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The longitudinal association of physical activity with symptoms of insomnia, sleep duration and daytime sleepiness - A European population-based study

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The longitudinal association of physical activity with symptoms of insomnia, sleep duration and daytime sleepiness - A European population-based study

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Abstract:

Objectives: To explore the relationship of physical activity during the past 10 years with insomnia, daytime sleepiness and estimated short or long sleep duration among middle aged adults.

Design: Population-based, multi-centre cohort study.

Setting: 21 centres in 9 European countries.

Methods: Included were 4339 participants in the third follow-up of the European Community Respiratory Health Survey (ECRHS III) who answered questions on physical activity at baseline (ECRHS II) and questions on physical activity, insomnia symptoms, sleep duration and daytime sleepiness at follow up (ECRHS III). Physical activity was assessed both in ECRHS III and 10 years before. Participants reported that they exercised with a frequency of at least two or more times a week for one hour a week or more were classified as being physically active. Change in activity status was categorised into four groups: persistently non-active, became inactive, became active and persistently active.

Main outcome measures: Insomnia, sleep time and daytime sleepiness in relation to physical activity.

Results: Altogether, 37% of participants were persistently non-active, 25% were persistently active, 20% became inactive and 18% became active from baseline to follow up. Participants that were persistently active were less likely to report difficulties initiating sleep (OR 0.60 (95% CI 0.45-0.78)), short sleep duration of ≤ 6 h/night (OR 0.71 (95% CI 0.59-0.85) and long sleep of (≥ 9 h/night (OR 0.53 (95% CI 0.33-0.84)) than persistently non active subjects after adjusting for age, sex, BMI, smoking history, and study centre. Daytime sleepiness and difficulties maintaining sleep were not related to physical activity.

Conclusion: Physically active people have a lower risk of insomnia symptoms and extreme sleep duration, both long and short.

Strengths and limitations of this study:

- The longitudinal study design, with the exposure (physical activity) measured 10 years before the outcome (sleep outcomes) allows testing the directionality of the association.
- Data was collected using standardized and validated procedures and instruments, increasing internal validity.
- Data was obtained from 9 European countries, increasing external validity of our findings.
- One limitation of our study is that sleep variables are only available at the follow-up, precluding testing their role on baseline physical activity.
- Insomnia symptoms, sleep length and daytime sleepiness were obtained from questionnaire and no doctor diagnosis or objective assessments were available.

Introduction

Disturbed sleep is common in the general population and impacts health and quality of life.¹⁻³ Chronic sleep disturbances are associated with cardiovascular disease, metabolic dysfunction, psychiatric disorders, and increased mortality.⁴⁻⁶

Regular exercise is associated with better health and several studies suggest that physical activity (PA) is beneficial on sleep and may improve symptoms of chronic insomnia.⁷⁻¹⁰ It is, however, unclear how large these benefits are and which factors moderate these benefits.¹¹ The positive association between PA and sleep might be subject to multiple moderating factors such as gender, age, BMI, fitness level, general health and the characteristics of the exercise. Therefore, sleep and PA probably influence each other through complex, reciprocal interactions including multiple physiological and psychological pathways.⁷

There is evidence that more PA is associated with less daytime sleepiness.¹²⁻¹⁷ Cross-sectional studies have shown that low PA is associated with increased likelihood of excessive daytime sleepiness (EDS)¹⁴⁻¹⁶ and that subjects participating in exercise are less likely to have EDS.^{12 17} In the elderly, increasing PA by doing home exercises has been shown to improve EDS and reduce the prevalence of insomnia symptoms¹³ and another study showed that increasing PA protected women from future insomnia.¹⁸ Other studies have contradictory findings. In an epidemiological study of 4.405 Koreans, daytime sleepiness was more common among those in the top quartile of PA compared to those in the lowest quartile group.¹⁹ Among patients with obstructive sleep apnoea increased PA was associated with lower disease severity and 28% decrease in EDS.²⁰ The daily association between PA and sleep duration was described in 2021 based on a systemic review and meta-analysis on 33 peer-reviewed papers showing that the night following an increased PA there was a lower total sleep time.²¹

There is a lack of epidemiological data from long-term follow-up of large cohorts studying the association of PA to sleep length, daytime sleepiness, and insomnia symptoms. Previous research on physical activity and sleep-related outcomes has several important limitations. Most studies are cross-sectional or with a short follow-up, preventing to elucidate if increased physical activity improves sleeping outcomes or reduced physical activity is a consequence of sleep problems. Finally, no studies have tested at the same time the effect of physical activity on sleep length, daytime sleepiness, and insomnia symptoms. Therefore, the aim of the

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3 present study was to assess the interrelationship between physical activity based on
4 frequency, duration and intensity and symptoms of insomnia, self-reported sleep
5 duration and daytime sleepiness among middle-aged subjects from 21 centres in 9
6 countries at two time periods 10 years apart, giving important longitudinal follow up
7 data.
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13 **Material and methods**

14 *Patient and Public Involvement:*

15 We studied participants in the second and third follow-up of the European Community
16 Respiratory Health Survey (ECRHS II and III, www.ecrsh.org), an international,
17 population-based, multicentre cohort study of asthma and allergy, which was first
18 performed in 1990. Detailed descriptions of the methods for ECRHS I and ECRHS II
19 have been published elsewhere.^{22 23} Briefly, participating centres first randomly
20 selected samples of 20 to 44-year-old subjects. Participants completed a short postal
21 questionnaire about asthma and asthma-like symptoms and from those who
22 responded, a random sample was selected to undergo a more detailed clinical
23 examination. In ECRHS II, subjects who had participated in the clinical phase of
24 ECRHS I (performed between 1991 – 1994) were invited to participate in follow-up.
25 The clinical phase of ECRHS II was performed between 1998 to 2002. ECRHS III is
26 the second follow-up and was performed from February 2011 to January 2014.²²⁻²⁴
27 The present study is based on data from ECRHS II and III (see figure 1 for flowchart).
28 Ethical approval for the study from local research ethics committees and written
29 consent from participants were obtained.
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44 *Health, habits, and measurements*

45 Subjects answered the core ECRHS questionnaires which included questions
46 on lifestyle, respiratory symptoms, smoking history, and general health. Current
47 smokers were defined as those who smoked tobacco regularly during the last month.
48 Former smokers were defined as smokers who denied having smoked regularly for a
49 month prior to the examination. Those who reported no regular smoking at or prior to
50 the examination were defined as never smokers. Height and weight were measured,
51 and body mass index (BMI) was calculated.²⁴
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Assessment of physical activity

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3 Physical activity was assessed in ECRHS II and III using questionnaire.²²

4 Participants were asked how often and for how many hours per week they usually
5 exercised so that they got out of breath or became sweaty. Participants who
6 exercised two or more times a week during at least 1 hour a week were classified
7 physically active. Change in activity status from baseline to follow up was categorised
8 into four PA groups: persistently non-active (non-active at both baseline and follow
9 up), became inactive (active at baseline and non-active at follow up), became active
10 (non-active at baseline and active at follow up) and persistently active (active at both
11 baseline and follow up).
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20 *Sleep questionnaires and measurements*

21 Sleep-related symptoms were assessed by using the Basic Nordic Sleep
22 Questionnaire²⁵, where participants were asked about frequency of insomnia
23 symptoms. Answers were on a scale of 1 – 5: (1) never or very seldom, (2) less than
24 once a week, (3) once to twice a week, (4) three to five times a week, (5) every day
25 or almost every day of the week. Insomnia symptoms were defined using answers to
26 three questions from the Basic Nordic Sleep Questionnaire “I have difficulties falling
27 asleep at night” (difficulties initiating sleep), “I wake up often during the night”
28 (difficulties maintaining sleep) and “I wake up early in the morning and can’t fall back
29 asleep” (early morning awakenings). Those who reported those symptoms of
30 insomnia ≥ 3 times a week (scores 4 and 5) were considered to have the
31 corresponding insomnia subtype. Daytime sleepiness was evaluated using the
32 Epworth Sleepiness Scale, a brief questionnaire that measures daytime sleepiness
33 based on the likelihood of falling asleep in eight different situations.²⁶ Participants
34 with Epworth sleepiness scale score > 10 were considered to have EDS. Participants
35 answered the question: how much sleep do you estimate that you get on average
36 each night? They were classified as short sleepers (≤ 6 hours/night), normal sleepers
37 (6–9 hours/night) and long sleepers (≥ 9 hours/night) according to their answers.
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53 *Statistical analysis*

54 Data are presented as number and percentage or mean \pm SD, depending on
55 distribution. For bivariate analysis, the χ^2 test and one-way analysis of variance were
56 used for nominal and continuous variables. Logistic regression was used for
57 multivariable analyses to estimate the association between physical activity and
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sleep related outcomes after adjusting for potential confounders such as sex, age, BMI and smoking status. STATA V.16 was used for all statistical analyses.

Results

Participants and level of physical activity

From a total of 5.850 participants in ECRHS II, we excluded those with missing data and included a total of 4.339 participants (48% men), see Figure 1. From baseline to 10 years later, 36.9% of participants were persistently non-active, 17.9% became physically active at follow-up, 20.3% of participants became inactive 24.9% were persistently active (Table 1).

Table 1. Characteristics and general health of the participants by the level of physical activity

| | Persistently non-active | Became inactive | Became active | Persistently active | p-value |
|------------------------------------|-------------------------|-----------------|---------------|---------------------|------------------|
| General characteristics | | | | | |
| N, % | 1601 (36.9) | 881 (20.3) | 775 (17.9) | 1082 (24.9) | |
| Men, % | 44.3 | 49.0 | 46.8 | 53.7 | <0.001 |
| Age, years | 55.0 ± 7.2 | 54.5 ± 7.1 | 53.4 ± 7.2 | 53.7 ± 7.2 | <0.001 |
| Body mass index, kg/m ² | 27.6 ± 5.2 | 27.1 ± 4.9 | 27.1 ± 4.8 | 27.0 ± 4.4 | 0.007 |
| Currently working, % | 82.7 | 85.8 | 88.9 | 90.4 | <0.001 |
| Smoking history | | | | | |
| Never, % | 42.4 | 43.4 | 44.3 | 47.6 | <0.001 |
| Former, % | 34.4 | 39.8 | 37.5 | 40.0 | |
| Current, % | 23.2 | 16.9 | 18.2 | 12.4 | |

There were geographical differences in the level of physical activity between the ECRHS countries (Figure 2). Participants in Norway were most likely to be persistently active, while participants in Spain, followed by Estonia, were most likely to be persistently non-active (Figure 2).

General characteristics and health

Persistently active participants were more often men, they were younger, and they had slightly lower BMI (Table 1). They were also less likely to be current smokers and more likely to be currently working (Table 1).

Insomnia symptoms

In unadjusted analysis, there was a significant difference in reporting difficulties initiating sleep, early morning awakenings and any insomnia symptom where those persistently active were least likely to report these symptoms. Also, persistently active subjects were the least likely to report two and three insomnia symptoms (Table 2).

Table 2. Insomnia symptoms, sleep duration and daytime sleepiness by level of physical activity.

| | Persistently non-active (n=1601) | Became inactive (n=881) | Became active (n=775) | Persistently Active (n=1082) | p-value |
|--|--|-----------------------------------|---------------------------------|--|------------------|
| Insomnia symptoms | | | | | |
| Difficulties initiating sleep (%) | 15.4 | 14.0 | 11.7 | 8.2 | <0.001 |
| Difficulties maintaining sleep (%) | 31.9 | 32.1 | 33.0 | 28.5 | 0.128 |
| Early morning awakenings (%) | 18.2 | 18.3 | 15.0 | 13.2 | 0.002 |
| Any insomnia symptom (%) | 41.0 | 41.5 | 39.5 | 34.9 | 0.006 |
| Numbers of insomnia symptoms | | | | | |
| None (%) | 58.4 | 58.2 | 61.0 | 64.9 | 0.001 |
| One (%) | 23.2 | 25.2 | 24.0 | 23.8 | |
| Two (%) | 11.9 | 10.6 | 10.0 | 7.8 | |
| Three (%) | 6.6 | 6.1 | 5.1 | 3.6 | |
| Sleep duration | | | | | |
| Sleep time (hours) | 6.8 ± 1.1 | 6.8 ± 1.0 | 6.9 ± 1.0 | 6.9 ± 0.9 | 0.234 |
| Sleep time, % | | | | | |
| Short sleepers (≤ 6 hours) | 35.9 | 31.9 | 20.7 | 26.9 | <0.001 |
| Normal sleepers (6 – 9 hours) | 59.2 | 64.6 | 66.9 | 70.9 | |
| Long sleepers (≥ 9 hours) | 4.9 | 3.5 | 3.4 | 2.2 | |
| Daytime sleepiness | | | | | |
| Epworth sleepiness scale score | 6.8 ± 4.1 | 7.2 ± 4.1 | 6.9 ± 4.1 | 6.9 ± 3.8 | 0.106 |
| Epworth sleepiness scale score >10 (%) | 17.2 | 19.4 | 17.7 | 15.6 | 0.176 |
| Data are presented as mean ± standard deviation or % where indicated. Significant differences are in bold (p<0.05). *p-value from Pearson's chi-square test (numerical variables) and one-way analysis of variance (continuous variables). | | | | | |

After adjusting for age, sex, BMI, smoking history and study centre, this negative association remained for difficulties initiating sleep (OR 0.58 (0.42-0.77)), any insomnia symptom (0.78 (0.65-0.94) and reporting two (OR 0.60 (0.43-0.82) and

three (OR 0.63 (0.41-0.98) insomnia symptoms (Table 3). Additionally, in adjusted analysis, persistently active subjects were significantly less likely to report difficulties initiating sleep (OR 0.80 (0.66-0.97) (Table 3).

Table 3. Independent association between the level of physical activity and medical disorders, insomnia symptoms, daytime sleepiness and sleep duration expressed as adjusted* odds ratios (95% CI) with the persistently non-active group as reference.

| | Became inactive (n=881) | Became active (n=775) | Persistently active (n=1082) |
|---|----------------------------|--------------------------|------------------------------------|
| Insomnia symptoms | | | |
| Difficulties initiating sleep | 0.97 (0.75-1.25) | 0.82 (0.62-1.08) | 0.58 (0.42-0.77) |
| Difficulties maintaining sleep | 0.96 (0.80-1.17) | 1.04 (0.85-1.27) | 0.80 (0.66-0.97) |
| Early morning awakenings | 1.09 (0.87-1.38) | 0.86 (0.63-1.03) | 0.80 (0.63-1.03) |
| Any insomnia symptom | 1.02 (0.85-1.22) | 0.95 (0.78-1.14) | 0.78 (0.65-0.94) |
| Numbers of insomnia symptoms | | | |
| One | 1.07 (0.86-1.32) | 0.99 (0.79-1.24) | 0.91 (0.74-1.12) |
| Two | 0.89 (0.66-1.20) | 0.86 (0.63-1.17) | 0.60 (0.43-0.82) |
| Three | 1.09 (0.74-1.59) | 0.94 (0.62-1.42) | 0.63 (0.41-0.98) |
| Daytime sleepiness | | | |
| Epworth sleepiness scale score >10 | 1.17 (0.94-1.47) | 1.00 (0.78-1.27) | 0.87 (0.69-1.10) |
| Sleep duration | | | |
| Short sleepers (≤ 6 hours) | 0.89 (0.73-1.07) | 0.85 (0.69-1.03) | 0.71 (0.58-0.85) |
| Normal sleepers (6-9 hours) | 1.18 (0.98-1.42) | 1.21 (1.00-1.47) | 1.55 (1.29-1.87) |
| Long sleepers (≥ 9 hours) | 0.74 (0.47-1.17) | 0.84 (0.53-1.33) | 0.48 (0.28-0.80) |
| *Adjusted for age, sex, BMI, smoking history and center. Significant differences are in bold. | | | |

Sleep duration and daytime sleepiness

In unadjusted analysis, there was a significant difference in short and long sleep duration between levels of activity. Those who were persistently active were most likely to be normal sleepers and the persistently non-active were least likely (70.9% vs. 59.2% respectively) (Table 2). After adjusting for age, sex, BMI, smoking history and study centre, these results remained significant for persistently active subjects. They were significantly more likely to be normal sleepers (OR 1.55 (1.29-1.87)) and significantly less likely to be short sleepers (OR 0.71 (0.58-0.85)) or long sleepers (0.48 (0.28-0.80)) (Table 3). Additionally, those who became active were more likely to be normal sleepers than those persistently non-active (OR 1.21 (1.00-1.47) (Table 3).

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3 However, there was not a significant association between the mean Epworth
4 sleepiness scale score or percentage with Epworth sleepiness scale score >10 and
5 level of physical activity (Tables 2 and 3).
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Discussion

The main results of this study were that participants who reported being physically active at the start and end of a 10 year follow up period were less likely to report insomnia symptoms at the follow-up. We also found that subjects that are persistently active are more likely to sleep the recommended 6-9 hours. This association remained statistically significant after adjusting for sex, age, smoking history, and BMI.

Our results are in line with previous studies that have shown a beneficial effect of physical activity on symptoms of insomnia (9, 10), but the current study additionally shows the importance of consistency in exercise over time because the association was lost in initially active subjects who became inactive. A recent meta-analysis examining the effects of acute and regular exercise on a range of sleep variables showed that acute exercise (less than one week of exercise) has a small beneficial effect on many objective measures of sleep such as total sleep time, symptoms of insomnia and sleep quality.⁷ Furthermore, this meta-analysis found greater benefits for regular exercise on both subjective and objective sleep parameters over time. Regular exercise had small beneficial effects on total sleep time and sleep efficiency, small-to-medium beneficial effects on sleep onset latency, and moderate beneficial effects on sleep quality.⁷

There are two recent systematic reviews and meta-analysis on the effects of PA on sleep⁷ and insomnia⁹ both substantially reviewing the same randomized controlled studies. Banno *et al.* included nine studies with a total of 557 participants.⁷ The majority of participants exercised 3 times or less per week and follow-up was 4 months or shorter in all studies except one. Their conclusion was that exercise could improve sleep, but higher quality research was needed.⁷ Five studies on insomnia and additionally six on insomnia symptoms showed shorter sleep latency and higher sleep efficacy, but the authors also acknowledged the small size of the literature and severe methodological limitations often based on selection bias.⁹ Most previous studies are also cross-sectional which can also be considered a limitation.

This study has a long follow up period (10 years) and indicates strongly that consistency in physically activity might be an important factor to optimize sleep duration and reduce symptoms of insomnia. Most other studies have had a much

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3 shorter follow up period⁷ which makes it more difficult to assess consistency in
4 activity over time.

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6 Our results indicate that those who are consistent in physical activity are also less
7 likely to be both short (<6h) and long sleepers (>9h). Those who are physically active
8 in general are also more likely to engage in a healthier lifestyle²⁷ which also can have
9 an effect on sleep. Lifestyle factors such as healthy diet and physical activity are
10 probably a part of a phenotype that characterizes those individuals who are generally
11 engaged in a healthy lifestyle. A recent review highlighted the importance of focusing
12 on the combination of sleep, diet and exercise when exploring healthy longevity.²⁸
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20 The three groups reporting low physical activity in either ECRHS survey or at both
21 time points are all reporting very similar prevalence of insomnia symptoms, extreme
22 sleep length and daytime sleepiness. This is somewhat surprising, especially that
23 those who are active at the follow-up but were not at baseline do have very similar
24 symptom profile as those who were inactive at both surveys. Our study found a
25 consistency in a behaviour like physical activity for more than a decade is strongly
26 related to less insomnia and more “normal” sleep length. The important information
27 concerning “the healthy phenotype” would be missed if the physical activity data were
28 available only at baseline or at follow-up but not at both time points. Under these
29 circumstances physical activity data would only have shown very limited association
30 with sleep.
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39 In a recent review based on 22 randomized controlled trials on the effects of regular
40 exercise (lasting at least 2 months on a regular basis) on self-reported sleep quality,
41 insomnia and daytime sleepiness, it was found that regular physical activity improved
42 subjective sleep quality, insomnia severity, and daytime sleepiness as measured only
43 with the Epworth sleepiness scale.²⁹ These results regarding insomnia symptoms are
44 in line with our study but the results on daytime sleepiness differ from our results. The
45 reason for this discrepancy could be due to different study populations since there
46 were only two studies in this review that measured daytime sleepiness using the
47 Epworth sleepiness scale, one study assessed this among the elderly, 60 years and
48 older¹³ and the other among overweight and obese men.³⁰ Another recent review of
49 32 randomized control trials on the effects of exercise on improving sleep
50 disturbances showed that exercise is beneficial in improving sleep quality, symptoms
51 of insomnia, restless legs, sleep apnoea and daytime sleepiness. However, exercise
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3 only had significant effects on sleepiness if it had lasted for more than 12 weeks
4 while the exercise period did not matter in regards of the association to sleep quality
5 and insomnia symptoms.³¹
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8 Another recent study showed that high or increasing levels of physical activity could
9 protect women from future insomnia.¹⁸ Therefore, exercise seems to have a stronger
10 association with sleep quality and insomnia than with sleepiness, which is in line with
11 our results. However almost all previous studies, have the limitation that the definition
12 of sleepiness is limited to the estimate the likelihood of falling asleep but not the
13 general feeling of sleepiness, that we have shown is also an important part of
14 sleepiness.^{32 33} Another recent review exploring the associations of exercise, sleep
15 and cognitive function among older adults showed interesting results. Physical
16 activity is associated with improved cognitive function but the association of sleep
17 and cognitive function seems to be U-shaped, as too much or too little sleep is
18 negatively associated with cognitive function.³⁴ It would therefore be interesting for
19 future studies to explore how cognitive function is affected by the association of
20 physical activity and sleep.
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32 This study has several strengths such as the population-based nature, the
33 longitudinal study design and the large sample collected in the same manner at many
34 centres in 9 different countries. Another strength is the use of standardized and
35 validated procedures and instruments. The long follow up period is also a strength
36 since data on physical activity is collected ten years apart and subjects are
37 categorized according to change in physical activity. This study is however not
38 without limitations. It is not possible to know whether those who are active at both
39 timepoints have been continuously physically active throughout the study period or
40 only at these two timepoints. Another limitation of our study is that sleep variables are
41 only available at the follow-up, and we only have information on insomnia symptoms
42 but not the diagnosis of insomnia disorder. Sleep length and daytime sleepiness are
43 also based on subjective data. Another limitation is that physical activity was only
44 measured using a questionnaire. Also, the questions included only vigorous physical
45 activity and the effect of moderate or low intensity activity could not be tested.
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3 In conclusion, physical activity over time is associated with lower prevalence of
4 insomnia symptoms and a more likelihood of sleeping the recommended 6-9 hours
5 per night.
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10 **Ethical statement:**

11 All participants participated voluntarily in the study. Ethical approval for the study
12 from local research ethics committees and written consent from participants were
13 obtained.
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19 **Contributors** EB and EHT drafted the paper, participated in designing the study and
20 performed the statistical analysis. CJ and EL designed the study, participated in
21 manuscript preparation and reviewed the paper on several stages. CJ also
22 contributed to the statistical analysis. BB participated in data collection and reviewing
23 the paper. KF, DLJ, PD, JP, JG-A, SDA, JH, KT, VGL, RJ contributed to the statistical
24 analysis and reviewed the paper. TG and CJ are the correspondence author, and he
25 designed the study, participated in manuscript preparation and reviewed the paper
26 on several stages.
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35 Research and Innovation programme under grant agreement No 633212.
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39 **Competing interests** None declared.
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43 **Data sharing statement** No additional data available.
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53 **References**

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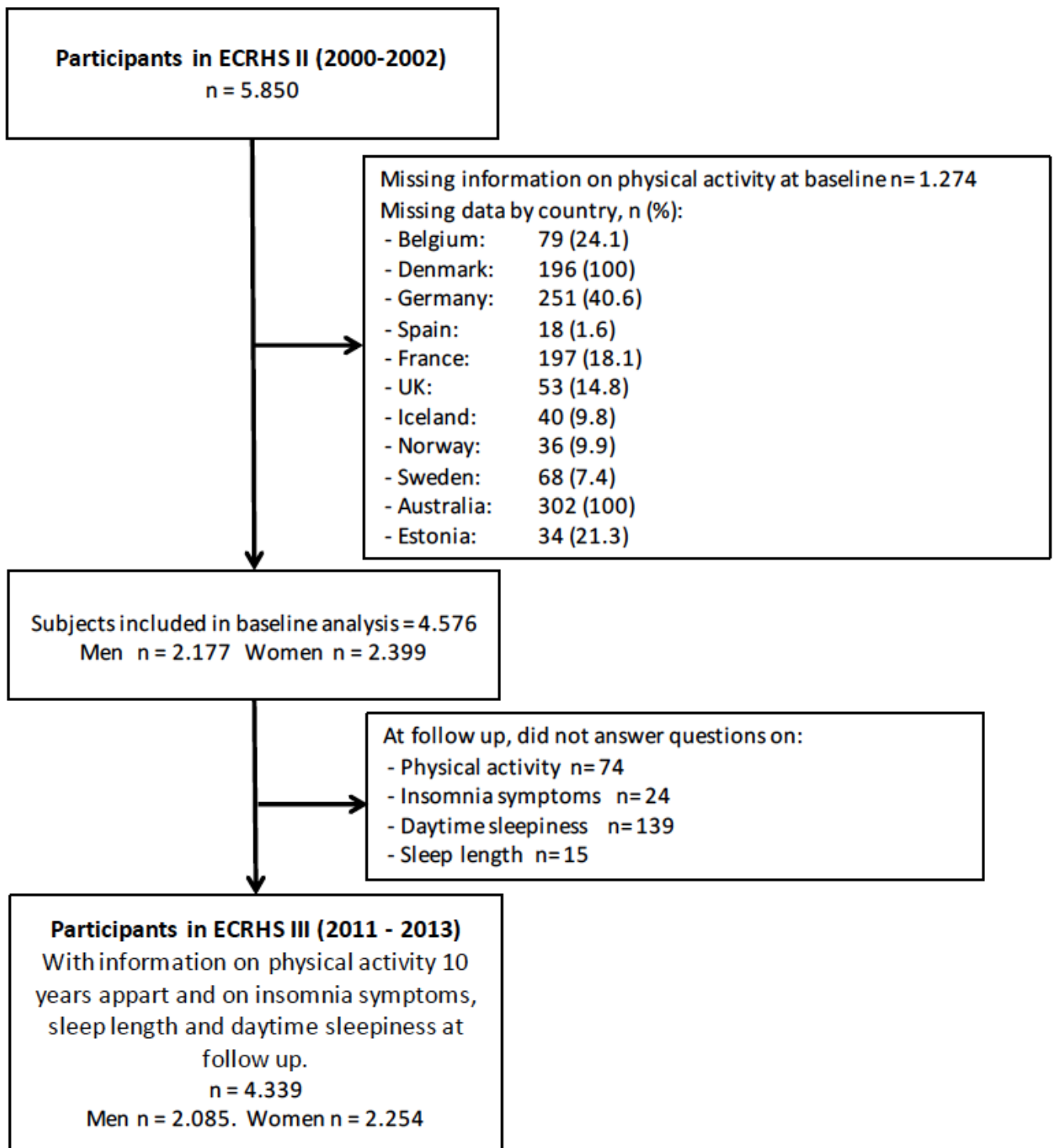
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Figure 1. Flow chart of the study population in the European community health survey (ECRSH)

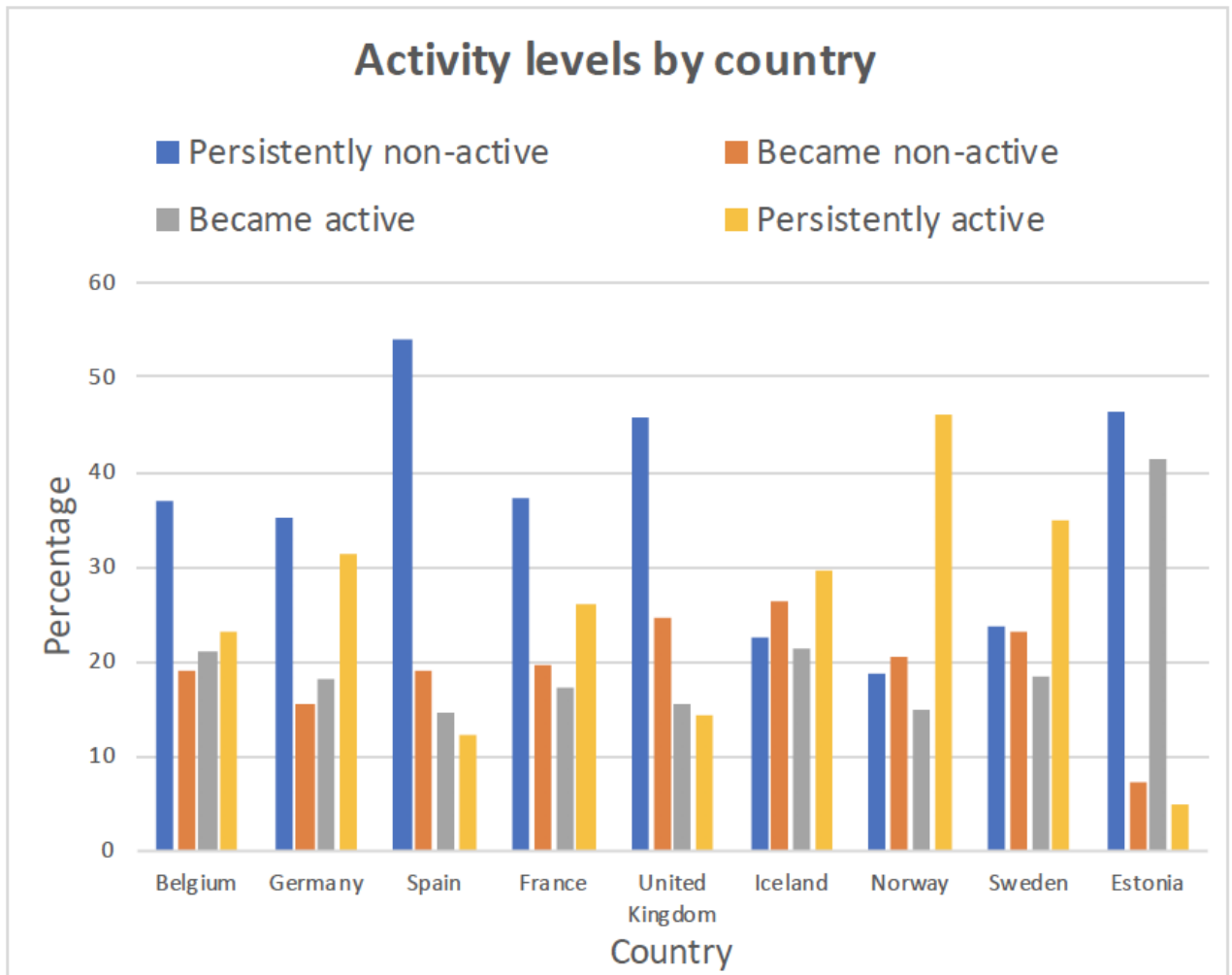


Figure 2. Activity levels by country

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Ethical approvals over lifetime of ECRHS 1,2, 3

Committee name and approval number

| Genetics | Centre Name & Country | ECRHS 1 | ECRHS 2 | ECRHS 3 |
|----------|---|---|---|--|
| N | Australia, Melbourne | Alfred Hospital Ethics Review Committee 24 / 91 | The Alfred Healthcare Group Ethics Committee 24/91. (amendment) | Monash University Human Research Ethics Committee Project # CF11/1818-2010001012 |
| N | Belgium, South Antwerp and Antwerp City | Not available | Not available | Comité voor Medische Ethiek UZA/UA 11/41/288 – UA |
| N | Denmark, Aarhus | Unable to find | N/A | De Videnskabetiske Komiteer for region Midtjylland. M-20110106 |
| Y | Estonia, Tartu | Cannot get the info, text redacted. | Research Ethics Committee of the University of Tartu (UT REC) 60/3-1998 | Research Ethics Committee of the University of Tartu (UT REC) 209T-17 and 225/M-24 |

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| N | France, Paris | Comité Consultatif National d'Ethique Pour les Sciences de la Vie et de la Santé, Section Technique, N/réf.AB/GM/91-298 - 19/07/91. INSERM-Biomedical research authorization n°91020 (01/03/91), Approval of the Commission Nationale Informatique et Liberté (CNIL (protection of the data) 05/08/91 | Comité consultatif de protection des personnes dans la recherche biomédicale de Bichat-Claude Bernard". 17/11/1999 | Etude ECRHS III: promotion CHU de Grenoble. Ethical approval CPP Sud est V 4 mars 2011. Approval Ministry of Health AFSSAPS n°B110053-70. |
| Y | France, Grenoble | Comité Consultatif National | Comité consultatif de protection des | Etude ECRHS III: promotion CHU |

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| | | <p>d'Ethique Pour les Sciences de la Vie et de la Santé, Section Technique, N/réf.AB/GM/91-298 - 19/07/91.</p> <p>INSERM-Biomedical research authorization n°91020 (01/03/91), Approval of the Commission Nationale Informatique et Liberté (CNIL (protection of the data) 05/08/91</p> | <p>personnes dans la recherche biomédicale de Bichat-Claude Bernard". 17/11/1999</p> | <p>de Grenoble. Ethical approval CPP Sud est V 4 mars 2011. Approval Ministry of Health AFSSAPS n°B110053-70.</p> |
| N | France, Montpellier | Comité Consultatif National d'Ethique Pour les Sciences de la Vie et de la | Comité consultatif de protection des personnes dans la recherche | Etude ECRHS III : promotion CHU de Grenoble. Ethical approval CPP Sud est V 4 |

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| N | France, Bordeaux | Comité Consultatif National d'Ethique Pour les Sciences de la Vie et de la Santé, Section Technique, | Comité consultatif de protection des personnes dans la recherche biomédicale de Bichat- | - Etude ECRHS III : promotion CHU de Grenoble. Ethical approval CPP |

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| Y | Germany, Hamburg | Ethikkommission der Ärztekammer Schleswig-Hollstein, Positive Votum, no number | Ethikkommission der Bayerischen Landesärztekammer (Positive Votum: Nr. 00079) | Ethikkommission der Bayerischen Landesärztekammer (Positive Votum: 10015 |

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| Y | Germany, Erfurt | Ethikkommission der Medizinischen Akademie Erfurt, Positive Votum, no number | Ethikkommission der Bayerischen Landesärztekammer (Positive Votum: Nr. 00079) | Ethikkommission der Bayerischen Landesärztekammer (Positive Votum: 10015) |
| N | Iceland, Reykjavik | ? | ? | National Bioethics committee of Iceland VSN-11-121-S3 |
| N | Italy, Pavia | No formal ethics committee-data unavailable | Ethics Committee of Internal Medicine and Medical Therapy Department, Pavia University (The approval was reported in the memorandum n. 4/1999) | Ethics Committee of IRCCS "San Matteo" Hospital Foundation, University of Pavia, Pavia (approval number 24215/2011) |
| N | Italy, Turin | | ? | ? |
| N | Italy, Verona | N/A | N/A | "Comitato Etico per la sperimentazione dell'Azienda Ospedaliera Universitaria |

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| N | Netherlands, Groningen | ? | ? | ? |
| N | Netherlands, Bergen-op-zoon | ? | ? | ? |
| N | Netherlands, Geleen | ? | ? | ? |
| Y | Norway, Bergen | The Regional Committee for Medical and Health Research Ethics West Norway Approval number: 42.91 | The Regional Committee for Medical and Health Research Ethics West Norway Approval number: 149.2000 | Regional Ethics Committee West Norway 2010/759 |
| | Barcelona, Spain | JA cannot find | Ethics Committee of the Parc de Salut Mar, Barcelona (Comité del etico d'investigacion clínica (CEIC)- Parc de Salut | Ethics Committee of the Parc de Salut Mar, Barcelona (Comité del etico d'investigacion clínica (CEIC)- Parc de Salut Mar, Barcelona (Approval |

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| | | | Forschung (UREK M175/99 123/00) | |
| N | Gothenburg, Sweden | Regional Ethical Review Board in Uppsala. 1990/257 and 1991/33 | Regional Ethical Review Board in Uppsala. 1999/313 | Regional Ethical Review Board in Uppsala. 2010/432 |
| Y | Uppsala, Sweden | Regional Ethical Review Board in Uppsala. 1990/257 and 1991/33 | Regional Ethical Review Board in Uppsala. 1999/313 | Regional Ethical Review Board in Uppsala. And the number of the decision is 2010/432 |
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| Y | Ipswich, UK | Ipswich District Hospital Ethics Committee | Suffolk | NRES committee London-Stanmore REC Ref: 11/LO/0965 |
| Y | Norwich, UK | Norfolk and Norwich Hospital Ethics Committee | Norfolk | NRES committee London-Stanmore REC Ref: 11/LO/0965 |

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| N | Caerphilly, UK | ? | ? | NRES committee London-Stanmore REC Ref: 11/LO/0965 |

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

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

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(e) Describe any sensitivity analyses

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60**Results**

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| 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 | 8, fig 1 |
| | | (b) Give reasons for non-participation at each stage | 8, fig 1 |
| | | (c) Consider use of a flow diagram | Fig 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1 |
| | | (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) | 6 |
| Outcome data | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time | 8-9 |
| | | <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure | N/A |
| | | <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures | N/A |
| 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 | Table 1, 2, 3 and page 8-9 |
| | | (b) Report category boundaries when continuous variables were categorized | See tables and methods |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | x |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N/A |

Discussion

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|------------------|----|--|--------|
| Key results | 18 | Summarise key results with reference to study objectives | 10 |
| 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 | 4, 12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 10-12 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10, 12 |

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 | 2 |
|---------|----|---|---|

*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.

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The association of longitudinal physical activity with current symptoms of insomnia, sleep duration and daytime sleepiness - A European population-based study

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| Secondary Subject Heading: | Global health |

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The association of longitudinal physical activity with current symptoms of insomnia, sleep duration and daytime sleepiness - A European population-based study

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Abstract:

Objectives: To explore the relationship of physical activity during the past 10 years with insomnia, daytime sleepiness and estimated short or long sleep duration among adults aged 39–67 years.

Design: Population-based, multi-centre cohort study.

Setting: 21 centres in 9 European countries.

Methods: Included were 4339 participants in the third follow-up of the European Community Respiratory Health Survey (ECRHS III) who answered questions on physical activity at baseline (ECRHS II) and questions on physical activity, insomnia symptoms, sleep duration and daytime sleepiness at follow up (ECRHS III). Physical activity was assessed both in ECRHS III and 10 years before. Participants reported that they exercised with a frequency of at least two or more times a week for one hour a week or more were classified as being physically active. Change in activity status was categorised into four groups: persistently non-active, became inactive, became active and persistently active.

Main outcome measures: Insomnia, sleep time and daytime sleepiness in relation to physical activity.

Results: Altogether, 37% of participants were persistently non-active, 25% were persistently active, 20% became inactive and 18% became active from baseline to follow up. Participants that were persistently active were less likely to report difficulties initiating sleep (OR 0.60 (95% CI 0.45-0.78)), short sleep duration of ≤ 6 h/night (OR 0.71 (95% CI 0.59-0.85) and long sleep of (≥ 9 h/night (OR 0.53 (95% CI 0.33-0.84)) than persistently non active subjects after adjusting for age, sex, BMI, smoking history, and study centre. Daytime sleepiness and difficulties maintaining sleep were not related to physical activity.

Conclusion: Physically active people have a lower risk of some insomnia symptoms and extreme sleep duration, both long and short.

Strengths and limitations of this study:

- The longitudinal study design, with the exposure (physical activity) measured 10 years before the outcome (sleep outcomes) allows testing the directionality of the association.
- Data was collected using standardized and validated procedures and instruments, increasing internal validity.
- Data was obtained from 9 European countries, increasing external validity of our findings.
- One limitation of our study is that sleep variables are only available at the follow-up, precluding testing their role on baseline physical activity.
- Insomnia symptoms, sleep length and daytime sleepiness were obtained from questionnaire and no sleep disorder diagnoses from medical providers or objective assessments were available.

Introduction

Disturbed sleep is common in the general population and impacts health and quality of life.(1-3) Chronic sleep disturbances are associated with cardiovascular disease, metabolic dysfunction, psychiatric disorders, and increased mortality.(4-6)

Physical activity and sleep: Regular exercise is associated with better health and several studies suggest that physical activity (PA) is beneficial on sleep and may improve symptoms of chronic insomnia.(7-10) It is, however, unclear how large these benefits are and which factors moderate these benefits.(11) The positive association between PA and sleep might be subject to multiple moderating factors such as gender, age, BMI, fitness level, general health and the characteristics of the exercise. Therefore, sleep and PA probably influence each other through complex, reciprocal interactions including multiple physiological and psychological pathways.(7)

Physical activity and daytime sleepiness: There is evidence that more PA is associated with less daytime sleepiness.(12-17) Cross-sectional studies have shown that low PA is associated with increased likelihood of excessive daytime sleepiness (EDS)(14-16) and that subjects participating in exercise are less likely to have EDS.(12, 17) In older adults, increasing PA by doing home exercises has been shown to improve EDS and reduce the prevalence of insomnia symptoms(13) and another study showed that increasing PA protected women from future insomnia.(18) Other studies have contradictory findings. In an epidemiological study of 4.405 Koreans, daytime sleepiness was more common among those in the top quartile of PA compared to those in the lowest quartile group.(19) Among patients with obstructive sleep apnoea increased PA was associated with lower disease severity and 28% decrease in EDS.(20) The daily association between PA and sleep duration was described in 2021 based on a systemic review and meta-analysis on 33 peer-reviewed papers showing that the night following an increased PA there was a lower total sleep time.(21)

Limitations of previous studies: There is a lack of epidemiological data from long-term follow-up of large cohorts studying the association of PA to sleep length, daytime sleepiness, and insomnia symptoms. Previous research on physical activity and

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3 sleep-related outcomes has several important limitations. Most studies are cross-
4 sectional or with a short follow-up, preventing to elucidate if increased physical
5 activity improves sleeping outcomes or reduced physical activity is a consequence of
6 sleep problems. Finally, the effect of physical activity on sleep length, daytime
7 sleepiness, and insomnia symptoms has not been studied simultaneously.
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13 Aims of the current study: Therefore, the aim of the present study was to assess the
14 interrelationship between physical activity based on frequency, duration and intensity
15 and symptoms of insomnia, self-reported sleep duration and daytime sleepiness
16 among middle-aged subjects from 21 centres in 9 countries at two time periods
17 10 years apart, giving important longitudinal follow up data.
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23 **Material and methods**

24 *Subjects:*

25 We studied participants in the second and third follow-up of the European Community
26 Respiratory Health Survey (ECRHS II and III, www.ecrhs.org), an international,
27 population-based, multicentre cohort study of asthma and allergy, which was first
28 performed in 1990. Detailed descriptions of the methods for ECRHS I and ECRHS II
29 have been published elsewhere.(22, 23) Briefly, participating centres first randomly
30 selected samples of 20 to 44-year-old subjects in order to follow them for the asthma,
31 allergy and lung diseases (See: www.ecrhs.org). Participants completed a short
32 postal questionnaire about asthma and asthma-like symptoms and from those who
33 responded, a random sample was selected to undergo a more detailed clinical
34 examination. In ECRHS II, subjects who had participated in the clinical phase of
35 ECRHS I (performed between 1991 – 1994) were invited to participate in follow-up.
36 The clinical phase of ECRHS II was performed between 1998 to 2002. ECRHS III is
37 the second follow-up and was performed from February 2011 to January 2014.(22-
38 24) The present study is based on data from ECRHS II and III (see figure 1 for
39 flowchart). Ethical approval for the study from local research ethics committees and
40 written consent from participants were obtained.
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56 *Health, habits, and measurements*

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58 Subjects answered the core ECRHS questionnaires which included questions
59 on lifestyle, respiratory symptoms, smoking history, and general health. Current
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3 smokers were defined as those who smoked tobacco regularly during the last month.
4 Former smokers were defined as smokers who denied having smoked regularly for a
5 month prior to the examination. Those who reported no regular smoking at or prior to
6 the examination were defined as never smokers. Height and weight were measured,
7 and body mass index (BMI) was calculated.(24)
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13 *Assessment of physical activity*

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15 Physical activity was assessed in ECRHS II and III using replies from questionnaire
16 in ECRHS II and III. The assessment of PA in ECRHS has previously been described
17 in details and how both frequency and duration of PA was used to divide the
18 population into categories.(22) In brief, participants were asked how often and for
19 how many hours per week they usually exercised so that they got out of breath or
20 became sweaty. Participants who exercised two or more times a week during at least
21 1 hour a week were classified physically active. Change in activity status from
22 baseline to follow up was categorised into four PA groups: persistently non-active
23 (non-active at both baseline and follow up), became inactive (active at baseline and
24 non-active at follow up), became active (non-active at baseline and active at follow
25 up) and persistently active (active at both baseline and follow up).
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36 *Sleep questionnaires and measurements*

37 Sleep-related symptoms were assessed by using the Basic Nordic Sleep
38 Questionnaire(25), where participants were asked about frequency of insomnia
39 symptoms. Answers were on a scale of 1 – 5: (1) never or very seldom, (2) less than
40 once a week, (3) once to twice a week, (4) three to five times a week, (5) every day
41 or almost every day of the week. Insomnia symptoms were defined using answers to
42 three questions from the Basic Nordic Sleep Questionnaire “I have difficulties falling
43 asleep at night” (difficulties initiating sleep), “I wake up often during the night”
44 (difficulties maintaining sleep) and “I wake up early in the morning and can’t fall back
45 asleep” (early morning awakenings). Those who reported those symptoms of
46 insomnia ≥ 3 times a week (scores 4 and 5) were considered to have the
47 corresponding insomnia subtype. Daytime sleepiness was evaluated using the
48 Epworth Sleepiness Scale, a brief questionnaire that measures daytime sleepiness
49 based on the likelihood of falling asleep in eight different situations.(26) Participants
50 with Epworth sleepiness scale score >10 were considered to have EDS. Participants
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3 answered the question: how much sleep do you estimate that you get on average
4 each night? They were classified as short sleepers (≤ 6 hours/night), normal sleepers
5 (6–9 hours/night) and long sleepers (≥ 9 hours/night) according to their answers.
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9 10 *Patient and public involvement*

11 The study's design did not involve patients or the general public. However, all
12 participating patients were informed about the research objectives, and their informed
13 consent was obtained. The survey was completed by participants voluntarily and no
14 input from patients was sought in interpreting or writing up the results. The results of
15 the research will not be disseminated to the patients.
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22 *Statistical analysis*

23 Data are presented as number and percentage or mean \pm SD, depending on
24 distribution. For bivariate analysis, the χ^2 test and one-way analysis of variance were
25 used for nominal and continuous variables. Logistic regression was used for
26 multivariable analyses to estimate the association between physical activity and
27 sleep related outcomes. The model was adjusted for potential confounders including
28 age, sex, BMI, smoking history and study center. In the analysis, all variables,
29 including study center (n=21), were treated as fixed effects. STATA V.16 was used
30 for all statistical analyses.
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39 **Results**

40 *Participants and level of physical activity*

41 From a total of 5.850 participants in ECRHS II, we excluded those with missing data
42 and included a total of 4.339 participants (48% men), see Figure 1. From baseline to
43 10 years later, 36.9% of participants were persistently non-active, 17.9% became
44 physically active at follow-up, 20.3% of participants became inactive 24.9% were
45 persistently active (Table 1). There were geographical differences in the level of
46 physical activity between the ECRHS countries (Figure 2). Participants in Norway
47 were most likely to be persistently active, while participants in Spain, followed by
48 Estonia, were most likely to be persistently non-active (Figure 2).
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58 *General characteristics and health*

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3 Persistently active participants were more often men, they were younger, and they
4 had slightly lower BMI (Table 1). They were also less likely to be current smokers
5 and more likely to be currently working (Table 1).
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9 10 *Insomnia symptoms*

11 In unadjusted analysis, there was a significant difference in reporting difficulties
12 initiating sleep, early morning awakenings and any insomnia symptom where those
13 persistently active were least likely to report these symptoms. Also, persistently
14 active subjects were the least likely to report two and three insomnia symptoms
15 (Table 2). After adjusting for age, sex, BMI, smoking history and study centre, this
16 negative association remained for difficulties initiating sleep (OR 0.58 (0.42-0.77)),
17 any insomnia symptom (OR 0.78 (0.65-0.94) and reporting two (OR 0.60 (0.43-0.82))
18 and three (OR 0.63 (0.41-0.98) insomnia symptoms (Table 3). Additionally, in
19 adjusted analysis, persistently active subjects were significantly less likely to report
20 difficulties initiating sleep (OR 0.80 (0.66-0.97) (Table 3). There were also
21 independent associations between insomnia symptoms and age, female gender and
22 BMI (Table 4).
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34 *Sleep duration and daytime sleepiness*

35 In unadjusted analysis, there was a significant difference in short and long sleep
36 duration between levels of activity. Those who were persistently active were most
37 likely to be normal sleepers and the persistently non-active were least likely (70.9%
38 vs. 59.2% respectively) (Table 2). After adjusting for age, sex, BMI, smoking history
39 and study centre, these results remained significant for persistently active subjects.
40 They were significantly more likely to be normal sleepers (OR 1.55 (1.29-1.87)) and
41 significantly less likely to be short sleepers (OR 0.71 (0.58-0.85)) or long sleepers
42 (OR 0.48 (0.28-0.80)) (Table 3). Additionally, those who became active were more
43 likely to be normal sleepers than those persistently non-active (OR 1.21 (1.00-1.47))
44 (Table 3).
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52 However, there was not a significant association between the mean Epworth
53 sleepiness scale score or percentage with Epworth sleepiness scale score >10 and
54 level of physical activity (Tables 2 and 3). Daytime sleepiness was also
55 independently associated with smoking (Table 4).
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Discussion

The main results of this study were that participants who reported being physically active at the start and end of a 10 year follow up period were less likely to report insomnia symptoms at the follow-up. We also found that subjects that are persistently active are more likely to sleep the recommended 6-9 hours. This association remained statistically significant after adjusting for sex, age, smoking history, and BMI. We also saw that persistently active participants were more often men, they were younger, and they had slightly lower BMI and were less likely to be current smokers and more likely to be currently working.

Our results are in line with previous studies that have shown a beneficial effect of physical activity on symptoms of insomnia (9, 10) but the current study additionally shows the importance of consistency in exercise over time because the association was lost in initially active subjects who became inactive. A recent meta-analysis examining the effects of acute and regular exercise on a range of sleep variables showed that acute exercise (less than one week of exercise) has a small beneficial effect on many objective measures of sleep such as total sleep time, symptoms of insomnia and sleep quality.(7) Furthermore, this meta-analysis found greater benefits for regular exercise on both subjective and objective sleep parameters over time. Regular exercise had small beneficial effects on total sleep time and sleep efficiency, small-to-medium beneficial effects on sleep onset latency, and moderate beneficial effects on sleep quality.(7)

There are two recent systematic reviews and meta-analysis on the effects of PA on sleep(7) and insomnia(9) both substantially reviewing the same randomized controlled studies. Banno *et al.* included nine studies with a total of 557 participants.(7) The majority of participants exercised 3 times or less per week and follow-up was 4 months or shorter in all studies except one. Their conclusion was that exercise could improve sleep, but higher quality research was needed.(7) Five studies on insomnia and additionally six on insomnia symptoms showed shorter sleep latency and higher sleep efficacy, but the authors also acknowledged the small size of the literature and severe methodological limitations often based on selection bias.(9) Most previous studies are also cross-sectional which can also be considered a limitation.

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3 Furthermore, a recent systematic review on physical activity and sleep showed that
4 moderate exercise had more promising outcome on sleep quality than vigorous
5 exercise. It is therefore important to further study the impact of the intensity of
6 physical activity in the context of age and gender when exploring the beneficial
7 impact on sleep.(27)
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13 This study has a long follow up period (10 years) and indicates strongly that
14 consistency in physically activity might be an important factor to optimize sleep
15 duration and reduce symptoms of insomnia. Most other studies have had a much
16 shorter follow up period(7) which makes it more difficult to assess consistency in
17 activity over time.
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22 Our results indicate that those who are consistent in physical activity are also less
23 likely to be both short (<6h) and long sleepers (>9h). Those who are physically active
24 in general are also more likely to engage in a healthier lifestyle (28) which also can
25 have an effect on sleep. Lifestyle factors such as healthy diet and physical activity
26 are probably a part of a phenotype that characterizes those individuals who are
27 generally engaged in a healthy lifestyle. A recent review highlighted the importance
28 of focusing on the combination of sleep, diet and exercise when exploring healthy
29 longevity.(29)
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38 The three groups reporting low physical activity in either ECRHS survey or at both
39 time points are all reporting very similar prevalence of insomnia symptoms, extreme
40 sleep length and daytime sleepiness. This is somewhat surprising, especially that
41 those who are active at the follow-up but were not at baseline do have very similar
42 symptom profile as those who were inactive at both surveys. Our study found a
43 consistency in a behaviour like physical activity for more than a decade is strongly
44 related to less insomnia and more “normal” sleep length. The important information
45 concerning “the healthy phenotype” would be missed if the physical activity data were
46 available only at baseline or at follow-up but not at both time points.
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55 In a recent review based on 22 randomized controlled trials on the effects of regular
56 exercise (lasting at least 2 months on a regular basis) on self-reported sleep quality,
57 insomnia and daytime sleepiness, it was found that regular physical activity improved
58 subjective sleep quality, insomnia severity, and daytime sleepiness as measured only
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3 with the Epworth sleepiness scale.(27) These results regarding insomnia symptoms
4 are in line with our study but the results on daytime sleepiness differ from our results.
5 The reason for this discrepancy could be due to different study populations since
6 there were only two studies in this review that measured daytime sleepiness using
7 the Epworth sleepiness scale, one study assessed this among the elderly, 60 years
8 and older(13) and the other among overweight and obese men.(30) Another recent
9 review of 32 randomized control trials on the effects of exercise on improving sleep
10 disturbances showed that exercise is beneficial in improving sleep quality, symptoms
11 of insomnia, restless legs, sleep apnoea and daytime sleepiness. However, exercise
12 only had significant effects on sleepiness if it had lasted for more than 12 weeks
13 while the exercise period did not matter in regards of the association to sleep quality
14 and insomnia symptoms.(31)

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Another recent study showed that high or increasing levels of physical activity could
protect women from future insomnia.(18) Therefore, exercise seems to have a
stronger association with sleep quality and insomnia than with sleepiness, which is in
line with our results. However almost all previous studies, have the limitation that the
definition of sleepiness is limited to the estimate the likelihood of falling asleep but
not the general feeling of sleepiness, that we have shown is also an important part of
sleepiness.(32, 33) Another recent review exploring the associations of exercise,
sleep and cognitive function among older adults showed that physical activity is
associated with improved cognitive function but the association of sleep and
cognitive function seems to be U-shaped, as too much or too little sleep is negatively
associated with cognitive function.(34) We did not explore cognitive function in the
current study but It would be interesting for future studies to explore further how
cognitive function is affected by the association of physical activity and sleep.

This study has several strengths such as the population-based nature, the
longitudinal study design and the large sample collected in the same manner at many
centres in 9 different countries. Another strength is the use of standardized and
validated procedures and instruments. The long follow up period is also a strength
since data on physical activity is collected ten years apart and subjects are
categorized according to change in physical activity. This study is however not
without limitations. It is not possible to know whether those who are active at both
timepoints have been continuously physically active throughout the study period or

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3 only at these two timepoints. Furthermore, physical activity was only measured using
4 a questionnaire. Another limitation of our study is that sleep variables are only
5 available at the follow-up, and we only have information on insomnia symptoms but
6 not the diagnosis of insomnia disorder. Sleep length and daytime sleepiness are also
7 based on subjective data. Therefore, even though the measurement of physical
8 activity is longitudinal, it may not be entirely appropriate to describe the associations
9 between physical activity and sleep outcomes as longitudinal. Also, there are
10 potential implications of residual confounders that can influence both physical activity
11 and sleep which were not explored in the current study (e.g. mental health,
12 musculoskeletal disorders/ chronic pain) which could influence the study findings.
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22 In conclusion, physical activity over time is associated with lower prevalence of
23 insomnia symptoms and with sleeping between 6-9 hours per night.
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For peer review only

Table 1. Characteristics and general health of the participants by the level of physical activity

| | Persistently non-active | Became inactive | Became active | Persistently active | p-value |
|------------------------------------|-------------------------|-----------------|---------------|---------------------|------------------|
| General characteristics | | | | | |
| N, % | 1601 (36.9) | 881 (20.3) | 775 (17.9) | 1082 (24.9) | |
| Men, % | 44.3 | 49.0 | 46.8 | 53.7 | <0.001 |
| Age, years | 55.0 ± 7.2 | 54.5 ± 7.1 | 53.4 ± 7.2 | 53.7 ± 7.2 | <0.001 |
| Body mass index, kg/m ² | 27.6 ± 5.2 | 27.1 ± 4.9 | 27.1 ± 4.8 | 27.0 ± 4.4 | 0.007 |
| Currently working, % | 82.7 | 85.8 | 88.9 | 90.4 | <0.001 |
| Smoking history | | | | | |
| Never, % | 42.4 | 43.4 | 44.3 | 47.6 | <0.001 |
| Former, % | 34.4 | 39.8 | 37.5 | 40.0 | |
| Current, % | 23.2 | 16.9 | 18.2 | 12.4 | |

Table 2. Insomnia symptoms, sleep duration and daytime sleepiness by level of physical activity.

| | Persistently non-active (n=1601) | Became inactive (n=881) | Became active (n=775) | Persistently Active (n=1082) | p-value |
|--|--|-----------------------------------|---------------------------------|--|------------------|
| Insomnia symptoms | | | | | |
| Difficulties initiating sleep (%) | 15.4 | 14.0 | 11.7 | 8.2 | <0.001 |
| Difficulties maintaining sleep (%) | 31.9 | 32.1 | 33.0 | 28.5 | 0.128 |
| Early morning awakenings (%) | 18.2 | 18.3 | 15.0 | 13.2 | 0.002 |
| Any insomnia symptom (%) | 41.0 | 41.5 | 39.5 | 34.9 | 0.006 |
| Numbers of insomnia symptoms | | | | | |
| None (%) | 58.4 | 58.2 | 61.0 | 64.9 | 0.001 |
| One (%) | 23.2 | 25.2 | 24.0 | 23.8 | |
| Two (%) | 11.9 | 10.6 | 10.0 | 7.8 | |
| Three (%) | 6.6 | 6.1 | 5.1 | 3.6 | |
| Sleep duration | | | | | |
| Sleep time (hours) | 6.8 ± 1.1 | 6.8 ± 1.0 | 6.9 ± 1.0 | 6.9 ± 0.9 | 0.234 |
| Sleep time, % | | | | | |
| Short sleepers (≤ 6 hours) | 35.9 | 31.9 | 20.7 | 26.9 | <0.001 |
| Normal sleepers (6 – 9 hours) | 59.2 | 64.6 | 66.9 | 70.9 | |
| Long sleepers (≥ 9 hours) | 4.9 | 3.5 | 3.4 | 2.2 | |
| Daytime sleepiness | | | | | |
| Epworth sleepiness scale score | 6.8 ± 4.1 | 7.2 ± 4.1 | 6.9 ± 4.1 | 6.9 ± 3.8 | 0.106 |
| Epworth sleepiness scale score >10 (%) | 17.2 | 19.4 | 17.7 | 15.6 | 0.176 |
| Data are presented as mean ± standard deviation or % where indicated. Significant differences are in bold (p<0.05). *p-value from Pearson's chi-square test (numerical variables) and one-way analysis of variance (continuous variables). | | | | | |

Table 3. Independent association between the level of physical activity and medical disorders, insomnia symptoms, daytime sleepiness and sleep duration expressed as adjusted* odds ratios (95% CI) with the persistently non-active group as reference. Bold text indicates statistical significance.

| | Became inactive (n=881) | Became active (n=775) | Persistently active (n=1082) |
|------------------------------------|-----------------------------------|---------------------------------|--|
| Insomnia symptoms | | | |
| Difficulties initiating sleep | 0.97 (0.75-1.25) | 0.82 (0.62-1.08) | 0.58 (0.42-0.77) |
| Difficulties maintaining sleep | 0.96 (0.80-1.17) | 1.04 (0.85-1.27) | 0.80 (0.66-0.97) |
| Early morning awakenings | 1.09 (0.87-1.38) | 0.86 (0.63-1.03) | 0.80 (0.63-1.03) |
| Any insomnia symptom | 1.02 (0.85-1.22) | 0.95 (0.78-1.14) | 0.78 (0.65-0.94) |
| Numbers of insomnia symptoms | | | |
| One | 1.07 (0.86-1.32) | 0.99 (0.79-1.24) | 0.91 (0.74-1.12) |
| Two | 0.89 (0.66-1.20) | 0.86 (0.63-1.17) | 0.60 (0.43-0.82) |
| Three | 1.09 (0.74-1.59) | 0.94 (0.62-1.42) | 0.63 (0.41-0.98) |
| Daytime sleepiness | | | |
| Epworth sleepiness scale score >10 | 1.17 (0.94-1.47) | 1.00 (0.78-1.27) | 0.87 (0.69-1.10) |
| Sleep duration | | | |
| Short sleepers (≤ 6 hours) | 0.89 (0.73-1.07) | 0.85 (0.69-1.03) | 0.71 (0.58-0.85) |
| Normal sleepers (6-9 hours) | 1.18 (0.98-1.42) | 1.21 (1.00-1.47) | 1.55 (1.29-1.87) |
| Long sleepers (≥ 9 hours) | 0.74 (0.47-1.17) | 0.84 (0.53-1.33) | 0.48 (0.28-0.80) |

*Adjusted for age, sex, BMI, smoking history and center. Significant differences are in bold.

Table 4. Associations between age, sex, BMI and smoking history and sleep related symptoms.

| | Age | Sex | BMI | Smoking history |
|------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Insomnia symptoms | | | | |
| Difficulties initiating sleep | 1.02 (1.01-1.03) | 2.16 (1.77-2.64) | 1.02 (1.01-1.05) | 0.81 (0.66-0.99) |
| Difficulties maintaining sleep | 1.04 (1.03-1.05) | 1.80 (1.56-2.07) | 1.01 (1.00-1.03) | 1.09 (0.95-1.26) |
| Early morning awakenings | 1.02 (1.01-1.03) | 1.52 (1.28-1.80) | 1.01 (1.00-1.03) | 1.02 (0.85-1.21) |
| Any insomnia symptom | 1.03 (1.02-1.04) | 1.75 (1.53-1.99) | 1.02 (1.01-1.03) | 1.07 (0.93-1.22) |
| Numbers of insomnia symptoms | | | | |
| One | 1.03 (1.01-1.04) | 1.47 (1.26-1.71) | 1.02 (1.00-1.03) | 1.15 (0.98-1.34) |
| Two | 1.04 (1.02-1.06) | 2.11 (1.69-2.64) | 1.02 (1.00-1.05) | 1.01 (0.80-1.26) |
| Three | 1.04 (1.02-1.06) | 2.62 (1.93-3.53) | 1.03 (0.99-1.06) | 0.89 (0.66-1.20) |
| Daytime sleepiness | | | | |
| Epworth sleepiness scale score >10 | 0.99 (0.98-1.00) | 0.95 (0.81-1.12) | 1.01 (0.99-1.03) | 1.28 (1.08-1.52) |
| Sleep duration | | | | |
| Short sleepers (≤ 6 hours) | 1.01 (0.99-1.02) | 0.88 (0.77-1.00) | 1.03 (1.02-1.05) | 0.83 (0.72-0.96) |
| Normal sleepers (6-9 hours) | 0.99 (0.98-0.99) | 1.08 (0.95-1.23) | 0.96 (0.95-0.98) | 1.20 (1.05-1.38) |
| Long sleepers (≥ 9 hours) | 1.03 (1.01-1.06) | 1.35 (0.96-1.89) | 1.02 (0.99-1.06) | 0.95 (0.67-1.34) |

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3 **Figure legends:**

4 **Figure 1.** Flow chart of the study population in the European community health survey
5 (ECRSH)
6

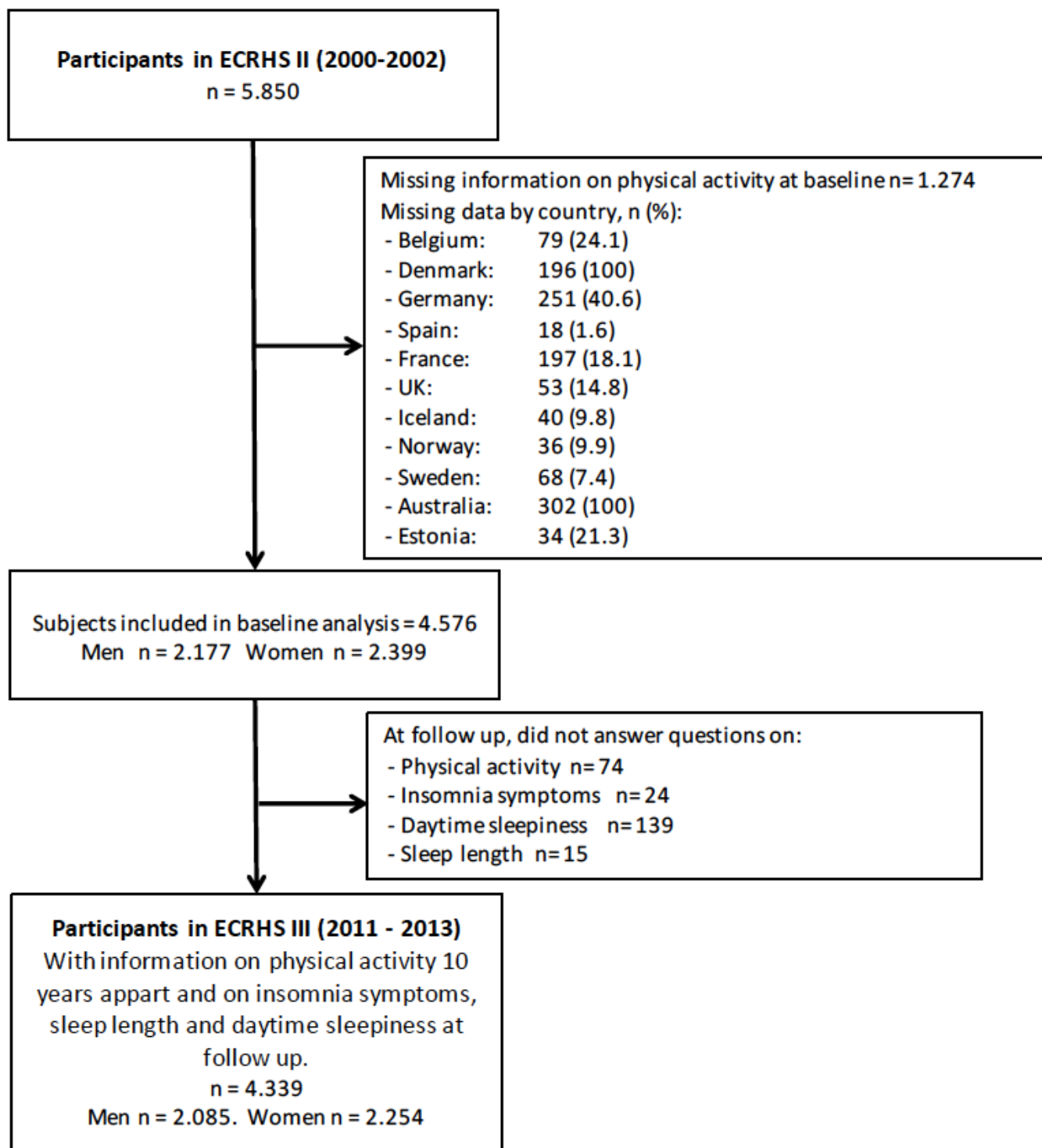
7
8 **Figure 2.** Activity levels by country
9

10 **Figure 3.** Prevalence of any insomnia symptom, short sleep duration (≤ 6 hours per night),
11 long sleep duration (≥ 9 hours per night) and daytime sleepiness (ESS >10) by country.
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Figure 1. Flow chart of the study population in the European community health survey (ECRSH)

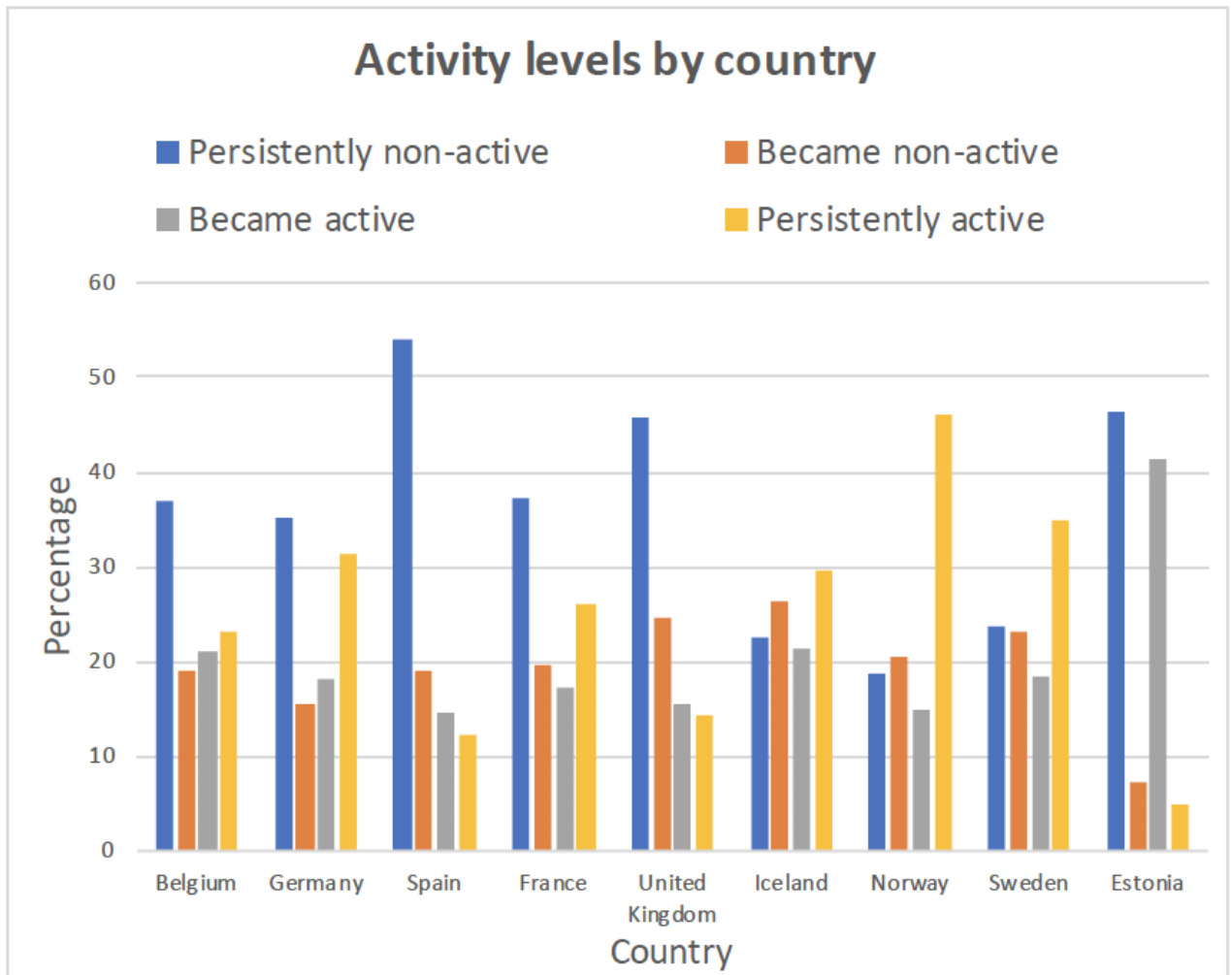


Figure 2. Activity levels by country

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

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

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(e) Describe any sensitivity analyses

Continued on next page



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| 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 | 8, fig 1 |
| | | (b) Give reasons for non-participation at each stage | 8, fig 1 |
| | | (c) Consider use of a flow diagram | Fig 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1 |
| | | (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) | 6 |
| Outcome data | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time | 8-9 |
| | | <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure | N/A |
| | | <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures | N/A |
| 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 | Table 1, 2, 3 and page 8-9 |
| | | (b) Report category boundaries when continuous variables were categorized | See tables and methods |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | x |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N/A |
| Discussion | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 10 |
| 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 | 4, 12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 10-12 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10, 12 |
| 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 | 2 |

*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.

BMJ Open

The association between physical activity over a 10-year period and current insomnia symptoms, sleep duration and daytime sleepiness – A European population-based study

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The association between physical activity over a 10-year period and current insomnia symptoms, sleep duration and daytime sleepiness – A European population-based study

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Abstract:

Objectives: To explore the relationship between physical activity over a 10-year period and current symptoms of insomnia, daytime sleepiness and estimated sleep duration in adults aged 39–67.

Design: Population-based, multi-centre cohort study.

Setting: 21 centres in 9 European countries.

Methods: Included were 4,339 participants in the third follow-up to the European Community Respiratory Health Survey (ECRHS III), who answered questions on physical activity at baseline (ECRHS II) and questions on physical activity, insomnia symptoms, sleep duration and daytime sleepiness at 10-years follow up (ECRHS III). Participants who reported that they exercised with a frequency of at least two or more times a week, for one hour a week or more, were classified as being physically active. Changes in activity status were categorised into four groups: persistently non-active; became inactive; became active; and persistently active.

Main outcome measures: Insomnia, sleep time and daytime sleepiness in relation to physical activity.

Results: Altogether, 37% of participants were persistently non-active, 25% were persistently active, 20% became inactive and 18% became active from baseline to follow up. Participants who were persistently active were less likely to report difficulties initiating sleep (OR 0.60 (95% CI 0.45-0.78)), a short sleep duration of ≤ 6 h/night (OR 0.71 (95% CI 0.59-0.85)) and a long sleep of ≥ 9 h/night (OR 0.53 (95% CI 0.33-0.84)) than persistently non-active subjects after adjusting for age, sex, BMI, smoking history and study centre. Daytime sleepiness and difficulties maintaining sleep were not related to physical activity status.

Conclusion: Physically active people have a lower risk of some insomnia symptoms and extreme sleep durations, both long and short.

Strengths and limitations of this study:

- The longitudinal study design, in which the exposure (physical activity) is measured 10 years prior to the sleep outcomes, enables an investigation into whether the consistency of physical activity over time has an impact on current symptoms of insomnia, sleep duration and daytime sleepiness.
- Data was collected using standardized and validated procedures and instruments, increasing its internal validity.
- Data was obtained from nine European countries, increasing the external validity of our findings.
- One limitation of our study is that sleep variables are only available at the follow up, which precluded testing their effect on baseline physical activity.
- Insomnia symptoms, sleep durations and daytime sleepiness data were obtained by questionnaire and no sleep disorder diagnoses from medical providers or objective assessments were available.

Introduction

Disturbed sleep is common in the general population and impacts health and quality of life.(1-3) Chronic sleep disturbances are associated with cardiovascular disease, metabolic dysfunction, psychiatric disorders, and increased mortality.(4-6)

Physical activity and sleep: Regular exercise is associated with better health and several studies suggest that physical activity (PA) is beneficial to sleep and may improve symptoms of chronic insomnia.(7-10) It is, however, unclear how significant these benefits are and which factors may have a moderating effect upon them.(11) The positive association between PA and sleep may be subject to multiple moderating factors such as gender, age, BMI, fitness level, general health and the characteristics of the type of exercise in question. Therefore, sleep and PA probably influence each other through complex, reciprocal interactions including multiple physiological and psychological pathways.(7)

Physical activity and daytime sleepiness: There is evidence that more PA is associated with less daytime sleepiness.(12-17) Cross-sectional studies have shown that low PA is associated with an increased likelihood of excessive daytime sleepiness (EDS)(14-16) and that subjects participating in exercise are less likely to have EDS.(12, 17) In older adults, increasing PA by doing home exercises has been shown to improve EDS and reduce the prevalence of insomnia symptoms(13), while another study showed that increasing PA protected women from future insomnia.(18) Other studies have contradictory findings. In an epidemiological study of 4,405 Koreans, daytime sleepiness was more common among those in the top quartile of PA compared to those in the lowest quartile group.(19) Among patients with obstructive sleep apnoea, increased PA was associated with a lower severity of disease and a 28% decrease in EDS.(20) The daily association between PA and sleep duration was described in 2021, based on a systematic review and meta-analysis of 33 peer-reviewed papers, which showed that, on the night following increased PA, there was a lower total sleep time.(21)

Limitations of previous studies: There is a lack of epidemiological data from long-term follow up studies of large cohorts exploring the association of PA with sleep length, daytime sleepiness and insomnia symptoms. Previous research on physical activity

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3 and sleep-related outcomes has several important limitations. Most studies are cross-
4 sectional or have a short follow-up interval, preventing the possibility of elucidating
5 whether increased physical activity improves sleeping outcomes or whether reduced
6 physical activity is a consequence of sleep problems. Finally, the effects of physical
7 activity on sleep length, daytime sleepiness, and insomnia symptoms have not been
8 studied simultaneously.
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15 Aims of the current study: Therefore, the aim of the present study was to assess the
16 interrelationship between physical activity, based on frequency, duration and
17 intensity, and symptoms of insomnia, self-reported sleep durations and daytime
18 sleepiness among middle-aged subjects from 21 centres in nine countries at two
19 moments in time, 10 years apart, providing important longitudinal follow-up data.
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25 **Material and methods**

26 *Subjects:*

27 We studied participants from the second and third follow-up surveys of the European
28 Community Respiratory Health Survey (ECRHS II and III, www.ecrhs.org), an
29 international, population-based, multi-centre cohort study of asthma and allergic
30 disease, which was first carried out in 1990. Detailed descriptions of the methods
31 used for ECRHS I and ECRHS II have been published elsewhere.(22, 23) Briefly,
32 participating centres randomly selected samples from subjects aged 20 to 44 in
33 order to track them for asthma, allergy and lung disease (See: www.ecrhs.org).
34 Participants completed a short postal questionnaire about asthma and asthma-like
35 symptoms and, from those who responded, a random sample was selected to
36 undergo a more detailed clinical examination. In ECRHS II, subjects who had
37 participated in the clinical phase of ECRHS I (performed between 1991 and 1994)
38 were invited to participate in the follow-up study. The clinical phase of ECRHS II was
39 carried out between 1998 and 2002. ECRHS III is the second follow-up study and
40 was carried out from February 2011 to January 2014.(22-24) The present study is
41 based on data from ECRHS II and III (see figure 1 for flowchart). Ethical approval for
42 the study from local research ethics committees, and written consent from
43 participants, were obtained.
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Health, habits and measurements

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Subjects answered the core ECRHS questionnaires, which included questions on lifestyle, respiratory symptoms, smoking history and general health. 'Current smokers' were defined as those who smoked tobacco regularly during the last month. 'Former smokers' were defined as smokers who denied having smoked regularly in the month prior to the examination. Those who reported no regular smoking at the time of, or prior to, the examination, were defined as 'never smokers'. The participants' height and weight were measured and their body mass index (BMI) was calculated.(24)

Assessment of physical activity

Physical activity was assessed in ECRHS II and III using replies from questionnaires. The assessment of PA in ECRHS has previously been described in detail, including how both the frequency and duration of PA were used to divide the population into categories.(22) In brief, participants were asked how often and for how many hours per week they usually exercised to the point that they became out of breath or sweaty. Participants who exercised two or more times a week, for at least 1 hour a week, were classified as physically active. Changes in activity status from baseline to follow up were categorised into four PA groups: persistently non-active (non-active at both baseline and follow up), became inactive (active at baseline and non-active at follow up), became active (non-active at baseline and active at follow up) and persistently active (active at both baseline and follow up).

Sleep questionnaires and measurements

Sleep-related symptoms were assessed using the Basic Nordic Sleep Questionnaire(25), where participants were asked about the frequency of insomnia symptoms. Answers were provided on a scale of 1–5: (1) never or very seldom, (2) less than once a week, (3) once to twice a week, (4) three to five times a week, (5) every day or almost every day of the week. Insomnia symptoms were defined using answers to three questions from the Basic Nordic Sleep Questionnaire: "I have difficulties falling asleep at night" (difficulties initiating sleep), "I wake up often during the night" (difficulties maintaining sleep) and "I wake up early in the morning and can't fall back asleep" (early morning awakenings). Those who reported these symptoms of insomnia ≥ 3 times a week (scores 4 and 5) were considered to have the

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3 corresponding insomnia subtype. Daytime sleepiness was evaluated using the
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6 Epworth Sleepiness Scale, a brief questionnaire that measures daytime sleepiness
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9 based on the likelihood of falling asleep in eight different situations.⁽²⁶⁾ Participants
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11 with an Epworth sleepiness scale score >10 were considered to have EDS.
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13 Participants were asked the question: how much sleep do you estimate that you get
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15 on average each night? According to their answers, they were classified as: short
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17 sleepers (≤ 6 hours/night), normal sleepers (6–9 hours/night) or long sleepers
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20 (≥ 9 hours/night).
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25 *Patient and public involvement*

26 The study's design did not involve patients or the general public. However, all
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28 participating patients were informed of the research objectives and their informed
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30 consent was obtained. The survey was completed by participants voluntarily and no
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32 input from patients was sought in interpreting or writing up the results. The results of
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34 the research will not be disseminated to the patients.
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37 *Statistical analysis*

38 Data are presented as numbers and percentages or mean \pm SD, depending on
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40 distribution. For bivariate analysis, the χ^2 test and one-way analysis of variance were
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42 used for nominal and continuous variables. Logistic regression was used for
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44 multivariable analyses to estimate the association between physical activity and
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46 sleep-related outcomes. The model was adjusted for potential confounders including
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48 age, sex, BMI, smoking history and study centre. In the analysis, all variables,
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50 including study centre (n=21), were treated as fixed effects. STATA V.16 was used
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52 for all statistical analyses.
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54 **Results**

55 *Participants and level of physical activity*

56 From a total of 5,850 participants in ECRHS II, we excluded those with missing data
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58 and included a total of 4,339 participants (48% men), see Figure 1. Figure 2 shows
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3 the prevalence of insomnia symptoms, short and long sleep durations, and daytime
4 sleepiness among subjects in the different countries included in the study. From
5 baseline to 10 years later, 36.9% of participants were persistently non-active, 17.9%
6 became physically active at follow up, 20.3% of participants became inactive, and
7 24.9% were persistently active (Table 1). There were geographical differences in the
8 level of physical activity between the ECRHS countries (Figure 3). Participants in
9 Norway were most likely to be persistently active, while participants in Spain,
10 followed by Estonia, were most likely to be persistently non-active (Figure 3).

11 12 13 14 15 16 17 18 19 *General characteristics and health*

20 Persistently active participants were more often men, they were younger, and they
21 had a slightly lower BMI (Table 1). They were also less likely to be current smokers
22 and more likely to be currently working (Table 1).

23 24 25 26 27 28 *Insomnia symptoms*

29 In unadjusted analysis, there was a significant difference in reporting difficulties
30 initiating sleep, early morning awakenings and any insomnia symptom where those
31 persistently active were least likely to report these symptoms. Also, persistently
32 active subjects were the least likely to report having two or three insomnia symptoms
33 (Table 2). After adjusting for age, sex, BMI, smoking history and study centre, this
34 negative association remained significant for difficulties initiating sleep (OR 0.58
35 (0.42-0.77)), any insomnia symptom (OR 0.78 (0.65-0.94) and reporting two (OR
36 0.60 (0.43-0.82) and three (OR 0.63 (0.41-0.98) insomnia symptoms (Table 3).
37 Additionally, in adjusted analysis, persistently active subjects were significantly less
38 likely to report difficulties initiating sleep (OR 0.80 (0.66-0.97) (Table 3). There were
39 also independent associations between insomnia symptoms and age, female gender
40 and BMI (Table 4).

41 42 43 44 45 46 47 48 49 50 51 *Sleep duration and daytime sleepiness*

52 In unadjusted analysis, there was a significant difference in short and long sleep
53 durations between levels of activity. Those who were persistently active were most
54 likely to be normal sleepers while the persistently non-active were least likely to be in
55 that category (70.9% vs. 59.2% respectively) (Table 2). After adjusting for age, sex,
56 BMI, smoking history and study centre, these results remained significant for
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3 persistently active subjects. They were significantly more likely to be normal sleepers
4 (OR 1.55 (1.29-1.87)) and significantly less likely to be short sleepers (OR 0.71 (0.58-
5 0.85)) or long sleepers (OR 0.48 (0.28-0.80)) (Table 3). Additionally, those who
6 became active were more likely to be normal sleepers than those who were
7 persistently non-active (OR 1.21 (1.00-1.47)) (Table 3).
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9 However, there was not a significant association between the mean Epworth
10 sleepiness scale score or percentage with an Epworth sleepiness scale score >10
11 and level of physical activity (Tables 2 and 3). Daytime sleepiness was also
12 independently associated with smoking (Table 4).
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Discussion

The main results of this study were that participants who reported being physically active at the start and end of a 10-year follow-up period were less likely to report insomnia symptoms at the follow up. We also found that subjects who are persistently active are more likely to sleep the recommended 6-9 hours. This association remained statistically significant after adjusting for sex, age, smoking history and BMI. We also found that persistently active participants were more often men, were younger, had a slightly lower BMI and were less likely to be current smokers and more likely to be currently working.

Our results are in line with previous studies that have shown the beneficial effect of physical activity on symptoms of insomnia (9, 10), but the current study additionally shows the importance of consistency in exercising over time, because the association was lost for initially active subjects who became inactive. A recent meta-analysis examining the effects of acute and regular exercise on a range of sleep variables showed that acute exercise (less than one week of exercise) has a small beneficial effect on many objective measures of sleep, such as total sleep time, insomnia symptoms and sleep quality.(7) Furthermore, this meta-analysis found greater benefits from regular exercise for both subjective and objective sleep parameters over time. Regular exercise had small beneficial effects on total sleep time and sleep efficiency, small-to-medium beneficial effects on sleep onset latency, and moderate beneficial effects on sleep quality.(7)

There are two recent systematic reviews and meta-analyses on the effects of PA on sleep(7) and insomnia(9), both substantially reviewing the same randomized controlled studies. Banno *et al.* included nine studies with a total of 557 participants.(7) The majority of participants exercised 3 times or less per week and the follow up interval was 4 months or shorter in all the studies except one. Their conclusion was that exercise could improve sleep, but that higher quality research was needed.(7) Five studies on insomnia, and, additionally, six on insomnia symptoms, showed shorter sleep latency and higher sleep efficacy, but the authors also acknowledged the small size of the literature and severe methodological limitations, often based on selection bias.(9) In addition, most previous studies are cross-sectional, which can also be considered a limitation.

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3 Furthermore, a recent systematic review of physical activity and sleep showed that
4 moderate exercise had a more promising outcome in terms of sleep quality than
5 vigorous exercise. It is therefore important to study further the impact of the intensity
6 of physical activity, in the context of age and gender, when exploring any beneficial
7 impact on sleep.(27)
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13 This study has a long follow-up period (10 years) and indicates strongly that
14 consistency in physical activity might be an important factor in optimizing sleep
15 duration and reducing the symptoms of insomnia. Most other studies have had a
16 much shorter follow-up period(7), which makes it more difficult to assess the
17 consistency of activity over time.
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22 Our results indicate that those who maintain a consistent level of physical activity are
23 also less likely to be both short (<6h) and long sleepers (>9h). Those who are
24 physically active in general are also more likely to engage in a healthier lifestyle (28),
25 which can likewise have an effect on sleep. Lifestyle factors, such as a healthy diet
26 and being physically active, are probably part of a phenotype that characterizes
27 those individuals who are generally engaged in a healthy lifestyle. A recent review
28 highlighted the importance of focusing on the combination of sleep, diet and exercise
29 when exploring healthy longevity.(29)
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38 The three groups reporting low physical activity in either of the ECRHS surveys, or at
39 both points in time, all report a very similar prevalence of insomnia symptoms,
40 extreme sleep lengths and daytime sleepiness. This is somewhat surprising,
41 especially given that those who were active in the follow-up survey but not at the
42 baseline have a very similar symptom profile to those who were inactive in both
43 surveys. Our study found that consistency in a behaviour such as physical activity for
44 more than a decade is strongly related to a lower incidence of insomnia and a more
45 “normal” sleep length. Important information concerning “the healthy phenotype”
46 would be missed if the physical activity data were available only at baseline or at
47 follow up but not at both time points.
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57 In a recent review based on 22 randomized controlled trials concerning the effects of
58 regular exercise (lasting at least two months on a regular basis) on self-reported
59 sleep quality, insomnia and daytime sleepiness, it was found that regular physical
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3 activity improved subjective sleep quality, insomnia severity and daytime sleepiness
4 as measured with the Epworth sleepiness scale.(30) These results regarding
5 insomnia symptoms are in line with our study, but the results on daytime sleepiness
6 differ from our results. The reason for this discrepancy could be due to different study
7 populations, as there were only two studies in this review that measured daytime
8 sleepiness using the Epworth sleepiness scale; one study assessed this among the
9 elderly, 60 years and older(13), and the other among overweight and obese men.(31)
10 Another recent review of 32 randomized control trials on the effects of exercise on
11 improving sleep disturbances showed that exercise is beneficial in improving sleep
12 quality, symptoms of insomnia, restless legs, sleep apnoea and daytime sleepiness.
13 However, exercise only had significant effects on sleepiness if it had lasted for more
14 than 12 weeks, while the exercise period did not matter in regards of the association
15 to sleep quality and insomnia symptoms.(32)

16 Another recent study showed that high or increasing levels of physical activity could
17 protect women from future insomnia.(18) Therefore, exercise seems to have a
18 stronger association with sleep quality and insomnia than with sleepiness, which is in
19 line with our results. However almost all previous studies, have the limitation that the
20 definition of sleepiness is limited to the estimate the likelihood of falling asleep but
21 not the general feeling of sleepiness, that we have shown is also an important part of
22 sleepiness.(33, 34) Another recent review exploring the associations of exercise,
23 sleep and cognitive function among older adults showed that physical activity is
24 associated with improved cognitive function but the association of sleep and
25 cognitive function seems to be U-shaped, as too much or too little sleep is negatively
26 associated with cognitive function.(35) We did not explore cognitive function in the
27 current study but It would be interesting for future studies to explore further how
28 cognitive function is affected by the association of physical activity and sleep.
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49 This study has several strengths such as the population-based nature, the
50 longitudinal study design and the large sample collected in the same manner at many
51 centres in 9 different countries. Another strength is the use of standardized and
52 validated procedures and instruments. The long follow up period is also a strength
53 since data on physical activity is collected ten years apart and subjects are
54 categorized according to change in physical activity. This study is however not
55 without limitations. It is not possible to know whether those who are active at both
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3 timepoints have been continuously physically active throughout the study period or
4 only at these two timepoints. Furthermore, physical activity was only measured using
5 a questionnaire. Another limitation of our study is that sleep variables are only
6 available at the follow-up, and we only have information on insomnia symptoms but
7 not the diagnosis of insomnia disorder. Sleep length and daytime sleepiness are also
8 based on subjective data. Therefore, even though the measurement of physical
9 activity is longitudinal, it may not be entirely appropriate to describe the associations
10 between physical activity and sleep outcomes as longitudinal. Also, there are
11 potential implications of residual confounders that can influence both physical activity
12 and sleep which were not explored in the current study (e.g. mental health,
13 musculoskeletal disorders/ chronic pain) which could influence the study findings.
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24 In conclusion, physical activity over time is associated with lower prevalence of
25 insomnia symptoms and with sleeping between 6-9 hours per night.
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5 **Data sharing statement:** Data are available on reasonable request. The data that
6 supports the findings of this study are available on request from the corresponding
7 author.
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13

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Table 1. Characteristics and general health of the participants by the level of physical activity

| | Persistently non-active | Became inactive | Became active | Persistently active | p-value |
|------------------------------------|-------------------------|-----------------|---------------|---------------------|------------------|
| General characteristics | | | | | |
| N, % | 1601 (36.9) | 881 (20.3) | 775 (17.9) | 1082 (24.9) | |
| Men, % | 44.3 | 49.0 | 46.8 | 53.7 | <0.001 |
| Age, years | 55.0 ± 7.2 | 54.5 ± 7.1 | 53.4 ± 7.2 | 53.7 ± 7.2 | <0.001 |
| Body mass index, kg/m ² | 27.6 ± 5.2 | 27.1 ± 4.9 | 27.1 ± 4.8 | 27.0 ± 4.4 | 0.007 |
| Currently working, % | 82.7 | 85.8 | 88.9 | 90.4 | <0.001 |
| Smoking history | | | | | |
| Never, % | 42.4 | 43.4 | 44.3 | 47.6 | <0.001 |
| Former, % | 34.4 | 39.8 | 37.5 | 40.0 | |
| Current, % | 23.2 | 16.9 | 18.2 | 12.4 | |

Table 2. Insomnia symptoms, sleep duration and daytime sleepiness by level of physical activity.

| | Persistently non-active (n=1601) | Became inactive (n=881) | Became active (n=775) | Persistently Active (n=1082) | p-value |
|--|--|-----------------------------------|---------------------------------|--|------------------|
| Insomnia symptoms | | | | | |
| Difficulties initiating sleep (%) | 15.4 | 14.0 | 11.7 | 8.2 | <0.001 |
| Difficulties maintaining sleep (%) | 31.9 | 32.1 | 33.0 | 28.5 | 0.128 |
| Early morning awakenings (%) | 18.2 | 18.3 | 15.0 | 13.2 | 0.002 |
| Any insomnia symptom (%) | 41.0 | 41.5 | 39.5 | 34.9 | 0.006 |
| Numbers of insomnia symptoms | | | | | |
| None (%) | 58.4 | 58.2 | 61.0 | 64.9 | 0.001 |
| One (%) | 23.2 | 25.2 | 24.0 | 23.8 | |
| Two (%) | 11.9 | 10.6 | 10.0 | 7.8 | |
| Three (%) | 6.6 | 6.1 | 5.1 | 3.6 | |
| Sleep duration | | | | | |
| Sleep time (hours) | 6.8 ± 1.1 | 6.8 ± 1.0 | 6.9 ± 1.0 | 6.9 ± 0.9 | 0.234 |
| Sleep time, % | | | | | |
| Short sleepers (≤ 6 hours) | 35.9 | 31.9 | 20.7 | 26.9 | <0.001 |
| Normal sleepers (6 – 9 hours) | 59.2 | 64.6 | 66.9 | 70.9 | |
| Long sleepers (≥ 9 hours) | 4.9 | 3.5 | 3.4 | 2.2 | |
| Daytime sleepiness | | | | | |
| Epworth sleepiness scale score | 6.8 ± 4.1 | 7.2 ± 4.1 | 6.9 ± 4.1 | 6.9 ± 3.8 | 0.106 |
| Epworth sleepiness scale score >10 (%) | 17.2 | 19.4 | 17.7 | 15.6 | 0.176 |
| Data are presented as mean ± standard deviation or % where indicated. Significant differences are in bold (p<0.05). *p-value from Pearson's chi-square test (numerical variables) and one-way analysis of variance (continuous variables). | | | | | |

Table 3. Independent association between the level of physical activity and medical disorders, insomnia symptoms, daytime sleepiness and sleep duration expressed as adjusted* odds ratios (95% CI) with the persistently non-active group as reference. Bold text indicates statistical significance.

| | Became inactive (n=881) | Became active (n=775) | Persistently active (n=1082) |
|---|-----------------------------------|---------------------------------|--|
| Insomnia symptoms | | | |
| Difficulties initiating sleep | 0.97 (0.75-1.25) | 0.82 (0.62-1.08) | 0.58 (0.42-0.77) |
| Difficulties maintaining sleep | 0.96 (0.80-1.17) | 1.04 (0.85-1.27) | 0.80 (0.66-0.97) |
| Early morning awakenings | 1.09 (0.87-1.38) | 0.86 (0.63-1.03) | 0.80 (0.63-1.03) |
| Any insomnia symptom | 1.02 (0.85-1.22) | 0.95 (0.78-1.14) | 0.78 (0.65-0.94) |
| Numbers of insomnia symptoms | | | |
| One | 1.07 (0.86-1.32) | 0.99 (0.79-1.24) | 0.91 (0.74-1.12) |
| Two | 0.89 (0.66-1.20) | 0.86 (0.63-1.17) | 0.60 (0.43-0.82) |
| Three | 1.09 (0.74-1.59) | 0.94 (0.62-1.42) | 0.63 (0.41-0.98) |
| Daytime sleepiness | | | |
| Epworth sleepiness scale score >10 | 1.17 (0.94-1.47) | 1.00 (0.78-1.27) | 0.87 (0.69-1.10) |
| Sleep duration | | | |
| Short sleepers (\leq 6 hours) | 0.89 (0.73-10.7) | 0.85 (0.69-1.03) | 0.71 (0.58-0.85) |
| Normal sleepers (6-9 hours) | 1.18 (0.98-1.42) | 1.21 (1.00-1.47) | 1.55 (1.29-1.87) |
| Long sleepers (\geq 9 hours) | 0.74 (0.47-1.17) | 0.84 (0.53-1.33) | 0.48 (0.28-0.80) |
| *Adjusted for age, sex, BMI, smoking history and center. Significant differences are in bold. | | | |

Table 4. Associations between age, sex, BMI and smoking history and sleep related symptoms.

| | Age | Sex | BMI | Smoking history |
|------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Insomnia symptoms | | | | |
| Difficulties initiating sleep | 1.02 (1.01-1.03) | 2.16 (1.77-2.64) | 1.02 (1.01-1.05) | 0.81 (0.66-0.99) |
| Difficulties maintaining sleep | 1.04 (1.03-1.05) | 1.80 (1.56-2.07) | 1.01 (1.00-1.03) | 1.09 (0.95-1.26) |
| Early morning awakenings | 1.02 (1.01-1.03) | 1.52 (1.28-1.80) | 1.01 (1.00-1.03) | 1.02 (0.85-1.21) |
| Any insomnia symptom | 1.03 (1.02-1.04) | 1.75 (1.53-1.99) | 1.02 (1.01-1.03) | 1.07 (0.93-1.22) |
| Numbers of insomnia symptoms | | | | |
| One | 1.03 (1.01-1.04) | 1.47 (1.26-1.71) | 1.02 (1.00-1.03) | 1.15 (0.98-1.34) |
| Two | 1.04 (1.02-1.06) | 2.11 (1.69-2.64) | 1.02 (1.00-1.05) | 1.01 (0.80-1.26) |
| Three | 1.04 (1.02-1.06) | 2.62 (1.93-3.53) | 1.03 (0.99-1.06) | 0.89 (0.66-1.20) |
| Daytime sleepiness | | | | |
| Epworth sleepiness scale score >10 | 0.99 (0.98-1.00) | 0.95 (0.81-1.12) | 1.01 (0.99-1.03) | 1.28 (1.08-1.52) |
| Sleep duration | | | | |
| Short sleepers (≤ 6 hours) | 1.01 (0.99-1.02) | 0.88 (0.77-1.00) | 1.03 (1.02-1.05) | 0.83 (0.72-0.96) |
| Normal sleepers (6-9 hours) | 0.99 (0.98-0.99) | 1.08 (0.95-1.23) | 0.96 (0.95-0.98) | 1.20 (1.05-1.38) |
| Long sleepers (≥ 9 hours) | 1.03 (1.01-1.06) | 1.35 (0.96-1.89) | 1.02 (0.99-1.06) | 0.95 (0.67-1.34) |

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3 **Figure legends:**

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5 **Figure 1.** Flow chart of the study population in the European community health
6 survey (ECRSH)

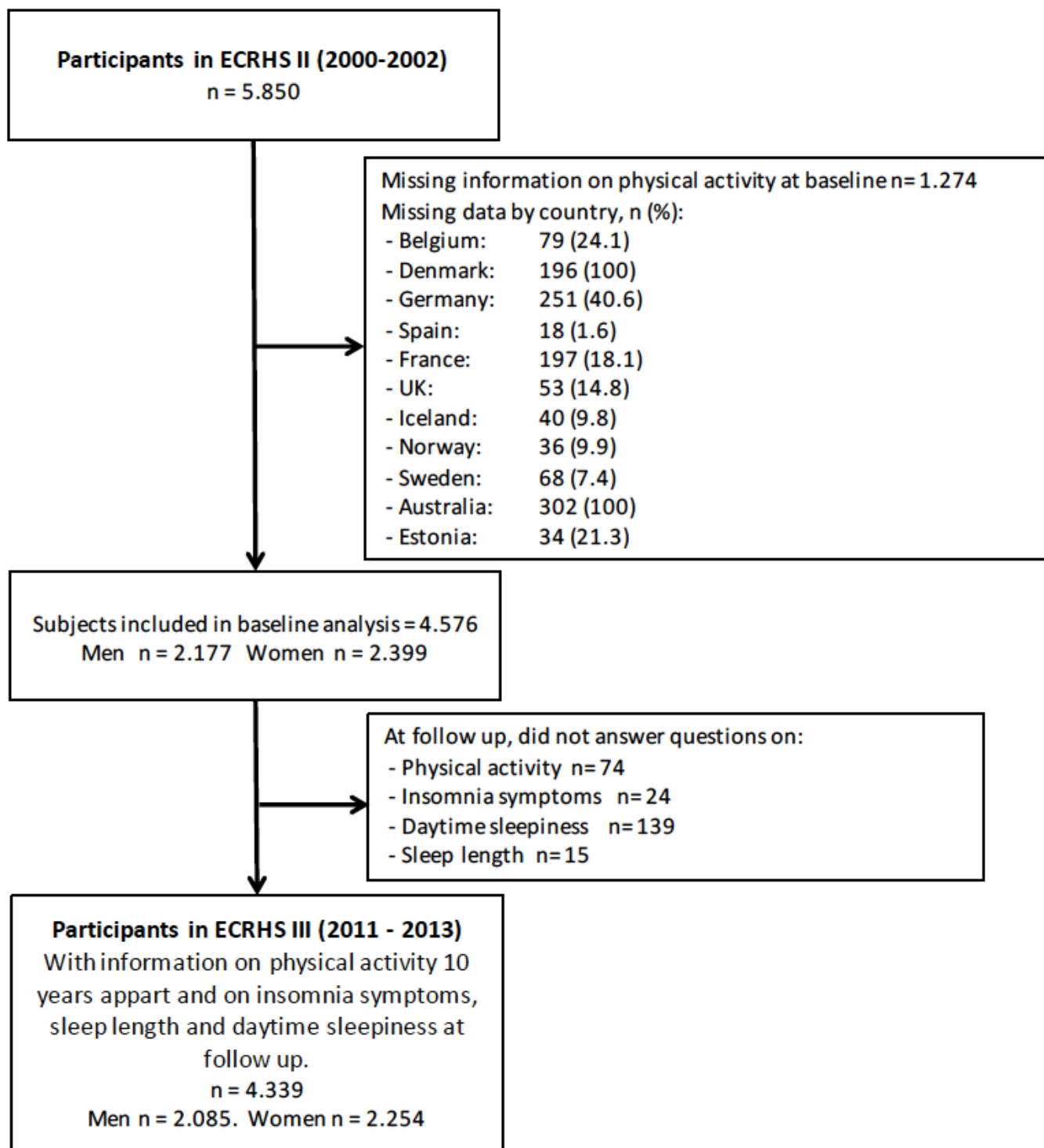
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8 **Figure 2.** Prevalence of any insomnia symptom, short sleep duration (≤ 6 hours per
9 night), long sleep duration (≥ 9 hours per night) and daytime sleepiness (ESS >10) by
10 country
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13 **Figure 3.** Activity levels by country
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Figure 1. Flow chart of the study population in the European community health survey (ECRSH)

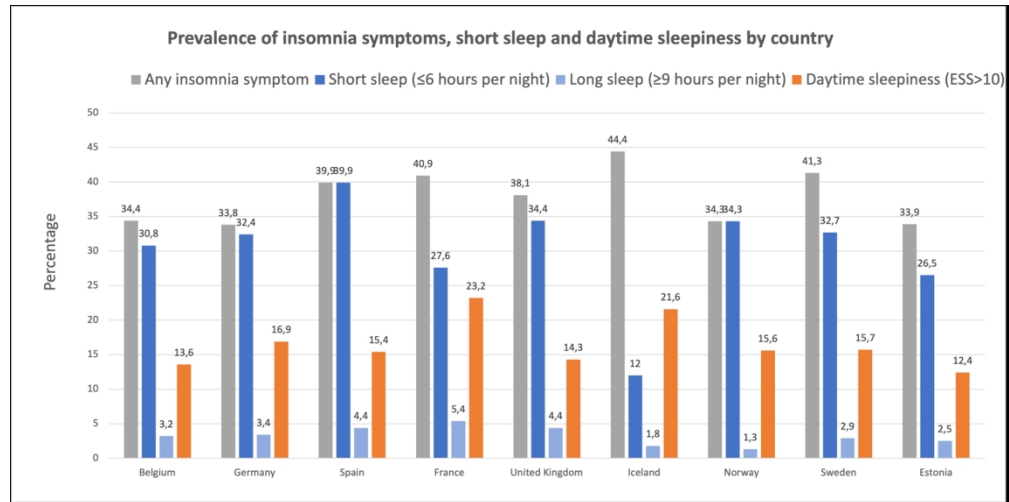


Figure 2. Prevalence of any insomnia symptom, short sleep duration (≤ 6 hours per night), long sleep duration (≥ 9 hours per night) and daytime sleepiness (ESS >10) by country

229x115mm (220 x 220 DPI)

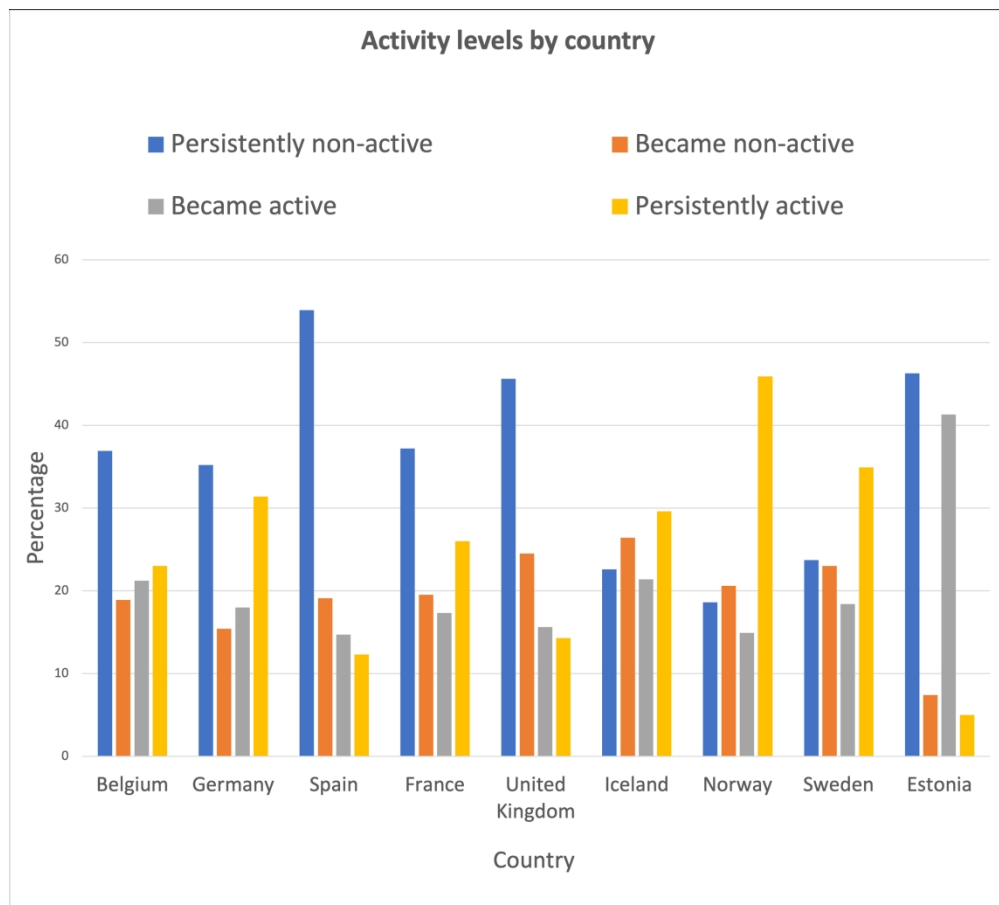


Figure 3. Activity levels by country

224x202mm (300 x 300 DPI)

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

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

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(e) Describe any sensitivity analyses

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60**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 | 8, fig 1 |
| | | (b) Give reasons for non-participation at each stage | 8, fig 1 |
| | | (c) Consider use of a flow diagram | Fig 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1 |
| | | (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) | 6 |
| Outcome data | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time | 8-9 |
| | | <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure | N/A |
| | | <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures | N/A |
| 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 | Table 1, 2, 3 and page 8-9 |
| | | (b) Report category boundaries when continuous variables were categorized | See tables and methods |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | x |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N/A |

Discussion

| | | | |
|------------------|----|--|--------|
| Key results | 18 | Summarise key results with reference to study objectives | 10 |
| 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 | 4, 12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 10-12 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10, 12 |

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 | 2 |
|---------|----|---|---|

*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.