

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Structural Brain Lesions and Restless Legs Syndrome: A cross-sectional population-based study
AUTHORS	Rist, Pamela; Tzourio, Christophe; Elbaz, Alexis; Soumare, Aicha; Dufouil, Carole; Mazoyer, Bernard; Kurth, Tobias

VERSION 1 - REVIEW

REVIEWER	Frederic Roche Clinical Physiology CHU Saint-Etienne
REVIEW RETURNED	06-Jul-2014

GENERAL COMMENTS	<p>This is an article quite interesting testing using cross sectional analysis the link between the presence of restless legs syndrome (RLS) and the fragility of the cerebral white matter in a large population aged 72 years.</p> <p>Methodology of brain RMI treatment suffers no criticism. The diagnosis of RLS was likely focused on a series of three questions that may ask questions about the real value of screening for this brief interview. This is the limitation of the study. It has not been tested the severity of RLS and biological information. The prevalence of RLS appears higher in this cohort. This is also true for the history of high blood pressure.</p> <p>These points need to be better discussed in the discussion.</p> <p>It is also possible that only patients with severe RLS have cerebral vascular fragility or that only the association of RLS associated with periodic limb movements may only be harmful.</p> <p>Thank you for comment to these specific points.</p> <p>It appears desirable to give a flow chart to better understand the population that remained in the study.</p> <p>Patients are not included different from those who remained in the final set presented here ?</p>
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REVIEWER	Klaus Berger University of Muenster, Germany
REVIEW RETURNED	07-Jul-2014

GENERAL COMMENTS	<p>The authors report results from the population-based 3C Study in France on the association between brain lesions and Restless Legs Syndrome. The analysis was restricted to one of the three cities where the study was conducted and within this city to participants still in the study at follow-up 5 and 6. 1.5 T brain MRI were performed among those without contraindications, RLS status was</p>
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	<p>assessed by questionnaire. The authors found no association between the amount of global and regional white matter lesion volume or silent infarcts and Restless Legs Syndrome. Based on a cross-sectional analysis this study adds to the few published studies on this specific association and is one of the very few that applies MRI in population-based studies while simultaneously assessing Restless Legs Syndrome status according to the minimal criteria.</p> <p>I only have very few comments</p> <ul style="list-style-type: none"> - References 22 and 23 are obviously wrong, please correct. - It seems that MRI was performed at baseline and the RLS assessment at wave 5 and 6 of the follow-up. What was the mean time interval between baseline and wave 5 of the follow-up? - No information is provided on the effects of selection for this specific analysis. Thus, some basic information how those participating in the MRI sub-study (N=1,924) differ from all Dijon participants and how those included in this specific analysis (N=1,268) differ from those in the MRI sub-study with regard to age, gender and comorbidity burden should be added to the result section. - The prevalences of structural brain lesions (number or volume of white matter lesions and stroke) is not provided and should be added either to table 1 or presented in an extra table. - The RLS prevalence in this specific study is rather high (17.2 %) compared to other population-based studies in the elderly. What are potential explanations for this high prevalence? A comment should be added to the discussion section.
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VERSION 1 – AUTHOR RESPONSE

Reviewer Name Frederic Roche

Institution and Country Clinical Physiology

CHU Saint-Etienne

France

Please state any competing interests or state 'None declared': None declared

This is an article quite interesting testing using cross sectional analysis the link between the presence of restless legs syndrome (RLS) and the fragility of the cerebral white matter in a large population aged 72 years.

Methodology of brain RMI treatment suffers no criticism. The diagnosis of RLS was likely focused on a series of three questions that may ask questions about the real value of screening for this brief interview. This is the limitation of the study. It has not been tested the severity of RLS and biological information. The prevalence of RLS appears higher in this cohort. This is also true for the history of high blood pressure.

These points need to be better discussed in the discussion.

As stated in the discussion section, we acknowledge that there is the potential for misclassification of RLS status. However, we have used the best available population-based measure of assessment. Unfortunately our RLS questions did not address RLS severity. We have added this to our limitations section (p 15-16).

Please see our comments to the second reviewer on the prevalence of RLS in our cohort. A high prevalence of high blood pressure in this cohort has also been observed in previous studies using data from the Three Cities Study.

It is also possible that only patients with severe RLS have cerebral vascular fragility or that only the association of RLS associated with periodic limb movements may only be harmful.

Thank you for comment to these specific points.

We do not have information on periodic limb movements available in this study. We have added this to our limitations section (p 15-16).

It appears desirable to give a flow chart to better understand the population that remained in the study.

We have added a flow chart to our paper as Figure 1.

Patients are not included different from those who remained in the final set presented here?

As in any study, the final study population may differ from the target study population. The question is rather whether there is any reason to believe why the study sample is a biased sample for answering the specific questions under study. We have evaluated whether baseline factors differ between those participating in our study compared with those who did not.

The average age and prevalence of female participants was similar across all three cohorts. The average age in all Dijon participants was 74.6 years compared to 72.5 in the MRI cohort and 71.6 among participants eligible for our analyses. 61.7% of the Dijon subjects were female while 60.1% of the MRI cohort and 62.5% of the subjects in our study were female. Full details of the baseline characteristics of all Dijon participants have been previously published (The 3C Study Group 2003). As mentioned in our discussion section, the comorbidity burden at baseline was somewhat lower among those in our analyses compared to all Dijon participants and participants in the MRI study. For example, those in our analyses had slightly lower prevalence of obesity, high blood pressure, and history of CVD at baseline and a higher prevalence of people who were physically active compared to all Dijon participants and the participants in the MRI study. The three groups were similar with respect to other covariates (for example prevalence of diabetes, smoking status, alcohol consumption and history of high cholesterol).

The 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology* 2003;22(6):316-25

Reviewer Name Klaus Berger

Institution and Country University of Muenster, Germany

Please state any competing interests or state 'None declared': None declared

The authors report results from the population-based 3C Study in France on the association between brain lesions and Restless Legs Syndrome. The analysis was restricted to one of the three cities where the study was conducted and within this city to participants still in the study at follow-up 5 and 6. 1.5 T brain MRI were performed among those without contraindications, RLS status was assessed by questionnaire. The authors found no association between the amount of global and regional white matter lesion volume or silent infarcts and Restless Legs Syndrome.

Based on a cross-sectional analysis this study adds to the few published studies on this specific association and is one of the very few that applies MRI in population-based studies while simultaneously assessing Restless Legs Syndrome status according to the minimal criteria.

I only have very few comments

- References 22 and 23 are obviously wrong, please correct.

We apologize for that mistake and have inserted the correct reference (p 20).

- It seems that MRI was performed at baseline and the RLS assessment at wave 5 and 6 of the follow-up. What was the mean time interval between baseline and wave 5 of the follow-up?

The mean time interval was approximately 10 years. We have added this information to our limitations section (p 15).

- No information is provided on the effects of selection for this specific analysis. Thus, some basic information how those participating in the MRI sub-study (N=1,924) differ from all Dijon participants and how those included in this specific analysis (N=1,268) differ from those in the MRI sub-study with regard to age, gender and comorbidity burden should be added to the result section.

As in any study, the final study population may differ from the target study population. The question is rather whether there is any reason to believe why the study sample is a biased sample for answering the specific questions under study.

The average age and prevalence of female participants was similar across all three cohorts. The average age in all Dijon participants was 74.6 years compared to 72.5 in the MRI cohort and 71.6 among participants eligible for our analyses. 61.7% of the Dijon subjects were female while 60.1% of the MRI cohort and 62.5% of the subjects in our study were female. Full details of the baseline characteristics of all Dijon participants have been previously published (The 3C Study Group 2003). As mentioned in our discussion section, the comorbidity burden at baseline was somewhat lower among those in our analyses compared to all Dijon participants and participants in the MRI study. For example, those in our analyses had slightly lower prevalence of obesity, high blood pressure, and history of CVD at baseline and a higher prevalence of people who were physically active compared to all Dijon participants and the participants in the MRI study. The three groups were similar with respect to other covariates (for example prevalence of diabetes, smoking status, alcohol consumption and history of high cholesterol).

The 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology* 2003;22(6):316-25

- The prevalences of structural brain lesions (number or volume of white matter lesions and stroke) is not provided and should be added either to table 1 or presented in an extra table.

We have provided the prevalence of stroke and the volume of white matter lesions by RLS status in Table 1 (pg 23-24).

- The RLS prevalence in this specific study is rather high (17.2 %) compared to other population-based studies in the elderly. What are potential explanations for this high prevalence? A comment should be added to the discussion section.

Although our RLS prevalence appears high, this is an older population than many previous studies. As proposed by others, the prevalence of RLS increases with age. Although the MEMO study had a lower prevalence of RLS, the number of cases is low compared to our so the prevalence estimate is much more unstable. A recent study in the city of Reykjavik showed a prevalence of RLS of 18.3% in their population (Benediktsdottir 2010).

Benediktsdottir B, Janson C, Lindberg E, et al. Prevalence of restless legs syndrome among adults in

Iceland and Sweden: Lung function, comorbidity, ferritin, biomarkers and quality of life. *Sleep medicine* 2010;11(10):1043-8 doi: 10.1016/j.sleep.2010.08.006[published Online First: Epub Date].