Author’s response to reviews

Title: Causes and consequences of cerebral small vessel disease. The RUN DMC study: a prospective cohort study. Study rationale and protocol

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Dear Prof Alam,

Thank you for giving us the opportunity to submit a revised version of our manuscript, entitled ‘Causes and consequences of cerebral small vessel disease. The RUN DMC study: a prospective cohort study. Study rationale and protocol’.

We added a point-by-point list of the changes made in the manuscript according to your suggestions and added a version of the manuscript in which the changes are highlighted.

We hope we sufficiently answered your remarks and hope the manuscript will now be accepted for publication as a ‘Study Protocol’in BMC Neurology in its current form.

Yours sincerely,

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Response to comments

Power calculation

We provided a more detailed sample size calculation in the ‘statistical analysis’ section:

‘Sample size calculation’ Based on the literature we expect about 60 incident dementia cases during the five year follow up (absolute risk 4-5%/year), as about half of our study population has a relatively high degree of WML. [63] We expect that each SD increase in MD increases this absolute risk of dementia by 2% per year. To detect this increased risk with a high probability of 90% at the 5% significance level we will need 380 participants at the end of the follow up, so therefore we included 500 participants at baseline and hope to end up with 400 participants at follow-up protocol (taking into account an expected loss to follow up of about 20%).’

Statistical analysis

We provided a more detailed description of the statistical analysis of the primary outcome measures we intend to carry out:

‘Analysis of primary outcome measures’ We will analyze mean baseline MD and FA and change in MD and FA on follow up imaging in relation to incident dementia and parkinsonism by Cox proportional hazard models adjusted for age, sex, education, depressive symptoms, total brain volume, white matter lesion volume and lacunar infarcts, where appropriate.’

Trial registration number

We did not provide a trial registration number as this manuscript describes the study rationale and protocol of a prospective cohort study on microstructural brain changes assessed by new imaging techniques in relation to incident dementia and incident parkinsonism. As this prospective cohort study does not concern a trial with ‘health related interventions’ we did not register our study in a Trial Register (in accordance with most papers describing study protocols in your journal).