

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Restless legs syndrome and all-cause mortality in four prospective cohort studies
AUTHORS	Szentkirályi, András; Winter, Anke; Schürks, Markus; Völzke, Henry; Hoffmann, Wolfgang; Buring, Julie; Gaziano, J.; Kurth, Tobias; Berger, Klaus

VERSION 1 - REVIEW

REVIEWER	Univ.-Prof. Dr. Birgit Högl Head of the Sleep Disorders Clinic Department of Neurology Innsbruck Medical University
REVIEW RETURNED	11-Jul-2012

GENERAL COMMENTS	<p>Overall, it is a very high ranking manuscript, 98%, and should be published with very high priority, only a few minor modifications. Please forward my review or integrate it into the system. .</p> <p>Comments to editor and to authors: This is a very well written manuscript of outstanding importance. The manuscript contains four independent, very well conducted, large epidemiological cohort studies which contribute extremely large numbers of subjects and show quite consistent results. The introduction shows, that the authors are very knowledgeable on the topic.</p> <p>The only minor drawback is the fact, that RLS mimics, which are conditions which may make a subject fulfill four diagnostic criteria for RLS without having RLS, are not thoroughly excluded, but this definite exclusion of mimics cannot be considered standard now. Even more, many of the older RLS prevalence studies which are still cited did not even consider the IRLSSG criteria.</p> <p>Overall, the study is very well conducted and the results extremely well analysed, overall the contributes a wealth of highly relevant new results for RLS.</p> <p>Issues Page 7, line 36 (physicians health study): Are these male or female physicians?</p> <p>Introduction 1st paragraph</p> <ul style="list-style-type: none">• Line 3: to move the leg. (should be: legs)• Line 19: the impairment of the dopaminergic system has an importance.. here, brain iron metabolism should also be mentioned briefly
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REVIEWER	Gian Luigi Gigli, MD Professor of Neurology University of Udine Medical School Udine, Italy No conflict of interest to be declared
REVIEW RETURNED	04-Sep-2012

GENERAL COMMENTS	<p>To date, studies on RLS and mortality were limited and wooly. This work, including a very large population coming from four different prospective studies, shows that RLS is not associated with an increased risk for all-cause mortality. The lack of an association between the sleep disorder and mortality was observed in each study using multivariate analyses that took several potential confounders into account. The paper is well written and statistical analysis is correct, but it is undermined by important limitations.</p> <p>1. RLS diagnosis was not based on a complete clinical interview and examination, but it was assessed by a self administered questionnaire aimed to detect the presence of all the essential criteria necessary to to define a subject as RLS affected. This may have resulted in RLS mimics incorrectly considered as affected by the sleep disorder. This limitation is recognized by the authors as well, although I acknowledge that performing a careful physical examination in 31,370 subjects is vary arduous.</p> <p>2. I consider instead more serious the lack of data concerning RLS frequency (that could be investigated using a simple question) and the lack of information on RLS severity (using the IRLSGSS). Information on RLS frequency could be very useful for the aim of this work.</p> <p>3. The authors should acknowledge that, although important, the follow up period is probably insufficiently extended to exclude definitely an increased mortality. In fact the relatively young age of the populations studied (means between 50.3 and 67.8 in the four groups) would require a very strong effect of RLS on mortality, in order to observe an increased rate in an average time span ranging between 6.5 and 11.1 years. This is particularly true for two youngest groups (Dortmund and Pomerania studies).</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Q1. The only minor drawback is the fact, that RLS mimics, which are conditions which may make a subject fullfill four diagnostic criteria for RLS without having RLS, are not thoroughly excluded, but this definite exclusion of mimics cannot be considered standard now. Even more, many of the older RLS prevalence studies which are still sited did not even consider the IRLSSG criteria.

A1. Indeed, RLS mimics could have been classified as RLS positive cases. Diabetic polyneuropathy

is a common mimic. Since we adjusted for diabetes in the multivariate model, it is not likely that this condition had a substantial influence on the results. Since we did not find any relationship between RLS and mortality, diabetic polyneuropathy has less relevance as potential RLS mimic and confounder. We also had information on leg cramps in one of the four studies, another common condition that might mimic RLS. Exclusion of these cases did not have any effect on the results. Nevertheless, the presence of potential RLS mimics is an important limitation. The issue is discussed in the revised manuscript.

Issues

2. Page 7, line 36 (physicians health study): Are these male or female physicians?

Participants were male in the physician health study, which has been noted in the revised text.

Introduction

1st paragraph

3. • Line 3: to move the leg. (should be: legs)
Corrected.

4. • Line 19: the impairment of the dopaminergic system has an importance.. here, brain iron metabolism should also be mentioned briefly

Brain iron metabolism is mentioned in the revised introduction.

Reviewer 2:

Q1. RLS diagnosis was not based on a complete clinical interview and examination, but it was assessed by a self administered questionnaire aimed to detect the presence of all the essential criteria necessary to to define a subject as RLS affected. This may have resulted in RLS mimics incorrectly considered as affected by the sleep disorder. This limitation is recognized by the authors as well, although I acknowledge that performing a careful physical examination in 31,370 subjects is vary arduous.

A1. Indeed, performing a full clinical interview in large population-based studies would have been extremely difficult. Nevertheless, we acknowledge the limitation in the discussion, and we have also made several steps to minimize the presence of some RLS mimics in the revised draft, please see our answer to the previous reviewer's first comment.

Q2. I consider instead more serious the lack of data concerning RLS frequency (that could be investigated using a simple question) and the lack of information on RLS severity (using the IRLSGSS). Information on RLS frequency could be very useful for the aim of this work.

A2. We agree, it would be interesting to look at RLS severity in these studies. Unfortunately, we did not have severity data except in the DHS. We could not find any significant association between RLS symptom frequency and mortality in DHS, even though the HR was higher in the more severe category. Similarly, the time elapsed since the onset of RLS was not related to the mortality hazard in DHS. These observations have been included in the revised manuscript.

Q3. The authors should acknowledge that, although important, the follow up period is probably insufficiently extended to exclude definitely an increased mortality. In fact the relatively young age of the populations studied (means between 50.3 and 67.8 in the four groups) would require a very strong

effect of RLS on mortality, in order to observe an increased rate in an average time span ranging between 6.5 and 11.1 years. This is particularly true for two youngest groups (Dortmund and Pomerania studies).

A3. Indeed, a longer follow-up time might have revealed a more subtle relationship with mortality, and this limitation has been noted in the revised manuscript. However, the HRs were quite close to 1, thus it is far from certain that a potential increase in effect size with a longer follow-up could have yielded a significant relationship. The only exception is the PHS, which consisted of the eldest participants. This also highlights the importance of the reviewer's comment. RLS-associated mortality hazard in elderly populations is of special interest, which needs further investigation as we have noted it in the revised draft.