# Transcranial Doppler ultrasonography for detection of cerebral white matter changes in a high-risk population

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KEY MESSAGES

1. In a high-risk population, the pulsatility index of the middle cerebral artery is associated with severity of white matter change (WMC). Nonetheless, its ability to differentiate those with and without significant subclinical WMC is only fair.
2. Using transcranial Doppler ultrasonography as a stand-alone screening instrument is not recommended to detect subclinical WMC.

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## Background

Age-related white matter change (WMC) is a manifestation of cerebral small vessel disease and the most common substrate of vascular dementia.[1] Overseas study showed that severe WMC was found in 20% of an elderly population.[2] Recent longitudinal studies and meta-analysis show that presence of WMC significantly increases the risk of dementia, and more severe WMC is associated with greater risk of cognitive decline.[3] WMC frequently coexists with other dementia diseases and aggravates their cognitive severity.[4] Non-demented elderly persons with WMC should be considered a high-risk group and require early management or monitoring.

Cerebral magnetic resonance imaging (MRI) is the standard imaging method to detect WMC. Nonetheless, it is not cost-effective for large-scale screening for subclinical WMC. Transcranial Doppler ultrasonography (TCD) is more convenient and less costly. It is portable and can be applied at the bedside or in outpatient clinics and community settings. The arterial pulsatility index (PI) is derived from the flow velocity of large arteries and is hypothesised to reflect vascular resistance distal to the examined artery. A study of 55 stroke patients showed that PI of the middle cerebral artery (MCA) correlated with severity of small vessel disease.[4] Another study in 100 acute stroke patients with WMC and 50 controls without WMC found that the mean PI of bilateral MCAs correlated with WMC volume. The area under the receiver operating curve (ROC) for mean MCA PI to differentiate those with and without WMC was 0.85 (95% confidence interval [CI], 0.78-0.91).[5] Nonetheless, data from the previous study cannot be generalised to stroke-free subjects as small arteries may dilate during the acute stroke phase to cause PI fluctuation.

The prevalence of dementia is estimated to increase by more than 300% over the next 30 years and be the greatest contributor to disability among the elderly in China.[6] WMC-related dementia is potentially preventable due to its vascular nature. We hypothesise that TCD is able to detect non-demented stroke-free subjects who have WMC. TCD can guide selective MRI scanning, enable early detection and management of at-risk subjects, and enhance their recruitment into WMC preventive trials.

### Study objectives

This study aimed to validate TCD PI for detecting WMC among non-demented stroke-free elderly subjects with high vascular risk, namely hypertension and/or diabetes mellitus. We hypothesised that MCA PI can significantly differentiate subjects with low and high WMC.

## Methodology

Potential subjects were recruited via advertisement at elderly centres. We screened 480 potentially eligible subjects (non-demented, stroke-free community-dwelling Chinese elderly having hypertension and/or diabetes mellitus) using TCD. Only 331 subjects who had at least one viable temporal window were recruited. Demographics were collected, and blood tests and cognitive function tests were performed using a standardised protocol. Brain MRI was arranged and WMC severity was rated according to the Fazekas scale and the age-related WMC scale. WMC volume was quantified automatically on axial FLAIR. By performing TCD through temporal windows on both sides of the brain, the MCA PI was

TABLE. Comparison of subjects with low and high white matter change (WMC)*

| Variable | Low WMC | High WMC | P value |
|---|---|---|---|
| Age (years) | 70.3±4.5 | 72.7±5.2 | <0.001 |
| Male | 77 (50.3) | 92 (55.8) | 0.322 |
| Education (years) | 8.5±4.8 | 8.1±4.9 | 0.519 |
| Hypertension | 141 (92.2) | 156 (94.5) | 0.391 |
| Diabetes mellitus | 52 (34.0) | 59 (36.0) | 0.711 |
| Pulsatility index of the middle cerebral artery | 1.06±0.18 | 1.16±0.27 | <0.001 |
| Age-related WMC total score | 1.9±1.9 | 4.9±3.0 | <0.001 |
| Fazekas score | 0.8±0.6 | 1.7±0.8 | <0.001 |
| WMC volume ($mm^3$) | 2161.73±994.65 | 12076.51±11737.85 | <0.001 |

* Data are presented as mean±SD or No. (%) of subjects

obtained.

Subjects with low (ie 1st and 2nd quartiles) or high (ie 3rd and 4th quartiles) WMC volume were compared for age, sex, education, presence of hypertension and diabetes mellitus, PI, Fazekas and age-related WMC scales, and WMC volumes using independent samples t-test. PI was correlated with continuous WMC volume and WMC quartiles using Spearman correlation analysis. A multivariate binomial logistic regression model was constructed to examine the association between PI and high WMC independent of age, sex, hypertension, and diabetes mellitus. A ROC analysis was conducted to examine the ability of MCA PI to differentiate high and low WMC. Statistical analyses were performed using SPSS version 14. Statistical significance was set at alpha = 0.05.

## Results

The mean MCA PI did not differ significantly between 274 subjects with bilateral temporal windows and 57 subjects with left- or right-side temporal window (p=0.531). MCA PI correlated with WMC volume (rho=0.171, P=0.002) and quartiles (rho=0.183, P=0.001). WMC volume was 2088, 3928, and 8080 $mm^3$ at the 25th, 50th, and 75th percentile, respectively. Group comparisons between subjects with high and low WMC are summarised in Table 1.

Compared with subjects with low WMC, those with high WMC were older and had higher MCA PI. In binomial logistic regression analysis, MCA PI was significantly associated with WMC in the upper quartiles (ie 3rd and 4th quartiles), independent of age, sex, and presence of hypertension and/or diabetes mellitus (odds ratio=4.53, 95% CI=1.35-15.24). ROC analysis showed that the area under the curve was 0.60 (95% CI=0.54-0.67, P=0.001, Fig). At an optimal cutoff of ≥0.97, its sensitivity was 82% and specificity was 32% in detecting high WMC. The positive and negative predictive values were 56.7% and 68.2%, respectively.

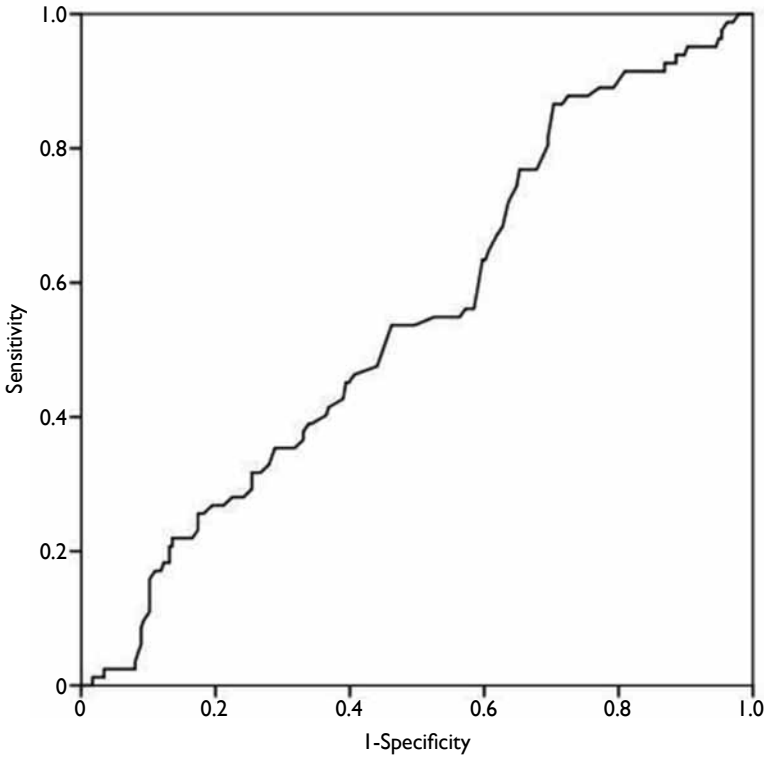


FIG. Receiver operating curve depicting the ability of pulsatility index of the middle cerebral artery to differentiate low from high white matter change subjects. The area under the curve is 0.60 (95% CI=0.54-0.67).

## Discussion

Our study shows that MCA PI correlates significantly with WMC volume both continuously and in quartiles. Moreover, the association between PI and high WMC is independent of age, sex, and vascular risk factors. Despite having a relatively high

sensitivity (82%), MCA PI has a low specificity (32%) and only fair area under the curve value and positive and negative predictive values.

The association between WMC and MCA PI can be explained by the pathophysiology of cerebral small vessel disease.[1,7] As arteriosclerosis narrows the lumen of small arteries and makes the thickened fibrotic vessels lose vasomotor reactivity, the vascular resistance and PI of small vessels increase. A strong association has been reported between mean MCA PI and WMC volume in quartiles among stroke patients with more severe WMC, with a high area under curve of 0.85.[8] Nonetheless, among community-dwelling stroke-free subjects with vascular risks, the ability of MCA PI to differentiate those with and without significant WMC was only fair (area under curve of 0.60 only).

Although the sample size was large and WMC severity was quantified by a fully automated method, this study had several limitations. First, 31.0% of the 480 potential subjects lacked temporal windows on both sides for TCD. Among the 331 subjects with at least one temporal window, 82.7% had viable temporal windows on both sides, whereas 9.7% and 7.6% had a temporal window on the left or right side only, respectively. The mean MCA PI did not differ significantly in those with bilateral or unilateral temporal windows. This implies that MCA PI obtained from a unilateral temporal window is comparable with that from bilateral temporal windows. Potential TCD limitations should also be considered in the calculation of PI, such as incorrect angle and suboptimal temporal window.[9] Furthermore, the sampling method was not randomised. As community dwellers were invited by word of mouth and recruited on a voluntary basis, the study subjects may have been more health-conscious and cooperative than an average community dweller with a similar vascular risk profile. The sample bias may partly account for the suboptimal sensitivity and specificity of the cut-off value. Other factors such as intracranial hypertension, respiratory parameters, haemoglobin level, and history of migraine might affect PI but were not investigated. Further studies should consider all these minor but significant factors.

## Conclusion

MCA PI is associated with WMC volume in community dwellers with a high vascular risk profile. Nonetheless, it cannot be recommended as a stand-alone screening tool to detect subclinical WMC among elderly subjects with vascular risk factors. Further research should explore whether a risk index that includes putative biomarkers for WMC (eg age, executive function performance, gait speed) combined with PI measure will be better able to detect significant subclinical WMC in high-risk subjects.

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