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Restless legs syndrome and all-cause mortality in four prospective cohort studies

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ABSTRACT

Objectives: To evaluate the association between restless legs syndrome and all-cause mortality.

Design: Four prospective cohort studies.

Setting: The Dortmund Health Study (DHS) and the Study of Health in Pomerania (SHIP) from Germany. The Women's Health Study (WHS) and the Physicians' Health Study (PHS) from the United States.

Participants: In DHS: a random sample (n=1,299) from the population of Dortmund; in SHIP: a sample (n=4,291) from residents living in West Pomerania were drawn by multistage random sampling design; in WHS: female health care professionals (n=31,370); in PHS: male physicians (n=22,926)

Main outcome measures: All-cause mortality.

Results: The prevalence of RLS ranged between 7.4% and 11.9% at baseline. During follow-up (ranging between 6 to 11 years) RLS was not associated with increased risk of all-cause mortality in any of the four cohorts. The multivariable-adjusted hazard ratios (95%CI) for all-cause mortality ranged from 0.21 (0.03-1.53) to 1.07 (0.93-1.23) across the four studies. The hazard ratios for all-cause mortality did not differ according to gender.

Conclusion: In these four independently conducted large prospective cohort studies from Germany and the United States, RLS did not increase the risk of all-cause mortality. These findings do not support the hypothesis that RLS is a risk factor of mortality of any cause.

Keywords: restless legs syndrome, prospective, cohort study, mortality

ARTICLE SUMMARY

Article focus

- The aim of this study is to evaluate the association between RLS and all cause mortality in four independent prospective cohort studies.

Key messages

- Results of our study do not indicate that RLS is associated with an increased risk for all-cause mortality
- The risk for all-cause mortality did not differ according to gender
- RLS should not be considered a risk factor for all-cause mortality

Strengths and limitations

- Strengths of the study are the inclusion of four different cohorts, the prospective study design, the standardized RLS assessment according to four minimal diagnostic criteria
- Limitations of the study are as follows: RLS information was self-reported and misclassification of cases was possible; no information on frequency, severity and duration of RLS symptoms was available; the cohorts consist of a predominately white population which may limit the generalisability of the results to other cohorts.

INTRODUCTION

Restless legs syndrome (RLS) is a common sleep-related movement disorder affecting about 7-10% of the general population in western countries.[1] RLS is characterised by an urge to move the leg, typically accompanied by uncomfortable leg sensations, and both feelings are relieved by leg movement. Symptoms emerge during inactivity and they are worst in evening or night hours. The prevalence and incidence of RLS increase with age, and women are more commonly affected.[1 2] The exact pathophysiological pathway of RLS remains unknown; the impairment of the central dopaminergic system has a key importance, but genetic risk variants have been also identified.[3] RLS is frequently associated with insomnia, impaired quality of life, and depression.[4-6]

In recent years, results from several cross-sectional studies suggested an association between RLS and chronic diseases, especially cardiovascular disorders, such as hypertension, stroke, and myocardial infarction.[7-11] These are frequent disorders in the elderly and associated with a clearly increased risk of mortality. The RLS prevalence and incidence also increase with age[2], and women are almost twice as often affected as men. However, the relation between RLS and mortality is unclear since prospective studies using the minimal criteria for RLS are lacking so far. The few existing studies either examined clinic-based populations or did not apply the minimal criteria for assessing RLS published in 1995.[12] RLS was reported to be a marker of higher mortality among patients with chronic renal disease,[13-15] a condition known to predispose to RLS. Among elderly community dwelling female residents RLS was found to be related to mortality.[16] Similarly, in a middle-aged sample from the general population RLS was a risk factor for mortality only in women according to a 20-year follow-up study.[17] Since case classification relies entirely on self-reported symptoms and disease characteristics, application of the minimal criteria for RLS, defined by the International RLS Study Group, is important to allow standardised RLS assessment across populations.

Despite the high prevalence and subjective burden of RLS, it often remains unrecognised in primary care. Given the high frequency of RLS in the general population, an association between RLS and all-cause mortality would have a substantial impact on the population level. Once diagnosed, RLS can be successfully treated in many cases. Thus, the evaluation of RLS as a novel modifiable mortality risk factor has considerable public health implications, and may result in more routine screening and monitoring of RLS.

Therefore, the aim of this study was to investigate whether RLS, assessed by the minimal criteria, is associated with an increased risk of all-cause mortality in four large, independent cohort studies, two from Germany and two from the United States, enabling an application of results across studies and countries.

METHODS

The following four prospective cohort studies were included in the analyses. All four studies applied the minimal diagnostic criteria for RLS by using the same short set of standardised questions,[12] either in German or in English.

The Dortmund Health Study

Primary aim of the Dortmund Health Study (DHS) was to determine the frequency of headache disorders, cardiovascular and other chronic diseases, and behaviour dependent risk factors in the population of the city of Dortmund in the western part of Germany.[18] From a total population of 591,000 a random sample of 3,820 persons aged 25-75 years was drawn from the municipal registry. Of those sampled, 395 persons were excluded because they had moved out of the study area, died, or did not have sufficient knowledge of the German language leaving 3,425 persons, who were eligible and invited to participate in a personal interview at the DHS study centre. If personal participation at the centre was impossible, a questionnaire with a subset of the otherwise identical questions was mailed to the participants.

The overall response at baseline was 66.9%, yielding 2,291 participants (1,312 with interview and 979 with questionnaire). RLS assessment at baseline was restricted to interviewed participants only, because the respective questions were not included in the questionnaire due to the reduced space available. Vital status of 13 subjects could not be identified during the follow-up. Eight had moved outside Germany and were not traceable, three of the remaining five had foreign nationalities and were likely to have moved abroad, and two were untraceable. Therefore, the analyses included the data of 1,299 participants from DHS.

The Study of Health in Pomerania

The Study of Health in Pomerania (SHIP) is an ongoing population-based study comprising three cities and 29 communities in the rural area close to the Baltic Sea (West Pomerania). It was designed to assess a broad range of health and quality of life indicators in the north-east region of Germany after the German reunification.[19] From the total population of 212,157 residents living in the study area in 1995, a sample of 7,008 men and women aged 20 to 79 stratified by five-year age groups was drawn using a multistage random sampling design. The final number of subjects participating in the study was 4,308 (response 68.8%). The baseline examination was conducted from 1997 to 2001, combining an interview, medical and dental examinations performed in one single visit in the study centre. RLS data at baseline were available from 4,291 participants.

The Women's Health Study

The Women's Health Study (WHS) was a randomised, placebo-controlled trial designed to test the risks and benefits of low-dose aspirin (100 mg every other day) and vitamin E (600 IU every other day) in the primary prevention of cardiovascular diseases (CVD) and cancer among apparently healthy women. The design and methods of the WHS have been described in detail previously.[20 21] Briefly, a total of 39,876 US female health care professionals aged 45

years or older at study entry (1992-1995) without a history of CVD, cancer, or other major illnesses were randomly assigned to receive active aspirin, active vitamin E, both active agents, or both placebos. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. After the trial's termination in March 2004, the women who were still alive and willing to participate entered an observational follow-up. The return date of the 108-month questionnaire containing questions on RLS was defined as new baseline for this analysis. Of the 33,092 women in active follow-up at 108 months, we excluded 1,722 women with missing RLS information, leaving a total of 31,370 women for this analysis.

The Physicians' Health Study

The Physicians' Health Study I (PHS I) was a randomised, double blind, placebo-controlled trial to test the benefits and risks of low dose aspirin (325mg) and beta-carotene (50 mg) in the primary prevention of CVD and cancer among 22,071 apparently healthy physicians aged 40 to 84 years at baseline in 1982.[22] Baseline information was self-reported and collected by means of a mailed questionnaire that asked about many cardiovascular risk factors and life style variables. Every six months in the first year and yearly thereafter, follow-up questionnaires were sent to the participants. Since the trials' termination in 1995, the men are continued to be followed either on an observational basis or as part of the Physician's Health Study II (PHS II).

Using methods successfully developed in the PHS I, the PHS II was launched in 1997.[23] The PHS II is an ongoing randomised, double-blind, placebo-controlled trial to test the effects of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (50 mg), and a daily multivitamin (Centrum Silver) in the prevention of total and prostate cancer, CVD, and age-related eye

disease among 14,641 US male physicians aged 55 years and older, including a total of 7,641 PHS I participants who were willing and eligible to enter the PHS II. Baseline information was self-reported and follow-up information was collected annually by mailed questionnaires. For the purpose of this analysis, we pooled data from the PHS I and PHS II, yielding a total of 29,071 participants. The return date of the questionnaire containing the RLS questions (216-month questionnaire for PHS I participants and 12-month questionnaire for PHS II participants) was defined as new baseline for this analysis. At this time point, 24,505 men were still in active follow-up. We excluded 1,579 men with missing information for all three RLS questions, leaving a total of 22,926 men at our defined baseline for our analysis.

RLS assessment

RLS is diagnosed according to the presence of specific symptoms. Participants in each study were asked to answer the following questions which were based on the minimal criteria published by the International Restless Legs Syndrome Study Group:[12] "Do you have unpleasant leg sensations (like crawling, paraesthesias, or pain) combined with a motor restlessness and an urge to move?", "Do these symptoms occur only at rest and does moving improve them?", "Are these symptoms worse in the evening or at night compared with the morning?" The three answer categories included "Yes", "No" or "Don't know". Participants were only classified as RLS positive if they answered all symptom questions with "Yes".
In DHS and SHIP RLS assessment was conducted in face-to-face interviews by trained and certified interviewers, while in WHS and PHS RLS information was retrieved by mailed standardised questionnaires. The same questions that were used to identify RLS symptoms in each study had been previously validated[24] and had already been used in prior reports[2 5 7 18 25]. Comparing the questionnaire-based classification of RLS with a physician's diagnosis as a gold standard showed good agreement (unweighted kappa=0.67, $p<0.001$) in the German MEMO (Memory and Morbidity in Augsburg Elderly) study.[24]

Ascertainment of mortality

Death from all causes was defined as our main outcome for the analyses. In both German cohorts, the vital status of participants, i.e. alive or deceased and the date of death, if applicable, was retrieved from the municipal registries at the follow-up. In both US cohorts, deaths of participants were identified by reports from family members or next of kin, or postal authorities, and searches of the National Death Index. Information on date and cause of death were confirmed through review of death certificates and medical records by an endpoints committee of physicians.

Socio-demographic data, lifestyle factors, and co-morbidities

Age, gender, and lifestyle factors, i.e. health related behaviours, were assessed during the interview in the German studies and with the mailed questionnaire in the WHS and PHS. In the DHS and SHIP, co-morbidities including diabetes mellitus, hypertension, cancer, myocardial infarction, and stroke were assessed as self-reports with specific questions asking for a physician-made diagnosis of the respective condition. In the WHS and PHS, these co-morbidities were also assessed by questionnaires, and the presence of myocardial infarction, stroke, and cancer was confirmed by medical record review. Body weight and height of the participants in the German studies were measured according to standard protocols, and in the US studies both items were self-reported.

Statistical analysis

Data of the four cohort studies were analysed separately using the following identical analysis approach. For each cohort, we calculated mean values for continuous and frequencies for categorical variables of baseline characteristics. Person-time was calculated from the return date of the questionnaire containing the RLS questions or date of interview, respectively, to

the date of death, last documented contact, or end of study, whatever occurred first. Cox proportional hazards models were used to evaluate the association between RLS status and mortality. Age- and multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. The multivariable models were adjusted for the following potential confounding factors: age, gender (DHS and SHIP), body mass index (BMI), smoking, exercise, history of diabetes, history of hypertension, myocardial infarction, stroke, and cancer. To provide comparability of results across studies, we additionally performed stratified analyses according to gender in the DHS and SHIP.

The proportional hazards assumption was tested by including an interaction term for RLS status and logarithm of follow-up time for mortality in age-adjusted models. We found no statistically significant violation.

In all multivariable models participants with missing covariate information were excluded. The models were reanalysed incorporating a missing value indicator in the outcome models for covariates if the number of participants with missing information was greater or equal to 100. We assigned participants with missing values to the covariate reference category if the number of missing information was less than 100. These analyses provided nearly identical results (data not shown).

All analyses were performed with Stata 11.0 (StataCorp, Tx, USA) in the DHS and SHIP. For all WHS and PHS analyses, we used SAS 9.1.3 (SAS Institute Inc, Cary, NC). All p-values were 2-tailed and $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Table 1 summarises the baseline characteristics of participants in the four different cohorts. The mean age in the cohorts ranged from 50.3 years in SHIP to 67.8 years in the PHS. The prevalence of RLS at baseline varied between 7.4% in DHS and 11.9% in WHS. Baseline

RLS prevalence was significantly higher among women than in men in both German cohorts (9.3% vs 5.2%, p=0.005 in DHS and 12.8% vs 7.3%, p<0.001 in SHIP).

RLS and mortality

The median follow-up time, the number of deaths, and the mortality rate for each study are presented in Table 2. The highest mortality rate was observed in the PHS (12.3 per 1,000 person-years) and the lowest mortality rate was measured in the WHS (2.8 per 1,000 person-years).

Tables 3 and 4 summarise the age- and multivariable-adjusted HRs (95%CI) for the association between RLS and mortality. RLS was not significantly associated with mortality in any of the four studies. Multivariable-adjusted HRs (95%CI) ranged from 0.21 (0.03-1.53) in the DHS to 1.07 (0.93-1.23) in the PHS. After gender stratification the adjusted HRs were similar among women and men in SHIP. Furthermore, when the interaction term between RLS and gender was added to the fully adjusted model, it was not significant (p=0.71). In DHS the estimation of the HR among women was not possible, because no women with RLS died during the follow-up.

DISCUSSION

In four independently conducted large prospective cohort studies from Germany and the US, RLS was not associated with all-cause mortality. The risk of death did not differ according to gender. In contrast to the few previous studies,[16 17] we applied standardised questions of the minimal diagnostic criteria to assess RLS and we also accounted for numerous explanatory variables.

Comparisons with other studies

Some clinic-based studies found a relationship between RLS and mortality among subjects with end-stage renal disease, either in dialysed[13 14] or transplanted patients.[15] There was no clear explanation for the findings, although the presence of RLS could be related to indicators of poorer health status, like higher level of uraemia, disease duration, and co-morbidity. However, those studies were conducted in a very specific patient group with very high morbidity and mortality, and thus the results can be hardly generalised to relatively healthier populations like ours.

In prior reports of community-dwelling elderly subjects, RLS symptoms indicated higher mortality only among women.[16] Mallon et al. found that RLS combined with daytime sleepiness was associated with increased mortality risk among women in a middle-aged population, although RLS without sleepiness was not significantly related to mortality.[17] There was no clear explanation for these findings, though it has been speculated that disturbed sleep, which frequently accompanies severe RLS, might contribute to the decreased lifespan of subjects with RLS. We had no data about daytime sleepiness or other sleep variables available to determine whether these factors modify the relationship between RLS and mortality.

Differences in sampling and population characteristics might have contributed to the discrepant findings between the previous and the present studies. More importantly, at the time of the baseline assessment of the two earlier studies, standard criteria for RLS did not exist. The urge to move the legs and relief of symptoms due to leg movement, two core symptoms of RLS, were not assessed. It should be also noted that the follow-up time of the study of Mallon et al.[17] was 20 years, much longer than any of our studies.

In contrast to these previous results, recently published analyses from the WHS and PHS cohorts do not suggest that RLS is associated with incident cardiovascular disease events including CVD mortality, either in women or men.[25]

Subjective and objective sleep disturbances are very common among subjects with RLS.[26 27] Both short sleep duration and frequent insomnia symptoms predict mortality according to population- and community-based studies.[28 29] Thus we cannot rule out that patients experiencing RLS combined with chronic severe sleep deprivation and/or insomnia may have a higher mortality risk over time. Future prospective studies with assessment of RLS severity as well as various sleep-related factors should further investigate this hypothesis.

Strengths and limitations

One of the strengths of the present work is the analysis of four independently conducted cohort studies. The lack of association observed across the four different studies indicates the robustness of our finding. Furthermore, RLS cases were classified according to the minimal criteria for RLS. There were differences in the sampling procedures, sample characteristics, and baseline data collection across the studies. However, the fact that the results of a null association were the same despite these differences underlines the robustness of the lack of association between RLS and mortality. Finally, we were able to take several important potential confounders into account, including behavioural risk factors and co-morbid conditions.

Several limitations have to be considered when interpreting our results. An important limitation is that, as in all large epidemiologic studies, case classification was based on a set of self-administered diagnostic questions instead of a complete clinical interview and examination. Therefore misclassification of RLS cases is possible. However, the set of RLS

questions used in our cohorts has been successfully used and validated in previous studies and the observed prevalences in our cohorts are similar to those reported in other population-based studies.[30] Furthermore, due to the low number of outcome events in DHS, the estimates for the association of RLS with mortality were less precise than in the other three cohorts. No information on frequency, severity and duration of RLS symptoms was available in the cohorts. Despite information on a large number of potential confounders, residual and unmeasureable confounding remains possible as our study is observational. However, we are not aware of any confounding factor that, if included in our final models, would result in increased risk of all-cause mortality among patients with RLS. Participants in all four cohorts were predominately white, which may limit the generalisability to other populations.

Clinical Implications

Results of these four independent large cohort studies do not suggest that RLS is a risk factor for mortality. However, previous studies indicate that RLS is associated with a variety of comorbidities, such as diabetes, higher body mass index, and cardiovascular diseases, which are established risk factors for mortality. Patients with RLS should be screened for RLS associated comorbidities and treated if necessary.

Unanswered questions and future research

RLS is a highly prevalent disease among the elderly, but the mechanisms causing the disease and its relationship with a diverse set of comorbidities remain poorly understood. Furthermore, the role of frequency, severity and duration of RLS symptoms on mortality and disease risk remains unclear. In addition, sleep deprivation and insomnia accompanying RLS may also influence mortality and comorbidity. Further studies are warranted to establish risk factors for incident RLS to be able to develop sufficient prevention strategies and to understand the complex relationship between RLS and its comorbid conditions.

In summary, results of four independent large, prospective cohort studies show that RLS is not associated with increased risk of all-cause mortality. Given the high prevalence of RLS in western populations, this is a positive result for all living with RLS.

Table 1: Baseline characteristics of participants

	Dortmund Health Study	Study of Health in Pomerania	Physicians' Health Study	Women's Health Study
Number of participants	1,299	4,291	22,926	31,370
Age, years (mean+/-SD)	52.2+/-13.8	50.3+/-16.4	67.8+/-9.0	63.6+/-6.9
Women, n (%)	688 (53.0)	2,185 (50.9)	0 (0)	31,370 (100)
RLS, n (%)	96 (7.4)	433 (10.1)	1,717 (7.5)	3,745 (11.9)
BMI, kg/m^2 (mean+/-SD)	27.5+/-5.0	27.3+/-4.8	25.9+/-3.7	27.1+/-5.5
Diabetes, diagnosed, n (%)	98 (7.5)	342 (8.0)	1,983 (8.7)	2,342 (7.5)
Hypertension, diagnosed, n (%)	461 (35.7)	1,729 (40.8)	12,079 (52.7)	15,223 (48.5)
Cancer, diagnosed, n (%)	59 (4.6)	53 (1.2)	2,306 (10.1)	1,818 (5.8)
Myocardial infarction, diagnosed, n (%)	49 (3.8)	146 (3.4)	797 (3.5)	248 (0.8)
Stroke, diagnosed, n (%)	29 (2.2)	98 (2.3)	490 (2.1)	251 (0.8)

SD: standard deviation; BMI: body mass index.

Table 2: Follow-up status of participants

	Dortmund Health Study	Study of Health in Pomerania	Physicians' Health Study	Women's Health Study
Number of participants	1,299	4,291	22,926	31,370
Median follow-up time [IQR]	6.9 [0.3]	11.1 [1.5]	8.7 [0.6]	6.5 [0.8]
Number of deaths (%)				
Total	55 (4.2)	540 (12.6)	2,287 (10.0)	542 (1.7)
Among participants with RLS	1 (1.0)	70 (16.2)	215 (12.5)	63 (1.7)
Among participants without RLS	54 (4.5)	470 (12.2)	2072 (9.8)	479 (1.7)
Mortality rate per 1,000 person per year (95% CI)	6.2 (4.7-8.1)	11.8 (10.9-12.9)	12.3 (11.8-12.8)	2.8 (2.5-3.0)

IQR: interquartile range; CI: confidence interval.

Table 3: Age-, gender- and multivariable-adjusted hazard ratios and 95% confidence intervals for mortality according to RLS status in the German cohorts

	Dortmund Health Study	Study of Health in Pomerania
	HR (95% CI)	HR (95% CI)
Age- and gender-adjusted models	n=1,299	n=4,291
Total	0.21 (0.03-1.49)	1.04 (0.81-1.34)
Male	0.42 (0.06-3.09)	1.00 (0.71-1.39)
Female	n.a.	1.13 (0.77-1.67)
Multivariable-adjusted* models	n=1,283	n=4,264
Total	0.21 (0.03-1.53)	0.99 (0.76-1.29)
Male	0.52 (0.07-3.95)	0.98 (0.68-1.39)
Female	n.a.	1.00 (0.66-1.50)

*Multivariable models were adjusted for age, gender, BMI, smoking, physical activity and histories of diabetes, hypertension, myocardial infarction, stroke and cancer.

HR: hazard ratio, CI: confidence interval, n.a.: not available.

Table 4: Age- and multivariable- adjusted hazard ratios and 95% confidence intervals for mortality according to RLS status in the US cohorts

	Women's Health Study	Physicians' Health Study
	HR (95% CI)	HR (95% CI)
Age-adjusted models	n=31,370	n=22,926
	0.98 (0.75-1.27)	1.10 (0.96-1.27)
Multivariable-adjusted* models	n=30,475	n=22,816
	0.93 (0.71-1.21)	1.07 (0.93-1.23)

*Multivariable models were adjusted for age, BMI, smoking, physical activity and histories of diabetes, hypertension, myocardial infarction, stroke and cancer.

HR: hazard ratio, CI: confidence interval.

Competing interests

None

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Patient consent

Obtained

Ethical approval

All participants in the four cohorts gave informed written consent and the study protocol was approved by the local ethics committees of the Medical Faculty at the University of Münster,

(for DHS), the University of Greifswald (for SHIP) and the institutional review board of Brigham and Women's Hospital, Boston (for WHS and PHS; Protocol #: 2008-P-000613/3).

Data sharing

No additional data available

Author's footnote

All authors had full access to all the data in the study, can take responsibility for the integrity of the data and accuracy of the data analysis, and approved the final version of the manuscript.

Contributor statement

AS developed the evaluation plan, made statistical analyses, interpretation of results, literature search, and drafted the manuscript. ACW designed the study, developed the evaluation plan, carried out statistical analyses, interpreted the results, performed literature search, and drafted the manuscript. HV contributed to data collection, interpretation of results, and critically revised the manuscript. WH contributed to data collection, interpretation of results, and critically revised the manuscript. MS designed the study, interpreted the results, and critically revised the manuscript. JB analysed and interpreted data, obtained funding, and critically revised the manuscript. JMG analysed and interpreted data, obtained funding, and critically revised the manuscript. TK designed the study, developed the evaluation plan, interpreted the results and contributed to drafting the manuscript. KB designed the study, developed the evaluation plan, made the statistical analysis, interpreted the results, and drafted the manuscript.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org

Restless legs syndrome and all-cause mortality in four prospective cohort studies

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Restless legs syndrome and all-cause mortality in four prospective cohort studies

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ABSTRACT

Objectives: To evaluate the association between restless legs syndrome and all-cause mortality.

Design: Four prospective cohort studies.

Setting: The Dortmund Health Study (DHS) and the Study of Health in Pomerania (SHIP) from Germany. The Women's Health Study (WHS) and the Physicians' Health Study (PHS) from the United States.

Participants: In DHS: a random sample (n=1,299) from the population of Dortmund; in SHIP: a sample (n=4,291) from residents living in West Pomerania were drawn by multistage random sampling design; in WHS: female health care professionals (n=31,370); in PHS: male physicians (n=22,926)

Main outcome measures: All-cause mortality.

Results: The prevalence of RLS ranged between 7.4% and 11.9% at baseline. During follow-up (ranging between 6 to 11 years) RLS was not associated with increased risk of all-cause mortality in any of the four cohorts. The multivariable-adjusted hazard ratios (95%CI) for all-cause mortality ranged from 0.21 (0.03-1.53) to 1.07 (0.93-1.23) across the four studies. The hazard ratios for all-cause mortality did not differ according to gender.

Conclusion: In these four independently conducted large prospective cohort studies from Germany and the United States, RLS did not increase the risk of all-cause mortality. These findings do not support the hypothesis that RLS is a risk factor of mortality of any cause.

Keywords: restless legs syndrome, prospective, cohort study, mortality

ARTICLE SUMMARY

Article focus

- The aim of this study is to evaluate the association between RLS and all cause mortality in four independent prospective cohort studies.

Key messages

- Results of our study do not indicate that RLS is associated with an increased risk for all-cause mortality
- The risk for all-cause mortality did not differ according to gender
- RLS should not be considered a risk factor for all-cause mortality

Strengths and limitations

- Strengths of the study are the inclusion of four different cohorts, the prospective study design, the standardized RLS assessment according to four minimal diagnostic criteria
- Limitations of the study are as follows: RLS information was self-reported and misclassification of cases was possible; no information on frequency, severity and duration of RLS symptoms was available; the cohorts consist of a predominately white population which may limit the generalisability of the results to other cohorts.

INTRODUCTION

Restless legs syndrome (RLS) is a common sleep-related movement disorder affecting about 7-10% of the general population in western countries.[1] RLS is characterised by an urge to move the legs, typically accompanied by uncomfortable leg sensations, and both feelings are relieved by leg movement. Symptoms emerge during inactivity and they are worst in evening or night hours. The prevalence and incidence of RLS increase with age, and women are more commonly affected.[1 2] The exact pathophysiological pathway of RLS remains unknown; the impairment of the central dopaminergic system and iron deficiency in the brain have a key importance, but genetic risk variants have been also identified.[3] RLS is frequently associated with insomnia, impaired quality of life, and depression.[4-6]

In recent years, results from several cross-sectional studies suggested an association between RLS and chronic diseases, especially cardiovascular disorders, such as hypertension, stroke, and myocardial infarction.[7-11] These are frequent disorders in the elderly and associated with a clearly increased risk of mortality. The RLS prevalence and incidence also increase with age[2], and women are almost twice as often affected as men. However, the relation between RLS and mortality is unclear since prospective studies using the minimal criteria for RLS are lacking so far. The few existing studies either examined clinic-based populations or did not apply the minimal criteria for assessing RLS published in 1995.[12] RLS was reported to be a marker of higher mortality among patients with chronic renal disease,[13-15] a condition known to predispose to RLS. Among elderly community dwelling female residents RLS was found to be related to mortality.[16] Similarly, in a middle-aged sample from the general population RLS was a risk factor for mortality only in women according to a 20-year follow-up study.[17] Since case classification relies entirely on self-reported symptoms and disease characteristics, application of the minimal criteria for RLS, defined by the International RLS Study Group, is important to allow standardised RLS assessment across populations.

Despite the high prevalence and subjective burden of RLS, it often remains unrecognised in primary care. Given the high frequency of RLS in the general population, an association between RLS and all-cause mortality would have a substantial impact on the population level. Once diagnosed, RLS can be successfully treated in many cases. Thus, the evaluation of RLS as a novel modifiable mortality risk factor has considerable public health implications, and may result in more routine screening and monitoring of RLS.

Therefore, the aim of this study was to investigate whether RLS, assessed by the minimal criteria, is associated with an increased risk of all-cause mortality in four large, independent cohort studies, two from Germany and two from the United States, enabling an application of results across studies and countries.

METHODS

The following four prospective cohort studies were included in the analyses. All four studies applied the minimal diagnostic criteria for RLS by using the same short set of standardised questions,[12] either in German or in English.

The Dortmund Health Study

Primary aim of the Dortmund Health Study (DHS) was to determine the frequency of headache disorders, cardiovascular and other chronic diseases, and behaviour dependent risk factors in the population of the city of Dortmund in the western part of Germany.[18] From a total population of 591,000 a random sample of 3,820 persons aged 25-75 years was drawn from the municipal registry. Of those sampled, 395 persons were excluded because they had moved out of the study area, died, or did not have sufficient knowledge of the German language leaving 3,425 persons, who were eligible and invited to participate in a personal interview at the DHS study centre. If personal participation at the centre was impossible, a questionnaire with a subset of the otherwise identical questions was mailed to the participants.

The overall response at baseline was 66.9%, yielding 2,291 participants (1,312 with interview and 979 with questionnaire). RLS assessment at baseline was restricted to interviewed participants only, because the respective questions were not included in the questionnaire due to the reduced space available. Vital status of 13 subjects could not be identified during the follow-up. Eight had moved outside Germany and were not traceable, three of the remaining five had foreign nationalities and were likely to have moved abroad, and two were untraceable. Therefore, the analyses included the data of 1,299 participants from DHS.

The Study of Health in Pomerania

The Study of Health in Pomerania (SHIP) is an ongoing population-based study comprising three cities and 29 communities in the rural area close to the Baltic Sea (West Pomerania). It was designed to assess a broad range of health and quality of life indicators in the north-east region of Germany after the German reunification.[19] From the total population of 212,157 residents living in the study area in 1995, a sample of 7,008 men and women aged 20 to 79 stratified by five-year age groups was drawn using a multistage random sampling design. The final number of subjects participating in the study was 4,308 (response 68.8%). The baseline examination was conducted from 1997 to 2001, combining an interview, medical and dental examinations performed in one single visit in the study centre. RLS data at baseline were available from 4,291 participants.

The Women's Health Study

The Women's Health Study (WHS) was a randomised, placebo-controlled trial designed to test the risks and benefits of low-dose aspirin (100 mg every other day) and vitamin E (600 IU every other day) in the primary prevention of cardiovascular diseases (CVD) and cancer among apparently healthy women. The design and methods of the WHS have been described in detail previously.[20 21] Briefly, a total of 39,876 US female health care professionals aged 45

years or older at study entry (1992-1995) without a history of CVD, cancer, or other major illnesses were randomly assigned to receive active aspirin, active vitamin E, both active agents, or both placebos. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. After the trial's termination in March 2004, the women who were still alive and willing to participate entered an observational follow-up. The return date of the 108-month questionnaire containing questions on RLS was defined as new baseline for this analysis. Of the 33,092 women in active follow-up at 108 months, we excluded 1,722 women with missing RLS information, leaving a total of 31,370 women for this analysis.

The Physicians' Health Study

The Physicians' Health Study I (PHS I) was a randomised, double blind, placebo-controlled trial to test the benefits and risks of low dose aspirin (325mg) and beta-carotene (50 mg) in the primary prevention of CVD and cancer among 22,071 apparently healthy male physicians aged 40 to 84 years at baseline in 1982.[22] Baseline information was self-reported and collected by means of a mailed questionnaire that asked about many cardiovascular risk factors and life style variables. Every six months in the first year and yearly thereafter, follow-up questionnaires were sent to the participants. Since the trials' termination in 1995, the men are continued to be followed either on an observational basis or as part of the Physician's Health Study II (PHS II).

Using methods successfully developed in the PHS I, the PHS II was launched in 1997.[23] The PHS II is an ongoing randomised, double-blind, placebo-controlled trial to test the effects of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (50 mg), and a daily multivitamin (Centrum Silver) in the prevention of total and prostate cancer, CVD, and age-related eye

disease among 14,641 US male physicians aged 55 years and older, including a total of 7,641 PHS I participants who were willing and eligible to enter the PHS II. Baseline information was self-reported and follow-up information was collected annually by mailed questionnaires. For the purpose of this analysis, we pooled data from the PHS I and PHS II, yielding a total of 29,071 participants. The return date of the questionnaire containing the RLS questions (216-month questionnaire for PHS I participants and 12-month questionnaire for PHS II participants) was defined as new baseline for this analysis. At this time point, 24,505 men were still in active follow-up. We excluded 1,579 men with missing information for all three RLS questions, leaving a total of 22,926 men at our defined baseline for our analysis.

RLS assessment

RLS is diagnosed according to the presence of specific symptoms. Participants in each study were asked to answer the following questions which were based on the minimal criteria published by the International Restless Legs Syndrome Study Group:[12] "Do you have unpleasant leg sensations (like crawling, paraesthesias, or pain) combined with a motor restlessness and an urge to move?", "Do these symptoms occur only at rest and does moving improve them?", "Are these symptoms worse in the evening or at night compared with the morning?" The three answer categories included "Yes", "No" or "Don't know". Participants were only classified as RLS positive if they answered all symptom questions with "Yes".
In DHS and SHIP RLS assessment was conducted in face-to-face interviews by trained and certified interviewers, while in WHS and PHS RLS information was retrieved by mailed standardised questionnaires. The same questions that were used to identify RLS symptoms in each study had been previously validated[24] and had already been used in prior reports[2 5 7 18 25]. Comparing the questionnaire-based classification of RLS with a physician's diagnosis as a gold standard showed good agreement (unweighted kappa=0.67, p<0.001) in the German MEMO (Memory and Morbidity in Augsburg Elderly) study.[24] In DHS there was a further

question related to the number of years elapsed since the onset of RLS symptoms. The frequency of RLS symptoms was also assessed in DHS with the following possible answer categories: ‘daily’, ‘3-6 times a week’, ‘1-2 times a week’, ‘1-3 times a month’, and ‘less than once a month’. The first two categories and the remaining three categories were subsequently collapsed for the analysis.

Ascertainment of mortality

Death from all causes was defined as our main outcome for the analyses. In both German cohorts, the vital status of participants, i.e. alive or deceased and the date of death, if applicable, was retrieved from the municipal registries at the follow-up. In both US cohorts, deaths of participants were identified by reports from family members or next of kin, or postal authorities, and searches of the National Death Index. Information on date and cause of death were confirmed through review of death certificates and medical records by an endpoints committee of physicians.

Socio-demographic data, lifestyle factors, and co-morbidities

Age, gender, and lifestyle factors, i.e. health related behaviours, were assessed during the interview in the German studies and with the mailed questionnaire in the WHS and PHS. In the DHS and SHIP, co-morbidities including diabetes mellitus, hypertension, cancer, myocardial infarction, and stroke were assessed as self-reports with specific questions asking for a physician-made diagnosis of the respective condition. In the WHS and PHS, these co-morbidities were also assessed by questionnaires, and the presence of myocardial infarction, stroke, and cancer was confirmed by medical record review. Body weight and height of the participants in the German studies were measured according to standard protocols, and in the US studies both items were self-reported. There was one question referring to the presence of leg cramps in SHIP.

Statistical analysis

Data of the four cohort studies were analysed separately using the following identical analysis approach. For each cohort, we calculated mean values for continuous and frequencies for categorical variables of baseline characteristics. Person-time was calculated from the return date of the questionnaire containing the RLS questions or date of interview, respectively, to the date of death, last documented contact, or end of study, whatever occurred first. Cox proportional hazards models were used to evaluate the association between RLS status and mortality. Age- and multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. The multivariable models were adjusted for the following potential confounding factors: age, gender (DHS and SHIP), body mass index (BMI), smoking, exercise, history of diabetes, history of hypertension, myocardial infarction, stroke, and cancer. To provide comparability of results across studies, we additionally performed stratified analyses according to gender in the DHS and SHIP.

The proportional hazards assumption was tested by including an interaction term for RLS status and logarithm of follow-up time for mortality in age-adjusted models. We found no statistically significant violation.

In all multivariable models participants with missing covariate information were excluded. The models were reanalysed incorporating a missing value indicator in the outcome models for covariates if the number of participants with missing information was greater or equal to 100. We assigned participants with missing values to the covariate reference category if the number of missing information was less than 100. These analyses provided nearly identical results (data not shown).

All analyses were performed with Stata 11.0 (StataCorp, Tx, USA) in the DHS and SHIP. For all WHS and PHS analyses, we used SAS 9.1.3 (SAS Institute Inc, Cary, NC). All p-values were 2-tailed and $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Table 1 summarises the baseline characteristics of participants in the four different cohorts. The mean age in the cohorts ranged from 50.3 years in SHIP to 67.8 years in the PHS. The prevalence of RLS at baseline varied between 7.4% in DHS and 11.9% in WHS. Baseline RLS prevalence was significantly higher among women than in men in both German cohorts (9.3% vs 5.2%, p=0.005 in DHS and 12.8% vs 7.3%, p<0.001 in SHIP).

RLS and mortality

The median follow-up time, the number of deaths, and the mortality rate for each study are presented in Table 2. The highest mortality rate was observed in the PHS (12.3 per 1,000 person-years) and the lowest mortality rate was measured in the WHS (2.8 per 1,000 person-years).

Tables 3 and 4 summarise the age- and multivariable-adjusted HRs (95%CI) for the association between RLS and mortality. RLS was not significantly associated with mortality in any of the four studies. Multivariable-adjusted HRs (95%CI) ranged from 0.21 (0.03-1.53) in the DHS to 1.07 (0.93-1.23) in the PHS. After gender stratification the adjusted HRs were similar among women and men in SHIP. Furthermore, when the interaction term between RLS and gender was added to the fully adjusted model, it was not significant (p=0.71). In DHS the estimation of the HR among women was not possible, because no women with RLS died during the follow-up. The presence of leg cramps is a potential RLS mimic, therefore a sensitivity analysis was conducted for SHIP excluding participants reporting leg cramps (n=380), which resulted in a multivariable-adjusted HR (95%CI) of 0.85 (0.61-1.19). When the frequency of RLS symptoms was entered into the model in DHS, the HR associated with the RLS frequency of no more than twice a week vs. no RLS symptoms was 0.39 (95%CI:

0.09-1.63); the HR for RLS frequency of at least three times a week vs. no RLS was 1.28 (95%CI 0.45-3.63). Finally, when the number of years elapsed since the onset of RLS symptoms was added to the multivariable-adjusted model, it was not associated with increased mortality hazard in DHS: HR=1.00 (95%CI 0.90-1.12).

DISCUSSION

In four independently conducted large prospective cohort studies from Germany and the US, RLS was not associated with all-cause mortality. The risk of death did not differ according to gender. In contrast to the few previous studies,[16 17] we applied standardised questions of the minimal diagnostic criteria to assess RLS and we also accounted for numerous explanatory variables.

Comparisons with other studies

Some clinic-based studies found a relationship between RLS and mortality among subjects with end-stage renal disease, either in dialysed[13 14] or transplanted patients.[15] There was no clear explanation for the findings, although the presence of RLS could be related to indicators of poorer health status, like higher level of uraemia, disease duration, and co-morbidity. However, those studies were conducted in a very specific patient group with very high morbidity and mortality, and thus the results can be hardly generalised to relatively healthier populations like ours.

In prior reports of community-dwelling elderly subjects, RLS symptoms indicated higher mortality only among women.[16] Mallon et al. found that RLS combined with daytime sleepiness was associated with increased mortality risk among women in a middle-aged population, although RLS without sleepiness was not significantly related to mortality.[17] There was no clear explanation for these findings, though it has been speculated that disturbed

sleep, which frequently accompanies severe RLS, might contribute to the decreased lifespan of subjects with RLS. We had no data about daytime sleepiness or other sleep variables available to determine whether these factors modify the relationship between RLS and mortality.

Differences in sampling and population characteristics might have contributed to the discrepant findings between the previous and the present studies. More importantly, at the time of the baseline assessment of the two earlier studies, standard criteria for RLS did not exist. The urge to move the legs and relief of symptoms due to leg movement, two core symptoms of RLS, were not assessed. It should be also noted that the follow-up time of the study of Mallon et al.[17] was 20 years, much longer than any of our studies.

In contrast to these previous results, recently published analyses from the WHS and PHS cohorts do not suggest that RLS is associated with incident cardiovascular disease events including CVD mortality, either in women or men.[25]

Subjective and objective sleep disturbances are very common among subjects with RLS.[26 27] Both short sleep duration and frequent insomnia symptoms predict mortality according to population- and community-based studies.[28 29] Thus we cannot rule out that patients experiencing RLS combined with chronic severe sleep deprivation and/or insomnia may have a higher mortality risk over time. Future prospective studies with assessment of RLS severity as well as various sleep-related factors should further investigate this hypothesis.

Strengths and limitations

One of the strengths of the present work is the analysis of four independently conducted cohort studies. The lack of association observed across the four different studies indicates the

robustness of our finding. Furthermore, RLS cases were classified according to the minimal criteria for RLS. There were differences in the sampling procedures, sample characteristics, and baseline data collection across the studies. However, the fact that the results of a null association were the same despite these differences underlines the robustness of the lack of association between RLS and mortality. Finally, we were able to take several important potential confounders into account, including behavioural risk factors and co-morbid conditions.

Several limitations have to be considered when interpreting our results. An important limitation is that, as in all large epidemiologic studies, case classification was based on a set of self-administered diagnostic questions instead of a complete clinical interview and examination. However, the set of RLS questions used in our cohorts has been successfully used and validated in previous studies and the observed prevalences in our cohorts are similar to those reported in other population-based studies.[30] We also note that conducting clinical interviews in large studies like these would have been extremely difficult. Still, the use of screening questions could have led to misclassification, and RLS mimics could have been falsely identified as RLS cases. We adjusted for the presence of diabetes, therefore diabetic neuropathy, a common potential RLS mimic, was not likely to influence the findings. In SHIP, excluding participants with leg cramps, another frequent RLS mimic, did not alter the results substantially. Nevertheless, there might be other potential mimics of RLS symptoms that could have an effect on the association between RLS and mortality. Due to the low number of outcome events in DHS, the estimates for the association of RLS with mortality were less precise than in the other three cohorts. The mean age was highest in PHS, where the follow-up time was also quite long, and this study showed the highest mortality hazard associated with RLS, even though it was still not significant. It is possible that a longer follow-up time might have revealed a more subtle association with RLS, especially in an

elderly population. Information on frequency and duration of RLS symptoms was available in only one of the cohorts. Despite adjustments for a large number of potential confounders, residual and unmeasureable confounding remains possible as our study is observational. However, we are not aware of any confounding factor that, if included in our final models, would result in increased risk of all-cause mortality among patients with RLS. Participants in all four cohorts were predominately white, which may limit the generalisability to other populations.

Clinical Implications

Results of these four independent large cohort studies do not suggest that RLS is a risk factor for mortality. However, previous studies indicate that RLS is associated with a variety of comorbidities, such as diabetes, higher body mass index, and cardiovascular diseases, which are established risk factors for mortality. Patients with RLS should be screened for RLS associated comorbidities and treated if necessary.

Unanswered questions and future research

RLS is a highly prevalent disease among the elderly, but the mechanisms causing the disease and its relationship with a diverse set of comorbidities remain poorly understood. According to DHS, the frequency and duration of RLS symptoms were not related to mortality, even though the effect size increased with symptom frequency. Since this was the smallest study with the youngest population, the potential role of RLS severity needs further clarification. In addition, sleep deprivation and insomnia accompanying RLS may also influence mortality and comorbidity. Further studies are warranted to establish risk factors for incident RLS to be able to develop sufficient prevention strategies and to understand the complex relationship between RLS and its comorbid conditions. Finally, RLS as a potential mortality hazard should

be further investigated with longer follow-up time and in high-risk populations, for example among elderly subjects.

In summary, results of four independent large, prospective cohort studies show that RLS is not associated with increased risk of all-cause mortality. Given the high prevalence of RLS in western populations, this is a positive result for all living with RLS.

Table 1: Baseline characteristics of participants

	Dortmund Health Study	Study of Health in Pomerania	Physicians' Health Study	Women's Health Study
Number of participants	1,299	4,291	22,926	31,370
Age, years (mean+/-SD)	52.2+/-13.8	50.3+/-16.4	67.8+/-9.0	63.6+/-6.9
Women, n (%)	688 (53.0)	2,185 (50.9)	0 (0)	31,370 (100)
RLS, n (%)	96 (7.4)	433 (10.1)	1,717 (7.5)	3,745 (11.9)
BMI, kg/m^2 (mean+/-SD)	27.5+/-5.0	27.3+/-4.8	25.9+/-3.7	27.1+/-5.5
Diabetes, diagnosed, n (%)	98 (7.5)	342 (8.0)	1,983 (8.7)	2,342 (7.5)
Hypertension, diagnosed, n (%)	461 (35.7)	1,729 (40.8)	12,079 (52.7)	15,223 (48.5)
Cancer, diagnosed, n (%)	59 (4.6)	53 (1.2)	2,306 (10.1)	1,818 (5.8)
Myocardial infarction, diagnosed, n (%)	49 (3.8)	146 (3.4)	797 (3.5)	248 (0.8)
Stroke, diagnosed, n (%)	29 (2.2)	98 (2.3)	490 (2.1)	251 (0.8)

SD: standard deviation; BMI: body mass index.

Table 2: Follow-up status of participants

	Dortmund Health Study	Study of Health in Pomerania	Physicians' Health Study	Women's Health Study
Number of participants	1,299	4,291	22,926	31,370
Median follow-up time [IQR]	6.9 [0.3]	11.1 [1.5]	8.7 [0.6]	6.5 [0.8]
Number of deaths (%)				
Total	55 (4.2)	540 (12.6)	2,287 (10.0)	542 (1.7)
Among participants with RLS	1 (1.0)	70 (16.2)	215 (12.5)	63 (1.7)
Among participants without RLS	54 (4.5)	470 (12.2)	2072 (9.8)	479 (1.7)
Mortality rate per 1,000 person per year (95% CI)	6.2 (4.7-8.1)	11.8 (10.9-12.9)	12.3 (11.8-12.8)	2.8 (2.5-3.0)

IQR: interquartile range; CI: confidence interval.

Table 3: Age-, gender- and multivariable-adjusted hazard ratios and 95% confidence intervals for mortality according to RLS status in the German cohorts

	Dortmund Health Study	Study of Health in Pomerania
	HR (95% CI)	HR (95% CI)
Age- and gender-adjusted models	n=1,299	n=4,291
Total	0.21 (0.03-1.49)	1.04 (0.81-1.34)
Male	0.42 (0.06-3.09)	1.00 (0.71-1.39)
Female	n.a.	1.13 (0.77-1.67)
Multivariable-adjusted* models	n=1,283	n=4,264
Total	0.21 (0.03-1.53)	0.99 (0.76-1.29)
Male	0.52 (0.07-3.95)	0.98 (0.68-1.39)
Female	n.a.	1.00 (0.66-1.50)

*Multivariable models were adjusted for age, gender, BMI, smoking, physical activity and histories of diabetes, hypertension, myocardial infarction, stroke and cancer.

HR: hazard ratio, CI: confidence interval, n.a.: not available.

Table 4: Age- and multivariable- adjusted hazard ratios and 95% confidence intervals for mortality according to RLS status in the US cohorts

	Women's Health Study	Physicians' Health Study
	HR (95% CI)	HR (95% CI)
Age-adjusted models	n=31,370	n=22,926
	0.98 (0.75-1.27)	1.10 (0.96-1.27)
Multivariable-adjusted* models	n=30,475	n=22,816
	0.93 (0.71-1.21)	1.07 (0.93-1.23)

*Multivariable models were adjusted for age, BMI, smoking, physical activity and histories of diabetes, hypertension, myocardial infarction, stroke and cancer.

HR: hazard ratio, CI: confidence interval.

Competing interests

None

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Patient consent

Obtained

Ethical approval

All participants in the four cohorts gave informed written consent and the study protocol was approved by the local ethics committees of the Medical Faculty at the University of Münster,

(for DHS), the University of Greifswald (for SHIP) and the institutional review board of Brigham and Women's Hospital, Boston (for WHS and PHS; Protocol #: 2008-P-000613/3).

Data sharing

No additional data available

Author's footnote

All authors had full access to all the data in the study, can take responsibility for the integrity of the data and accuracy of the data analysis, and approved the final version of the manuscript.

Contributor statement

AS developed the evaluation plan, made statistical analyses, interpretation of results, literature search, and drafted the manuscript. ACW designed the study, developed the evaluation plan, carried out statistical analyses, interpreted the results, performed literature search, and drafted the manuscript. HV contributed to data collection, interpretation of results, and critically revised the manuscript. WH contributed to data collection, interpretation of results, and critically revised the manuscript. MS designed the study, interpreted the results, and critically revised the manuscript. JB analysed and interpreted data, obtained funding, and critically revised the manuscript. JMG analysed and interpreted data, obtained funding, and critically revised the manuscript. TK designed the study, developed the evaluation plan, interpreted the results and contributed to drafting the manuscript. KB designed the study, developed the evaluation plan, made the statistical analysis, interpreted the results, and drafted the manuscript.

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Restless legs syndrome and all-cause mortality in four prospective cohort studies

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ABSTRACT

Objectives: To evaluate the association between restless legs syndrome and all-cause mortality.

Design: Four prospective cohort studies.

Setting: The Dortmund Health Study (DHS) and the Study of Health in Pomerania (SHIP) from Germany. The Women's Health Study (WHS) and the Physicians' Health Study (PHS) from the United States.

Participants: In DHS: a random sample (n=1,299) from the population of Dortmund; in SHIP: a sample (n=4,291) from residents living in West Pomerania were drawn by multistage random sampling design; in WHS: female health care professionals (n=31,370); in PHS: male physicians (n=22,926)

Main outcome measures: All-cause mortality.

Results: The prevalence of RLS ranged between 7.4% and 11.9% at baseline. During follow-up (ranging between 6 to 11 years) RLS was not associated with increased risk of all-cause mortality in any of the four cohorts. The multivariable-adjusted hazard ratios (95%CI) for all-cause mortality ranged from 0.21 (0.03-1.53) to 1.07 (0.93-1.23) across the four studies. The hazard ratios for all-cause mortality did not differ according to gender.

Conclusion: In these four independently conducted large prospective cohort studies from Germany and the United States, RLS did not increase the risk of all-cause mortality. These findings do not support the hypothesis that RLS is a risk factor of mortality of any cause.

Keywords: restless legs syndrome, prospective, cohort study, mortality

ARTICLE SUMMARY

Article focus

- The aim of this study is to evaluate the association between RLS and all cause mortality in four independent prospective cohort studies.

Key messages

- Results of our study do not indicate that RLS is associated with an increased risk for all-cause mortality
- The risk for all-cause mortality did not differ according to gender
- RLS should not be considered a risk factor for all-cause mortality

Strengths and limitations

- Strengths of the study are the inclusion of four different cohorts, the prospective study design, the standardized RLS assessment according to four minimal diagnostic criteria
- Limitations of the study are as follows: RLS information was self-reported and misclassification of cases was possible; no information on frequency, severity and duration of RLS symptoms was available; the cohorts consist of a predominately white population which may limit the generalisability of the results to other cohorts.

INTRODUCTION

Restless legs syndrome (RLS) is a common sleep-related movement disorder affecting about 7-10% of the general population in western countries.[1] RLS is characterised by an urge to move the legs, typically accompanied by uncomfortable leg sensations, and both feelings are relieved by leg movement. Symptoms emerge during inactivity and they are worst in evening or night hours. The prevalence and incidence of RLS increase with age, and women are more commonly affected.[1 2] The exact pathophysiological pathway of RLS remains unknown; the impairment of the central dopaminergic system and iron deficiency in the brain haves a key importance, but genetic risk variants have been also identified.[3] RLS is frequently associated with insomnia, impaired quality of life, and depression.[4-6]

In recent years, results from several cross-sectional studies suggested an association between RLS and chronic diseases, especially cardiovascular disorders, such as hypertension, stroke, and myocardial infarction.[7-11] These are frequent disorders in the elderly and associated with a clearly increased risk of mortality. The RLS prevalence and incidence also increase with age[2], and women are almost twice as often affected as men. However, the relation between RLS and mortality is unclear since prospective studies using the minimal criteria for RLS are lacking so far. The few existing studies either examined clinic-based populations or did not apply the minimal criteria for assessing RLS published in 1995.[12] RLS was reported to be a marker of higher mortality among patients with chronic renal disease,[13-15] a condition known to predispose to RLS. Among elderly community dwelling female residents RLS was found to be related to mortality.[16] Similarly, in a middle-aged sample from the general population RLS was a risk factor for mortality only in women according to a 20-year follow-up study.[17] Since case classification relies entirely on self-reported symptoms and disease characteristics, application of the minimal criteria for RLS, defined by the International RLS Study Group, is important to allow standardised RLS assessment across populations.

Despite the high prevalence and subjective burden of RLS, it often remains unrecognised in primary care. Given the high frequency of RLS in the general population, an association between RLS and all-cause mortality would have a substantial impact on the population level. Once diagnosed, RLS can be successfully treated in many cases. Thus, the evaluation of RLS as a novel modifiable mortality risk factor has considerable public health implications, and may result in more routine screening and monitoring of RLS.

Therefore, the aim of this study was to investigate whether RLS, assessed by the minimal criteria, is associated with an increased risk of all-cause mortality in four large, independent cohort studies, two from Germany and two from the United States, enabling an application of results across studies and countries.

METHODS

The following four prospective cohort studies were included in the analyses. All four studies applied the minimal diagnostic criteria for RLS by using the same short set of standardised questions,[12] either in German or in English.

The Dortmund Health Study

Primary aim of the Dortmund Health Study (DHS) was to determine the frequency of headache disorders, cardiovascular and other chronic diseases, and behaviour dependent risk factors in the population of the city of Dortmund in the western part of Germany.[18] From a total population of 591,000 a random sample of 3,820 persons aged 25-75 years was drawn from the municipal registry. Of those sampled, 395 persons were excluded because they had moved out of the study area, died, or did not have sufficient knowledge of the German language leaving 3,425 persons, who were eligible and invited to participate in a personal interview at the DHS study centre. If personal participation at the centre was impossible, a questionnaire with a subset of the otherwise identical questions was mailed to the participants.

The overall response at baseline was 66.9%, yielding 2,291 participants (1,312 with interview and 979 with questionnaire). RLS assessment at baseline was restricted to interviewed participants only, because the respective questions were not included in the questionnaire due to the reduced space available. Vital status of 13 subjects could not be identified during the follow-up. Eight had moved outside Germany and were not traceable, three of the remaining five had foreign nationalities and were likely to have moved abroad, and two were untraceable. Therefore, the analyses included the data of 1,299 participants from DHS.

The Study of Health in Pomerania

The Study of Health in Pomerania (SHIP) is an ongoing population-based study comprising three cities and 29 communities in the rural area close to the Baltic Sea (West Pomerania). It was designed to assess a broad range of health and quality of life indicators in the north-east region of Germany after the German reunification.[19] From the total population of 212,157 residents living in the study area in 1995, a sample of 7,008 men and women aged 20 to 79 stratified by five-year age groups was drawn using a multistage random sampling design. The final number of subjects participating in the study was 4,308 (response 68.8%). The baseline examination was conducted from 1997 to 2001, combining an interview, medical and dental examinations performed in one single visit in the study centre. RLS data at baseline were available from 4,291 participants.

The Women's Health Study

The Women's Health Study (WHS) was a randomised, placebo-controlled trial designed to test the risks and benefits of low-dose aspirin (100 mg every other day) and vitamin E (600 IU every other day) in the primary prevention of cardiovascular diseases (CVD) and cancer among apparently healthy women. The design and methods of the WHS have been described in detail previously.[20 21] Briefly, a total of 39,876 US female health care professionals aged 45

years or older at study entry (1992-1995) without a history of CVD, cancer, or other major illnesses were randomly assigned to receive active aspirin, active vitamin E, both active agents, or both placebos. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. After the trial's termination in March 2004, the women who were still alive and willing to participate entered an observational follow-up. The return date of the 108-month questionnaire containing questions on RLS was defined as new baseline for this analysis. Of the 33,092 women in active follow-up at 108 months, we excluded 1,722 women with missing RLS information, leaving a total of 31,370 women for this analysis.

The Physicians' Health Study

The Physicians' Health Study I (PHS I) was a randomised, double blind, placebo-controlled trial to test the benefits and risks of low dose aspirin (325mg) and beta-carotene (50 mg) in the primary prevention of CVD and cancer among 22,071 apparently healthy male physicians aged 40 to 84 years at baseline in 1982.[22] Baseline information was self-reported and collected by means of a mailed questionnaire that asked about many cardiovascular risk factors and life style variables. Every six months in the first year and yearly thereafter, follow-up questionnaires were sent to the participants. Since the trials' termination in 1995, the men are continued to be followed either on an observational basis or as part of the Physician's Health Study II (PHS II).

Using methods successfully developed in the PHS I, the PHS II was launched in 1997.[23] The PHS II is an ongoing randomised, double-blind, placebo-controlled trial to test the effects of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (50 mg), and a daily multivitamin (Centrum Silver) in the prevention of total and prostate cancer, CVD, and age-related eye

disease among 14,641 US male physicians aged 55 years and older, including a total of 7,641 PHS I participants who were willing and eligible to enter the PHS II. Baseline information was self-reported and follow-up information was collected annually by mailed questionnaires. For the purpose of this analysis, we pooled data from the PHS I and PHS II, yielding a total of 29,071 participants. The return date of the questionnaire containing the RLS questions (216-month questionnaire for PHS I participants and 12-month questionnaire for PHS II participants) was defined as new baseline for this analysis. At this time point, 24,505 men were still in active follow-up. We excluded 1,579 men with missing information for all three RLS questions, leaving a total of 22,926 men at our defined baseline for our analysis.

RLS assessment

RLS is diagnosed according to the presence of specific symptoms. Participants in each study were asked to answer the following questions which were based on the minimal criteria published by the International Restless Legs Syndrome Study Group:[12] "Do you have unpleasant leg sensations (like crawling, paraesthesias, or pain) combined with a motor restlessness and an urge to move?", "Do these symptoms occur only at rest and does moving improve them?", "Are these symptoms worse in the evening or at night compared with the morning?" The three answer categories included "Yes", "No" or "Don't know". Participants were only classified as RLS positive if they answered all symptom questions with "Yes".
In DHS and SHIP RLS assessment was conducted in face-to-face interviews by trained and certified interviewers, while in WHS and PHS RLS information was retrieved by mailed standardised questionnaires. The same questions that were used to identify RLS symptoms in each study had been previously validated[24] and had already been used in prior reports[2 5 7 18 25]. Comparing the questionnaire-based classification of RLS with a physician's diagnosis as a gold standard showed good agreement (unweighted kappa=0.67, p<0.001) in the German MEMO (Memory and Morbidity in Augsburg Elderly) study.[24] In DHS there was a further

question related to the number of years elapsed since the onset of RLS symptoms. The frequency of RLS symptoms was also assessed in DHS with the following possible answer categories: 'daily', '3-6 times a week', '1-2 times a week', '1-3 times a month', and 'less than once a month'. The first two categories and the remaining three categories were subsequently collapsed for the analysis.

Ascertainment of mortality

Death from all causes was defined as our main outcome for the analyses. In both German cohorts, the vital status of participants, i.e. alive or deceased and the date of death, if applicable, was retrieved from the municipal registries at the follow-up. In both US cohorts, deaths of participants were identified by reports from family members or next of kin, or postal authorities, and searches of the National Death Index. Information on date and cause of death were confirmed through review of death certificates and medical records by an endpoints committee of physicians.

Socio-demographic data, lifestyle factors, and co-morbidities

Age, gender, and lifestyle factors, i.e. health related behaviours, were assessed during the interview in the German studies and with the mailed questionnaire in the WHS and PHS. In the DHS and SHIP, co-morbidities including diabetes mellitus, hypertension, cancer, myocardial infarction, and stroke were assessed as self-reports with specific questions asking for a physician-made diagnosis of the respective condition. In the WHS and PHS, these co-morbidities were also assessed by questionnaires, and the presence of myocardial infarction, stroke, and cancer was confirmed by medical record review. Body weight and height of the participants in the German studies were measured according to standard protocols, and in the US studies both items were self-reported. There was one question referring to the presence of leg cramps in SHIP.

Statistical analysis

Data of the four cohort studies were analysed separately using the following identical analysis approach. For each cohort, we calculated mean values for continuous and frequencies for categorical variables of baseline characteristics. Person-time was calculated from the return date of the questionnaire containing the RLS questions or date of interview, respectively, to the date of death, last documented contact, or end of study, whatever occurred first. Cox proportional hazards models were used to evaluate the association between RLS status and mortality. Age- and multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. The multivariable models were adjusted for the following potential confounding factors: age, gender (DHS and SHIP), body mass index (BMI), smoking, exercise, history of diabetes, history of hypertension, myocardial infarction, stroke, and cancer. To provide comparability of results across studies, we additionally performed stratified analyses according to gender in the DHS and SHIP.

The proportional hazards assumption was tested by including an interaction term for RLS status and logarithm of follow-up time for mortality in age-adjusted models. We found no statistically significant violation.

In all multivariable models participants with missing covariate information were excluded. The models were reanalysed incorporating a missing value indicator in the outcome models for covariates if the number of participants with missing information was greater or equal to 100. We assigned participants with missing values to the covariate reference category if the number of missing information was less than 100. These analyses provided nearly identical results (data not shown).

All analyses were performed with Stata 11.0 (StataCorp, Tx, USA) in the DHS and SHIP. For all WHS and PHS analyses, we used SAS 9.1.3 (SAS Institute Inc, Cary, NC). All p-values were 2-tailed and $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Table 1 summarises the baseline characteristics of participants in the four different cohorts. The mean age in the cohorts ranged from 50.3 years in SHIP to 67.8 years in the PHS. The prevalence of RLS at baseline varied between 7.4% in DHS and 11.9% in WHS. Baseline RLS prevalence was significantly higher among women than in men in both German cohorts (9.3% vs 5.2%, p=0.005 in DHS and 12.8% vs 7.3%, p<0.001 in SHIP).

RLS and mortality

The median follow-up time, the number of deaths, and the mortality rate for each study are presented in Table 2. The highest mortality rate was observed in the PHS (12.3 per 1,000 person-years) and the lowest mortality rate was measured in the WHS (2.8 per 1,000 person-years).

Tables 3 and 4 summarise the age- and multivariable-adjusted HRs (95%CI) for the association between RLS and mortality. RLS was not significantly associated with mortality in any of the four studies. Multivariable-adjusted HRs (95%CI) ranged from 0.21 (0.03-1.53) in the DHS to 1.07 (0.93-1.23) in the PHS. After gender stratification the adjusted HRs were similar among women and men in SHIP. Furthermore, when the interaction term between RLS and gender was added to the fully adjusted model, it was not significant (p=0.71). In DHS the estimation of the HR among women was not possible, because no women with RLS died during the follow-up. The presence of leg cramps is a potential RLS mimic, therefore a sensitivity analysis was conducted for SHIP excluding participants reporting leg cramps (n=380), which resulted in a multivariable-adjusted HR (95%CI) of 0.85 (0.61-1.19). When the frequency of RLS symptoms was entered into the model in DHS, the HR associated with the RLS frequency of no more than twice a week vs. no RLS symptoms was 0.39 (95%CI:

0.09-1.63); the HR for RLS frequency of at least three times a week vs. no RLS was 1.28 (95%CI 0.45-3.63). Finally, when the number of years elapsed since the onset of RLS symptoms was added to the multivariable-adjusted model, it was not associated with increased mortality hazard in DHS: HR=1.00 (95%CI 0.90-1.12).

DISCUSSION

In four independently conducted large prospective cohort studies from Germany and the US, RLS was not associated with all-cause mortality. The risk of death did not differ according to gender. In contrast to the few previous studies,[16 17] we applied standardised questions of the minimal diagnostic criteria to assess RLS and we also accounted for numerous explanatory variables.

Comparisons with other studies

Some clinic-based studies found a relationship between RLS and mortality among subjects with end-stage renal disease, either in dialysed[13 14] or transplanted patients.[15] There was no clear explanation for the findings, although the presence of RLS could be related to indicators of poorer health status, like higher level of uraemia, disease duration, and co-morbidity. However, those studies were conducted in a very specific patient group with very high morbidity and mortality, and thus the results can be hardly generalised to relatively healthier populations like ours.

In prior reports of community-dwelling elderly subjects, RLS symptoms indicated higher mortality only among women.[16] Mallon et al. found that RLS combined with daytime sleepiness was associated with increased mortality risk among women in a middle-aged population, although RLS without sleepiness was not significantly related to mortality.[17] There was no clear explanation for these findings, though it has been speculated that disturbed

sleep, which frequently accompanies severe RLS, might contribute to the decreased lifespan of subjects with RLS. We had no data about daytime sleepiness or other sleep variables available to determine whether these factors modify the relationship between RLS and mortality.

Differences in sampling and population characteristics might have contributed to the discrepant findings between the previous and the present studies. More importantly, at the time of the baseline assessment of the two earlier studies, standard criteria for RLS did not exist. The urge to move the legs and relief of symptoms due to leg movement, two core symptoms of RLS, were not assessed. It should be also noted that the follow-up time of the study of Mallon et al.[17] was 20 years, much longer than any of our studies.

In contrast to these previous results, recently published analyses from the WHS and PHS cohorts do not suggest that RLS is associated with incident cardiovascular disease events including CVD mortality, either in women or men.[25]

Subjective and objective sleep disturbances are very common among subjects with RLS.[26 27] Both short sleep duration and frequent insomnia symptoms predict mortality according to population- and community-based studies.[28 29] Thus we cannot rule out that patients experiencing RLS combined with chronic severe sleep deprivation and/or insomnia may have a higher mortality risk over time. Future prospective studies with assessment of RLS severity as well as various sleep-related factors should further investigate this hypothesis.

Strengths and limitations

One of the strengths of the present work is the analysis of four independently conducted cohort studies. The lack of association observed across the four different studies indicates the

robustness of our finding. Furthermore, RLS cases were classified according to the minimal criteria for RLS. There were differences in the sampling procedures, sample characteristics, and baseline data collection across the studies. However, the fact that the results of a null association were the same despite these differences underlines the robustness of the lack of association between RLS and mortality. Finally, we were able to take several important potential confounders into account, including behavioural risk factors and co-morbid conditions.

Several limitations have to be considered when interpreting our results. An important limitation is that, as in all large epidemiologic studies, case classification was based on a set of self-administered diagnostic questions instead of a complete clinical interview and examination. ~~Therefore misclassification of RLS cases is possible.~~ However, the set of RLS questions used in our cohorts has been successfully used and validated in previous studies and the observed prevalences in our cohorts are similar to those reported in other population-based studies.[30] We also note that conducting clinical interviews in large studies like these would have been extremely difficult. Still, the use of screening questions could have led to misclassification, and RLS mimics could have been falsely identified as RLS cases. We adjusted for the presence of diabetes, therefore diabetic neuropathy, a common potential RLS mimic, was not likely to influence the findings. In SHIP, excluding participants with leg cramps, another frequent RLS mimic, did not alter the results substantially. Nevertheless, there might be other potential mimics of RLS symptoms that could have an effect on the association between RLS and mortality. ~~Furthermore, d~~Due to the low number of outcome events in DHS, the estimates for the association of RLS with mortality were less precise than in the other three cohorts. The mean age was highest in PHS, where the follow-up time was also quite long, and this study showed the highest mortality hazard associated with RLS, even though it was still not significant. It is possible that a longer follow-up time might have

revealed a more subtle association with RLS, especially in an elderly population. ~~No~~ ~~i~~Information on frequency~~, severity~~ and duration of RLS symptoms was available in only one of the cohorts. Despite ~~information on a~~adjustments for a large number of potential confounders, residual and unmeasureable confounding remains possible as our study is observational. However, we are not aware of any confounding factor that, if included in our final models, would result in increased risk of all-cause mortality among patients with RLS. Participants in all four cohorts were predominately white, which may limit the generalisability to other populations.

Clinical Implications

Results of these four independent large cohort studies do not suggest that RLS is a risk factor for mortality. However, previous studies indicate that RLS is associated with a variety of comorbidities, such as diabetes, higher body mass index, and cardiovascular diseases, which are established risk factors for mortality. Patients with RLS should be screened for RLS associated comorbidities and treated if necessary.

Unanswered questions and future research

RLS is a highly prevalent disease among the elderly, but the mechanisms causing the disease and its relationship with a diverse set of comorbidities remain poorly understood. According to DHS, ~~Furthermore, the role of~~ the frequency~~, severity~~ and duration of RLS symptoms were not related to ~~on~~ mortality, even though the effect size increased with symptom frequency. Since this was the smallest study with the youngest population, the potential role of RLS severity ~~and disease risk remains unclear.~~ needs further clarification. In addition, sleep deprivation and insomnia accompanying RLS may also influence mortality and comorbidity. Further studies are warranted to establish risk factors for incident RLS to be able to develop sufficient prevention strategies and to understand the complex relationship between RLS and

its comorbid conditions. Finally, RLS as a potential mortality hazard should be further investigated with longer follow-up time and in high-risk populations, for example among elderly subjects.

In summary, results of four independent large, prospective cohort studies show that RLS is not associated with increased risk of all-cause mortality. Given the high prevalence of RLS in western populations, this is a positive result for all living with RLS.

Table 1: Baseline characteristics of participants

	Dortmund Health Study	Study of Health in Pomerania	Physicians' Health Study	Women's Health Study
Number of participants	1,299	4,291	22,926	31,370
Age, years (mean+/-SD)	52.2+/-13.8	50.3+/-16.4	67.8+/-9.0	63.6+/-6.9
Women, n (%)	688 (53.0)	2,185 (50.9)	0 (0)	31,370 (100)
RLS, n (%)	96 (7.4)	433 (10.1)	1,717 (7.5)	3,745 (11.9)
BMI, kg/m^2 (mean+/-SD)	27.5+/-5.0	27.3+/-4.8	25.9+/-3.7	27.1+/-5.5
Diabetes, diagnosed, n (%)	98 (7.5)	342 (8.0)	1,983 (8.7)	2,342 (7.5)
Hypertension, diagnosed, n (%)	461 (35.7)	1,729 (40.8)	12,079 (52.7)	15,223 (48.5)
Cancer, diagnosed, n (%)	59 (4.6)	53 (1.2)	2,306 (10.1)	1,818 (5.8)
Myocardial infarction, diagnosed, n (%)	49 (3.8)	146 (3.4)	797 (3.5)	248 (0.8)
Stroke, diagnosed, n (%)	29 (2.2)	98 (2.3)	490 (2.1)	251 (0.8)

SD: standard deviation; BMI: body mass index.

Table 2: Follow-up status of participants

	Dortmund Health Study	Study of Health in Pomerania	Physicians' Health Study	Women's Health Study
Number of participants	1,299	4,291	22,926	31,370
Median follow-up time [IQR]	6.9 [0.3]	11.1 [1.5]	8.7 [0.6]	6.5 [0.8]
Number of deaths (%)				
Total	55 (4.2)	540 (12.6)	2,287 (10.0)	542 (1.7)
Among participants with RLS	1 (1.0)	70 (16.2)	215 (12.5)	63 (1.7)
Among participants without RLS	54 (4.5)	470 (12.2)	2072 (9.8)	479 (1.7)
Mortality rate per 1,000 person per year (95% CI)	6.2 (4.7-8.1)	11.8 (10.9-12.9)	12.3 (11.8-12.8)	2.8 (2.5-3.0)

IQR: interquartile range; CI: confidence interval.

Table 3: Age-, gender- and multivariable-adjusted hazard ratios and 95% confidence intervals for mortality according to RLS status in the German cohorts

	Dortmund Health Study	Study of Health in Pomerania
	HR (95% CI)	HR (95% CI)
Age- and gender-adjusted models	n=1,299	n=4,291
Total	0.21 (0.03-1.49)	1.04 (0.81-1.34)
Male	0.42 (0.06-3.09)	1.00 (0.71-1.39)
Female	n.a.	1.13 (0.77-1.67)
Multivariable-adjusted* models	n=1,283	n=4,264
Total	0.21 (0.03-1.53)	0.99 (0.76-1.29)
Male	0.52 (0.07-3.95)	0.98 (0.68-1.39)
Female	n.a.	1.00 (0.66-1.50)

*Multivariable models were adjusted for age, gender, BMI, smoking, physical activity and histories of diabetes, hypertension, myocardial infarction, stroke and cancer.

HR: hazard ratio, CI: confidence interval, n.a.: not available.

Table 4: Age- and multivariable- adjusted hazard ratios and 95% confidence intervals for mortality according to RLS status in the US cohorts

	Women's Health Study	Physicians' Health Study
	HR (95% CI)	HR (95% CI)
Age-adjusted models	n=31,370	n=22,926
	0.98 (0.75-1.27)	1.10 (0.96-1.27)
Multivariable-adjusted* models	n=30,475	n=22,816
	0.93 (0.71-1.21)	1.07 (0.93-1.23)

*Multivariable models were adjusted for age, BMI, smoking, physical activity and histories of diabetes, hypertension, myocardial infarction, stroke and cancer.

HR: hazard ratio, CI: confidence interval.

Competing interests

None

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Patient consent

Obtained

Ethical approval

All participants in the four cohorts gave informed written consent and the study protocol was approved by the local ethics committees of the Medical Faculty at the University of Münster,

(for DHS), the University of Greifswald (for SHIP) and the institutional review board of Brigham and Women's Hospital, Boston (for WHS and PHS; Protocol #: 2008-P-000613/3).

Data sharing

No additional data available

Author's footnote

All authors had full access to all the data in the study, can take responsibility for the integrity of the data and accuracy of the data analysis, and approved the final version of the manuscript.

Contributor statement

AS developed the evaluation plan, made statistical analyses, interpretation of results, literature search, and drafted the manuscript. ACW designed the study, developed the evaluation plan, carried out statistical analyses, interpreted the results, performed literature search, and drafted the manuscript. HV contributed to data collection, interpretation of results, and critically revised the manuscript. WH contributed to data collection, interpretation of results, and critically revised the manuscript. MS designed the study, interpreted the results, and critically revised the manuscript. JB analysed and interpreted data, obtained funding, and critically revised the manuscript. JMG analysed and interpreted data, obtained funding, and critically revised the manuscript. TK designed the study, developed the evaluation plan, interpreted the results and contributed to drafting the manuscript. KB designed the study, developed the evaluation plan, made the statistical analysis, interpreted the results, and drafted the manuscript.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org