear diagnostic criteria, selection independent of the exposure of interest (for example, underlying disease, age and history of hypertension, which might influence BMB prevalence), blinded assessment and minimize confounding influences (such as a prior history of stroke) (Schulz and Grimes, 2002; Grimes and Schulz, 2005).

Data extraction

We extracted: attributes of each study's design for critical appraisal; details of the MRI sequences used; and the prevalence of BMBs in different disease groups, disease subgroups and risk factor groups. When we extracted data on risk factors to quantify their influence of risk factors on the occurrence of BMBs, we rated them as 'evaluated' (Table 2).

Table 2 Critical appraisal of studies of BMBs included in this review

Study	BMB size (mm)	Participants defined?	Participants generalizable?	Classification of BMB distribution defined?	Risk factors for BMB development defined?	Assessment of BMB blinded to clinical data?	Appropriate comparison groups?	Risk factors evaluated				
								Gender	Hypertension	Diabetes mellitus	Cardiac ischaemia	Smoking
Healthy												
Jeerakathil *et al*., 2004	<10	■	■	■	■	■	–	■	■	■	□	■
Horita *et al*., 2003	<10	■	■	?	?	?	–	■	■	■	□	■
Tsushima *et al*., 2002	<10	■	■	■	■	?	–	■	■	■	■	■
Roob *et al*., 1999*b*	2–5	■	■	■	■	?	–	■	■	■	■	■
Cerebrovascular diseases: stroke (mixed types of stroke or subtypes not distinguished)												
Alemany *et al*., 2006	<5	□	□	■	■	■	□	□	■	■	■	□
Imaizumi *et al*., 2004*b*	<7	■	■	■	■	?	–	□	□	□	□	□
Kidwell *et al*., 2004	<5	□	□	■	–	■	–	□	□	□	□	□
Lee *et al*., 2004*a*	<5	■	□	■	□	■	–	■	□	■	■	■
Lee *et al*., 2004*b*	<5	■	□	■	□	■	–	■	□	■	■	■
Lee *et al*., 2004*c*	<5	□	□	■	□	?	□	□	□	□	□	□
Lee *et al*., 2004*d*	<5	■	□	■	■	?	–	□	□	□	■	□
Lee *et al*., 2004*e*	⩽5	■	□	■	□	■	–	■	□	■	□	■
Naka *et al*., 2004	□	■	□	□	□	■	–	□	□	□	□	□
Kato *et al*., 2002	□	□	□	■	–	□	□	□	□	□	□	□
Kim *et al*., 2002	<5	■	□	□	■	■	□	□	□	□	□	□
Yanagawa *et al*., 2001	□	■	□	□	□	?	■	□	□	□	□	□
Kinoshita *et al*., 2000	□	□	■	■	–	?	□	□	□	□	□	□
Cerebrovascular diseases: intracerebral haemorrhages												
Lee *et al*., 2006	□	□	□	□	□	■	–	■	■	■	□	■
Greenberg *et al*., 2004	⩽5	■	□	■	■	■	■	□	□	□	□	□
Imaizumi *et al*., 2004*a*	<7	■	□	■	■	?	□	□	□	□	□	□
Jeong *et al*., 2004	<5	■	□	□	■	■	–	■	■	■	■	■
Wong *et al*., 2003	□	■	□	■	□	■	□	□	□	□	□	□
Roob *et al*., 2000	2–5	■	□	■	■	■	□	■	■	■	□	□
Greenberg *et al*., 1999	□	■	□	■	–	■	–	□	□	□	□	□
Tanaka *et al*., 1999	2–5	□	□	■	■	?	□	□	□	□	□	□
Greenberg *et al*., 1996	<10	□	□	■	–	?	□	■	□	□	□	□
Offenbacher *et al*., 1996	2–5	■	■	□	–	–	–	□	□	□	□	□
Cerebrovascular diseases: ischaemic stroke and/or transient ischaemic attack												
Imaizumi *et al*., 2005	<7	■	■	■	■	?	□	□	□	□	□	□
Schonewille *et al*., 2005	<10	■	□	■	□	?	–	□	■	■	□	□
Werring *et al*., 2005	<10	□	□	■	□	■	□	■	■	■	□	■
Fan *et al*., 2004	<5	■	■	■	□	?	–	■	■	■	■	■
Werring *et al*., 2004	<10	■	□	■	□	■	■	□	□	□	□	□
Fan *et al*., 2003	2–5	■	□	■	□	?	–	■	■	■	■	■
Kwa *et al*., 1998	2–5	■	□	■	■	■	□	□	□	□	□	□

Continued

Table 2 *Continued*

Study	BMB size (mm)	Participants defined?	Participants generalizable?	Classification of BMB distribution defined?	Risk factors for BMB development defined?	Assessment of BMB blinded to clinical data?	Appropriate comparison groups?	Risk factors evaluated				
								Gender	Hypertension	Diabetes mellitus	Cardiac ischaemia	Smoking
Cerebrovascular diseases: ischaemic stroke (thrombolysed with IV tPA)												
Kakuda *et al*., 2005	<5	■	□	□	–	■	–	■	■	■	□	■
Derex *et al*., 2004	<5	■	□	■	□	■	–	■	□	□	□	□
Kidwell *et al*., 2002	<5	■	□	□	–	■	–	□	□	□	□	□
Nighoghossian *et al*., 2002	2–5	■	□	□	□	■	–	■	■	■	□	■
Other cerebrovascular disease groups												
Ishikawa *et al*., 2005	□	■	■	□	–	?	–	■	□	□	□	□
Kikuta *et al*., 2005	<10	□	■	□	–	?	□	■	□	□	□	□
Van Den Boom *et al*., 2005	⩽10	□	■	■	■	?	□	□	□	□	□	□
Hanyu *et al*., 2003*b*	>2	■	■	■	□	?	□	□	□	□	□	□
Dichgans *et al*., 2002	2–10	□	■	■	–	?	□	□	□	□	□	□
Jeong *et al*., 2002	□	□	□	■	□	■	–	■	■	■	□	■
Lesnik Oberstein *et al*., 2001	⩽10	□	■	■	■	■	–	■	■	■	■	■
Heterogeneous populations												
Kim *et al*., 2005	<5	□	□	■	■	■	–	□	□	□	□	□
Yokoyama *et al*., 2005	2–5	■	□	□	□	?	□	□	□	□	□	□
Walker *et al*., 2004	2–5	□	□	■	–	■	–	□	□	□	□	□
Tsushima *et al*., 2003	<10	□	□	■	■	?	–	□	□	□	□	□
Lee *et al*., 2002	<5	□	□	□	■	■	–	□	□	□	□	□
Tsushima *et al*., 2000	<10	□	□	■	□	■	–	□	□	□	□	□
Chan *et al*., 1996	□	□	□	■	■	■	□	□	□	□	□	□
Cognitive disorders												
Hanyu *et al*., 2003*a*	□	■	□	■	□	■	□	□	□	□	□	□
Nakata *et al*., 2002	□	■	■	□	□	?	–	□	□	□	□	□

Note: Filled squares denote characteristics fulfilled; open squares denote characteristics not fulfilled; question mark symbol denotes unknown; minus symbol denotes not applicable.

Statistical analysis

Where multiple publications arose from the same case series, we included only the largest or single most relevant study in pooled estimates of prevalence and subgroup analyses. We calculated the prevalence of BMBs by dividing the number of participants harbouring at least one BMB by the total number of study participants. We obtained 95% confidence intervals (95% CIs) for prevalence estimates and odds ratios (OR) to quantify the influence of risk factors on the occurrence of BMBs using Confidence Interval Analysis software (Bryant, 2000). In our quantitative syntheses, studies were not weighted, but simply summed.

Results

The electronic search of Ovid Medline and Embase identified 473 articles, of which 115 concerned BMBs either in people who were healthy or in patients with stroke, related conditions or other non-traumatic neurological diseases. Of these 115 articles, 57 were excluded for the following reasons: 18 case reports, three animal studies, four letters to an editor, five studies on stroke without data on BMBs, 25 narrative reviews on subjects other than BMBs (for example imaging techniques or stroke in general) and two narrative reviews on BMBs. There were 58 eligible studies: two of these were republications of the same series (Roob *et al.*, 1999*a*; van den Boom *et al.*, 2003) and one appeared to be a precursor of a subsequent study (Imaizumi *et al.*, 2001), leaving 55 studies suitable for inclusion. After excluding one study that did not use T_2^*-weighted MRI for BMB diagnosis (Hiroki *et al.*, 2004), we were left with 54 included studies relating to 53 different groups of participants, who numbered 9073 in total. The salient methodological features of the included studies are summarized in Table 2.

What was the quality of the included studies?

Appropriate imaging to diagnose BMB

Although one study did not specify imaging parameters (Kim *et al.*, 2005), in the rest the magnet strength ranged from 0.5 tesla (T) (Yokoyama *et al.*, 2005), 1 T (six studies) and 1.5 T (45 studies), to 3 T (Kikuta *et al.*, 2005) (Supplementary Table 2). Among the 54 studies, four studies used T_2^*-EPI sequences (Tanaka *et al.*, 1999; Kinoshita *et al.*, 2000; Lesnik Oberstein *et al.*, 2001; Kidwell *et al.*, 2004). The sequences varied, even between studies using the same magnet strength, possibly reflecting manufacturer preferences. For example (Supplementary Table 2): at 1.5 T, repetition time (TR) varied from 200 ms to 2598 ms and echo time (TE) from 14 ms to 50 ms; flip angle ranged from 10 to 90°; slice thickness was 1.4–10 mm where specified (11 studies did not mention slice thickness); slice gap ranged from 0 mm to 2.5 mm (13 studies did not state slice gap); and matrix size varied from 192×256 to 256×256 (not stated in 22 studies).

Clear definition of BMBs and their size

All but two studies defined BMBs (Jeong *et al.*, 2002; Lee *et al.*, 2006), and most defined BMBs consistently. Most indicated an awareness of mimics of BMBs, but only 14 studies included CT brain in their protocols to rule out calcification mimicking BMBs (Kwa *et al.*, 1998; Tanaka *et al.*, 1999; Kinoshita *et al.*, 2000; Tsushima *et al.*, 2000; Kim *et al.*, 2002; Fan *et al.*, 2003; Wong *et al.*, 2003; Imaizumi *et al.*, 2004*a*; Imaizumi *et al.*, 2004*b*; Jeong *et al.*, 2004; Ishikawa *et al.*, 2005; Imaizumi *et al.*, 2005; Schonewille *et al.*, 2005; Alemany *et al.*, 2006). BMB maximum diameter was arbitrarily and inconsistently defined: 12 (23%) studies did not describe size at all, nine (17%) specified 2–5 mm, 15 (27%) specified $\leqslant$5 mm, three (6%) specified $\leqslant$7 mm, one (2%) specified 2–10 mm, 12 (23%) specified $\leqslant$10 mm and one (2%) only mentioned a minimum diameter of 2 mm (Table 2).

Clear definition of participants' diagnosis

Thirty-three (62%) studies clearly defined their study group (Table 2): 12 studies did not accurately define their population, whilst eight did define their disease group but failed to distinguish participants with first-ever stroke from those with recurrent stroke. Four (8%) studies involved 1411 healthy adults, 41 studies (75%) involved a total of 3972 participants with cerebrovascular diseases and 460 controls, two studies (4%) involved 97 participants with Alzheimer's disease and 55 controls and seven (13%) other studies concerned 3078 people with a variety of diagnoses, neurological or otherwise. Of the 12 studies that identified lacunar infarcts as an ischaemic stroke subtype, most used risk-factor-based definitions, or radiological criteria only, or did not specify their definition: two studies used the NINDS criteria (NINDS, 1990; Kato *et al.*, 2002; Naka *et al.*, 2004), three used the TOAST criteria (Adams *et al.*, 1993; Kim *et al.*, 2002; Werring *et al.*, 2004; Werring *et al.*, 2005), three studies did not describe their classification (Kinoshita *et al.*, 2000; Hanyu *et al.*, 2003*b*; Lee *et al.*, 2004*e*) and three used imaging to classify stroke subtype (Fan *et al.*, 2004; Imaizumi *et al.*, 2004*b*; Imaizumi *et al.*, 2005), two of which mentioned that participants with a source of embolism were excluded (Imaizumi *et al.*, 2004*b*; Imaizumi *et al.*, 2005). Only one study defined lacunar infarction primarily on clinical grounds, with MRI support in most cases (Schonewille *et al.*, 2005).

Generalizability of participants

Inevitably, all studies of BMBs suffer investigation bias because of the requirement for brain MRI, which precludes the inclusion of the very ill, but quite apart from this, only 16 (30%) studies had reasonable external validity (Table 2). Some of the major reasons for poor generalizability were failure to separate people with first-ever from those with recurrent stroke and the lack of a clinical definition of some stroke subtypes (with or without imaging support). A major, recurrent problem with studies of non-traumatic ICH was the failure to clearly describe the pattern and uptake of further radiological investigation in order to

clearly distinguish the various causes of ICH; we have therefore used the catch-all term 'non-traumatic' ICH, rather than the more ambiguous terms 'primary'/'spontaneous' ICH.

Anatomical areas clearly defined

The anatomical distribution of BMBs was mentioned in 38 studies (71%) (Table 2). Only eight studies described the anatomical limits of each location precisely, but there was little consistency between these studies (Dichgans *et al.*, 2002; Jeong *et al.*, 2002; Hanyu *et al.*, 2003*a*; Tsushima *et al.*, 2003; Derex *et al.*, 2004; Lee *et al.*, 2004*a*; Lee *et al.*, 2004*b*; Alemany *et al.*, 2006). For example, 'infratentorial' (brainstem and cerebellar) BMBs have been grouped with or separated from 'deep' (basal ganglia) BMBs, and corticosubcortical areas have not been given a clear anatomical substrate.

Observer agreement quantified

No study assessed the observer agreement for BMB size. One study assessed the observer agreement for classifying BMB location (Lee *et al.*, 2004e). Nine studies quantified observer agreement about the presence of BMBs, using various statistical tests (Supplementary Table 3). The level of intra-observer agreement (in three studies) was excellent, and appeared to be greater than the level of inter-observer agreement (in eight studies), which ranged from fair to excellent.

Risk factors clearly defined, blinded assessment and appropriate comparison groups

(i) *Clinical risk factors*: Forty (75%) studies explored BMB occurrence in different subgroups by age and/or gender and/or conventional vascular risk factors (Table 2). These were compared with a control sample (for example, those with a risk factor versus those without) and/or external comparisons with a different control group. Only 29 (55%) studies mentioned that the evaluations of BMBs were blinded to clinical data (Table 2). Twenty (38%) explored the association with age, 25 (47%) with gender, 20 (38%) with hypertension, 21 (40%) with diabetes mellitus, 9 (17%) with ischaemic heart disease and 16 (30%) with smoking (Table 2). Definitions of risk factors varied widely between studies. For example, in the 20 studies with data about hypertension, the cut-offs for hypertension varied from 140/90 mmHg to 160/95 mmHg, and the identification of hypertension relied on pre-stroke measurements and/or antihypertensive treatment in 10 studies, but post-stroke measurements in the other 10 studies. Twenty-three (43%) studies used a comparison group, 20 of which were imperfect (Table 2): 14 did not mention whether comparison groups were matched for factors either known or suspected to influence BMB occurrence (for example age and hypertension) and six used imperfect matching. However, some studies tried to take potential influences into account using multivariate analyses instead of matched controls.

(ii) *Pharmacological influences*: There were eight studies of the influence of antiplatelet drugs, four studies of the influence of anticoagulants and four studies of the impact of thrombolytics on BMBs. None of these evaluated dosage or duration of treatment, and only one had a comparison group (which did not help evaluate the influence of treatment on BMBs).

(iii) *Radiological associations*: The main radiological features studied in relation to BMBs were 'lacunes' and leucoaraiosis/white-matter hyperintensities. In 20 studies the definition of lacunes was based on MRI findings; only three studies differentiated asymptomatic from symptomatic lesions (Imaizumi *et al.*, 2004*a*; Imaizumi *et al.*, 2004*b*; Imaizumi *et al.*, 2005). Some studies reported simply the presence or absence of radiological lacunes (Offenbacher *et al.*, 1996; Kwa *et al.*, 1998; Tanaka *et al.*, 1999; Nighoghossian *et al.*, 2002; Hanyu *et al.*, 2003*a*; Fan *et al.*, 2004; Yokoyama *et al.*, 2005), some quantified the mean number of lacunes (Lesnik Oberstein *et al.*, 2001; Kim *et al.*, 2002; Hanyu *et al.*, 2003*b*; Fan *et al.*, 2004; Jeong *et al.*, 2004) and others categorized the number of lacunes using a grading scale (Lee *et al.*, 2004*c*; Lee *et al.*, 2004*d*).

Ideal design of prognosis studies

There were eight studies of BMBs as potential determinants of prognosis. Four studies, meeting most of our desired criteria (Table 1), tried to determine whether BMBs influence haemorrhagic transformation of ischaemic stroke (Kidwell *et al.*, 2002; Nighoghossian *et al.*, 2002; Derex *et al.*, 2004; Kakuda *et al.*, 2005). The other four studies concerned BMBs as predictors of stroke recurrence, but these met few of our desired criteria (Fan *et al.*, 2003; Tsushima *et al.*, 2003; Greenberg *et al.*, 2004; Imaizumi *et al.*, 2004*b*).

With these limitations in mind, we have used the existing evidence to tackle the major clinical questions about BMBs.

How frequent are BMBs?

Prevalence in 'healthy' adults

Four studies involving 1411 participants used brain MRI to determine the prevalence of BMBs in 'healthy people', either as part of screening schemes in Japan for people without neurological diseases, or asymptomatic volunteers from the Framingham and Offspring cohorts, or random recruits from the community (excluding those with history of neuropsychiatric disease) (Roob *et al.*, 1999*b*; Tsushima *et al.*, 2002; Horita *et al.*, 2003; Jeerakathil *et al.*, 2004). Overall, 70 of 1411 adults (5.0%, 95% CI 3.9–6.2%)

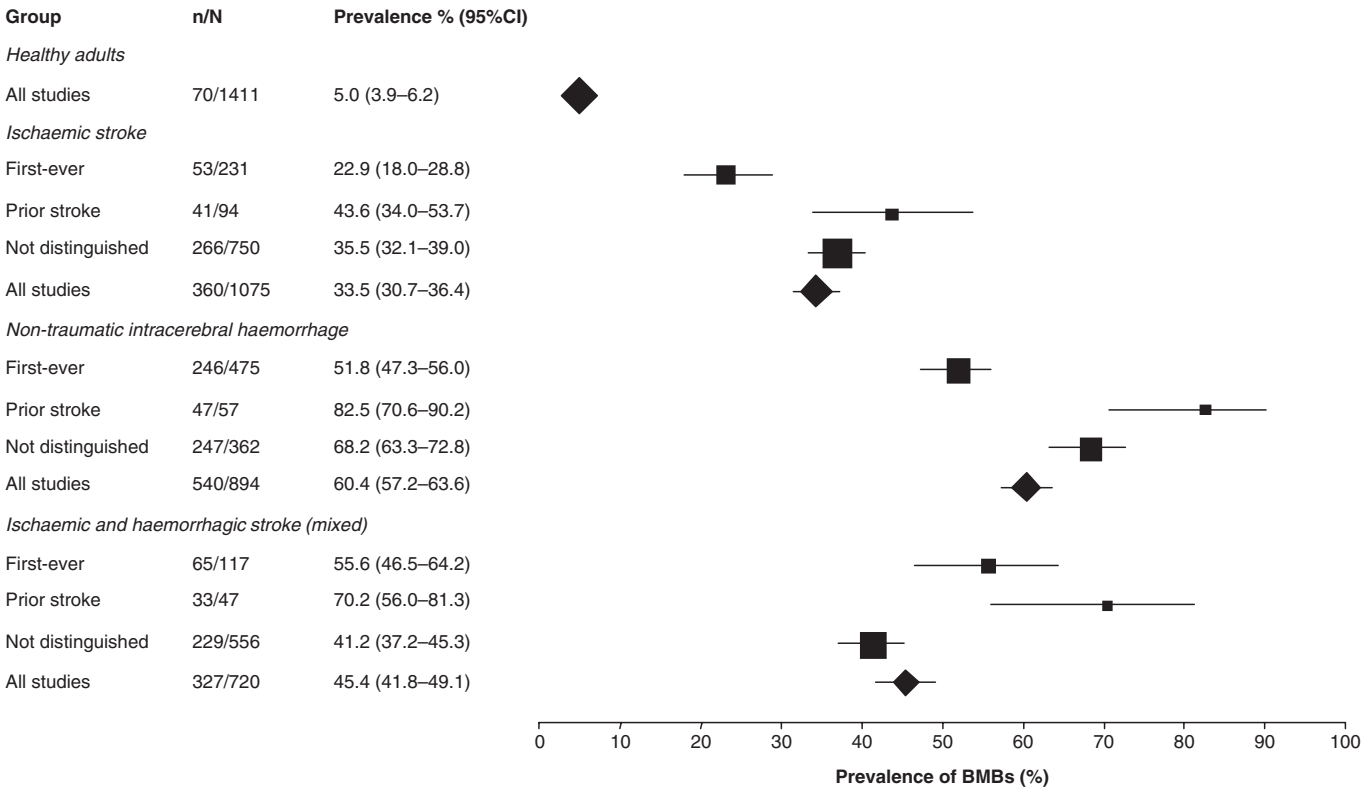

Fig. 2 The prevalence of BMBs in different groups of people. Point estimates are represented by boxes for individual disease categories and diamonds for summed disease categories. The area of each point estimate is proportional to the size of each study. The error bars represent 95% confidence intervals (95% CI). *N* = sample size, *n* = number of study participants with one BMB or more. Note data from each study only appear once.

harboured one or more BMBs (Fig. 2); there was no difference between the prevalence in Asians (4.6%, 95% CI 3.2–6.4%) (Tsushima *et al.*, 2002; Horita *et al.*, 2003) and non-Asians (5.3%, 95% CI 3.9–7.2%) (Roob *et al.*, 1999*b*; Jeerakathil *et al.*, 2004). Aspects of study design may account for some heterogeneity among these studies: the mean ages were 64.4 years (Jeerakathil *et al.*, 2004), 60 years (Roob *et al.*, 1999*b*), 56.4 years (Horita *et al.*, 2003) and 52.9 years (Tsushima *et al.*, 2002); furthermore, the prevalences of hypertension were 24.9% (Tsushima *et al.*, 2002), 28.8% (Jeerakathil *et al.*, 2004), 31.8% (Roob *et al.*, 1999*b*) and 46.4% (Horita *et al.*, 2003).

Prevalence among people with any cerebrovascular disease

Of the 41 studies involving people with any cerebrovascular disease, there were 948 participants in 10 studies of ICH (858 cases and 90 controls), 255 participants in four studies of acute ischaemic stroke, 796 participants in seven studies of ischaemic stroke and transient ischaemic attack (TIA) (598 ischaemic stroke, 43 TIA and 155 controls), 2041 participants in 13 studies with mixtures of stroke types (843 ICH, 877 ischaemic stroke, 156 stroke type not specified, 165 controls), 72 participants in two studies of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) (56 with CADASIL and 16 controls) (Lesnik Oberstein *et al.*, 2001; Dichgans *et al.*, 2002), 86 participants in two studies of moyamoya disease (52 with moyamoya and 34 controls) (Ishikawa *et al.*, 2005; Kikuta *et al.*, 2005), 27 participants in one study of hereditary cerebral haemorrhage with amyloidosis-Dutch type (Van Den Boom *et al.*, 2005) and 207 participants in two studies of multiple lacunar strokes and vascular dementia (Jeong *et al.*, 2002; Hanyu *et al.*, 2003b). Twenty-six studies (25 groups of participants) provided data about the prevalence of BMBs in a total of 2689 people with symptomatic stroke (Fig. 2) (Greenberg *et al.*, 1996; Offenbacher *et al.*, 1996; Tanaka *et al.*, 1999; Kinoshita *et al.*, 2000; Roob *et al.*, 2000; Yanagawa *et al.*, 2001; Kato *et al.*, 2002; Kidwell *et al.*, 2002; Nighoghossian *et al.*, 2002; Fan *et al.*, 2003; Wong *et al.*, 2003; Derex *et al.*, 2004; Fan *et al.*, 2004; Jeong *et al.*, 2004; Kidwell *et al.*, 2004; Lee *et al.*, 2004*a*; Lee *et al.*, 2004*b*; Lee *et al.*, 2004*c*; Lee *et al.*, 2004*d*; Lee *et al.*, 2004*e*; Naka *et al.*, 2004; Kakuda *et al.*, 2005; Schonewille *et al.*, 2005; Werring *et al.*, 2005; Alemany *et al.*, 2006; Lee *et al.*, 2006). For 720 (27%) of these people, we were unable to distinguish whether they had ischaemic stroke or ICH, and the overall prevalence of BMBs in this group was 45.4% (95% CI 41.8–49.1%), with individual studies reporting prevalences from 21% (Kidwell *et al.*, 2004) to 60% (Lee *et al.*, 2004*a*; Lee *et al.*, 2004*b*).

Prevalence among people with ischaemic stroke

Based on data extracted from 16 studies, involving 1075 participants (Fig. 2), the prevalence of BMBs among people with ischaemic stroke was 33.5% (95% CI 30.7–36.4%) (Kinoshita *et al.*, 2000; Tsushima *et al.*, 2000; Yanagawa *et al.*, 2001; Kato *et al.*, 2002; Kidwell *et al.*, 2002; Nighoghossian *et al.*, 2002; Fan *et al.*, 2003; Hanyu *et al.*, 2003*b*; Derex *et al.*, 2004; Fan *et al.*, 2004; Lee *et al.*, 2004*e*; Naka *et al.*, 2004; Kakuda *et al.*, 2005; Schonewille *et al.*, 2005; Werring *et al.*, 2005; Alemany *et al.*, 2006). Individual studies reported prevalences ranging from 12% (Kidwell *et al.*, 2002) to 71% (Kinoshita *et al.*, 2000). The prevalence of BMBs among Asians with ischaemic strokes was 41.5% (95% CI 37.8–45.4%) whereas the prevalence among non-Asians was 21.5% (95% CI 17.9–25.6%), although this may be explained in part by a higher prevalence of hypertension in Asian participants (79 versus 61% in non-Asians). One study found the prevalence of BMBs to be significantly lower in people with TIA than in people with ischaemic stroke, although it was unclear whether the latter had first-ever or recurrent ischaemic stroke, which could have affected the observed difference (Werring *et al.*, 2005).

Prevalence among different ischaemic stroke subtypes

Only two studies, which happened to be of Asians, reported the prevalences of BMBs according to the NINDS stroke subtype, which relies in part on the hypothesized underlying mechanism of the stroke (NINDS, 1990; Kato *et al.*, 2002; Naka *et al.*, 2004). The prevalence of BMBs was 53.5% (95% CI 44.9–61.9%) among lacunar strokes, 36.0% (95% CI 26.7–46.6%) among atherothrombotic strokes, and 19.4% (95% CI 29.5–60.4%) among cardioembolic strokes. Among those with multiple lacunar infarcts the prevalence of BMBs was 62.2% (95% CI 53.2–70.4%) (Kinoshita *et al.*, 2000; Hanyu *et al.*, 2003*b*). Only one study used a definition of lacunar stroke based on both clinical features and an appropriately-located infarct on brain MRI, and this study found the prevalence of BMBs to be 45.7% (95% CI 32.3–59.8%) (Schonewille *et al.*, 2005). The prevalence of BMBs amongst people with CADASIL was 37.5% (95% CI 26.0–50.6%) (Lesnik Oberstein *et al.*, 2001; Dichgans *et al.*, 2002), and the prevalence of BMBs amongst Asians with moyamoya disease was 21.2% (95% CI 12.2–34.0%) (Ishikawa *et al.*, 2005; Kikuta *et al.*, 2005).

Prevalence among people with non-traumatic intracerebral haemorrhage

Based on data extracted from 15 studies involving 894 participants with ICH, the prevalence of BMBs was 60.4% (95% CI 57.2–63.6%) (Fig. 2) (Greenberg *et al.*, 1996; Offenbacher *et al.*, 1996; Tanaka *et al.*, 1999; Kinoshita *et al.*, 2000; Roob *et al.*, 2000; Tsushima *et al.*, 2000; Yanagawa *et al.*, 2001; Kato *et al.*, 2002; Wong *et al.*, 2003; Jeong *et al.*, 2004; Lee *et al.*, 2004*c*; Lee *et al.*, 2004*e*; Naka *et al.*, 2004; Alemany *et al.*, 2006; Lee *et al.*, 2006). Individual studies reported prevalences ranging from 23% (Offenbacher *et al.*, 1996) to 90% (Wong *et al.*, 2003). The prevalence of BMBs among Asians with ICH was 67.5% (95% CI 63.6–71.1%), which was higher than the prevalence among non-Asians of 47.1% (95% CI 41.6–57.2%), again possibly due to confounding by the higher prevalence of hypertension in the Asians studies. The individual studies were quite heterogeneous; for example, it was unclear whether underlying or traumatic causes of ICH had been excluded, and some studies described BMBs only in specific ICH subtypes: three were studies of lobar ICH (Greenberg *et al.*, 1996; Greenberg *et al.*, 1999; Greenberg *et al.*, 2004), one studied only deep ICH (Imaizumi *et al.*, 2004*a*), and another only included supratentorial ICH (Lee *et al.*, 2006).

Prevalence among people with first-ever versus recurrent stroke

Figure 2 demonstrates that BMBs were more prevalent amongst people with recurrent than those with first-ever strokes (be they ischaemic, haemorrhagic or a mixture of the two). This conclusion is derived from only 1021 (38%) of the 2689 study participants in the analysis, because study authors did not distinguish first-ever from recurrent strokes in the other 1668 participants. These findings highlight the importance of studying homogeneous groups of people at uniform points in their disease (Table 1), but they strongly suggest that BMBs are a biomarker of ongoing cerebrovascular disease.

Prevalence in other disease groups

The prevalence of BMBs among people with Alzheimer's disease was 26.8% (95% CI 19.0–36.4%) (Nakata *et al.*, 2002; Hanyu *et al.*, 2003*a*). It was impossible to describe a meaningful prevalence among the studies that included other heterogeneous populations (Table 2).

Do definitions of BMB size and the MR sequence parameters used to image BMBs influence the apparent prevalence of BMBs?

There appeared to be a trend for BMB prevalence to increase with increasing MRI magnet strength (Supplementary Table 2), but the estimates were too imprecise to permit firm conclusions. In healthy people, BMB prevalence ranged from 3.9% (95% CI 2.8–5.4%) when using a 1.0 T magnet (Tsushima *et al.*, 2002; Jeerakathil *et al.*, 2004) to 7.0% (95% CI 5.0–9.6%) when using a 1.5 T magnet (Roob *et al.*, 1999*b*; Horita *et al.*, 2003). In studies of people with cerebrovascular diseases, BMB prevalence varied from 41.6% (95% CI 34.5–49.1%) when using a 1.0 T magnet to 46.9% (95% CI 44.9–48.9%) when using a 1.5 T magnet.

There does not appear to be a clear relationship between different definitions of BMB size (Table 2) and their apparent prevalence, although the estimates are too imprecise to permit firm conclusions. In healthy people, BMB prevalence was 6.4% (95% CI 4.1–9.9%) in studies where maximum BMB diameter was <5 mm (one study); contrary to our expectations, BMB prevalence fell to 4.6% (95% CI 3.5–6.0%) in three studies where maximum BMB diameter was <10 mm. In people with cerebrovascular diseases, BMB prevalence was 42.0% (95% CI 39.7–44.3%) in studies where maximum BMB diameter was <5 mm (20 studies); again, contrary to our expectations, BMB prevalence fell to 36.1% (95% CI 28.7–44.1%) in the three studies where maximum BMB diameter was <10 mm.

MRI slice gap (Supplementary Table 2) does not appear to influence BMB prevalence, although estimates were too imprecise to draw firm conclusions. In healthy people, BMB prevalence varied from 5.3% (95% CI 3.9–7.2%) in studies where the gap was <1 mm (Roob *et al.*, 1999*b*; Jeerakathil *et al.*, 2004) to 3.1% (95% CI 1.9–5.2%) in studies where the gap was 2–3 mm (Tsushima *et al.*, 2002). In people with cerebrovascular diseases, BMB prevalence was 40.8% (95% CI 37.3–44.5%) if the gap was <1 mm (eight studies), it rose to 53.9% (95% CI 49.4–58.3%) if the gap was 1–1.9 mm (three studies), and BMB prevalence was 52.1% (95% CI 48.6–55.6%) if the gap was 1.9–3 mm (seven studies).

Using more than one imaging plane may affect the number of lesions reported. Unfortunately, only three studies mentioned that axial and/or coronal slices were performed (Dichgans *et al.*, 2002; Nakata *et al.*, 2002; Alemany *et al.*, 2006).

Most of the studies from which data on prevalence could be extracted used a slice thickness around 5 mm, therefore the impact of slice thickness could not be evaluated. There was no obvious interaction between size definition, magnet strength and radiological parameters, although we did not perform a statistical analysis to test this.

Are vascular risk factors, gender or age associated with BMBs?

We have extracted data, where possible, from all four studies of healthy people and from studies of any type of cerebrovascular disease on the prevalence of BMBs in subgroups of risk factors, age and gender (Table 2). In all four cohorts of healthy people, data were available on some of the risk factors for cerebrovascular disease among all 1411 participants. Hypertension and diabetes mellitus were associated with BMBs, whereas gender, smoking and ischaemic heart disease were not (Table 3). In 12 studies of people with cerebrovascular diseases, hypertension was again associated with BMBs (although the association was a little weaker than in the healthy cohorts), whereas gender, ischaemic heart disease and diabetes mellitus were not; smoking appeared to be negatively associated with BMBs. We performed sensitivity analyses to explore the influence of BMB size cut-offs and blinded assessment of BMBs on the findings for adults with cerebrovascular diseases; the association of BMBs with hypertension was robust, but the precision was too low to comment on the other associations. Individual studies of healthy people found the prevalence of BMBs increased with increasing age, with only one exception (Tsushima *et al.*, 2002). Because the individual studies did not report BMB prevalence in 10-year, mid-decade age bands, it was not possible for us to combine data to confirm this pattern. We could not demonstrate a clear relationship between BMB prevalence and average (mean) age in 17 studies of healthy adults and people with cerebrovascular diseases.

Is antiplatelet or anticoagulant treatment associated with a higher prevalence of BMBs?

Some studies provide data about the use of antiplatelet/anticoagulant agents at the time of brain MRI examination, usually without information about the duration of treatment. From such studies, it does not appear that antiplatelet agents are associated with an increased risk of possessing BMBs (OR 1.20, 95% CI 0.84–1.68%), from a pooled analysis of 630 people with ischaemic stroke (Nighoghossian *et al.*, 2002; Schonewille *et al.*, 2005), ICH (Jeong *et al.*, 2004; Lee *et al.*, 2006), cohorts of mixed ischaemic and haemorrhagic stroke (Jeong *et al.*, 2002; Lee *et al.*, 2004*e*; Alemany *et al.*, 2006) and CADASIL (Lesnik Oberstein *et al.*, 2001). Nor does it appear that anticoagulant treatment is associated with an increased risk of possessing BMBs (OR 1.79, 95% CI 0.72–4.46%), from

Table 3 Influence of comorbid conditions on the prevalence of BMBs

Risk factor	Healthy adults			Adults with cerebrovascular diseases		
	Studies	Sample size	Odds ratio, 95% CI	Studies	Sample size	Odds ratio, 95% CI
Male gender	4	1411	1.4, 0.9–2.3	16	1275	1.2, 0.98–1.5
Hypertension	4	1411	3.9, 2.4–6.4	12	1037	2.3, 1.7–3.0
Smoking	4	1411	1.0, 0.5–2.0	11	1107	0.7, 0.5–0.9
Ischaemic heart disease	2	730	1.9, 0.8–4.4	7	628	0.6, 0.4–1.02
Diabetes mellitus	4	1411	2.2, 1.2–4.2	14	1303	0.9, 0.7–1.1

a pooled analysis of 210 people with ischaemic stroke (Schonewille *et al.*, 2005), ICH (Jeong *et al.*, 2004), a cohort of mixed ischaemic and haemorrhagic stroke (Alemany *et al.*, 2006) and people with heterogeneous disorders (Walker *et al.*, 2004).

Are radiological lacunes and leucoaraiosis associated with BMBs?

Several studies have explored whether BMBs co-segregate with radiological lacunes (lesions 10–15 mm in diameter, isointense with cerebrospinal fluid) and white-matter hyperintensities on brain MRI. BMBs were associated with radiological lacunes in two studies of 489 healthy people (OR 12.2, 95% CI 5.4–27.5%) (Roob *et al.*, 1999*b*; Horita *et al.*, 2003), and in two studies of 154 people with cerebrovascular diseases (OR 3.1, 95% CI 1.6–6.0%) (Roob *et al.*, 2000; Alemany *et al.*, 2006). Leucoaraiosis was rated in 16 studies, but different scales were used: the Fazekas scale in eight studies (Fazekas *et al.*, 1987), the Scheltens scale in three studies (Scheltens *et al.*, 1993), the Wahlund scale in two studies (Wahlund *et al.*, 2001), a personal scale in one other study and two studies used semi-automated measurements (Jeerakathil *et al.*, 2004; Van Den Boom *et al.*, 2005). BMBs were associated with higher white matter hyperintensity scores (dichotomized as Fazekas grade 0–1 versus 2–3): among healthy people (OR 4.6, 95% CI 1.7–12.6%) (Roob *et al.*, 1999*b*) and among people with cerebrovascular diseases (OR 6.2, 95% CI 4.2–9.1%) (Roob *et al.*, 2000; Nighoghossian *et al.*, 2002; Jeong *et al.*, 2004; Lee *et al.*, 2004*a*, *e*). The number of BMBs, depending on their location, could be a marker of severity of any microangiopathy (Imaizumi *et al.*, 2004*a*); however, the paucity of other studies exploring the influence of the numerical burden of BMBs, and whether their distribution is related to the anatomical location of stroke, precludes any firm conclusions.

Is the distribution of BMBs diagnostically useful?

Studies of the diagnostic utility of BMBs were difficult to interpret because authors varied in their classifications of BMB distribution, they varied in their description of either the presence or the mean number of BMBs per location, and some used different grading systems. None of these classifications of BMB distribution has been validated. Twenty-two studies simply described the prevalence of BMBs by location, but 16 studies explored the relationship of BMB location (often dichotomized as deep versus lobar) to other variables. Most studies explored the relationship between BMB location and features of small-vessel diseases (such as hypertension and radiological lacunes) but the widely varying definitions, case mix and small numbers precluded further analyses. Some studies also focused on the relationship between distribution of BMBs and underlying diagnosis (for example, cerebral amyloid angiopathy), but none of these described the sensitivity/specificity of BMB distribution.

Are BMBs associated with an increased risk of future stroke occurrence/recurrence?

Four studies examined the association between BMBs and future stroke risk, three in Asian populations (Fan *et al.*, 2003; Tsushima *et al.*, 2003; Imaizumi *et al.*, 2004*b*) and one in a non-Asian population (Greenberg *et al.*, 2004). These four studies were conducted in distinct groups of people: 2019 with heterogeneous diseases (Tsushima *et al.*, 2003), 337 with lacunar infarction (clinical syndrome, with diffusion-weighted MRI confirmation) or ICH (Imaizumi *et al.*, 2004*b*), 121 with ischaemic stroke (Fan *et al.*, 2003), and 94 lobar ICH (Greenberg *et al.*, 2004). Compared with our desired design (Table 1), the studies were mostly prospective, but only two assessed objective outcomes blind to BMBs (Fan *et al.*, 2003; Greenberg *et al.*, 2004), and—when described—most simply quantified completeness of follow-up over variable periods (ranging up to an average of 3 years) rather than completeness of follow-up at a specified time.

These limited data suggest that BMBs may predict subsequent recurrent lacunar infarction or ICH in those with lacunar infarction or ICH (Imaizumi *et al.*, 2004*b*), as well as predicting recurrent ICH in those with lobar ICH, for whom the larger the number of BMBs the greater the future risk (Greenberg *et al.*, 2004). BMBs 'possibly' predict the future occurrence of haemorrhagic stroke for those with ischaemic stroke (Fan *et al.*, 2003). The methods of analysis and the numbers of outcomes in these studies precluded an analysis of future risk stratified by differences in drug treatment.

Does treatment with antiplatelet, anticoagulant or thrombolytic agents increase the future risk of intracerebral haemorrhage for people with BMBs?

Scant data are available to answer this important question. Four studies explored the association between BMBs and the risk of haemorrhagic transformation following intravenous tissue plasminogen activator (tPA) for acute ischaemic stroke. Three studies with a total of only 155 participants found no increase in haemorrhagic transformation following tPA treatment (Kidwell *et al.*, 2002; Nighoghossian *et al.*, 2002; Derex *et al.*, 2004; Kakuda *et al.*, 2005), but they were underpowered to detect such an effect. The fourth study, of 100 people with ischaemic stroke treated with antiplatelet or anticoagulant or thrombolytic drugs, suggested that BMBs (detected on MRI after treatment was started) increased the risk of future haemorrhagic transformation of cerebral infarction or

ICH, but it too was underpowered to provide reliable data (Nighoghossian *et al.*, 2002).

Discussion

Research into BMBs is proliferating rapidly, but the variable quality of studies' methods has led to several potentially avoidable biases.

Methodological quality of BMB research

The main limitations in study design have been: failure to differentiate first-ever from recurrent and ischaemic from haemorrhagic stroke; failure to distinguish clinical stroke from asymptomatic lesions identified on imaging; poor generalizability of study participants (for example, prevalences of hypertension ranged from 25% to 46% in cohorts of healthy people); poor matching of control/comparison groups on factors known, or suspected, to influence BMB occurrence; variation in MRI parameters used; inconsistent cut-offs for BMB size and infrequent blinding of assessors to other factors of interest. These biases notwithstanding, confounding factors might also account for some studies' observations (for example the apparent difference in BMB prevalence between Asians and non-Asians might be related to the recruitment of many of the Asians from hypertension clinics, thereby raising the prevalence of hypertension, and so BMBs). In addition to bias and confounding, small sample sizes make chance a further explanation for some studies' findings.

Other findings of this review

We found that the prevalence of BMBs is greatest in those with ICH (60%, 95% CI 57–64%), less so in those with ischaemic stroke (34%, 95% CI 31–36%), and least of all in apparently healthy adults (5%, 95% CI 4–6%). More importantly, BMBs were more prevalent among recurrent strokes than first-ever strokes. Furthermore, BMBs were associated with hypertension (OR 3.9, 95% CI 2.4–6.4%) and diabetes mellitus (OR 2.2, 95% CI 1.2–4.2%) in otherwise healthy adults. In adults with cerebrovascular diseases, BMBs were also associated with hypertension (OR 2.7, 95% CI 2.0–3.5%), which was robust in sensitivity analyses; furthermore, smoking appeared to be negatively associated with BMBs, which may be an artefact of the association of smoking with large vessel disease if BMBs are indeed part of a non-atheromatous microangiopathy. We cannot exclude the influence of reporting bias, if studies that did not find an association were less likely to cross-tabulate data to enable our subgroup analyses. Although several individual studies found that BMB prevalence increased with age, a pooled analysis to confirm this was not possible.

On the basis of this objective evidence, BMBs do not have any major implications for clinical practice at present. There were insufficient data to determine whether the distribution of BMBs is diagnostically useful, and whether treating people who have BMBs with antiplatelet drugs, anticoagulants, or thrombolytics increases their risk of subsequent haemorrhage. Although the data are sparse and rely on only two studies, it seems that BMBs may confer a higher risk of recurrent haemorrhage in people with ICH (Imaizumi *et al.*, 2004*b*; Greenberg *et al.*, 2004). This, of course, provokes variation in practice; for example, some authors have already incorporated the existence of BMBs into their decisions about thrombolysis for acute ischaemic stroke (Hjort *et al.*, 2005; Kang *et al.*, 2005).

Strengths and weaknesses of this review

Our systematic literature search and transparent study quality assessment revealed a dearth of high quality studies. In an attempt to minimize the influence of bias and chance, we applied strict inclusion/exclusion criteria. Although the studies of BMBs in healthy people and those with cerebrovascular diseases are somewhat heterogeneous, we have pooled broadly comparable studies. The advantage of this approach is that it minimizes the various biases of the individual studies and increases the precision of our findings, but the main disadvantage is that the pooled analyses consist of indirect comparisons between stroke types and subtypes from different populations. This approach was not taken by previous narrative reviews (Fiehler, 2006; Koennecke, 2006; Viswanathan and Chabriat, 2006). Our approach has also enabled us to explore the influence of variations in study design using subgroup analyses of, for example, MRI parameters and definitions of BMB size, and test the major findings of this review using sensitivity analyses. In order to investigate the interplay between several different variables with a multivariate analysis, individual participant data would have been required; this remains a recommendation for future studies.

In the seven months following our literature search, 15 further articles about BMBs were published, including a further narrative review (Fiehler, 2006). However, none of these substantially alters our conclusions. Notably, there are two further studies suggesting that BMBs predict future stroke (Boulanger *et al.*, 2006; Naka *et al.*, 2006). Unfortunately, both of these studies suffer from the same problems with bias, confounding and chance that we have identified in the BMB literature: both studies mixed first-ever and recurrent strokes; and sample sizes were small which precluded a powerful multivariate analysis and made 95% CIs wide (Boulanger *et al.*, 2006; Naka *et al.*, 2006); furthermore, one failed to use GRE T_2^*-weighted MRI sequences in all participants (Boulanger *et al.*, 2006). Another study found that BMBs are independently associated with blood pressure and glycaemic control in a large cohort study of adults with CADASIL (Viswanathan *et al.*, 2006).

Future research: design, research questions, and reporting

We recommend that future studies aspire to the ideal design described in Table 1 (elaborated subsequently). In particular, the use of GRE T_2^*-weighted MRI sequences is compulsory, and all other MRI parameters should be clearly specified. The internal validity of each study and ability to compare it with other studies is enhanced by a clear radiological definition of BMB appearance and size. Given that 23% of the studies in this review did not define BMB size, in future this should be clearly stated and a maximum diameter of up to 10 mm seems reasonable (but authors could explore the influence on their findings by choosing a smaller maximum diameter of 5 mm using sensitivity analyses). Validity is further enhanced by a homogeneous sample of participants, a clear inception point of first-ever stroke, a description of measures taken to identify an underlying cause in studies of ICH, and a clear distinction between radiologically-supported clinically-symptomatic stroke (and its subtypes, identified independent of risk factors) and asymptomatic radiological stroke. Control groups should be matched on factors that probably influence BMB occurrence (age, hypertension, diabetes mellitus and possibly smoking).

Do MRI parameters influence BMB detection?

Due to the incomplete reporting of radiological parameters (ranging from 21% to 40%), it was difficult to evaluate their influence on BMB detection. Most studies used GRE T_2^*-weighted sequences but four used T_2^*-EPI sequences. We chose to include the latter because the spatial resolution shown in those articles seemed satisfactory, although we were concerned at the potential loss of sensitivity in T_2^*-EPI if only a few images are averaged. To date, no study compared the impact of those different sequences on the prevalence or number of lesions detected. In sensitivity analyses excluding the four studies using T_2^*-EPI, our results were the same. Although we could not prove it, significant differences in BMB detection may have arisen from the huge variation in flip angle (10–90°) influencing susceptibility weighting, and the variations in slice thickness and slice gap affecting the ability to detect small BMBs. Information was sparse about other technical factors such as pixel sizes, whether BMB were rated in one or more planes, and whether BMBs were assessed on computer or cut film, although they may well contribute to the variation in reported prevalence of BMBs. Future studies should explore their influence on BMB detection using sensitivity analyses.

Prevalence of BMBs in different stroke subtypes

This review lends tentative support to the hypothesis that BMBs are another expression of an intrinsic cerebral small vessel disease. There were associations between BMBs and both radiological lacunes (most of which appeared to be asymptomatic) as well as white matter hyperintensities/leucoaraiosis on brain MRI. However, the apparent association between BMBs and the clinical syndrome of lacunar stroke, in the few studies that examined this, may be confounded by the use of risk factor-based definitions of ischaemic stroke subtypes. Studies comparing BMB prevalence in different stroke subtypes should use risk factor-free subtype definitions with imaging support, to avoid confounding. If BMBs are a biomarker of small vessel disease, further histological and imaging studies should be encouraged to better understand their underlying pathology (Fazekas *et al.*, 1999; Tanaka *et al.*, 1999).

Are BMBs diagnostically useful?

The existence, number, size and/or distribution of BMBs may be valuable in the ante-mortem diagnosis of disorders such as cerebral amyloid angiopathy. To date, there are no studies of BMBs' diagnostic sensitivity, specificity and positive predictive value when compared against a reference standard (for example, pathological examination), therefore basing such diagnoses on BMBs requires caution, until reliable classifications of BMB distribution based on clear anatomical definitions have been developed and shown to have good observer agreement.

Do BMBs have prognostic value?

The existence and quantitative burden of BMBs may have prognostic value in adults with lobar ICH (Greenberg *et al.*, 2004), other types of ICH, ischaemic stroke (Boulanger *et al.*, 2006; Naka *et al.*, 2006) and cognitive dysfunction (Greenberg *et al.*, 2004; Werring *et al.*, 2004; Cordonnier *et al.*, 2006). We found a shortage of data on the association of BMBs with adverse effects of antiplatelet, anticoagulant and thrombolytic drug treatment, although this is a frequent clinical dilemma.

Reporting of future studies

Standardized reporting of BMB studies would improve the ability of future systematic reviews (and hopefully individual patient data meta-analyses) to pool similar studies and subgroups within them. Prospective studies with large sample size and near-complete follow up are far less biased than retrospective collection of small amounts of data, and allow determination of the independent predictive power of BMBs, after adjusting for known predictors of stroke recurrence. Clearly defined outcome events enhance study validity, whilst their assessment blinded to prognostic factors of interest avoids expectation bias on the part of the observers. Reporting the prevalence of BMBs in mid-decade age bands, amongst various risk factor groups (for example, hypertension and diabetes mellitus), according to the receipt of antiplatelet and anticoagulant drugs, and cross-tabulating these categories will enable a powerful analysis of their separate and combined influences. Individual studies would benefit from use of risk-factor

free stroke subtyping, multivariate analyses of factors that might influence BMB occurrence, and stroke recurrence. In order to examine the association between the distribution of BMBs and cerebrovascular disorders and prognosis, studies should report not only the prevalences, but also the number of BMBs, in the different anatomical areas, pending the development of a classification scheme that is shown to be easy to use and to involve minimal observer variation.

Conclusions

- The methodological quality of the literature on BMBs is generally poor.
- BMBs are more frequent in people with cerebrovascular diseases than in so-called 'healthy' adults.
- BMBs are more frequent in ICH than in ischaemic stroke.
- The prevalence of BMBs is higher in recurrent than first-ever stroke.
- Hypertension, radiological lacunes and leucoaraiosis appear to be robust associations with BMBs.
- Firm conclusions about the diagnostic utility of BMBs and their influence on prognosis and the effects of treatment are not possible, but these are the major priorities for future studies, which must be well-designed.

Supplementary material

Supplementary data are available at *Brain* Online.

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