MRI Markers of Neurodegenerative and Neurovascular Changes in Relation to Postoperative Delirium and Postoperative Cognitive Decline

Ilse M.J. Kant, M.Sc., Jeroen de Bresser, M.D., Ph.D., Simone J.T. van Montfort, M.Sc., Arjen J.C. Slooter, M.D., Ph.D., Jeroen Hendrikse, M.D., Ph.D.

Postoperative delirium (POD) and postoperative cognitive decline (POCD) are common in elderly patients. The aim of the present review was to explore the association of neurodegenerative and neurovascular changes with the occurrence of POD and POCD. Fifteen MRI studies were identified by combining multiple search terms for POD, POCD, and brain imaging. These studies described a total of 1,422 patients and were all observational in design. Neurodegenerative changes (global and regional brain volumes) did not show a consistent association with the occurrence of POD (four studies) or POCD (two studies). In contrast, neurovascular changes (white matter hyperintensities and cerebral infarcts) were more consistently associated with the occurrence of POD (seven studies) and POCD (five studies). In conclusion, neurovascular changes appear to be consistently associated with the occurrence of POD and POCD, and may identify patients at increased risk of these conditions. Larger prospective studies are needed to study the consistency of these findings and to unravel the underlying pathophysiological mechanisms. (Am J Geriatr Psychiatry 2017; 25:1048–1061)

Key Words: Postoperative delirium, postoperative cognitive decline, neurovascular brain changes, neurodegenerative brain changes, magnetic resonance imaging

Highlights

- Fifteen studies were identified that assessed structural MRI markers in relation to POD and POCD.
- Neurodegenerative brain changes do not show a clear association with the occurrence of POD or POCD.
- Neurovascular brain changes show a more consistent association with the occurrence of POD and POCD.
- Neurovascular brain changes may identify patients at increased risk of POD and POCD.

Received February 21, 2017; revised June 8, 2017; accepted June 20, 2017. From the Department of Radiology (IMJK, JB, JH); and the Intensive Care Medicine (IMJK, SJTM, AJCS), UMC, Utrecht, The Netherlands. Send correspondence and reprint requests to Ilse M.J. Kant, UMC Utrecht, Heidelberglaan 100, Postbus 85500, 3508 GA Utrecht, The Netherlands. e-mail: i.kant-2@umcutrecht.nl

http://dx.doi.org/10.1016/j.jagp.2017.06.016

Postoperative delirium (POD) and postoperative cognitive decline (POCD) are common in elderly patients. POD is a neuropsychiatric disorder characterized by an acute disturbance in attention and cognition that has an incidence of 15% to 53% in the first days after surgery.[1,2] Risk factors include increased age, dementia, and coexisting medical conditions.[2] Furthermore, the occurrence of POD during the hospital stay is associated with an increased risk of POCD.[3,4]

POCD is generally regarded as postoperative decline in memory and executive functioning that can last for weeks to months after surgery and might even persist for years.[5] To date, there is no exact operational definition of POCD, despite a consensus statement on the assessment of POCD after cardiac surgery.[6] This leads to a variable reported incidence of POCD of 20% to 50% in the first postoperative weeks. Three to 6 months after surgery the prevalence of POCD is around 10%.[3,5,7,8] Risk factors for the occurrence of POCD are increased age, increased duration of surgery and anesthesia, postoperative complications, a low level of education, a history of depression, or cerebrovascular disease.[7–9]

Both POD and POCD have considerable impact on the healthcare system, as they can lead to prolonged hospital admission, a reduced quality of life, and increased dependency.[4,10] To apply preventive measures and better balance the risks and benefits of surgery, we should be able to more accurately identify preoperative patients at increased risk of POD or POCD. Evidence to accurately predict these conditions preoperatively is lacking, however.

In population-based studies of patients with (mild) cognitive impairment, structural brain imaging has shown the potential to detect subgroups of patients at risk for increased cognitive decline.[11] Structural brain imaging markers that are widely used to assess neurodegenerative changes are global and regional brain tissue volumes, and markers to estimate neurovascular changes are white matter hyperintensities (WMH) and cortical and lacunar infarcts.[12–14] Because neurodegenerative and neurovascular changes may be related to increased vulnerability of patients for future cognitive decline, we reviewed studies that tested the hypothesis if these markers may identify patients at increased risk of POD and POCD.

The aim of this review was to explore the association of neurodegenerative and neurovascular changes on imaging, with the occurrence of POD and POCD.

METHODS

Study Selection

We searched for studies published up to January 2017 that assessed the association of structural neurodegenerative and neurovascular imaging markers (computed tomography or magnetic resonance imaging [MRI]) with POD or POCD. Because there is no universally accepted definition of POCD, we combined search terms for postoperative cognitive dysfunction and cognitive decline. The performed PubMed and Embase search can be found in Appendix A. All titles and abstracts obtained by the search were screened. Studies in animals, children, neurosurgery patients, ex vivo studies, case studies with fewer than 10 participants, studies with POCD measurements within 1 week after surgery, and studies with a definition of delirium before publication of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition criteria[15] were excluded. The references of all remaining studies were also screened and additional relevant studies were included. The resulting studies were fully read by two independent raters (IK and JB) to evaluate inclusion in the present review. All disagreements were assessed in a consensus meeting with a third rater (AS).

Quality Assessment

The assessment of study quality was based on a method that was developed for observational studies on delirium.[16] We have adapted these criteria for use in studies on POD and POCD (see Table 1). All included studies in our review were assessed on these criteria by two independent raters (IK and JB), and disagreements in a consensus meeting with a third rater (AS).

RESULTS

Included Studies

Fifteen studies were included in the present study (for details see Figure 1). Together these investigations described the results of 1,422 patients. These studies described the association of preoperative (seven studies) and postoperative (two studies) brain MRI markers with POD, and the association of preoperative

TABLE 1. Quality Criteria

Criterion	Description
1	Main aim of the study is to identify neuroimaging features of POD or POCD.
2	Prospective study design.
3	Sampling bias minimized; at least one-third of potential volunteers recruited.
4	POD diagnosed by valid criteria or POCD diagnosed by a cognitive test battery.
5	For case-control studies: non-POD/non-POCD subjects with similar characteristics to the patients. For cohort studies: appropriate information on subject characteristics, including possible confounders.
6	Use of validated methods of scan assessment.
7	Adequate quality control of scan results (e.g., use of two independent raters, reporting of inter-rater variability or quantitative assessment of scans).
8	Blinding of scan rater (i.e., no volunteer information available to the rater or quantitative assessment of scans).
9	Scan report detail. Quantitative assessment or the presence of at least two of the following in a qualitative assessment: cerebral atrophy, WMH, or pathological abnormalities.
10	Use of appropriate statistical methods to compare patients with POD/POCD with patients without POD/POCD.
11	Inclusion of an appropriate power calculation.

Notes: Table adapted from Soiza et al.[16] Criterion 1 was rated as 0 if studies were nested in a larger study. Criterion 5 was rated as 0 if POD and non-POD or POCD and non-POCD characteristics were not described separately. Criterion 7 was rated as 1 if one of the brain markers for POD or POCD met with this criterion.

FIGURE 1. Flow-diagram showing the search and assessment of studies included in this review.

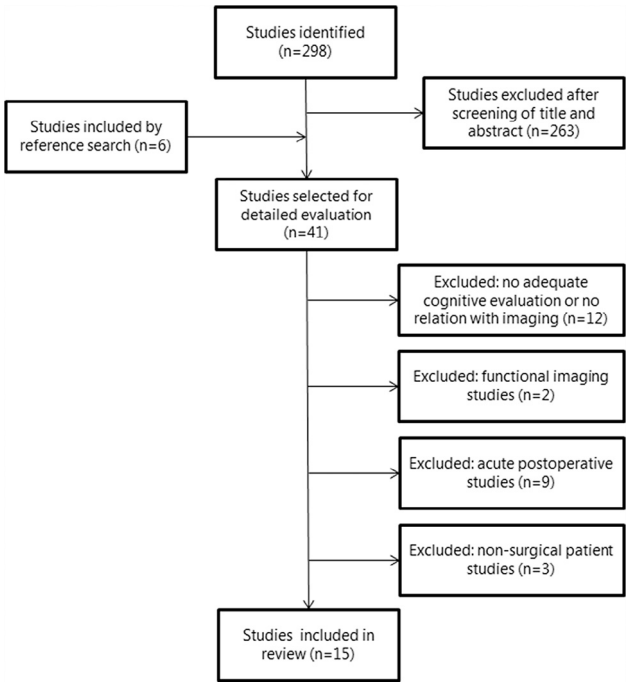
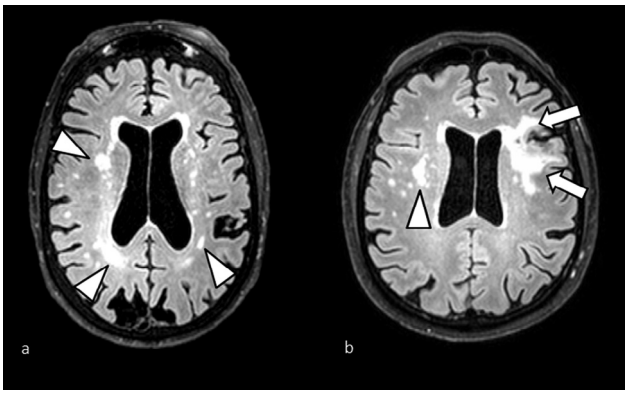


FIGURE 2. Two example figures of neurovascular brain changes. An example patient [A] of larger (arrowheads) and smaller white matter hyperintensities on a T2-weighted axial Fluid Attenuated Inversion Recovery (FLAIR) image. Some atrophy is also present with brain sulci clearly visible and central atrophy with ventricle enlargement. Another example patient [B] with a combination of white matter hyperintensities (arrowhead) and a larger cortical-subcortical infarct (arrows) on a T2-weighted FLAIR image.



(four studies) and postoperative (two studies) brain MRI markers with POCD. Appendix B includes background information on brain MRI methods and the neurodegenerative and neurovascular changes that were included in this review. Figure 2 shows some examples of these brain changes. No studies on brain computed tomography markers were included, because all of these studies met the exclusion criteria. All included studies were observational in design. For the assessment of study quality see Tables 1 and 2. For an overview of the included studies, see Table 3 for

TABLE 2. Assessment of Study Quality

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Brown et al., 2015[17]	0	1	0	1	1	1	1	1	1	1	1	10
Cavallari et al., 2015[18]	0	1	0	1	1	1	1	1	1	1	1	9
Cavallari et al., 2016[19]	0	1	0	1	1	1	1	0	0	1	0	6
Hatano et al., 2013[20]	1	0	1	1	1	1	1	1	0	1	0	8
Ito et al., 2012[21]	0	1	0	0	0	0	1	1	0	0	0	3
Maekawa et al., 2008[22]	0	1	1	1	0	0	0	1	1	0	0	5
Maekawa et al., 2014[23]	1	1	1	1	1	1	1	1	1	1	0	10
Nanba et al., 2012[24]	1	1	1	1	1	1	1	1	1	1	0	10
Omiya et al., 2015[25]	1	1	1	1	1	1	0	1	1	1	1	10
Otomo et al., 2013[26]	1	1	1	1	1	1	1	1	1	1	1	11
Patel et al., 2015[27]	0	1	0	1	1	0	0	1	1	1	0	5
Price et al., 2014[28]	1	1	0	1	0	1	1	1	1	1	1	10
Root et al., 2013[29]	1	0	0	1	1	1	1	1	1	1	0	8
Shioiri et al., 2016[30]	1	1	0	1	1	1	1	1	0	1	0	8
Shiori et al., 2010[31]	1	1	0	1	1	1	1	1	0	1	0	8

Notes: All included studies in our review were assessed on eleven quality criteria (see Table 1).

neurodegenerative changes and Table 4 for neurovascular changes.

MRI Markers of Neurodegenerative Changes in Relation to POD and POCD

Preoperative MRI Markers of Neurodegenerative Changes in Relation to POD

Three studies examined the association of preoperative global brain volume and the occurrence of POD (see Table 3).[18,29,30] Root et al. and Cavallari et al. did not find an association between preoperative global brain volumes and the occurrence of POD. Shioiri et al. found a smaller preoperative cortical brain volume in patients who developed POD compared with nondelirious patients. Cavallari et al. (hippocampal volume) and Shiori et al. (frontal, temporal, parietal, occipital, limbic, sublobar area, cerebellar, and brainstem volume[32]) also examined the association of regional brain volume and POD.[18,30] Cavallari et al. did not find an association between preoperative hippocampal volume and the occurrence of POD.[18] Shioiri et al. found an association between a smaller preoperative cortical brain volume in the temporal and limbic brain regions and the occurrence of POD.

Preoperative MRI Markers of Neurodegenerative Changes in Relation to POCD

There are no studies on the association between preoperative global, subcortical, or cortical brain volume and the occurrence of POCD. Two studies, however, examined the association between regional brain volumes and the occurrence of POCD. The studies of Price et al. and Maekawa et al. examined the association between preoperative regional brain volumes and the occurrence of POCD (see Tables 2 and 3). In the study of Price et al. no associations were found between preoperative hippocampal and entorhinal cortex volumes and POCD. Maekawa et al. found a relation between a smaller cortical volume of the medial temporal lobe and POCD.

Postoperative MRI Markers of Neurodegenerative Changes in Relation to POD and POCD

Only one study investigated the association between postoperative global brain volume and POD (see Tables 2 and 3).[17] The authors showed that a larger ventricular size was associated with the occurrence of POD. No other studies were found that examined the association between postoperative global, subcortical, cortical, or regional brain volumes and POD or POCD.

Overview of Evidence for MRI Markers of Neurodegenerative Changes in Relation to POD and POCD

Of the four studies that were performed on the association of preoperative global, cortical, and subcortical brain volume and the occurrence of POD, two were prospective studies (N = 146 and N = 84) with a

TABLE 3. Neurodegenerative Changes and POD/POCD

Author, Year	Study Design[a]	Number of Participants	Age in years[b]	Female Sex N (%)	Type of surgery	Delirium Assessment Tool or Cognitive Evaluation	Outcome (Time of Assessment)
Brown et al., 2015[17]	P	79	70 ± 8	22 (27%)	Cardiac surgery	Validated chart review	POD (during hospital stay)
Cavallari et al. 2015[18]	P	146	76 ± 4	87 (60%)	Elective non-cardiac surgery	CAM and chart review	POD (daily during hospital stay)
Root et al. 2013[29]	R	23, 24 non-delirious	73 (54–86)	26 (55%)	Lung surgery	Chart review	POD (within 4 days after surgery)
Shioiri et al. 2016[30]	P	84	64 (27–84)	32 (38%)	Cardiac surgery	Psychiatrist (DSM-IV)	POD (daily during hospital stay)
Maekawa et al. 2014[23]	P	28	73 ± 8	9 (32%)	Cardiac surgery	Cognitive tests of several domains	POCD (2 weeks after surgery)
Price et al. 2014[28]	P	31 patients, 12 non-surgery controls	71 ± 7	19 (45%)	Knee arthroplasty surgery	Cognitive tests of several domains	POCD (3 weeks and 3 months after surgery)

Author, Year	Preoperative Cognitive Status	MRI Sequence	MRI Markers	MRI Analysis	Conclusion	Comments
Brown et al., 2015[17]	Analysis adjusted for preoperative cognitive status	T1, FLAIR, DWI (2–23 days postoperative)	Ventricular size, cortical sulcal width	Qualitative (0–9 scale)	Postoperative increased ventricular size was associated with POD	Nested study in a larger prospective RCT
Cavallari et al. 2015[18]	Patients with dementia or low cognitive performance were excluded	FLAIR, T1 (preoperative)	Grey, white, CSF and hippocampal volume	Quantitative (FreeSurfer)	Global brain volume and hippocampal volume were not associated with POD	Part of the SAGES study
Root et al. 2013[29]	Patients with dementia or evidence of cognitive decline in chart were excluded	T1, FLAIR (preoperative)	Grey matter, white matter and CSF volumevolume	Quantitative (SPM8)	Global brain volume was not associated with POD	Scanning protocol was different for delirious and non-delirious patients
Shioiri et al. 2016[30]	No patients with dementia (MMSE < 24) were included	T1, T2 (preoperative)	Grey and white matter volume	Quantitative (SPM8, VBM8)	Lower global and regional brain volume were associated with POD	
Maekawa et al. 2014[23]	Patients with dementia (MMSE < 24) were excluded	3D T1, T2, FLAIR, 3D TOF (preoperative)	Medial temporal lobe volume	Quantitative (SPM8, VBM)	Lower volume of the temporal lobe was associated with POCD	
Price et al. 2014[28]	Patients with preoperative dementia were excluded	3D T1, FLAIR (preoperative)	Hippocampal and entorhinal cortex volume	Semi-quantitative (manually delineated by experienced raters)	Hippocampal and entorhinal cortex volumes were not associated with POCD	

Notes: CAM: Confusion Assessment Method; FLAIR: Fluid Attenuated Inversion Recovery; RCT: randomized controlled trial; SAGES: Successful Ageing after Elective Surgery study.

[a]Prospective (P) or retrospective (R).

[b]Age in years presented as mean ± SD or median and range.

TABLE 4. Neurovascular Changes and POD/POCD

Author, Year	Study Design[a]	Number of Participants	Age[b]	Female Sex N (%)	Type of Surgery	Delirium Assessment Tool Or Cognitive Evaluation	Outcome (Time of Assessment)
Brown et al., 2015[17]	P	79	70 ± 8	22 (27%)	Cardiac surgery	Validated chart review	POD (unknown)
Cavallari et al. 2016[19]	P	136	76 ± 4	80 (59%)	Elective non-cardiac surgery	CAM and chart review	POD (daily during hospital stay)
Cavallari et al., 2015[18]	P	146	76 ± 4	87 (60%)	Elective non-cardiac surgery	CAM and chart review	POD (daily during hospital stay)
Hatano et al. 2013[20]	R	130	67 ± 11	41 (32%)	Cardiac surgery	Chart review	POD (unknown)
Ito et al. 2012[21]	P	224 patients with infarcts, 225 patients without infarcts	70 (60–85)	141 (31%)	Cardiac surgery	Hasegawa dementia scale	POCD (unknown)
Maekawa et al. 2008[22]	P	247	70 ± 9	91 (58%)	Cardiac surgery	Cognitive tests of several domains	POCD (one week after surgery)
Maekawa et al. 2014[23]	P	28	73 ± 8	9 (32%)	Cardiac surgery	Delirium rating scale and DSM-IV, cognitive tests of several domains	POD (daily assessment until day 7) and POCD (2 weeks after surgery)
Nanba et al., 2012[24]	P	70	68 ± 8	7 (10%)	Carotid endarterectomy	Cognitive tests of several domains	POCD (one month after surgery)
Omiya et al., 2015[25]	P	98	69 ± 7	Not reported	Cardiac surgery	Delirium assessments	POD (6–24 h after surgery)
Otomo et al. 2013[26]	P	153	72 ± 7	44 (29%)	Cardiac surgery	Delirium rating scale, DSM-IV	POD (daily assessment until day 7)
Patel et al., 2015[27]	P	77	63 ± 10	5 (6%)	Cardiac surgery	Cognitive tests of several domains	POCD (6–8 weeks after surgery)
Price et al. 2014[28]	P	31 patients with surgery, 12 without surgery	71 ± 7	19 (45%)	Knee arthroplasty surgery	Cognitive tests of several domains	POCD (three weeks and three months after surgery)
Root et al. 2013[29]	R	23 delirious, 24 non-delirious patients	73 (54–86)	26 (55%)	Lung surgery	Chart review	POD (within 4 days after surgery)
Shioiri et al. 2010[31]	P	116	64 (27–84)	38 (33%)	Cardiac surgery	Psychiatrist (DSM-IV)	POD (daily assessment until discharge)

(*continued on next page*)

TABLE 4. (*continued*)

Author, Year	Preoperative Cognitive Status	MRI Sequence	MRI Markers	MRI Analysis	Conclusion	Comments
Brown et al., 2015[17]	Analysis adjusted for preoperative cognitive status	T1, FLAIR, DWI (5–8 days after surgery)	WMH severity	Qualitative (severity scale 0–9)	WMH severity was not associated with POD	Nested study in a larger prospective RCT, duration of delirium assessment based on chart review is unclear
Cavallari et al. 2016[19]	Patients with dementia or low cognitive performance were excluded	DTI (preoperative)	White matter integrity (fractional anisotropy and mean diffusivity)	Quantitative (Freesurfer, SPM8)	A lower fractional anisotropy of the cerebellum, hippocampus, thalamus and basal forebrain was associated with POD incidence and severity	Part of the SAGES study
Cavallari et al., 2015[18]	Patients with dementia or low cognitive performance were excluded	FLAIR, T1 (preoperative)	WMH volume	Semi-quantitative (expectation maximization algorithm)	Global brain volume and hippocampal volume were not associated with POD	Part of the SAGES study
Hatano et al. 2013[20]	No information provided	FLAIR (preoperative)	WMH severity	Qualitative (Fazekas score)	Severity of WMH is associated with POD	Duration of delirium assessment based on chart review is unclear
Ito et al. 2012[21]	Patients with preoperative cognitive impairment were not included	T1, T2 (preoperative)	Cerebral infarcts	Qualitative rating on T1 and T2	POCD was more common in the patient group with silent cerebral brain infarcts	Time of POCD measurement is unclear
Maekawa et al. 2008[22]	Patients with preoperative cognitive impairment (HDS < 24) were not excluded	DWI (preoperative)	Acute cerebral infarcts	Qualitative rating	There was no association between preoperative infarcts on DWI and POCD at one week after surgery	
Maekawa et al. 2014[23]	Patients with dementia (MMSE < 24) were excluded	T1, T2, FLAIR (preoperative)	WMH severity, cerebral infarcts	Qualitative (Fazekas score)	WMH severity and presence of infarcts were associated with POCD	
Nanba et al., 2012[24]	No information provided	DTI (preoperative and one month oostoperative)	White matter integrity (fractional anisotropy)	Quantitative (SPM5)	Fractional anisotropy values were associated with POCD	

(*continued on next page*)

TABLE 4. (*continued*)

Author, Year	Preoperative Cognitive Status	MRI Sequence	MRI Markers	MRI Analysis	Conclusion	Comments
Omiya et al., 2015[25]	No information provided	T2, FLAIR, T2*, DWI (two weeks postoperative)	New cerebral infarcts, WMH severity	Qualitative (Fazekas scale)	New cerebral infarcts and deep WMH were associated with POD	
Otomo et al. 2013[26]	Patients with preoperative cognitive impairment (HDS < 24) were not excluded	FLAIR, T2 (preoperative)	Cerebral infarcts	Qualitative rating	Pre-existing multiple cerebral infarcts were associated with POD	
Patel et al., 2015[27]	No information provided	FLAIR, DWI (pre- and 6–8 weeks postoperative)	Number and volume of new cerebral infarcts	Semi-quantitative contouring	New cerebral infarcts were not associated with POCD	
Price et al. 2014[28]	Patients with preoperative dementia were excluded	T1, FLAIR (preoperative)	Combined WMH and lacunar infarct volumes	Quantitative (semi-automatic volume measurement)	Combined WMH and lacunar volumes were associated with POCD	
Root et al. 2013[29]	Patients with dementia or evidence of cognitive decline in chart were excluded	T1, FLAIR (preoperative)	WMH volume	Semi-quantitative (MRIcron)	WMH volume was associated with POD	Scanning protocol was different for patients and controls
Shioiri et al. 2010[31]	No patients with dementia (MMSE < 24) were included	DTI, T1, T2 (preoperative)	White matter integrity (fractional anisotropy)	Quantitative (SPM12)	Reduced fractional anisotropy in four regional areas was associated with POD	

Notes: CAM: Confusion Assessment Method; FLAIR: Fluid Attenuated Inversion Recovery; RCT: randomized controlled trial; SAGES: Successful Ageing after Elective Surgery study.

[a]Prospective (P) or retrospective (R).

[b]Age in years presented as mean ± SD or median (range).

high-quality study design that included preoperative imaging, performed quantitative analysis of MRI scans and excluded demented patients (see Table 3).[18,30] These two studies found contradicting results, however. The two other studies that also examined the association of preoperative global, cortical, and subcortical brain volume and the occurrence of POD had fewer included patients, a lower study quality, and also showed contradicting results.[17,29] One of these studies was probably underpowered as it included only a small number of non-small cell lung cancer patients (N = 23).[29] The other of these studies (N = 79) performed only postoperative imaging and only performed qualitative MRI analyses rather than quantitative analyses.[17]

Both studies that examined the association of regional brain volumes and the occurrence of POCD had a relatively low number of included patients (N = 31 and N = 28) and were possibly underpowered.[23,28] These studies showed some leads on certain specific brain regions in the medial temporal lobe that are potential markers, but there is only limited evidence regarding these associations.

In summary, MRI markers of neurodegenerative changes (global and regional brain volumes) are not consistently associated with the occurrence of POD or POCD.

MRI Markers of Neurovascular Changes in Relation to POD and POCD

Preoperative MRI Markers of Neurovascular Changes in Relation to POD

In three studies, the association between preoperative WMH and the occurrence of POD was investigated[18,20,29] (see Table 4 for details). Two studies reported an association between WMH and the occurrence of POD.[20,29] In contrast to these findings, the largest prospective study by Cavallari et al. did not find an association between preoperative WMH volume and the occurrence of POD.[18]

In two studies, the association of preoperative old cortical brain infarcts and the occurrence of POD was assessed.[23,26] In both studies the presence of cortical brain infarcts was rated qualitatively (no infarcts, a single infarct, multiple infarcts in one location, or multiple infarcts in several locations). It was reported that the presence of preoperative cortical brain infarcts was associated with the occurrence of POD.[23,26]

Two prospective studies were performed that examined the association between preoperative structural white matter integrity and the occurrence of POD (see Table 4).[19,31] Shioiri et al. found an association between preoperative reduced fractional anisotropy values in the left frontal lobe and left thalamus and occurrence of POD. Cavallari et al. described an association between reduced fractional anisotropy values of different brain regions (cerebellum, hippocampus, basal forebrain, and part of the thalamus) and occurrence of POD.

Preoperative MRI Markers of Neurovascular Changes in Relation to POCD

Two studies examined the association between preoperative WMH and the occurrence of POCD (see Table 4).[23,28] Maekawa et al. showed that the severity of WMH was associated with the occurrence of POCD. Price et al. reported that the combined WMH and lacunar infarct volume was associated with decline of executive functions 3 weeks postoperatively, and showed a trend 3 months postoperatively.

Ito et al. examined the association between preoperative old cortical brain infarcts and the occurrence of POCD.[21] They grouped their participants not on POCD status, but on infarct status (silent brain infarcts, symptomatic brain infarcts, or no brain infarcts). In the group with silent brain infarcts, POCD was more common than in the group without brain infarcts. Maekawa et al. performed preoperative diffusion-weighted imaging and examined whether acute infarcts were associated with the occurrence of POCD[22] (Tables 2 and 4). They found no association between preoperative acute brain infarcts and POCD.

Postoperative MRI Markers of Neurovascular Changes in Relation to POD

One study examined the relation between postoperative WMH and POD (see Table 4).[17] Two studies examined the relation between acute postoperative cerebral infarcts and POD.[17,25] Omiya et al. described that acute postoperative infarcts larger than 2 mm were associated with POD.[25] Brown et al., however, found no association between acute postoperative cerebral infarcts and POD.[17]

Postoperative MRI Markers of Neurovascular Changes in Relation to POCD

Multiple studies have examined the association between acute postoperative cerebral infarcts and POCD. Patel et al. have recently published an extensive review regarding this subject in patients after cardiac surgery.[33] Therefore, we will not include a detailed description of all these individual studies in this review. In the review of Patel et al., most studies showed no association between acute postoperative cerebral infarcts and POCD.[33] Additionally, another more recent study by Patel et al. was performed on the relation between new WMH and acute cerebral infarcts on postoperative MRI scans (compared with preoperative MRI scans) and the occurrence of POCD[37] (see Table 4). No association was found between the presence, size, and number of new WMH or acute infarcts and the occurrence of POCD. A prospective study performed by Nanba et al. examined the relation between white matter integrity and the occurrence of POCD.[24] Patients who developed POCD had reduced postoperative fractional anisotropy values on the side of the carotid artery surgery.

Overview of Evidence for MRI Markers of Neurovascular Changes in Relation to POD and POCD

Six studies examined the association between WMH and POD and found some conflicting evidence.[17,18,20,23,25,29] The study with the largest number of included patients (N = 146) that had a high quality prospective design and used quantitative MRI analyses did not find an association between preoperative WMH and occurrence of POD (see Tables 2 and 4).[18] The other studies that examined the association between WMH and POD included fewer patients (N = 23, N = 28, N = 79, N = 98, N = 130). Most of these studies had a good study design and performed qualitative MRI analyses instead of quantitative analyses (see Appendix B and Table 2). Therefore, most evidence was found for an association between WMH volume and occurrence of POD. Two studies were performed on preoperative old cerebral infarcts.[23,26] Both studies were of high quality, but one had a low number of included patients and both included few patients with cerebral infarcts (N = 28 and N = 153) (see Table 2). Moreover, the nature of these infarcts (e.g., cortical, subcortical, or lacunar) was not specified (see Appendix B). Both studies found an association between cerebral infarcts and occurrence of POD.[23,26] Two prospective studies (N = 116 and N = 136) were performed that examined the association between markers of white matter integrity and POD.[19,31] Both studies were of high quality, excluded patients with dementia, and found an association between markers of white matter integrity and POD.

Two studies consisting of only few patients (N = 28, N = 31) examined the association between preoperative WMH and POCD.[23,28] In one of these studies, the follow-up period to diagnose POCD was relatively short,[23] which might have led to an underestimation of POCD incidence. Both studies found an association between preoperative WMH and occurrence of POCD. Only one study, with a relatively low quality design, examined the association between cerebral infarcts and POCD (see Table 2).[21] In that study an association was found between cerebral infarcts and occurrence of POCD. Only one study was performed that examined the association between markers of white matter integrity and POCD.[24] This prospective study (N = 70) had a relatively low quality mostly because of study design and patient selection (only patients who underwent carotid endarterectomy). This study showed an association between markers of white matter integrity and occurrence of POCD. In summary, most studies on neurovascular changes found an association with POD or POCD.

DISCUSSION

Neurovascular changes (WMH and cerebral infarcts) are most consistently associated with the occurrence of POD and POCD.[17,19–26,28–29,31] Neurodegenerative changes (global and regional brain volumes) are not consistently associated with the occurrence of POD or POCD.[17,18,23,28–30]

MRI Markers of Neurovascular Changes in Relation to POD and POCD

The finding that MRI markers of neurovascular changes are most consistently related to the occurrence of POD and POCD is in agreement with population-based studies that have shown an association between MRI markers of neurovascular changes and cognitive impairment.[11,34] The imaging signs of neurovascular disease detected by structural MRI sequences

might represent the tip of the iceberg of a larger burden of brain tissue changes related to neurovascular disease. We hypothesize that patients with a larger burden of brain tissue lesions (infarcts, WMH) are more vulnerable to hemodynamic changes during the operative period. Alternatively, in these patients there may be a progression of brain tissue lesions (with, for instance, new infarcts) during the postoperative period. In the direct postoperative period new acute ischemic lesions on diffusion-weighted imaging may also be related to POCD and POD.[33,35] From recent studies it is known that cognitive reserve (including education) may be an additional factor in the relation between brain tissue lesions and (postoperative) cognitive changes.[36] Still, the associations of preoperative neurovascular changes and both POD and POCD should be further investigated in larger studies by assessing promising neurovascular markers, such as WMH burden and presence of cerebral infarcts, and taking into account cerebral hemodynamics, new ischemic lesions, and cognitive reserve.

MRI Markers of Neurodegenerative Changes in Relation to POD and POCD

In most studies, no association was found between neurodegenerative changes on MRI scans and POD and POCD. Although some smaller studies suggested a relationship, this could not be confirmed in larger studies such as the recent SAGES study on brain atrophy and POD. It should be noted that in the SAGES study no relation was found between WMH and POD either, and that white matter structure assessed on diffusion tensor imaging (DTI) might be related to occurrence of POD. Based on the current findings we conclude that if a relation between (regional) brain MRI volume and POD and POCD is present, this relation is possibly weak. In most studies on POD and POCD in this review, demented patients were excluded (see Tables 3 and 4). Demented patients are known to have an increased risk of POD and POCD, and vice versa.[2] Because of a lack of studies with preoperative imaging and long-term follow-up, it remains unclear whether patients suffering from POD and POCD are on a trajectory of cognitive decline and dementia.

Strengths and Limitations

This is the first review to study the association of MRI markers of neurodegenerative and neurovascular changes of both POD and POCD. The review is strengthened by the systematic search for studies and the detailed quality assessments of all included studies. Therefore, our review provides a detailed overview of the current knowledge in this field.

A limitation of the included studies is the limited sample size of some of these studies. This resulted in only a few cases of POD or POCD and therefore limited the power of these studies. Other limitations of the included studies in our review were the heterogeneous study designs and applied quantification techniques, which made it impossible to pool studies in a meta-analysis. Therefore, we chose to group the imaging findings according to groups of underlying pathophysiological mechanisms (neurodegenerative and neurovascular changes). Another limitation could be that the POD assessment varied between studies, from a daily assessment by trained research staff to a retrospective chart review. In particular, diagnosis of POD by a retrospective chart review only might have led to an underestimation of POD in some studies. The heterogeneous definition and assessment of POCD made comparison of cognitive test results between studies difficult.

Future Recommendations

From the results of our review it became clear that large prospective studies are needed to study the consistency of the reported associations between brain MRI markers and the occurrence of POD and POCD. To ensure comparability to existing literature, we recommend that future studies perform preoperative MRI, daily delirium screening in the immediate postoperative period, and cognitive tests preoperatively, at 3 months, and at 1 year follow-up. Furthermore, a matched control group should be included, especially to control for learning effects of the cognitive tests. We recommend performing POCD assessment by previously published recommendations.[37] Furthermore, we would like to recommend the use of 3-D T1-weighted and 3-D FLAIR MRI sequences to assess brain structural changes, combined with more advanced magnetic resonance brain imaging to also assess more advanced aspects of brain structure, such as DTI. This review has shown that neurovascular brain changes show the most consistent association with POD and POCD. The presence of lacunar and cortical infarcts was related to the occurrence of POD and POCD in all

studies that assessed this marker. WMH volume shows potential as a marker for both POD and POCD. In a few studies with limited participants, white matter integrity also shows potential as a marker for POD and POCD. We would like to recommend that future studies perform quantitative analysis of WMH volume and qualitative assessment of cerebral infarcts. Functional and hemodynamic MRI markers of the brain vasculature, which were beyond the scope of our review, may also be promising markers to assess in the context of POD and POCD.[38,39] These markers include measurements of brain perfusion with arterial spin labeling MRI sequences, measurement of flow in the larger brain feeding arteries, functional resting-state MRI connectivity markers, functional MRI studies and blood-oxygen-level dependent MRI measures combined with a vascular stimulus such as carbon dioxide to measure the cerebrovascular reserve of the brain vasculature.[40,41]

To date, there is insufficient evidence for implementation of these results in clinical practice. Future clinical studies on risk scores need to be performed to be able to assess the added clinical value. In the future, a preoperative assessment could be used to predicts a patient's risk for the development of POD or POCD. This assessment could assist in the decision to operate on a patient at high risk of POD or POCD or could influence postoperative management and monitoring. Because of cost restraints, preoperative MRI scans could potentially be reserved only for patients at high risk of POD or POCD following a clinical assessment.

Conclusions

Neurovascular changes appear to be consistently associated with the occurrence of POD and POCD. In the future, these changes may even help to identify patients at increased risk of POD and POCD. Larger prospective studies are needed to study this in more detail and to unravel the underlying pathophysiological mechanisms.

The research of Jeroen Hendrikse has received funding from the European Research Council under the European Union's Horizon 2020 Programme (H2020) / ERC grant agreement n°637024 (HEARTOFSTROKE) and by the Netherlands Organisation for Scientific Research (NWO) under grant n°91712322.

The authors have no disclosures to report.

APPENDIX A: SEARCH TERMS

Pubmed:((“postoperative period”[MeSH Terms] OR (“postoperative”[All Fields] AND “period”[All Fields]) OR “postoperative period”[All Fields] OR “postoperative”[All Fields]) AND (“delirium”[MeSH Terms] OR “delirium”[All Fields])) OR ((“postoperative period”[MeSH Terms] OR (“postoperative”[All Fields] AND “period”[All Fields]) OR “postoperative period”[All Fields] OR “postoperative”[All Fields]) AND “cognitive”[All Fields]) AND (decline[All Fields] OR impairment[All Fields] OR “dysfunction”[All Fields]) AND ((“tomography, x-ray computed”[MeSH Terms] OR (“tomography”[All Fields] AND “x-ray”[All Fields] AND “computed”[All Fields]) OR “x-ray computed tomography”[All Fields] OR (“computed”[All Fields] AND “tomography”[All Fields]) OR “computed tomography”[All Fields]) OR (“magnetic resonance imaging”[MeSH Terms] OR (“magnetic”[All Fields] AND “resonance”[All Fields] AND “imaging”[All Fields]) OR “magnetic resonance imaging”[All Fields] OR “mri”[All Fields]))

Embase:postoperative AND period AND (“delirium”/exp OR delirium) OR “postoperative cognitive dysfunction”/exp OR “postoperative cognitive dysfunction” OR “postoperative cognitive decline”/exp OR “postoperative cognitive decline” AND (“imaging”/exp OR imaging OR (magnetic AND (“resonance”/exp OR resonance) AND (“imaging”/exp OR imaging)) OR (computed AND (“tomography”/exp OR tomography))) AND (“mri”/exp OR mri)

APPENDIX B: BRAIN MRI METHODS AND MARKERS

Neurodegenerative markers

The most important MRI methods (i.e., MRI sequences) for structural MRI are the 3D T1-weighted (volumetric) MRI and T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI sequences (either 2D or 3D). The 3D T1-weighted MRI provides excellent contrast between brain tissue and cerebrospinal fluid (CSF) and between gray and white matter. With 3D T1-weighted MRI, gray matter is hypointense (dark) compared to white matter and cerebrospinal fluid is hypointense relative to both white and gray matter.

MRI scans can be used by automated brain segmentation methods to segment different brain volumes.[42] Brain segmentation methods can determine the total intracranial volume, which is often used as a reference. Therefore, it is important that the 3D T1-weighted MRI sequence has a good contrast between the inner surface of the skull (tabula interna) and the intracranial compartments. Quantification of brain volumes is further enhanced when an MRI scan is acquired with thin slices that are contiguous. 3D methods are most optimal, as a complete volume is acquired. In most studies the 3D T1-weighted MRI sequence is used with automated segmentation methods to determine brain tissue volumes, but it can also be used in combination with other sequences. Typically, all brain volumes (total brain volume, white matter volume, gray matter volume) are normalized by the total intracranial volume to make the brain volume measurements independent of head size. Total brain volume is a widely studied MRI marker for neurodegenerative diseases such as Alzheimer disease.[43] In these diseases, the breakdown of neurons causes brain volume loss, which can be quantified on structural MRI. Brain volume could therefore be associated with an increased risk of POD or POCD. Regional brain volume loss of the medial temporal lobe, especially of the hippocampus and the entorhinal cortex, has previously been identified as a regional structural brain MRI marker for Alzheimer disease and is associated with mild cognitive impairment.[44] These regional brain MRI markers might therefore also be associated with an increased risk of POD or POCD.

Neurovascular markers

White matter hyperintensities (WMH) are common findings on brain MRI scans in the elderly[45] and also occur in otherwise healthy individuals. WMH and lacunes of presumed vascular origin are regarded as brain MRI markers of small vessel disease.[34,45] These markers are related to cognitive decline in patients with mild cognitive impairment.[46] Cerebral cortical infarcts are also associated with cognitive deficits.[47] The presence of one or a combination of these brain MRI markers could therefore increase the vulnerability for POD or POCD. The T2-weighted FLAIR MRI sequence provides excellent delineation of cerebral cortical infarcts, WMH, and lacunes. With the T2-weighted FLAIR sequence, the CSF is nulled (hypointense) and infarcts and WMH are typically hyperintense compared with other brain tissue. When quantitative assessment of these brain abnormalities is of interest, 3D (volumetric) T2-weighted FLAIR sequences have advantages over 2D MRI sequences. Other structural MRI sequences that are often acquired are classic T2-weighted sequences without CSF suppression (as present in T2-weighted FLAIR sequences). T2*-weighted or susceptibility-weighted imaging (SWI) MRI sequences are sensitive to the detection of cerebral hemorrhage and microbleeds. Diffusion-weighted imaging (DWI) can show (acute) cerebral infarcts and diffusion tensor imaging (DTI) can be used as a method to quantify white matter integrity. In the current review we will focus on T1-weighted, T2-weighted FLAIR, DWI, and DTI sequences, because these are the most performed structural MRI sequences.

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. Washington, DC: APA, 2013
2. Inouye SK: Delirium in older persons. N Engl J Med 2006; 354:1157–1165
3. Rudolph JL, Marcantonio ER, Culley DJ, et al: Delirium is associated with early postoperative cognitive dysfunction. Anaesthesia 2008; 63:941–947
4. Saczynski JS, Marcantonio ER, Quach L, et al: Cognitive trajectories after postoperative delirium. N Engl J Med 2012; 367:30–39
5. Rasmussen LS: Postoperative cognitive dysfunction: incidence and prevention. Best Pract Res Clin Anaesthesiol 2006; 20:315–330
6. Murkin JM, Newman SP, Stump DA, et al: Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg 1995; 59:1289–1295
7. Moller JT, Cluitmans P, Rasmussen LS, et al: Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet 1998; 351:857–861
8. Monk TG, Weldon BC, Garvan CW, et al: Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108:18–30
9. Ancelin ML, De Roquefeuil G, Ledésert B, et al: Exposure to anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. Br J Psychiatry 2001; 178:360–366
10. Abelha FJ, Luís C, Veiga D, et al: Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. Crit Care 2013; 17:R257
11. De Bruijn RF, Akoudad S, Cremers LGM, et al: Determinants, MRI correlates, and prognosis of mild cognitive impairment: the Rotterdam Study. J Alzheimers Dis 2014; 42(suppl 3):S239–S249
12. De Bresser J, Tiehuis AM, van den Berg E, et al: Progression of cerebral atrophy and white matter hyperintensities in patients with type 2 diabetes. Diabetes Care 2010; 33:1309–1314

13. Fox NC, Freeborough PA, Rossor MN: Visualisation and quantification of rates of atrophy in Alzheimer's disease. Lancet 1996; 348:94–97
14. Karas GB, Burton EJ, Rombouts SA, et al: A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. Neuroimage 2003; 18:895–907
15. American Psychiatric Association (APA): Diagnostic and Statistical Manual of Mental Disorders. Third ed. Washington, DC: APA, 1980
16. Soiza RL, Sharma V, Ferguson K, et al: Neuroimaging studies of delirium: a systematic review. J Psychosom Res 2008; 65:239–248
17. Brown CH, Faigle R, Klinker L, et al: The association of brain MRI characteristics and postoperative delirium in cardiac surgery patients. Clin Ther 2015; 37:2686–2699, e9
18. Cavallari M, Hshieh TT, Guttmann CRG, et al: Brain atrophy and white matter hyperintensities are not significantly associated with incidence and severity of postoperative delirium in older persons without dementia. Neurobiol Aging 2015; 36:2122–2129
19. Cavallari M, Dai W, Guttmann CRG, et al: Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI. Brain 2016; 139(Pt 4):1282–1294
20. Hatano Y, Narumoto J, Shibata K, et al: White-matter hyperintensities predict delirium after cardiac surgery. Am J Geriatr Psychiatry 2013; 21:938–945
21. Ito A, Goto T, Maekawa K, et al: Postoperative neurological complications and risk factors for pre-existing silent brain infarction in elderly patients undergoing coronary artery bypass grafting. J Anesth 2012; 26:405–411
22. Maekawa K, Goto T, Baba T, et al: Abnormalities in the brain before elective cardiac surgery detected by diffusion-weighted magnetic resonance imaging. Ann Thorac Surg 2008; 86:1563–1569
23. Maekawa K, Baba T, Otomo S, et al: Low pre-existing gray matter volume in the medial temporal lobe and white matter lesions are associated with postoperative cognitive dysfunction after cardiac surgery. PLoS ONE 2014; 9:e87375
24. Nanba T, Ogasawara K, Nishimoto H, et al: Postoperative cerebral white matter damage associated with cerebral hyperperfusion and cognitive impairment after carotid endarterectomy: a diffusion tensor magnetic resonance imaging study. Cerebrovasc Dis 2012; 34:358–367
25. Omiya H, Yoshitani K, Yamada N, et al: Preoperative brain magnetic resonance imaging and postoperative delirium after off-pump coronary artery bypass grafting: a prospective cohort study. Can J Anaesth 2015; 62:595–602
26. Otomo S, Maekawa K, Goto T, et al: Pre-existing cerebral infarcts as a risk factor for delirium after coronary artery bypass graft surgery. Interact Cardiovasc Thorac Surg 2013; 17:799–804
27. Patel N, Horsfield MA, Banahan C, et al: Impact of perioperative infarcts after cardiac surgery. Stroke 2015; 46:680–686
28. Price CC, Tanner JJ, Schmalfuss I, et al: A pilot study evaluating pre-surgery neuroanatomical biomarkers for postoperative cognitive decline after total knee arthroplasty in older adults. Anesthesiology 2014; 120:601–613
29. Root JC, Pryor KO, Downey R, et al: Association of pre-operative brain pathology with post-operative delirium in a cohort of non-small cell lung cancer patients undergoing surgical resection. Psychooncology 2013; 22:2087–2094
30. Shioiri A, Kurumaji A, Takeuchi T, et al: A decrease in the volume of gray matter as a risk factor for postoperative delirium revealed by an atlas-based method. Am J Geriatr Psychiatry 2016; 24:528–536
31. Shioiri A, Kurumaji A, Takeuchi T, et al: White matter abnormalities as a risk factor for postoperative delirium revealed by diffusion tensor imaging. Am J Geriatr Psychiatry 2010; 18:743–753
32. Lancaster JL, Woldorff MG, Parsons LM, et al: Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 2000; 10:120–131
33. Patel N, Minhas JS, Chung EML: The presence of new MRI lesions and cognitive decline after cardiac surgery: a systematic review. J Card Surg 2015; 30:808–812
34. Van Dijk EJ, Prins ND, Vrooman HA, et al: Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam scan study. Stroke 2008; 39:2712–2719
35. Abawi M, Nijhoff F, Agostoni P, et al: TCT-722 clinical effect of new cerebral ischemic lesions on the occurrence of postoperative delirium after transcatheter aortic valve implantation (abstract). J Am Coll Cardiol 2016; 68:B292
36. Jokinen H, Melkas S, Madureira S, et al: Cognitive reserve moderates long-term cognitive and functional outcome in cerebral small vessel disease. J Neurol Neurosurg Psychiatry 2016; 87:1296–1302
37. Rasmussen LS: The assessment of postoperative cognitive function. Acta Anaesthesiol Scand 2001; 45:275–289
38. Floyd TF, McGarvey M, Ochroch EA, et al: perioperative changes in cerebral blood flow after cardiac surgery: influence of anemia and aging. Ann Thorac Surg 2003; 76:2037–2042
39. Wilson DA, Mocco J, Ambrosio ALD, et al: Post-carotid endarterectomy neurocognitive decline is associated with cerebral blood flow asymmetry on post-operative magnetic resonance perfusion brain scans. Neurol Res 2008; 30:302–306
40. Choi SH, Lee H, Chung TS, et al: Neural network functional connectivity during and after an episode of delirium. Am J Psychiatry 2012; 169:498–507
41. Viticchi G, Falsetti L, Vernieri F, et al: Vascular predictors of cognitive decline in patients with mild cognitive impairment. Neurobiol Aging 2012; 33:1127, e1-e9
42. De Bresser J, Portegies MP, Leemans A, et al: A comparison of MR based segmentation methods for measuring brain atrophy progression. Neuroimage 2011; 54:760–768
43. Mak E, Su L, Williams GB, et al: Longitudinal assessment of global and regional atrophy rates in Alzheimer's disease and dementia with Lewy bodies. Neuroimage Clin 2015; 7:456–462
44. Du AT, Schuv N, Amend D, et al: Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001; 71:441–447
45. Wardlaw JM, Smith EE, Biessels GJ, et al: Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013; 12:822–838
46. Gorelick PB, Scuteri A, Black SE, et al: Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42:2672–2713
47. Aggarwal NT, Schneider JA, Wilson RS, et al: Characteristics of MR infarcts associated with dementia and cognitive function in the elderly. Neuroepidemiology 2012; 38:41–47