

Effects of cerebral hypoperfusion on the cerebral white matter: a meta-analysis

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Decreased cerebral blood flow (CBF) in aging is known to induce aging-related cerebral deteriorations, such as neuronal degeneration, white matter (WM) alterations, and vascular deformations. However, the effects of cerebral hypoperfusion on WM alterations remain unclear. This study investigates the relationship between cerebral hypoperfusion and WM total volume changes by assessing the trends in CBF and WM changes by meta-analysis. In this meta-analysis, the differences in CBF were compared according to cerebral hypoperfusion type and the effect of cerebral hypoperfusion on the total volume of WM changes in rodents. Using subgroup analysis, 13 studies were evaluated for comparing CBF according to the type of cerebral hypoperfusion; 12 studies were evaluated for comparing the effects of cerebral hypoperfusion on the total volume of WM changes. Our meta-analysis shows that the total volume of WM decreases with a decrease in CBF. However, the reduction in the total volume of WM was greater in normal aging mice than in the cerebral hypoperfusion model mice. These results suggest that the reduction of cerebral WM volume during the aging process is affected by other factors in addition to a decrease in CBF.

Key words: aging, cerebral blood flow, cerebral hypoperfusion, meta-analysis, white matter

INTRODUCTION

Cerebral hypoperfusion induces physical alterations in the white matter (WM) of the brain during the aging process (Hase et al., 2017). Age-related WM alterations appear in the magnetic resonance imaging (MRI) scans as an increased intensity or a decline in the volume of WM areas (Fazekas et al., 1988; Salat, 2011). The bright WM areas on the brain MRI are called white matter hyperintensities (WMHs) (Rane et al., 2018). The increase in WMHs is a clinically important indicator of aging and neurodegenerative disease because they are accompanied by symptoms such as cognitive impairment and reduced executive functions (Lo et al., 2012; Crane et al., 2015). Current studies mainly report the relationship between cerebral blood flow (CBF) reduction and WM changes by measuring WMHs (Shi et al., 2016). However, reports on the change in the total

volume of WM tissue following age-related low CBF are limited. Therefore, it is essential to determine the relationship between cerebral hypoperfusion and changes in the total volume of WM during normal aging.

The natural decrease in CBF during aging is accompanied by vascular alteration and neuronal change. The aged brain shows an increase in tortuous arterioles and the accumulation of collagen in the vessels (Brown et al., 2002; Kang et al., 2016). In addition, myelin alteration and breakdown, degeneration of oligodendrocytes, and increase in oligodendrocyte progenitor cells (OPCs) are representative neuronal changes in aging, which eventually induces WM lesions (Kohama et al., 2012; Liu et al., 2017). Based on these findings, CBF reduction may not be considered as the sole reason for WM lesions in the aged brain.

However, previous studies have revealed a close relationship between CBF reduction and WM chang-

es. To clarify the relationship between CBF and WM alterations, the WM alterations induced by only CBF must be analyzed. In human studies, it is difficult to study WM alterations occurring only in a single condition of low blood flow. Therefore, an experimental cerebral hypoperfused animal model is needed for understanding the association between CBF and WM alterations.

In this systematic review, we aim to evaluate the association between cerebral hypoperfusion and WM changes in rodents by we meta-analyzed on published studies on the measurements of CBF and the total volume of WM in cerebral hypoperfusion model mice and aging mice.

Systematic review, data collection and analysis

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. An electronic literature search was conducted using the PubMed and Cochrane library March 1996 to October 2019, with search key terms such as ‘chronic hypoperfusion’ and ‘aging brain white matter’. Only English publications were included. Online searching of the databases was performed in October 2019. The keyword search was last accomplished on November 6, 2019. After the literature search, appropriate data were selected. In addition, reference citations in reviews and primary papers were reviewed. All the searches were restricted to rodent studies.

The setting conditions for this meta-analysis according to the possible population, intervention, and outcome (PICO) approach are as follows. Population is rodents, and intervention is normal aging and cerebral hypoperfusion. The comparison for each intervention is a young and sham condition, respectively. The outcomes of this meta-analysis are CBF and the total volume of WM.

Exclusion criteria were as follows: studies published before 1996; reviews, duplicate publications, and studies that did not include full-text articles; human studies, animal studies except for rodents, and genetically modified animals. Experimental animals with other diseases, such as heart failure, diabetes, or high blood pressure owing to aging or treatment; among the CBF and WM measurement methods, studies that were not objective in the numerical calculation, and studies in which CBF and WM measurements were not clear; and *in vitro* and *ex vivo* studies.

Initial studies were conducted by eliminating duplications and included only inclusion studies based on title-abstract-full text screening. All studies report-

ing mean and standard deviation (SD) were included in the meta-analysis (Shi et al., 2016). Two authors independently screened the data. All data were checked for title, abstract, full-text, and appropriateness. The primary outcomes were the weighted mean differences in CBF between the hypoperfusion group and control group. The secondary outcomes were weighted mean differences in WM volume in the same groups.

The meta-analyses were conducted using Review Manager version 5.3 software (RevMan 5.3, Copenhagen, Denmark). To analyze the effect of hypoperfusion on CBF and the total volume of WM alterations across studies, the results were calculated for each comparison with 95% confidence intervals (CI) using the random-effects methods. The outcomes in the included studies were meta-analysis using the mean difference (MD). Heterogeneity between study results was assessed by calculating the I^2 statistic. A P -value < 0.05 was considered statistically significant.

The quality of the measures of selected studies was assessed using a modified version of the CAMARADES’ study quality checklist (Fig. 1) (Sadigh-Eteghad et al., 2017).

Second, to assess the risk of bias in the selected studies, the RevMan 5.3 program was used (Fig. 2).

A funnel plot was used for evaluating publication bias.

Study selection

A total of 6,792 publications were initially found and 178 duplicate publications were reviewed. For eligibility, 6,614 publications were assessed based on the title and abstract; 4,967 publications were excluded based on the title level, and 1,062 publications were excluded based on the abstract level. A total of 585 studies were evaluated based on full text; 503 were excluded, and 82 were assessed for eligibility. A total of 25 studies were included in the meta-analysis based on the eligibility criteria. A PRISMA flow chart summarizing the search and selection process is presented in Fig. 3.

The comparisons were segregated according to the cerebral hypoperfusion type and effect of cerebral hypoperfusion on WM change.

Two types of cerebral hypoperfusion were established for comparing CBF according to the low blood flow type; 13 studies were included. In the case of normal aging, the age of mice was accurately indicated in three studies (3/13) (Farkas et al., 2011; Suenaga et al., 2015; Ding et al., 2019). In the other nine cases, the most common carotid arteries (CCAs) were operated for inducing cerebral hypoperfusion (9/13). Five studies conducted suture ligation, (Ouchi et al., 1998;

Ohmori et al., 2011; Kitamura et al., 2012; Park et al., 2019; Xie et al., 2019) and four studies used micro-coils with an inner diameter of 0.18 mm (Shibata et al., 2004; Nishio et al., 2010; Patel et al., 2017; Dominguez et al., 2018). One study used facial vein ligation with sutures for inducing cerebral hypoperfusion (Chen et al., 2009). The induction period was described when cerebral hypoperfusion was induced by surgery. Characteristics such as species, gender, number of groups, age (weight), anesthesia methods, and measurement units are also described in Table 1.

For comparing WM changes, two types of cerebral hypoperfusion of cerebral hypoperfusion were established similar to CBF comparison. To evaluate WM changes, the total volume of WM were compared. A total of 12 studies were included. In the case of normal aging, the age of mice was accurately indicated in nine studies (9/12) (Sun et al., 2005; Maheswaran et al., 2009; Yang et al., 2009; Shao et al., 2010; Shi et al., 2011; Nemeth et al., 2014; Yang et al., 2015a; 2015b; Ding et al., 2019). Two studies were used micro-coils with an inner diameter of 0.18 mm for both CCAs; (Holland et al., 2011; 2015), one study used a 30 G needle on the left internal carotid artery for inducing cerebral hypoperfusion (Nemeth et al., 2014). The characteristics of the

included studies of the effects of cerebral hypoperfusion on WM change are described in Table 2. One study overlapped for each comparison but described separately for each comparison (Table 2).

Meta-analysis of the effects of cerebral hypoperfusion type on CBF

The meta-analysis of CBF according to cerebral hypoperfusion was conducted using two subgroup analyses. In the subgroups, the analysis was divided into different cerebral hypoperfusion types (normal aging or hypoperfusion model). In both the cerebral hypoperfusion types, CBF decreased compared to the control group. CBF moderately decreased in the normal aging group than in the young group (MD - 9.56 ; 95% CI - 11.64 to - 7.49 ; $P < 0.00001$) (Fig. 4A). CBF also decreased in the hypoperfusion model group than in the sham group (MD - 23.37 ; 95% CI - 32.24 to - 14.51 ; $P < 0.00001$) (Fig. 4C). The CBF reduction was more severe in the hypoperfusion model group than in the normal aging group. The evidence of heterogeneity was evaluated using I^2 . The heterogeneity for normal aging and hypoperfusion model was $I^2 = 0\%$ (aging and young group)

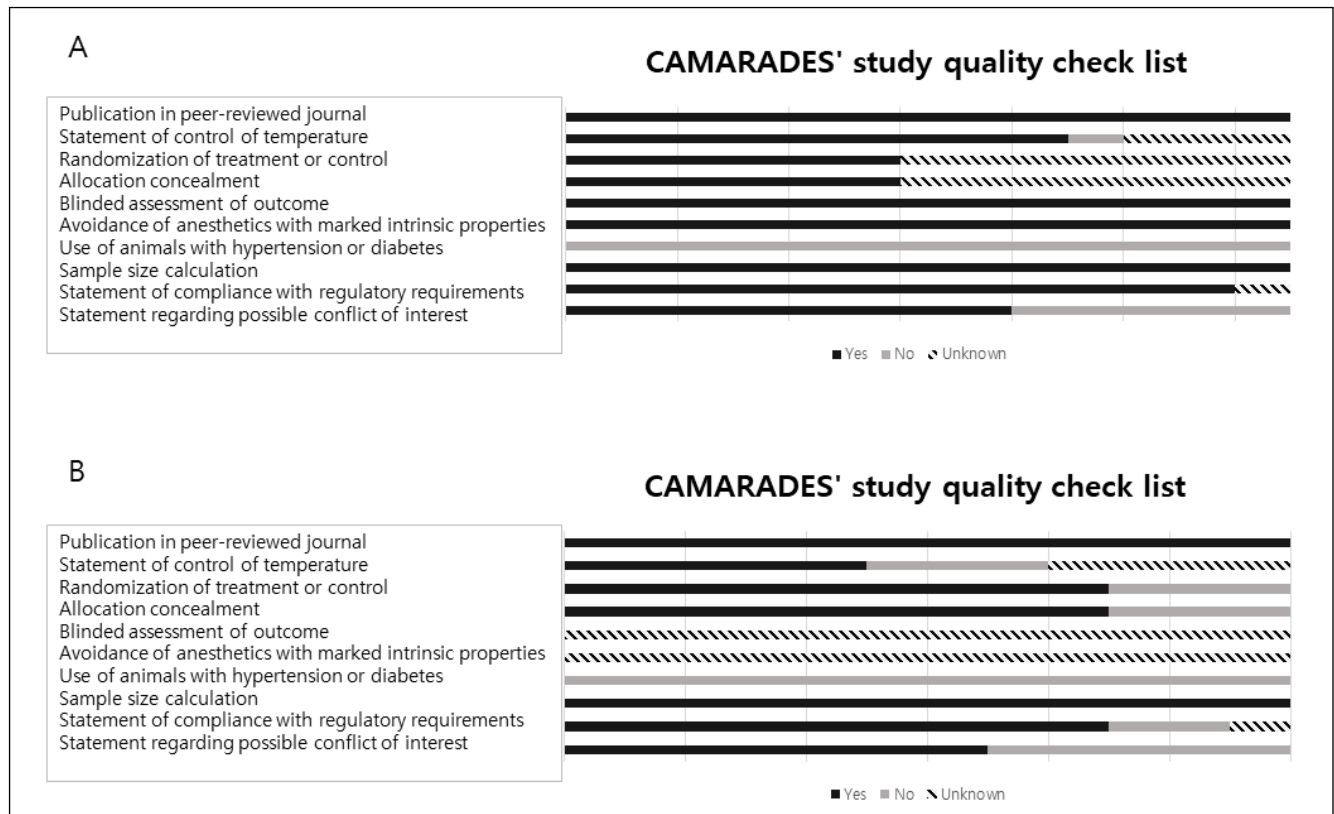


Fig. 1. Risk of bias of the included rodent studies according to the modified CAMARADES' study quality checklist. (A) CAMARADES' study quality checklist from selected studies of CBF change. (B) CAMARADES' study quality checklist from selected studies of the total volume of WM change.

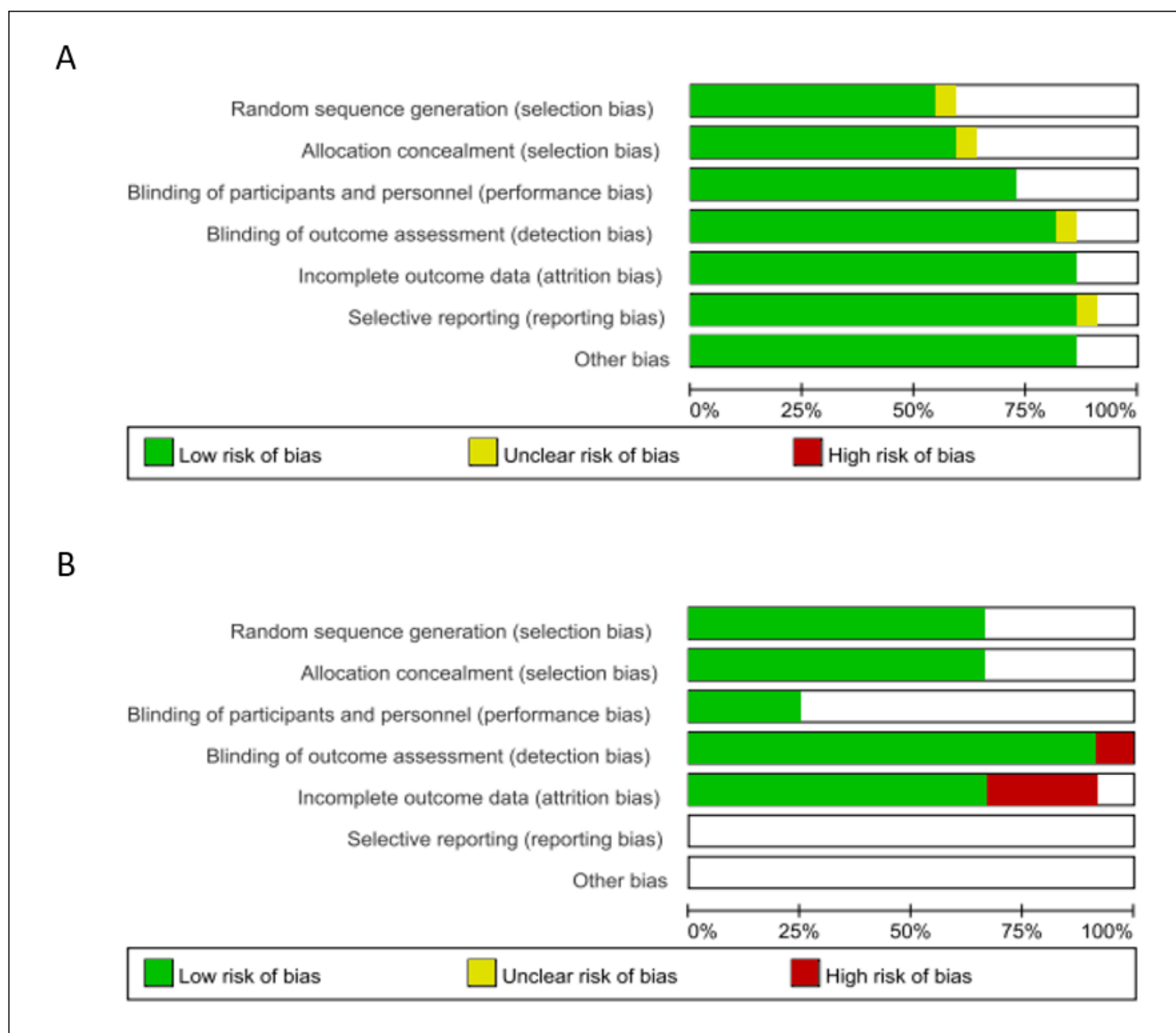


Fig. 2. Risk of bias chart from the included studies. (A) Bias risk chart from the selected studies of CBF change. (B) Bias risk chart from the selected studies of the total volume of WM change.

and $I^2=97\%$ (hypoperfusion and sham group), respectively. A funnel plot was used for evaluating the publication bias of the studies included in each meta-analysis (Fig. 4B, 4D).

Meta-analysis of cerebral hypoperfusion on WM change

The meta-analysis of cerebral hypoperfusion on WM change was conducted using three subgroup analyses. In the subgroups, the analysis was divided for different cerebral hypoperfusion types, such as CBF comparisons. In both cerebral hypoperfusion types, WM vol-

ume decreased compared to the control group, similar to the CBF comparisons. For the analysis of studies with different units of measurement, in case of aging and young group was divided into two analysis. The WM volume in most of the studies tended to decrease in the normal aging group than in the young group (MD - 24.46 ; 95% CI - 39.15 to - 9.76 ; $P<0.00001$) (Fig. 5A) (MD - 0.07 ; 95% CI - 0.16 to - 0.03 ; $P=0.16$) (Fig. 5C). The WM volume also decreased in the hypoperfusion model group than in sham group (MD - 0.04 ; 95% CI - 0.05 to - 0.03 ; $P<0.00001$) (Fig. 5E). The WM volume reduction in the normal aging group was more than in the hypoperfusion model group. The evidence of heterogeneity was evaluated using I^2 . The heterogeneity between normal

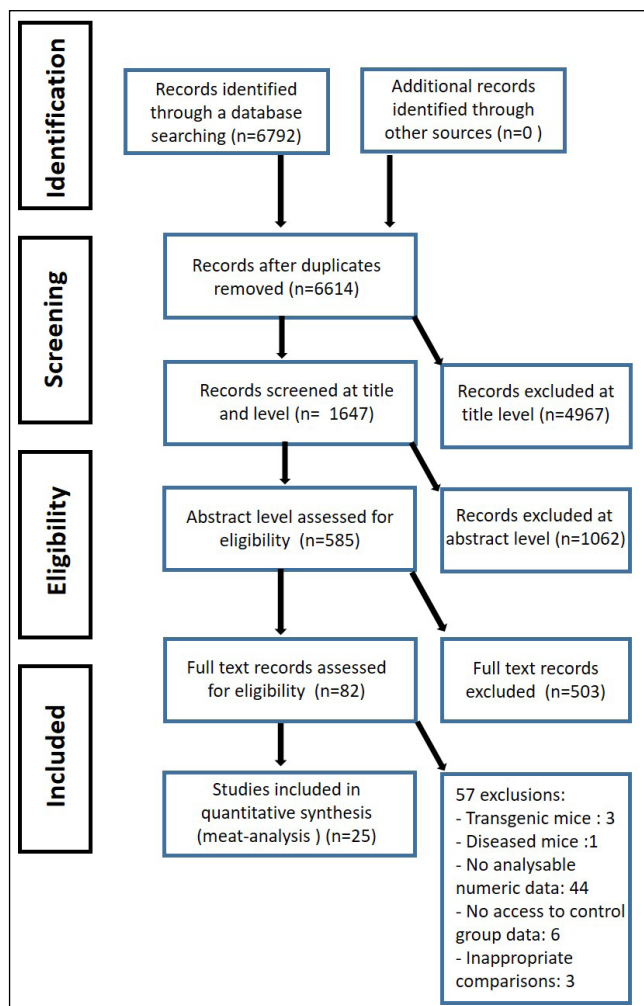


Fig. 3. PRISMA flow chart of literature search and data selection.

aging group and young group was $I^2=100\%$ and $I^2=35\%$, respectively. The heterogeneity between hypoperfusion model group and sham group was $I^2=0\%$. A funnel plot was used for evaluating publication bias of each subgroup analysis (Figs 5B, 5D, 5F).

Meta-analysis of cerebral hypoperfusion on WM

This meta-analysis showed that the total volume of WM decreased during cerebral hypoperfusion in rodents. In the majority of studies, the total volume of WM tended to decrease in the normal aging than in the young group. In addition, the subgroup analysis showed that the total volume of WM reduction in the normal aging mice was higher than that in the cerebral hypoperfusion model mice group. These results suggest that the reduction in WM volume during normal aging is regulated by cerebral hypoperfusion and other factors involved.

Cerebral hypoperfusion during aging is considered to be one of the causes of neurodegenerative brain disease and cerebral vascular disease (Farkas et al., 2007; Zhao and Gong, 2015). However, the effects of aging and cerebral hypoperfusion on the brain are still not clearly distinguished. In human studies, there is a limit to applying a single condition of cerebral hypoperfusion over a long period of time. To investigate the effect of a single condition of CBF reduction on the brain, a selection of studies that artificially induced cerebral hypoperfusion in experimental animals is necessary. The chronic hypoperfusion mouse model induced by common carotid artery stenosis (BCAS) has been evaluated as a reliable model for studying vascular dementia, such as cerebral hypoperfusion (Ihara and Tomimoto 2011; Bink et al., 2013; Madigan et al., 2016). In addition, the cerebral hypoperfusion model using microcoils can be used for studying WM lesions caused by cerebral hypoperfusion that show a moderate CBF reduction and low mortality (Shibata et al., 2004). We meta-analyzed studies using normal aging mice, BCAS model mice, and microcoils used model mice. The results of our analysis showed that CBF levels were slightly lower in the cerebral hypoperfusion model mice than in the normal aging mice.

Age-related changes in WM are common based on animal and human research (Brickman et al., 2009). The decrease in CBF has been known to be closely related to cerebral WM changes during aging (Crane et al., 2015). Several studies have reported that the cerebral hypoperfusion model presents WM lesions, abnormal inflammatory hyper-activation, and changes in neuronal morphology (Yoshizaki et al., 2008; Hattori et al., 2014; Mitome-Mishima et al., 2014; Wang et al., 2016; Park and Lee, 2018; Somredngan and Thong-Asa, 2018). The cerebral WM alterations were measured by the change in WMHs using MRI (Fazekas et al., 1988; Salat, 2011). Previous clinical studies have shown that WMHs increase with decreasing CBF (Bahrani et al., 2017; Rane et al., 2018). These findings indicate that the changes in the macroscopic properties of cerebral WM are caused by cerebral hypoperfusion. However, Gurol (2013) reported the highest probability that WMHs may reduce blood flow. Moreover, Shi et al. (2016) reported that CBF reduction was greater in patients with severe WMHs, and suggested that cerebral hypoperfusion is more likely a consequence of WM change than the cause. Hence, the causal relationship between cerebral hypoperfusion and WM changes is still controversial. Therefore, we used a cerebral hypoperfusion model to determine whether cerebral hypoperfusion induces WM change.

The changes in WM are represented by the change in the volume of WM on MRI examination. WM atrophy is positively related to WMHs, which is a marker in the

Table 1. Summary of the characteristics of included studies of the comparison of cerebral hypoperfusion type of CBF change.

	Study	Species	Age or weight	Methods of anesthesia	Methods of measuring CBF	Units of CBF	Method of hypoperfusion induction	Induction period	Comparison	Measuring area
1	Farkas E et al., 2011	Wistar rats	Young (2 months; n=6), old (10 months; n=8)	Chloral hydrate (400 mg/kg, i.p.)	LDF	%	–	–	Aging/ young	Cerebral cortex
2	Suenaga J et al., 2015	C57bl/6j	Young (10 weeks; n=4), old (18 months; n=4)	1.5% isoflurane	Laser speckle contrast imager	%	–	–	Aging/ young	Cerebral cortex
3	Ding G et al., 2019	Wistar rats	Young (2-3 months; n=10) old (14-15 months; n=10)	1.0-1.5% isoflurane	MRI (PASL)	C	–	–	Aging/ young	Cerebral cortex
4	Ouchi Y et al., 1998	Wistar rats	Sham (200-350 g; n=6), hypoperfusion (200-350 g; n=6)	Chloral hydrate (300 mg/kg, i.p.)	MRI	mL/100g/min	Both cca double-ligated with silk sutures	1 months	Hypoperfusion model / sham	Frontal cortex
5	Shibata M et al., 2004	C57bl/6j	Sham (10 weeks; n=7), hypoperfusion (10 weeks; n=12)	Sodium pentobarbital (50 mg/kg, i.p.)	LDF	%	Both cca twisted with 0.18 mm microcoils	2 h	Hypoperfusion model / sham	Cerebral cortex
6	Chen L et al., 2009	Sprague Dawley rats	Sham (300-400 g; n=25), hypoperfusion (300-400 g; n=35)	0.7% α -chloralose, 0.7% sodium bitorate, and 14% urethane (0.5 mL per 100 g of rat weight, i.p.)	Laser Doppler needle	%	Right anterior facial vein was ligated with 10-0 nylon suture	12 weeks	Hypoperfusion model / sham	Occipital lobe
7	Nishio K et al., 2010	C57bl/6j	Sham (16 weeks; n=5), hypoperfusion (16 weeks; n=6)	Sodium pentobarbital (50 mg/kg, i.p.)	LSF	%	Both cca twisted with 0.18 mm microcoils	3 months	Hypoperfusion model / sham	Cerebral cortex
8	Ohmori Y et al., 2011	Wistar rats	Sham (300-350 g; n=10), hypoperfusion (300-350 g; n=10)	4% halothane	LDF	%	Both cca ligated with 4-0 silk sutures	21 days	Hypoperfusion model / sham	Frontal lobe
9	Kitamura A et al., 2012	Wistar-Kyoto rats	Sham (12-14 weeks; n=6), hypoperfusion (12-14 weeks; n=6)	1.5% isoflurane	LSF	%	Both cca ligation with silk suture	28 days	Hypoperfusion model / sham	Frontal cortex
10	Dominguez R et al., 2018	C57bl/6j	Sham (12 weeks; n=14), hypoperfusion (12 weeks; n=14)	2% isoflurane	LDF	%	Both cca twisted with 0.18mm microcoils	Immediately after surgery	Hypoperfusion model / sham	Cerebral cortex
11	Park JH et al., 2019	Wistar rats	Sham (8 weeks; n=22), hypoperfusion (8 weeks; n=22)	2% isoflurane	LDF	%	Both cca double-ligated with silk sutures	28 days	Hypoperfusion model / sham	Cerebral cortex
12	Xie X et al., 2019	Sprague-Dawley rats	Sham (3 months; n=8), hypoperfusion (3 months; n=8)	3% sodium pentobarbital (0.1ml/ 100g)	MRI	%	Both cca double-ligated with silk sutures	28 days	Hypoperfusion model / sham	Parietal cortex

Note: All the studies were carried out with the male mice. CCA: common carotid artery; CBF: cerebral blood flow; i.p.: intraperitoneal injection; M: male; MRI: magnetic resonance imaging; n: the number of animals; LDF: Laser doppler flowmeter; LSF: Laser speckle flowmetry; PASL: pulsed arterial spin labeling.

traumatic brain injury, depression model, and chronic neurodegeneration (Gao et al., 2017; Marion et al., 2019). Brain atrophy is known to occur not only in neurodegenerative diseases such as Alzheimer's disease but also in natural aging processes. Imaging studies have reported that brain atrophy predicts CBF reduction (van Es et al., 2010; Zonneveld et al., 2015). However, most studies have revealed an association between cortical atrophy and CBF (Schmidt et al., 2005; Chen et al., 2011). In a meta-analysis by Melazzini et al. (2021)

a significant positive correlation was present between WMHs and age in individuals older than 50 years. In addition, a meta-analysis by Shi et al. (2016) reported the relationship between low CBF and WMHs severity. Few studies have examined changes in the WM volume. However, the change in both WMHs and WM volume occurs in the normal aging process, so it is also necessary to clarify the association between CBF reduction and the total volume of WM (de Leeuw et al., 2001; Bennett and Madden, 2014). In our review, we evaluated the as-

Table 2. Summary of the characteristics of included studies of the comparison of cerebral hypoperfusion effects on the total volume of WM change.

	Study	Species	Gender	Age or weight	Methods of anesthesia	Methods of measuring WM	Units of WM	Method of hypoperfusion induction	Induction period	Comparison	Measuring area
1	Yang S et al., 2009	Long-Evans rats	F	Young (6-8 months; n=5), old (27 months; n=8)	4% chloral hydrate (1 ml/100 g)	Stereological measurements	mm ³	–	–	Aging / young	White matter
2	Maheswaran S et al., 2009	C57Bl/6	M	Young (6 months; n=11), old (14 months; n=11)	5% isoflurane	MRI	mm ³	–	–	Aging / young	Corpus callosum
3	Shao WH et al., 2010	Long-Evans rats	F	Young (7 months; n=10), old (27 months; n=10)	4% chloral hydrate (10 mL/kg)	Stereological measurements	mm ³	–	–	Aging / young	White matter
4	Shi XY et al., 2011	Long-Evans rats	F	Young (6-8 months; n=5), old (27 months; n=5)	4% chloral hydrate	MRI	mm ³	–	–	Aging / young	White matter
5	Yang S et al., 2015a	Sprague-Dawley rats	F	Young (6 months; n=10), old (14 months; n=12)	4% chloral hydrate (10 ml/kg)	Stereological measurements	mm ³	–	–	Aging / young	White matter
6	Yang S et al., 2015b	Sprague-Dawley rats	M	Young (6 months; n=12), old (24 months; n=12)	4% chloral hydrate (1 ml/100 g)	MRI	mm ³	–	–	Aging / young	White matter
7	Ding G et al., 2019	Wistar rats	M	Young (2-3 months; n=10), old (14-15 months; n=10)	1.0-1.5% isoflurane	MRI	ms	–	–	Aging / young	Corpus callosum
8	Song SK et al., 2004	Swiss Webster	–	Young (3 months; n=10), old (15 months; n=8)	5% isoflurane	MRI	10 ⁻³ mm ² /s	–	–	Aging / young	Corpus callosum
9	Sun SW et al., 2005	B6/SJL	M, F	Young (8 months; n=8), old (18 months; n=8)	5% isoflurane	MRI	μm ² /ms	–	–	Aging / young	Corpus callosum
10	Nemeth CL et al., 2014	Wistar rats	M	Young (3 months; n=7), old (16 months; n=7) /sham (3 months; n= 9), hypoperfusion (3 months; n= 9)	isoflurane	MRI	FA	30 G needle to the left internal carotid artery	14 days	Aging / young + hypoperfusion / sham	Corpus callosum
11	Holland PR et al., 2011	C57Bl/6	M	Sham (n=8), hypoperfusion (n=15), 25-30 g	5% isoflurane	MRI	FA	Both cca twisted with 0.18 mm microcoils	1 months	Hypoperfusion model / sham	Corpus callosum
12	Holland PR et al., 2015	C57Bl/6	M	Sham (25-30 g; n=11), hypoperfusion (25-30 g; n=20)	5% isoflurane	MRI	FA	Both cca twisted with 0.18 mm microcoils	6 months	Hypoperfusion model / sham	Corpus callosum

CCA: common carotid artery; F: female; FA: fractional anisotropy; i.p.: intraperitoneal injection; M: male; MRI: Magnetic resonance imaging; n: the number of animals; WM: white matter.

sociation between cerebral hypoperfusion and changes in WM volume in studies that measured the total volume of WM.

Our meta-analysis shows the correlation between a decrease in CBF and a change in WM volume in a rodent cerebral hypoperfusion model. The total volume of WM slightly decreased in the cerebral hypoperfusion model mice than in the sham mice, which showed that CBF reduction alone can affect WM changes. However, in the comparison of the aging group and young

group, WM volume is clearly different. The results of our analysis show an average WM volume reduction of approximately 10% in most of the aging group of the included studies. Therefore, it was shown that WM atrophy occurs more certainly in the normal aging condition than in the cerebral hypoperfusion induction condition. These results show that WM volume decreases as CBF decreases, which indicates that CBF is closely related to the changes in WM. However, it can be speculated that the change in WM is also affected by

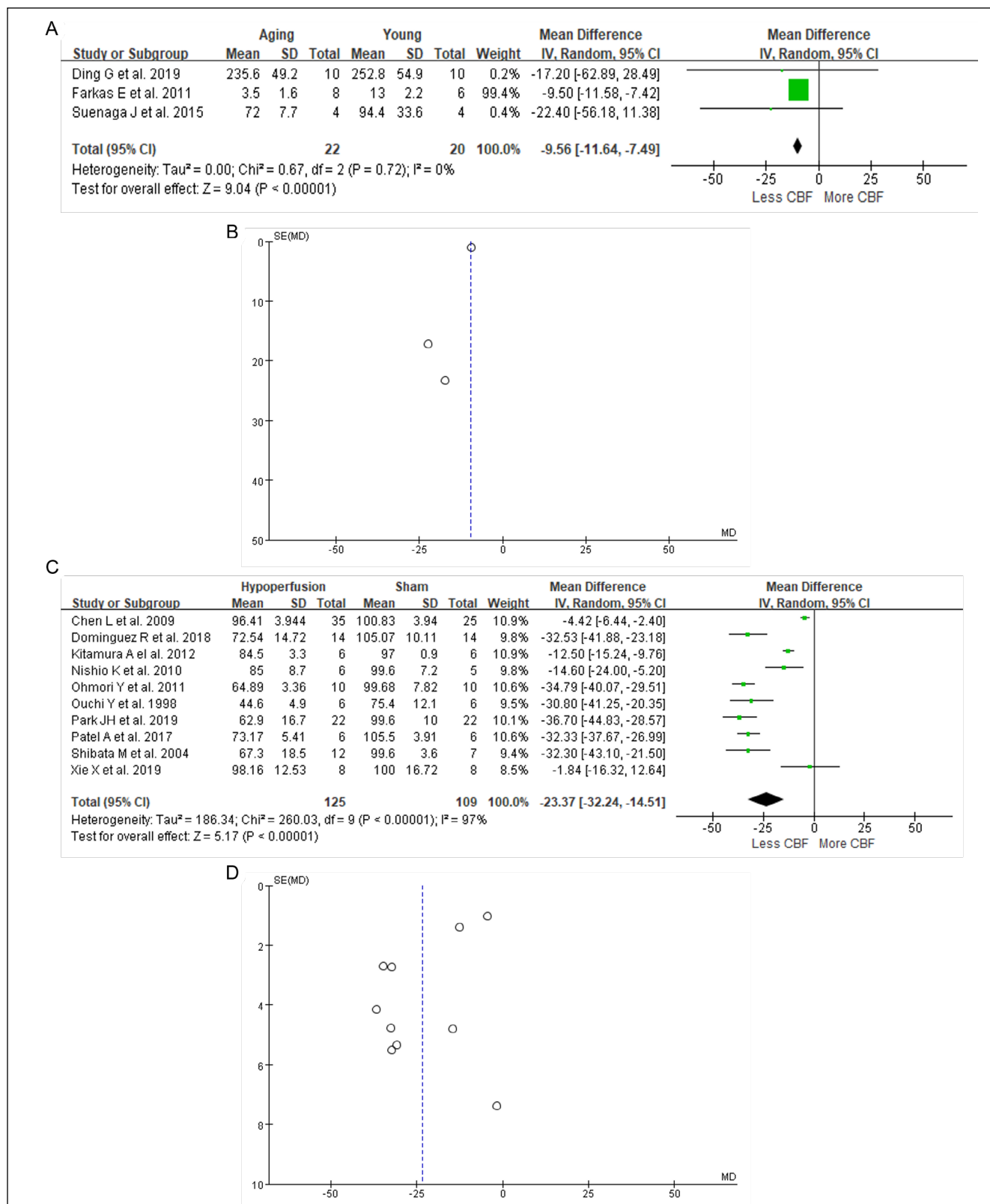
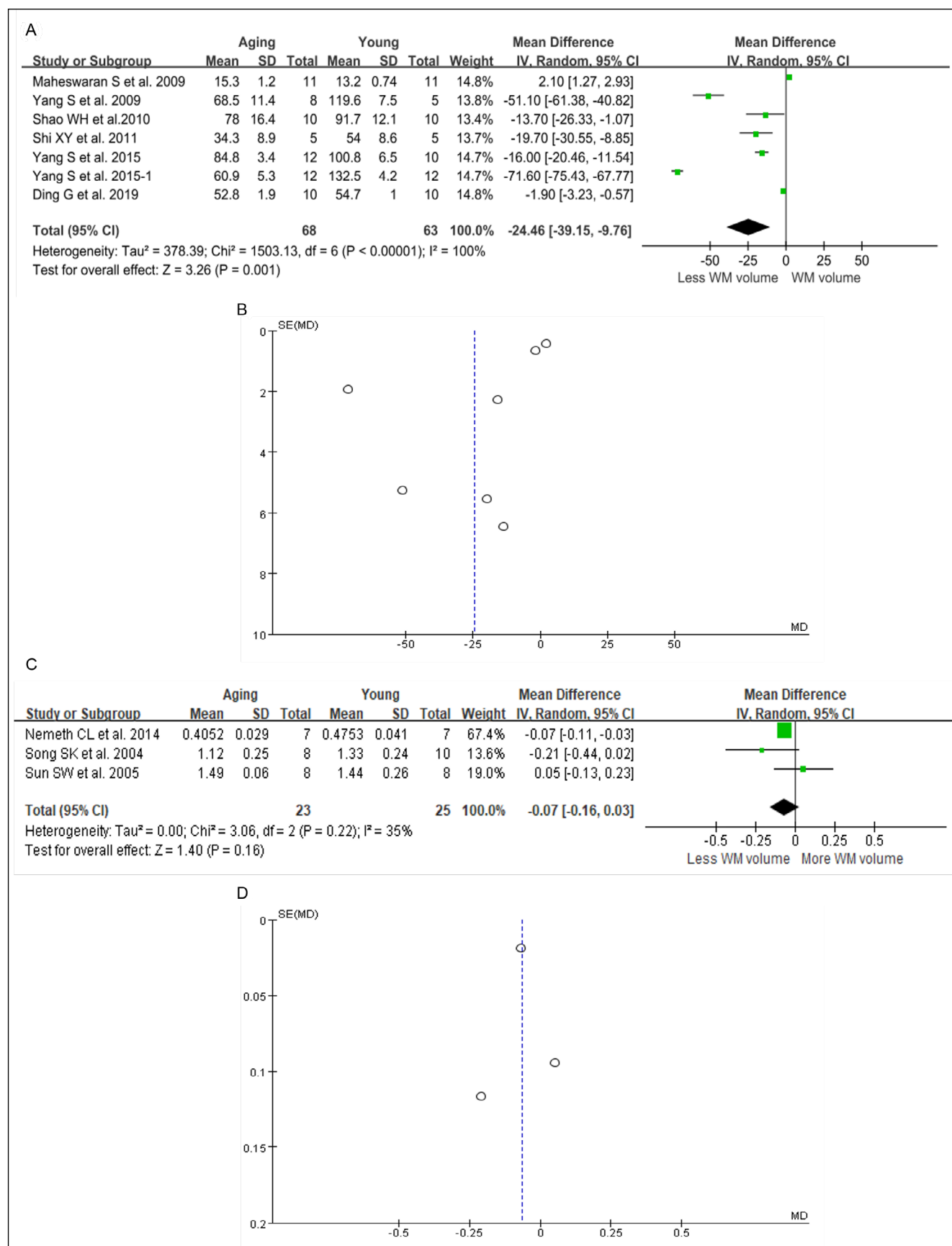


Fig. 4. Meta-analysis of CBF difference according to cerebral hypoperfusion type. (A) Comparison of changes in CBF was analyzed between normal aging and young group using forest plot. (B) Funnel plot used for evaluating publication bias for the included studies of a forest plot (A). (C) Comparison of changes in CBF was analyzed between hypoperfusion model and sham group using forest plot. (D) Funnel plot used for evaluating publication bias for the included studies of a forest plot (C). CBF, cerebral blood flow.



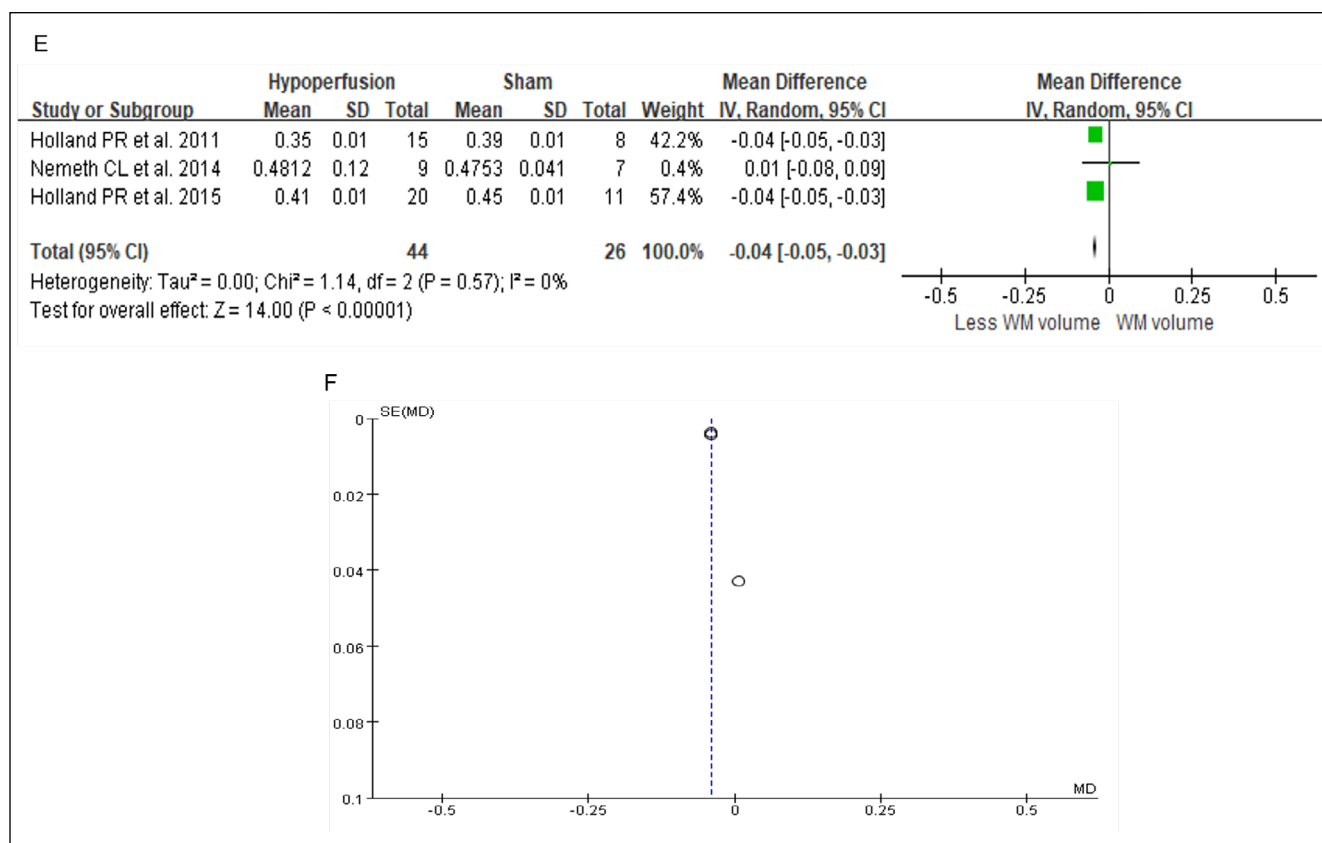


Fig. 5. Meta-analysis of cerebral hypoperfusion effects on the total volume of WM change between cerebral hypoperfusion (aging, hypoperfusion model) and control (young, sham) groups. (A) Comparison of changes in the total volume of WM was analyzed between normal aging and young group using forest plot. (B) Funnel plot used for evaluating publication bias for the included studies of a forest plot (A). (C) Comparison of changes in the total volume of WM was analyzed between normal aging and young group using forest plot. (D) Funnel plot used for evaluating publication bias for the included studies of a forest plot (C). (E) Comparison of changes in the total volume of WM was analyzed between hypoperfusion model and sham group using forest plot. (F) Funnel plot used for evaluating publication bias for the included studies of a forest plot (E). WM, white matter.

other aging processes because the decrease in the total volume of WM appears to be greater in aging mice. The changes in neurons, blood vessels, and other factors owing to aging can affect WM changes. Further analysis of other factors affecting WM changes will help identifying the mechanism of WM changes owing to cerebral hypoperfusion.

Our analysis has several limitations. First, only a few studies were included in this meta-analysis. Particularly, in the comparison of the differences in CBF according to cerebral hypoperfusion type, there were only three studies in the normal aging group. Second, for the cerebral hypoperfusion model, the induction period was short. Because chronic cerebral hypoperfusion has been associated with the aging process, a chronic level of cerebral hypoperfusion induction period is more appropriate for comparing cerebral hypoperfusion in the aging process using a cerebral hypoperfusion model (Santiago et al., 2018). The induction periods of the cerebral hypoperfusion model in our study were as

follows: two studies were performed for 12 weeks, five studies for approximately four weeks, one experiment for 2 h after the surgery, and two studies were measured for CBF immediately after the surgery. To understand the effect of chronic cerebral hypoperfusion on WM changes, further studies with prolonged cerebral hypoperfusion periods are needed. Third, in the comparisons of the effect of cerebral hypoperfusion on WM changes, the number of cerebral hypoperfusion model studies was relatively small than that in normal aging studies. Owing to several limitations of animal experiments, only a few studies measured the total volume of WM in the cerebral hypoperfusion model. Finally, the studies included in each comparison had relatively high heterogeneity. Because of the characteristics of animal experiments, various surgical and measurement methods were used, so most of the included studies were not measured on the same scale. Therefore, the studies that belonged to the same comparison were evaluated as having a high heterogeneity.

CONCLUSION

In conclusion, despite the large heterogeneities across included studies, this systematic review shows that the tendency for a reduction in the total volume of WM is affected by a decrease in CBF. Particularly, a greater more decrease in the WM volume in aging mice than in the cerebral hypoperfusion model. These results support the existing studies that WM changes in aging are regulated by not only in cerebral hypoperfusion but also in various other factors (Liu et al., 2017; Bagi et al., 2018). In other words, a decrease in CBF in aging is one of the causes affecting WM change, and it is expected that other factors including alteration of vascular and neuronal cell will also affect the change in WM volume. If further analysis of other factors will be performed in the future, the mechanism of WM alterations during aging processes will be clarified. These results will also help to identify the cause of cerebral changes during aging at the clinical level.

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