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Sir,

Our aim in developing the Vascular Cognitive Impairment Neuropathological Guidelines (VCING) was to establish criteria that we could show to be highly reproducible between neuropathologists in different centres, for post-mortem assessment of the likelihood that cognitive impairment was attributable to cerebrovascular pathology. To ensure reproducibility, we performed blinded post-mortem assessment of sections of brain tissue that were circulated to nine neuropathologists in centres across the UK. The advantage of this approach was that it enabled us to develop a protocol that can easily and reliably be applied in centres other than those participating in the VCING project. However, as noted by Oveisgharan and Hachinski (Oveisgharan and Hachinski, 2016), our approach did impose certain practical constraints on the scope and scale of the study. In particular, it restricted our assessment to variables that could be evaluated by
examination of histological sections, and limited the number of cases that it was practicable to assess (as each case required the assessment of 151 separate variables by 9 neuropathologists).

We agree that other studies have found moderate to severe atherosclerosis of the carotid arteries or circle of Willis to be associated not only with microinfarcts, lacunar infarcts and larger cerebral infarcts (Arvanitakis et al., 2016b; Dolan et al., 2010; Reed et al., 1994; Reed et al., 1988) but also dementia (Arvanitakis et al., 2016a; Dolan et al., 2010). Although atherosclerosis of the basal arteries was, for the stated reasons, not one of the variables included in our modelling of the risk of cognitive impairment, we have now reanalysed the data after incorporating information on circle of Willis atherosclerosis (recorded by the examining neuropathologist for all but 3 of the cases) in our predictive models. In our cohort, we find moderate/severe atherosclerosis to be a significant predictor of MMSE < 27 (p = 0.02), even in the presence of the other three most strongly predictive covariates (moderate/severe occipital leptomeningeal cerebral amyloid angiopathy, moderate/severe arteriolosclerosis in occipital white matter, and at least one large infarct), but not to predict a clinical diagnosis of dementia, MMSE < 24, or cognitive impairment, the last of these being the primary outcome measure in our study.

There is evidence that atherosclerosis of the circle of Willis may be a risk factor for Alzheimer's disease (Beach et al., 2007; Honig et al., 2005; Roher et al., 2003; Yarchoan et al., 2012) and, as noted above, it is associated with cerebral infarcts that are themselves a risk factor for vascular cognitive impairment. Dolan et al. (2010) found that intracranial atherosclerosis was associated with an increased risk of dementia that was independent of Alzheimer's disease pathology or cerebral infarcts in the Baltimore Longitudinal Study of Aging cohort, but it remains to be established whether circle of Willis atherosclerosis is truly an independent determinant of vascular cognitive impairment. We suggest that this merits further research, and would encourage studies to assess the reproducibility of the VCING model in much larger cohorts, preferably with standardised prospective collection of cognitive data.

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**References**


Oveisgharan S, Hachinski V. Atherosclerosis and vascular cognitive impairment neuropathological guideline. Brain 2016; ???: ???.


