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Do cerebral microbleeds increase the risk of dementia? A systematic review and meta-analysis

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ABSTRACT

Background: Dementia is a neurological disorder that commonly affects the elderly. Cerebral microbleeds (CMBs) are small, tiny lesions of the cerebral blood vessels and have been suggested as a possible risk factor for dementia. However, data about the association between CMBs and dementia risk are inconsistent and inconclusive. Therefore, we conducted this systematic review and meta-analysis to investigate the association between CMBs and dementia and highlight the possible explanations.

Methods: We followed the standard PRISMA statement and the Cochrane Handbook guidelines to conduct this study. First, we searched medical electronic databases for relevant articles. Then, we screened the retrieved articles for eligibility, extracted the relevant data, and appraised the methodological quality using the Newcastle-Ottawa Scale. Finally, the extracted data were pooled as risk ratios (RR) and hazard ratios (HR) in the random-effects meta-analysis model using the Review Manager software.

Results: We included nine studies with 14,221 participants and follow-up periods > 18 months. Overall, CMBs significantly increased the risk of developing dementia (RR 1.84, 95% CI [1.27–2.65]). This association was significant in the subgroups of studies on high-risk populations (RR 2.00, 95% CI [1.41–2.83], n = 1657 participants) and those in the general population (RR 2.30, 95% CI [1.25–4.26], n = 12,087 participants) but not in the memory clinic patients. Further, CMBs increased the risk of progressing to incident dementia over time (HR 2, 95% CI [1.54–2.61]).

Conclusion: Individuals with CMBs have twice the risk of developing dementia or progressing to MCI than those without CMBs. The detection of CMBs will help identify the population at higher risk of developing dementia. Physicians should educate individuals with CMBs and their families on the possibility of progressing to dementia or MCI. Regular cognitive assessments, cognitive training, lifestyle modifications, and controlling other dementia risk factors are recommended for individuals with CMBs to decrease the risk of cognitive decline and dementia development.

1. Introduction

Dementia is a neurological disorder that includes cognitive deterioration, memory, thinking, social abilities, problem-solving ability, and personal behavior changes (Chertkow et al., 2013). Symptoms of dementia also include emotional disturbances, language problems, and other symptoms that interfere with the patient's daily activity (Chertkow et al., 2013). Dementia can be classified into many subtypes

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according to the presentations and etiology. The common types of dementia are Alzheimer's disease (AD) dementia representing 56%, vascular dementia representing 11%, and mixed dementia representing 21% (Alladi et al., 2011; Wu et al., 2018).

According to the World Health Organization and Alzheimer's disease International, a new case of dementia develops every three seconds. Globally, the prevalence of dementia was 46.8 million in 2015, and the numbers are expected to increase over time. Furthermore, most dementia patients live in low and middle-income countries (ADI, 2022). Therefore, addressing dementia is a neurological priority with a global health dimension.

Primary prevention is key to decreasing the global burden of dementia. Therefore, identifying the risk factors of dementia is essential for neurologists, neurosurgeons, and public health experts. One of the risk factors reported for dementia is cerebral Microbleeds (CMBs), defined as small, rounded, and tiny lesions of the cerebral blood vessels (Akoudad et al., 2016; Romero et al., 2017; Martinez-Ramirez et al., 2014; Ding et al., 2017). CMBs represent the blood degradation products in the small blood vessels. They can be visualized by classic magnetic resonance imaging (MRI) or gradient-echo sequences of MRI with more sensitivity (Kim and Lee, 2013).

CMBs are indicators of underlying small vessel disease (SVD), and they have a strong association with other conditions such as severe hypertension (can be used as an indicator of end-organ damage), cerebral amyloid angiopathy, and cerebral infarcts (Greenberg et al., 2009). Other uncommon causes of CMBs include infective endocarditis, thrombotic thrombocytopenic purpura, post-radiation therapy, reversible encephalopathy syndrome, traumatic brain injury, moyamoya disease, sickle cell anemia, β-thalassemia, and obstructive sleep apnea (Noorbakhsh-Sabet et al., 2017).

Multiple studies have examined the association between CMBs and the risk of dementia but reported conflicting results due to difference in the follow-up period, outcome measures, risk factors, and the number of included patients/participants. For example, Romero et al. (2017) reported a significant association (Romero et al., 2017), but other studies did not support the same association (Benedictus et al., 2015; Staekenborg et al., 2009). Given that the literature data are inconsistent and inconclusive, we conducted this systematic review and meta-analysis to synthesize evidence from published prospective cohort studies about the association between CMBs and the development of dementia.

2. Materials and methods

The study was conducted according to the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions (Page et al., 2021; Moher et al., 2009; Higgins et al., 2019).

2.1. Search strategy

We searched MEDLINE through PubMed, SCOPUS, Web of Science, and Global Health Library databases for potentially relevant studies until December 2019, using search terms created by searching in Medical Subject Headings (MeSH) and the terms used in the paper published by Charidimou et al., 2018 (Charidimou et al., 2018): *((microbleed*) OR (microhemorrhag*) OR (microhemorrhag*) OR ("dot-like")) AND (MRI OR SWI OR T2 * OR suscept* OR hemosid*) AND ((brain OR cerebr* OR (cerebral small vessel disease) OR (vascular dementia) OR (Alzheimer disease) OR (Alzheimer's disease) OR cognit* OR dement*))*. The identified citations were retrieved and imported to the Endnote X8 software package (Thompson Reuter, USA).

The title and abstract of all retrieved papers were screened according to our predefined eligibility criteria by four independent review authors [MS, BR, AG, MS], who also reviewed the full text for eligibility. Then, the results of the possible eligible studies were reviewed by our other author [ASH] independently, and the final list of the included studies was decided by discussion and consensus.

2.2. Eligibility criteria

Studies satisfying our prespecified PIOS criteria were included in the systematic review as follows:

1) **P**opulation: studies conducted on the general population, high-risk population, or patients in memory clinics
2) **I**ndicator: studies where the indicator was the presence of CMBs, detected by MRI using the standard criteria, at the baseline as the predictor (risk factor) with sufficient follow-up periods for the development of dementia (outcome)
3) **O**utcome: studies where the outcome of interest was the development of dementia (any major subtype)
4) **S**tudy design: studies whose design was observational prospective cohort studies with no limitation on the age or gender of the participants.

We excluded studies for the following reasons:

1) Different study designs such as case reports, cross-sectional studies, and review papers
2) Studies that enrolled patients with AD at the baseline
3) Studies that report atypical AD
4) Studies that included mixed groups (AD and mild cognitive impairment (MCI))
5) Conference abstracts that were not available as full-text articles
6) Studies whose data were not reliable for extraction and analysis
7) Studies reporting multiple outcomes of interest, including dementia, but no separate data were provided for the dementia outcome separately

2.3. Outcome measures

The primary outcome of interest was the development of dementia or AD dementia, measured by repeated neuropsychological clinical evaluation (Benedictus et al., 2015; van Uden et al., 2016), Mini-Mental State Examination (MMSE) (Romero et al., 2017; Ding et al., 2017; Miwa et al., 2016, 2014) with scores < 24, or comprehensive battery of cognitive testing (Romero et al., 2017), and geriatric mental schedule (Akoudad et al., 2016). While the secondary outcome was the development of incident dementia over time.

2.4. Data extraction

Four review authors [MS, BR, AG, and MS] extracted the required data independently, and then another review author [ASH] resolved the conflicts. We extracted the following data from each study: study design, number of participants, baseline characteristics (including age, sex, and body mass index), follow-up period, education level, vascular risk factors (including hypertension, smoking, diabetes, hyperlipidemia), apolipoprotein E (APOE) gene status, and baseline MMSE.

Data were retrieved from each of the nine included studies and entered into a combined excel file containing all the requested data categories after each study's quality was evaluated against the NOS's criteria. Most baseline data were presented using the same units and measures (mean SD or range). Additionally, the MMSE and vascular risk variables were consistent across all studies (mean SD or n [%]).

The following procedures were carried out for the the1ry and 2ry outcomes:

1. Dividing each study into two arms: Controlled (CMBs) and Experimental (No CMBs)

2. Next, from each study, we calculated the incidence of dementia as the proportion of patients who experienced episodes and the overall number of participants in each research arm.

2.5. Quality assessment of the included studies

We assessed the methodological quality of each study in terms of three domains: selection, comparability, and outcome, as described in the Newcastle Ottawa scale (NOS) (Peterson et al., 2011). The selection domain includes four items that assess the representativeness of the selected cohort and the integrity of the selection process. The comparability domain was formed of one item examining the confounders' adjustments. Finally, the outcome domain includes three items that assess the quality of outcome measures and adequacy of the follow-up period.

2.6. Data synthesis and analysis

The meta-analysis was performed using Review Manager (RevMan) version 5.3. We used the random effect model with the inverse variance method in the meta-analysis. The association between CMBs and the development of dementia was expressed as the Risk Ratios (RR) and its corresponding 95% confidence intervals (CI). For studies reporting the risk of progression to incident all-cause dementia over time, the effect size was pooled as HRs and their corresponding 95% CI.

2.7. Subgroup analysis

We conducted a subgroup analysis according to the type of the study population: (1) studies on patients attending the memory clinic, (2) studies on high-risk population, and (3) studies on the general population "asymptomatic patients".

2.8. Assessing heterogeneity

We examined the statistical heterogeneity (inconsistency) across studies by visual inspection of the forest plot and using the I square test (I^2). We classified the values of the I^2 test as follows: $< 25\%$ is a low degree, from 25% to 50% is a moderate degree, and $> 50\%$ is a high degree of heterogeneity. Additionally, Funnel plots were used to detect the possibility of publication bias in the meta-analysis.

3. Results

3.1. Study selection

We identified 1965 citations through our search in the four databases that were deducted to 1601 citations after removing the duplicates using the Endnote X8 software package (Thompson Reuter, USA). Based on the title and abstract screening, additional 1582 citations did not meet our inclusion criteria and were excluded. For the remaining 19 abstracts, the full-text articles were retrieved and evaluated for eligibility. Of the remaining 19 studies, only nine studies with 14,221 patients were eligible for inclusion in this systematic review. Results of the search and study selection steps are shown in the PRISMA flow diagram (Fig. 1).

3.2. Baseline characteristics of the included studies

We classified the included studies based on the type of the study population. Two of the included studies included memory clinics patients (n = 486 participants) (Benedictus et al., 2015; Staekenborg et al., 2009), three studies were conducted in high-risk populations (n = 1657

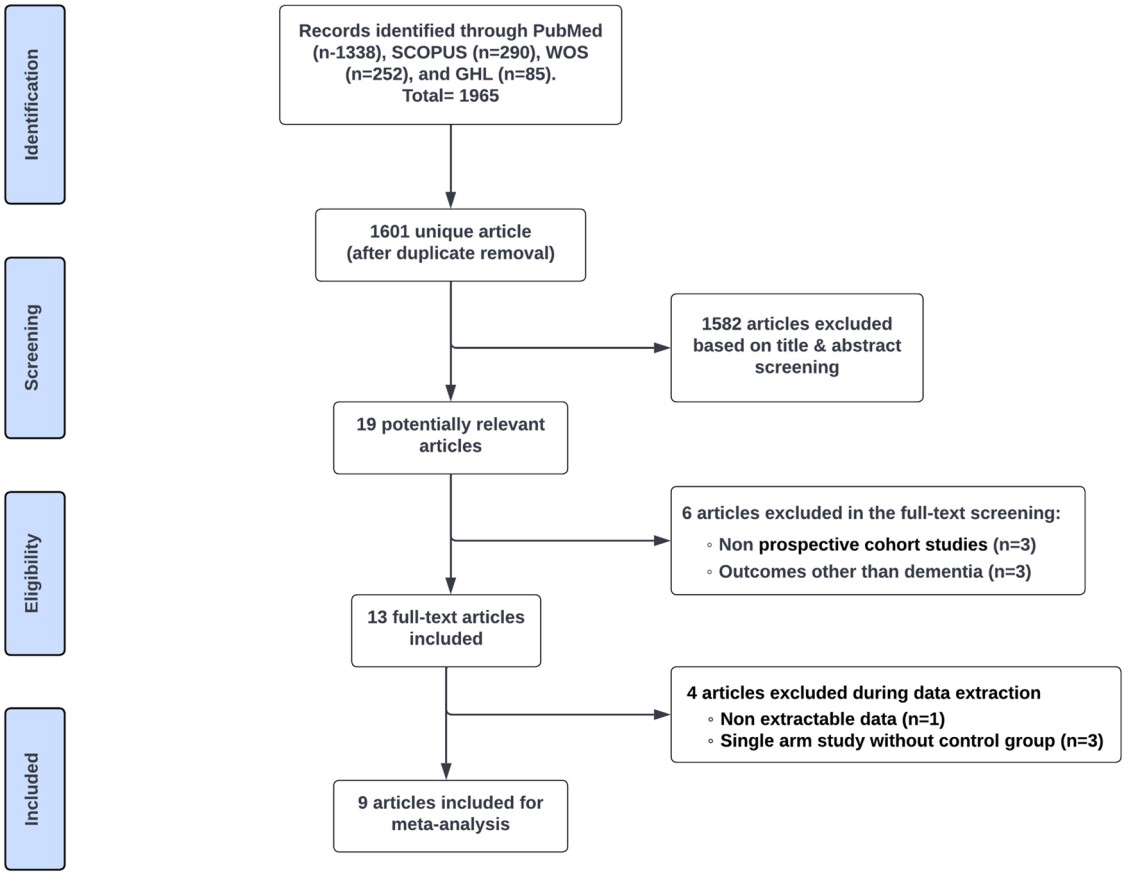

Fig. 1. The PRISMA flow diagram of the study selection process.

participants) (van Uden et al., 2016; Miwa et al., 2016, 2014), and the remaining four studies enrolled participants from the general population (n = 12,087 participants) (Akoudad et al., 2016; Romero et al., 2017; Ding et al., 2017; Kirsch et al., 2009). All the included studies were published between 2009 and 2017. Overall, 14,221 participants were enrolled in all studies, with sample sizes ranging from 23 to 3911 participants per study. The mean age of the participants was 70 years and the follow-up period for all studies was ≥ 18 months. Detailed characteristics of the included studies' populations are shown in Table 1.

3.3. Risk of bias and quality of evidence assessment

The quality score of NOS was good in all the included studies, with a score of 7 or 8 out of 9. The participants (exposed cohort) were representative of their communities in all studies. Other than age and sex, all studies were controlled for other factors such as medial temporal lobe atrophy, education, baseline MMSE, APOE status, vascular risk factors, and total cholesterol level. The follow-up periods were ≥ 18 months in all studies, which is long enough for the event of interest (dementia) to develop, and most of the participants completed their follow-up period. The results of the quality assessment are shown in Table 2.

3.4. Meta-analysis of the association between CMBs and dementia

The meta-analysis was done on two memory clinic studies with 486 participants, three high-risk studies with 1657 participants, and four studies from the general population with 8820 participants. These included studies provided relevant data on the association between the CMBs and the development of dementia. The overall meta-analysis without subgrouping showed that individuals with CMBs were

Table 1
Baseline characteristics of the included studies' population; n = Number of participants; FU = follow-up period; APOE = Apolipoprotein E; MMSE = mini-mental state examination.

Study	Study arms	n	Age, mean (SD) / Range	Female, %	FU period, years, mean (SD)	Vascular risk factors				APOE state, n (%)	Baseline MMSE, mean (SD)
						Hypertension, n (%)	Smokers, n (%)	Diabetes, n (%)	Hyperlipidemia, n (%)	Any ε4 allele	
Benedictus 2015	Stable	281	61 (9)	48%	3 (2)	83 (29)	—	24 (8)	54 (19)	—	28 (2)
	Progressors	53	69 (7)	42%	4 (3)	21 (40)	—	4 (7)	16 (30)	—	28 (2)
Van Uden 2015	Dementia	42	74.6 (6.5)	43%	5.2 (0.7)	—	—	—	—	—	27.1 (1.7)
	Non-dement	458	64.8 (8.5)	42%		—	—	—	—	—	28.2 (1.6)
Romero 2017	No CMB	1156	71 (8)	66%	6.8 (2.7)	717 (62)	69 (6)	150 (13)	—	243 (21)	—
	CMB	140	76 (7)	45%	5.8 (2.8)	107 (76)	9 (6)	24 (17)	—	37 (26)	—
Akoudad 2016	MBs absent (Cognitive decline analysis)	2780	59.0 (7.6)	55%	4.8 (1.4)	1446 (52.0)	1900 (68.3)	210 (7.6)	—	735 (28.2)	—
	MBs present (Cognitive decline analysis)	477	62.8 (8.5)	52.80%	—	297 (62.3)	351 (73.6)	37 (7.8)	—	141 (31.4)	—
	MBs absent (Incident dementia analysis)	3911	62.4 (10.4)	55.50%	—	2304 (58.9)	2706 (69.2)	330 (8.4)	—	884 (28.6)	—
	MBs present (Incident dementia analysis)	930	69.8 (71.7)	52.90%	—	678 (72.9)	678 (72.9)	98 (10.5)	—	233 (32.0)	—
Miwa 2015	tHcy ≤ 9.2 mol/L	328	65.4 (8.3)	54%	7.3 (3.2)	237 (72)	32 (9.8)	76 (23)	186 (57)	53 (21)	28.3 (1.6)
	tHcy > 9.2 mol/L	315	69 (8.1)	28%	—	271 (86)	69 (21)	96 (30)	197 (62)	53 (21)	28.2 (1.8)
Miwa 2014	No CMBs	401	67.3 (8.1)	44%	7 (2.6)	294 (73)	67 (17)	96 (24)	265 (66)	78 (19)	28.2 (1.9)
	CMBs	113	68.1 (8.8)	31%	—	94 (83)	18 (16)	27 (24)	67 (59)	23 (20)	27.7 (2.0)
staekenborg 2009	Nonconverters	80	68 (9)	39%	1.8 (1.1)	—	—	—	—	—	27 (2)
	Converters	72	72 (7)	56%	2.2 (1.3)	—	—	—	—	—	26 (2)
Kirsch 2009	Normal	33	71.2 (54–84)	57.60%	2.8 (0.98)	—	—	—	—	—	—
	MCI	23	75.5 (64–87)	34.80%	2.16 (1)	—	—	—	—	—	—
	Demented	26	78.9 (67–88)	53.80%	2.23 (1.04)	—	—	—	—	—	—
Ding 2017	No-CMBs	2165	74.5 (4.8)	61.50%	5.2 (0.2)	1651 (76.3)	230 (10.7)	197 (9.1)	—	555 (25.7)	27.75 (0.88)
	1 CMB	311	75.4 (4.7)	48.20%	—	256 (82.3)	30 (9.7)	29 (9.4)	—	78 (25.1)	27.75 (0.88)
	2 CMBs	68	75.4 (4.4)	44.10%	—	59 (86.8)	10 (14.7)	5 (7.4)	—	26 (38.2)	27.25 (0.88)
	≥ 3 CMBs	58	75.4 (4.7)	63.20%	—	52 (89.7)	6 (10.3)	10 (17.2)	—	26 (36.2)	27.25 (0.88)

Table 2
Results of the risk of bias assessment using the NOS; Good quality = 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain; Fair quality = 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality = 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Study	Selection				Comparability	Outcome			Quality Score
	Representativeness of Exposed Cohort	Selection of the Non-Exposed Cohort from Same Source as exposed	Ascertainment of exposure	Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts	Assessment of outcome	Follow-up long enough for outcomes to occur (FU $\geq$ 2 years)	Adequacy of follow-up	
Benedictus, 2015	Representative Sample includes patients who came to memory clinic because of their cognitive impairment. *	Yes *	MRI *	Yes *	Study was adjusted for age, sex, medial temporal lobe atrophy, and magnetic resonance imaging field strength using Cox proportional hazard model *	Independent blind assessment. *	Yes *	79% completed 1-year follow-up for neuropsychological assessment.	**Good**
Van Uden, 2015	Representative sample shows non-demented participants with an age between 50 and 85 years at baseline. *	Yes *	MRI *	Yes *	Age, gender, education, baseline MMSE, Hippocampal volume were adjusted for Cox proportional hazard model *	Independent blind assessment. *	Yes *	90% participated in the 5-years follow up with full description of the lost participants. *	**Good**
Romero, 2017	Participants were truly representative of dementia-free from Framingham Heart Study. *	Yes *	MRI *	Yes *	Age, sex, APOE status, and education, and vascular risk factors were adjusted for multivariable models *	Independent blind assessment. *	Yes *	126 participants were excluded for lack of follow up information in second data collection and the rest of participants complete the study. *	**Good**
Akoudad, 2016	Participants were truly representative as they aged $\geq$ 45 years, were invited to undergo home interviews and various physical and laboratory examination.*	Yes *	MRI *	Yes *	Age, sex, and education. Additionally, APOE ε4, a propensity score of cardiovascular risk were adjusted for regression models *	Independent blind assessment. *	Yes *	Follow-up for dementia was completed in 4841 participants.	**Good**
Miwa, 2015	The sample was truly representative of people with vascular risk factors. *	Yes *	MRI *	Yes *	Age, gender, BMI, MMSE, smoking, hypertension, and previous CVDs were adjusted for Logistic regression model. *	Record. *	Yes *	Complete follow-up for all participants. *	**Good**
Miwa, 2014	The sample was truly representative of people with vascular risk factors. *	Yes *	MRI *	Yes *	Age, sex, education, and APOE status were adjusted for Cox proportional hazards regression model. *	Record. *	Yes *	Complete follow-up for all participants. *	**Good**
Staekenborg, 2009	152 participants were recruited consecutively with MCI from the out-patient memory clinic of the Alzheimer Centre of the VU University Medical Centre. *	Yes *	MRI *	Yes *	Age and sex were adjusted for Cox Regression model *	Record. *	Yes *	All patients were annually re-examined for possible alteration in cognitive function with a mean follow-up of (1 +/- 2) years. *	**Good**
Kirsch, 2009	1348 individuals from several local communities were screened to recruit	Yes *	MRI *	Yes *	Age and presence of BMB were adjusted for	Record. *	Yes *	Complete follow-up for all participants. *	**Good**

(*continued on next page*)

Table 2 (*continued*)

Study	Selection				Comparability	Outcome			Quality Score
	Representativeness of Exposed Cohort	Selection of the Non-Exposed Cohort from Same Source as exposed	Ascertainment of exposure	Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts	Assessment of outcome	Follow-up long enough for outcomes to occur (FU ≥ 2 years)	Adequacy of follow-up	
	elderly cognitively normal and mild cognitively impaired (MCI) as study participants.*				logistic regression model *				
Ding, 2017	2602 representative participants aged 66–93 years and free of prevalent dementia. *	Yes *	MRI *	Yes *	Age, sex, follow-up time interval, coil type, primary education, hypertension, and total cholesterol were adjusted for logistic regression model *	Record. *	Yes *	98% participants attended the follow-up assessment with provided description of those lost. *	**Good**

associated with overall 1.84 times increased risk of developing dementia than those without CMBs (RR 1.84, 95% CI [1.27–2.65], P = 0.001, Fig. 2).

In the subgroup meta-analysis, the two memory clinic studies (Benedictus et al., 2015; Staekenborg et al., 2009) showed no association between CMBs and the development of dementia with no statistical heterogeneity between the studies (RR 1.02, 95% CI [0.68–1.51], P = 0.94). On the other hand, the three studies from the high-risk population (van Uden et al., 2016; Miwa et al., 2016, 2014) showed a double-fold increase in the risk of dementia in CMBs (RR 2.00, 95% CI [1.41–2.83], P < 0.0001) with no statistical heterogeneity (I^2 =0%, P = 0.55). The remaining four studies from the general population (Akoudad et al., 2016; Romero et al., 2017; Ding et al., 2017; Kirsch et al., 2009) also showed an increase in the risk of dementia in CMBs (RR

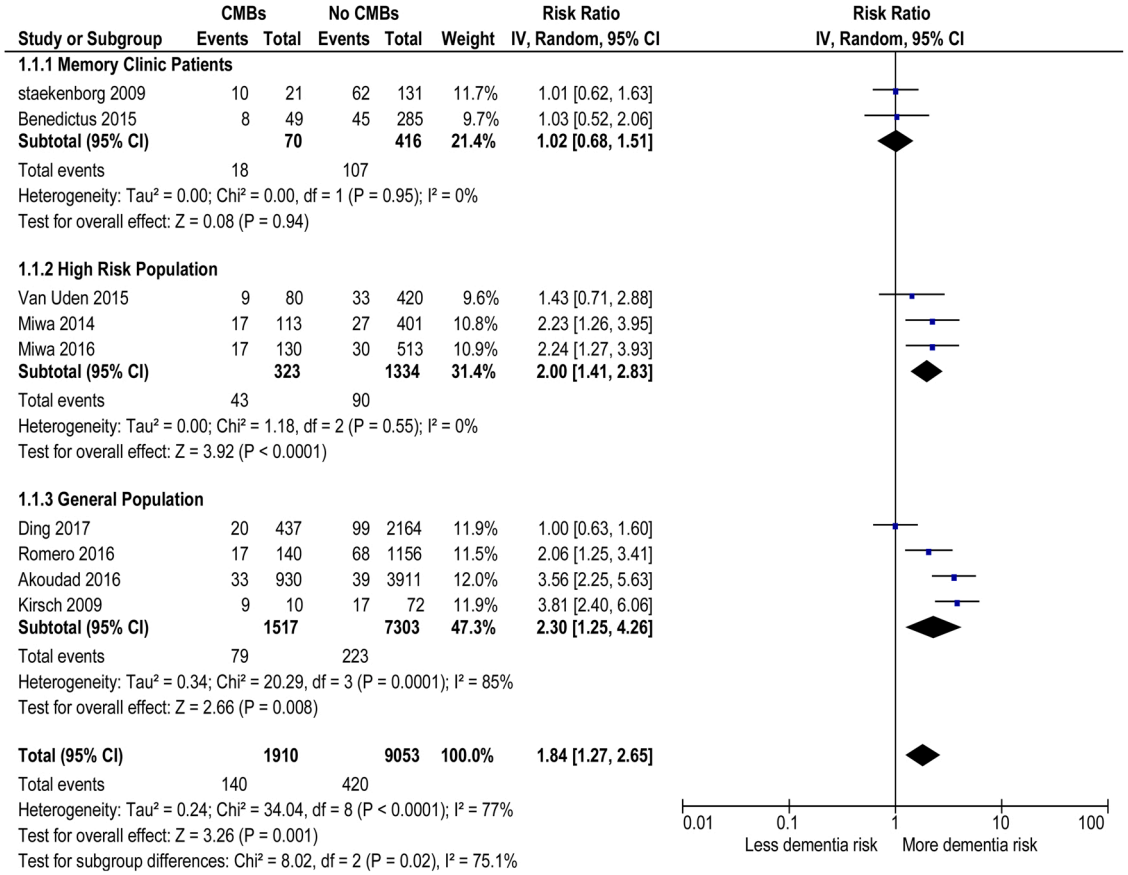

Fig. 2. Forest plot showing the risk of dementia in CMBs and no CMBs groups expressed as the risk ratio and the 95% CI; CMBs=Cerebral Microbleeds; IV=Inverse Variance; CI=Confidence Interval.

2.30, 95% CI [1.25–4.26], P = 0.001), but with substantial statistical heterogeneity (I^2 =77%, P = 0.0001). The results of the meta-analysis are shown in Fig. 2.

3.5. Meta-analysis of the hazard ratios of incident dementia over time

Unlike the primary analysis, some studies reported the adjusted HR of incident dementia over time during the follow-up. When these effect estimates were pooled in the meta-analysis model, we found a statistically significant association between CMBs and all-cause dementia (HR =2, 95% CI [1.54–2.61], P < 0.0001) with no heterogeneity between the included studies (I^2 =0%). Additionally, both the subgroups of studies on high-risk patients and those on the general population showed similar significant associations (pooled adjusted HR of 1.63 and 2.19) with no significant heterogeneity in both subgroups (I^2 =0%). The subgroup of the memory clinic population was not represented in this analysis because the two memory clinic studies (Benedictus et al., 2015; Staekenborg et al., 2009) did not report the adjusted HR and could not be estimated or extracted, so these studies were not included in this secondary analysis. The results of this meta-analysis of adjusted HRs are shown in Fig. 3.

3.6. Publication bias

According to Egger et al. (1997), the assessment of publication bias using the funnel plot and Egger's test is not reliable for meta-analysis with fewer than ten included studies. Therefore, in the present study, we could not confirm the existence of publication bias. For the explanatory purpose, the funnel plot of the meta-analysis model of the primary outcome is provided in supplementary file 1. By visual inspection, the distribution of studies around the effect estimate does not suggest the existence of publication bias.

4. Discussion

4.1. Summary of the key findings

This meta-analysis showed that individuals with CMBs have twice the risk of dementia compared to those without CMBs. These results were evident in the subgroups of studies on high-risk populations and those on the general population (asymptomatic individuals) but not in the studies on memory clinic patients. In addition, the results were concordant in both the primary crude analysis (event rates represented as RRs) and the secondary analysis of incident dementia over time (expressed as adjusted HRs).

4.2. Explanation of the study findings

CMBs are an indicator of underlying pathology in SVD (Greenberg et al., 2009), but the direct impact of CMBs on cognitive brain functions has not been fully understood. The literature provides some possible explanations for the association between CMBs and dementia, as follows: First, CMBs were found to contribute to network disruption and tissue damage in early cognitive decline patients as early AD (Heringa et al., 2014; Werring et al., 2004); Second, CMBs may affect cognitive function mainly through the underlying brain microangiopathy and vasculopathy, which change according to their number and locations (Poels et al., 2012); Finally, the CMBs-associated hypertensive vasculopathy and amyloid angiopathy may accelerate the process of cognitive deterioration.

In the subgroup of memory clinic patients, the association between CMBs and dementia was not statistically significant. This could be explained by: (1) the relatively smaller sample in this subgroup (n = 486 patients) compared to the high-risk and general population subgroups (n = 1457 and 8820 participants, respectively); (2) the shorter follow-up period in Staekenborg et al. (2009) (average=1.8 years) compared to other studies, the shorter follow-up period might not be sufficient for dementia to manifest; (3) Staekenborg et al. (2009) did not report their participants' baseline vascular risk factors. These factors have been reported in many studies as important risk factors for dementia as hypertension (Skoog et al., 1996; Starr et al., 1993; Bellew et al., 2004), smoking (Shinton and Beevers, 1989; Ott et al., 1998; Merchant et al., 1999; Tyas et al., 2003), diabetes (Brands et al., 2005; Young et al., 2006), and hyperlipidemia (Maki et al., 2005; Evans et al., 2000; Moroney et al., 1999); (4) Both studies in the memory clinic subgroup did not report the baseline APOE status of their participants, unlike the other groups. APOE is considered a principal risk factor for dementia development (Saunders et al., 1993; Blacker et al., 1997; Martins et al., 2005; Duron and Hanon, 2008); and (5) Different outcome measures for dementia were used in the follow-up. Since the two studies on memory clinic patients did not report the APOE status or vascular risk factors, we cannot confirm whether participants in these studies had lowered risk for dementia compared to the general population.

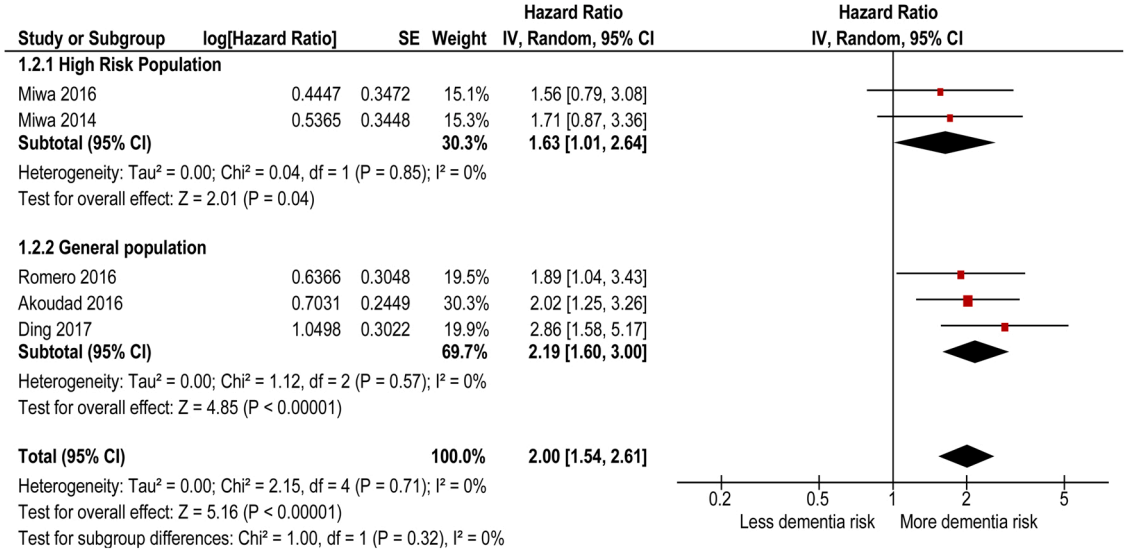

Fig. 3. Forest plot showing the progression to incident dementia (all cause-dementia) in CMBs and no CMBs groups expressed as the hazard ratio and the 95% CI; CMBs=Cerebral Microbleeds; IV=Inverse Variance; CI=Confidence Interval; SE=standard error.

4.3. Agreement and disagreement with previous studies

Our study results are in agreement with those of Charidimou et al. (2018) and Jiang et al., 2019 (Jiang et al., 2019). Both studies showed that CMBs were associated with a higher risk of dementia. Still, our study had a larger sample size and a more robust analysis and reported a stronger association than Charidimou et al. (2018) study. Despite us sharing most of the included studies with Charidimou et al (Charidimou et al., 2018)., we included an additional two studies in our systematic review, which increased the statistical power of the analysis (Miwa et al., 2016; Kirsch et al., 2009). Despite using a validated outcome measure in all studies, using discrete outcome measures and the difference in follow-up periods and data reporting may contribute to the statistical heterogeneity among study results.

4.4. Significance of the study

This study expands the literature by providing statistically robust evidence that CMBs are associated with dementia and progression to cognitive decline. These results are important for clinical practice. The detection of CMBs might help identify the population at higher risk of developing dementia. Therefore, physicians should educate patients with CMBs and their families on the possibility of progressing to dementia or cognitive decline. Patients may subject to regular follow-up and cognitive assessments. Further, cognitive training, lifestyle modifications, and controlling other dementia risk factors might be recommended for individuals with CMBs to decrease the risk of cognitive decline.

4.5. Strength points and limitations

This study has several strength points: (1) we followed the standard guidelines when conducting this study, the PRISMA statement and Cochrane Handbook, (2) we searched multiple electronic databases to identify the relevant studies, (3) we analyzed the dementia events (as RR) and the progression to incident all-cause dementia over time (as HR), and (4) we included more studies compared to the previously published meta-analyses which provide a larger sample size and more robust evidence.

Nonetheless, this study has a few limitations. First, the included studies were heterogeneous in the baseline characteristics and the outcome measures used. Second, we analyzed the data of CMBs vs. no CMBs without meta-regression for the number or location of CMBs. Because meta-regression analysis requires at least ten studies, and most studies did not report the number and location of CMBs, this additional analysis was not feasible to conduct. Therefore, this meta-analysis was limited by the small number of included studies. Because prospective cohort studies on dementia require a long follow-up period, they are expensive in time and money. In addition, only five out of the nine included studies reported the effect size of progression to all cause-dementia.

4.6. Recommendations for future research

We recommend future cohort studies on CMBs and dementia have the following characteristics:

- *A large sample size, following our recommendations for sample size calculation for cohort studies* (Khaled Fahim and Negida, 2019)
- *A longer follow up period > 5 years to allow for dementia to occur*
- *Enrolling the middle-aged population (existing studies focused on the elderly)*
- *Excluding individuals with other dementia risk factors or balancing these risk factors at baseline by using a matched design to avoid confounding bias*
- *Calculating the RR or HR after adjusting for age, sex, and any significant risk factors in the analysis*
- *Including the progression of MCI as a secondary endpoint*
- *Conducting a detailed neurocognitive assessment to illustrate which neurocognitive domains are mainly affected in CMBs patients*
- *Comparing mortality between CMBs vs. non-CMBs individuals*

Furthermore, future basic science research is needed to understand the pathology of CMBs and how they affect cognition. This will be helpful for prevention programs.

4.7. Conclusion

Individuals with CMBs have twice the risk of developing dementia than those without CMBs. Physicians should educate individuals with CMBs and their families on the possibility of progressing to dementia or cognitive decline. Regular cognitive assessments, cognitive training, lifestyle modifications, and controlling other dementia risk factors are recommended for individuals with CMBs to decrease the risk of cognitive decline.

Ethical approval

Not required. The study does not involve human participants or animal subjects.

CRediT authorship contribution statement

ASH: Contributed to search strategy formulation, statistical analysis, interpretation of the results, manuscript writing, and tabulation. **EIB**: Contributed to drafting and revising the manuscript. **ASH, MS, BR, AG, MS**: Screened the retrieved titles and abstracts, full-text screening, data extraction and revision, and ROB assessment and tabulation. **HG, AN**: Study concept and design, study supervision, revise the draft, All authors except **HG and AN** participated in all steps of study selection and data extraction.

Conflicts of Interest

None.

Acknowledgments

None to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ibneur.2022.12.009.

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