Association between sleep disorders and osteoarthritis: a case-control study of 351,932 adults in the United Kingdom

Louis Jacob, PhD[a,b,c]; Lee Smith, PhD[d]; Marcel Konrad, PhD[e]; Karel Kostev, PhD[f]

[a] Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Dr. Antoni Pujadas, 42, Sant Boi de Llobregat, Barcelona 08830, Spain

[b] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain

[c] Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux 78180, France

[d] The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK

[e] FOM University of Applied Sciences for Economics and Management, Frankfurt, Germany

[f] Epidemiology, IQVIA, Frankfurt, Germany

Correspondence:

Prof. Dr. rer. med. Karel Kostev

Epidemiology

IQVIA

Unterschweinstiege 2-14

60549 Frankfurt am Main

Germany

Tel.: +49-(0)69-66 04-4878

karel.kostev@iqvia.com

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Louis Jacob contributed to the design of the study, managed the literature searches, wrote the first draft of the manuscript, and corrected the manuscript. Lee Smith and Marcel Konrad contributed to the design of the study and corrected the manuscript.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract

This study aimed to analyze the association between sleep disorders and osteoarthritis in adults in the United Kingdom. This case-control study included patients aged ≥18 years who were diagnosed with osteoarthritis for the first time in one of 256 general practices in the United Kingdom between 1997 and 2016 (index date). Patients without osteoarthritis were matched (1:1) to those with osteoarthritis by sex, age, index year, general practice, observation time prior to index date (in years), obesity, injuries, and other types of arthritis. For patients without osteoarthritis, the index date was a randomly selected visit date between 1997 and 2016. The presence of sleep disorders prior to index date was assessed in the two groups. Finally, conditional logistic regression analyses were conducted to investigate the association between sleep disorders and osteoarthritis. This case-control study included 351,932 adults (61.5% women; mean [SD] age 64.9 [14.2] years). Overall, there was a significant association between sleep disorders and osteoarthritis (OR = 1.25, 95% CI = 1.22-1.29). This finding was corroborated in all sex and age subgroups except in patients aged >80 years. In terms of the type of sleep disorder, nonorganic sleep disorders, hypersomnia and sleep apnea were associated to a significant extent with higher odds of developing osteoarthritis. Finally, the relationship between sleep disorders and osteoarthritis was significant in all osteoarthritis subgroups except in that of patients with knee osteoarthritis. Based on these results, it can be concluded that sleep disorders may play a role in the development of osteoarthritis.

Keywords: sleep disorders; osteoarthritis; case-control study; United Kingdom.

Introduction

Osteoarthritis is a degenerative joint disease characterized by several pathological changes such as progressive destruction of the articular cartilage, formation of osteophytes and inflammation of the synovium (Chen et al., 2017). In 2017, the global age-standardized prevalence of osteoarthritis was 3,754 cases per 100,000 persons, a figure that is expected to increase in the years to come due to population aging (Safiri et al., 2020). Osteoarthritis has a negative impact on quality of life (Moskowitz, 2009), multimorbidity (Swain et al., 2020) and mortality (Wang et al., 2020), and is associated with substantial direct and indirect costs (Salmon et al., 2019). In view of these facts, further research is warranted to better identify risk factors and protective factors with respect to osteoarthritis.

A significant body of research has focused on the association between osteoarthritis and sleep disorders in recent years (Cho et al., 2020; Fertelli and Tuncay, 2019; Fu et al., 2019; Jeong et al., 2019; Jung et al., 2018; Koyanagi et al., 2014; Martinez et al., 2019; Taylor et al., 2018; Wilcox et al., 2000). For example, a study in the United States including 300 veterans with hip or knee osteoarthritis found that the prevalence of insomnia-related symptoms was around 53% in the sample (Taylor et al., 2018). Another US study involving 429 older adults with knee pain or radiographic knee osteoarthritis showed that the prevalence of weekly problems with sleep onset, sleep maintenance and early morning awakening was 31%, 81% and 51%, respectively (Wilcox et al., 2000). The deleterious effects of osteoarthritis on sleep are likely mediated by pain and poor levels of well-being. Interestingly, two studies have also suggested that sleep disorders may increase the occurrence of osteoarthritis (Cho et

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al., 2020; Jung et al., 2018). This association may be due to obesity (Itani et al., 2011; Reyes et al., 2016), hypertension (Guo et al., 2013; Zhang et al., 2017), diabetes (Gangwisch et al., 2007; Louati et al., 2015), or psychiatric disorders (Freeman et al., 2020; Huang et al., 2016). Although these two studies have advanced the field, they are subject to several limitations that need to be acknowledged at this point. First, both studies focused on sleep duration and not on sleep disorders, and this may have impacted the results. Second, these studies were conducted in South Korea, and it may therefore not be possible to extrapolate their findings to other countries. Taking these limitations into account, there is a clear need to collect additional data illustrating the relationship between sleep disorders and osteoarthritis.

In view of this, the goal of the present case-control study was to analyze the association between sleep disorders and osteoarthritis in patients treated in general practices in the United Kingdom. Given that the prevalence of insomnia has increased in the general population in the United Kingdom in recent decades (Calem et al., 2012), investigating the relationship between sleep disorders and osteoarthritis in this country is a public health priority.

Materials and Methods

Database

Data from the Disease Analyzer database (IQVIA) were used for this study. The Disease Analyzer database contains sociodemographic, clinical and pharmaceutical data obtained directly and in an anonymized format from general and specialized practices in the United Kingdom (Ogdie et al., 2012). Clinical data are coded using the

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International Classification of Diseases, 10th revision (ICD-10), while pharmaceutical data are obtained using the European Pharmaceutical Market Research Association (EPhMRA) Anatomical Therapeutic Chemical Classification (ATC) system. The quality of the data is assessed regularly on the basis of several criteria such as the completeness of documentation and the linkage between diagnoses and prescriptions. Finally, practices from the United Kingdom included in the Disease Analyzer database are selected based on several characteristics (i.e., age of practitioner, community size category of the practice and region of the practice) (Ogdie et al., 2012).

Study population

This case-control study included adults aged ≥18 years who were diagnosed for the first time with osteoarthritis (ICD-10: M15-M19) in one of 256 general practices (1,721 physicians) in the United Kingdom between January 1997 and December 2016 (index date). Patients without osteoarthritis were matched (1:1) to those with osteoarthritis by sex, age, index year, general practice, observation time prior to index date (in years), obesity (ICD-10: E66), injuries excluding head and thorax injuries (S00-S99 and T07 excluding S00-S09 and S20-S29), and other types of arthritis (M00-M14, M45-M49, M32, and L40.5). For patients without osteoarthritis, the index date was a randomly selected GP visit date between January 1997 and December 2016 (Figure 1). Finally, the study followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Supplementary Table 1).

Study variables

Study variables included sleep disorders (independent variable), osteoarthritis (dependent variable), sex, age, observation time prior to index date, obesity, injuries

(excluding head and thorax injuries), and other types of arthritis. The presence of sleep disorders prior to index date was assessed, where sleep disorders corresponded to nonorganic sleep disorders (ICD-10: F51), insomnia (G47.0), hypersomnia (G47.1), disorders of the sleep-wake schedule (G47.2), and sleep apnea (G47.3). Since the misdiagnosis of sleep disorders is relatively common in primary care practices (Grandner and Chakravorty, 2017), unspecified sleep disorder (G47.9) was not included in the analyses. Osteoarthritis included polyosteoarthritis (ICD-10: M15), hip osteoarthritis (M16), knee arthritis (M17), and other and unspecified osteoarthritis (M18 and M19).

Statistical analyses

Baseline characteristics (i.e., sex, age, observation time prior to index date, obesity, injuries, and other types of arthritis) were compared for adults with and without osteoarthritis using McNemar tests for categorical variables and Wilcoxon signed-rank tests for continuous variables. Conditional regression analyses were also conducted to assess the association between sleep disorders and osteoarthritis in the overall population and in specific sociodemographic (i.e., female, male, ≤50 years, 51-60 years, 61-70 years, 71-80 years, and >80 years), sleep disorder (i.e., nonorganic sleep disorders, insomnia, hypersomnia, disorders of the sleep-wake schedule, and sleep apnea) and osteoarthritis subgroups (i.e., polyosteoarthritis, hip osteoarthritis, knee osteoarthritis, and other and unspecified osteoarthritis). The results of the logistic conditional regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Finally, there was no missing data. P-values of less than 0.05 were considered statistically significant. All analyses were performed using SAS 9.4.

Results

This case-control study included 175,966 patients with osteoarthritis and 175,966 patients without osteoarthritis. In total, 61.5% of subjects were women, and the mean (standard deviation) age was 64.9 (14.2) years (Table 1). The mean (standard deviation) observation time prior to index date was 6.7 (4.9) years. In addition, the prevalence of obesity, injuries and other types of arthritis was 10.0%, 29.3% and 13.0%, respectively. Finally, an history of any sleep disorder was documented in 6.6% of osteoarthritis patients and in 5.4% of those without osteoarthritis. For more than 80% of patients with a history of sleep disorders, these conditions were documented only once or a few times within the same one-year timeframe. The results of the conditional logistic regression analyses are displayed in Table 2. Overall, there was a positive and significant association between sleep disorders and osteoarthritis (OR = 1.25, 95% CI = 1.22-1.29). This finding was corroborated in all sex and age subgroups except in patients aged >80 years (OR = 0.94, 95% CI = 0.88-1.01), with ORs decreasing with increasing age. In terms of the type of sleep disorder, nonorganic sleep disorders (OR = 1.51, 95% CI = 1.44-1.58), hypersomnia (OR = 1.79, 95% CI = 1.44-2.22) and sleep apnea (OR = 3.79, 95% CI = 3.20-4.50) were associated to a significant extent with higher odds of developing osteoarthritis. Finally, the relationship between sleep disorders and osteoarthritis was significant in all osteoarthritis subgroups except in that of patients with knee osteoarthritis (OR=0.97, 95% CI = 0.86-1.10).

Discussion

Main findings

This study of almost 352,000 patients from the United Kingdom showed that the prevalence of sleep disorders was 6.6% in those with osteoarthritis and 5.4% in those without osteoarthritis. The regression analysis also revealed that there was a positive and significant association between sleep disorders and osteoarthritis (OR = 1.25, 95% CI = 1.22-1.29). To the best of the knowledge of the authors, this is one of the largest studies to date in this area, and it is also one of the first studies to focus on clinically diagnosed sleep disorders rather than sleep duration.

Interpretation of the findings

The present case-control study is in line with previous studies conducted in other settings. One cross-sectional study of 11,540 individuals from South Korea found that sleeping ≤5 hours per night was associated to a significant extent with higher odds of developing osteoarthritis (men: OR = 1.38-2.28; women: OR =1.26-1.63) (Jung et al., 2018). Another study including 8,918 adults living in the same country revealed that there was a cross-sectional association between getting ≤6 hours of sleep per night and developing osteoarthritis (OR = 1.20, 95% CI = 1.03-1.39; comparison group: 7-8 hours of sleep per night) (Cho et al., 2020). The present study not only corroborates these findings in the United Kingdom, but also shows that the relationship between sleep disorders and osteoarthritis relationship is significant in all sex and age groups except in that of patients aged >80 years. The lack of significant results in older patients and the decrease in the ORs with increasing age may be due to the fact that osteoarthritis is relatively common in old age, even in the absence of sleep disorders (Anderson and Loeser, 2010). In terms of individual sleep disorders, the association was positive for all conditions but only significant for nonorganic sleep disorders,

hypersomnia and sleep apnea, possibly due to a lack of statistical power. Finally, the association between sleep disorders and osteoarthritis was significant for all types of osteoarthritis except knee osteoarthritis; further research is needed to better understand this unexpected result.

Several key mediating factors are likely involved in the association between sleep disorders and osteoarthritis. One longitudinal study including 22,743 employees from Japan found that sleeping less than five hours per night was associated with a 1.20- and 1.71-fold increase in the risk of obesity in men and women respectively (Itani et al., 2011). Meanwhile, it was observed in a population-based cohort of 1,764,061 individuals living in Spain that overweight and obesity significantly increased the risk of hip, knee and hand osteoarthritis (Reyes et al., 2016). A second potential mediator is hypertension. Indeed, a systematic review and meta-analysis of 21 studies including a total of 225,858 adults revealed that short sleep duration was cross-sectionally and longitudinally associated with hypertension (Guo et al., 2013). Furthermore, it was observed in another meta-analysis of eight studies that there was a significant association between hypertension and both radiographic and symptomatic knee osteoarthritis (Zhang et al., 2017). Interestingly, the relationship between sleep disorders and osteoarthritis may also involve diabetes. As a matter of fact, short sleep duration is a risk factor for diabetes (Gangwisch et al., 2007), while diabetes favors the occurrence of osteoarthritis (Louati et al., 2015). Besides, previous research also tends to indicate that psychiatric disorders may play a substantial role in the relationship between sleep disorders and osteoarthritis. In fact, sleep disorders frequently lead to poor mental health (Freeman et al., 2020). Interestingly, a longitudinal population-based study including 328,872 participants from Taiwan further found that psychiatric

conditions were associated with a 1.42-fold increase in the risk of osteoarthritis (Huang et al., 2016). Finally, one should bear in mind that the association between sleep disorders and osteoarthritis is bidirectional, and that osteoarthritis may lead to sleep disorders. The effects of osteoarthritis on sleep may involve pain (Finan et al., 2013; Neogi, 2013) and adverse mental health outcomes (Gupta et al., 2009; Sharma et al., 2016).

Clinical implications and directions for future research

Based on the results of this study, it can be concluded that sleep disorders may favor the occurrence of osteoarthritis. In this context, measures are needed to tackle the negative impact of sleep disorders, including the early diagnosis and management of these chronic conditions. Previous research has indicated that sleep disorders are frequently underdiagnosed (Grandner and Chakravorty, 2017; Kapur et al., 2002), and sleep-related symptoms should therefore be assessed on a regular basis in primary care practices. Following the diagnosis of sleep disorders, personalized and individualized treatment and management are necessary (e.g., cognitive behavior therapy for insomnia, sleep-wake schedule and melatonin/bright light therapy regimen for delayed sleep phase syndrome, and dopaminergic agonists for restless legs syndrome) (Ramar and Olson, 2013). In terms of future research, additional studies of a longitudinal nature are needed to confirm these results and to identify potential mediators involved in the association between sleep disorders and osteoarthritis (e.g., obesity, hypertension, diabetes, and psychiatric disorders).

Strengths and limitations

The major strengths of this study are the sample size and the use of data obtained in general practices. Nonetheless, the study findings must be interpreted in the light of several limitations. First, although no data from such practices were available it is possible that a substantial proportion of patients may have been diagnosed with sleep disorders in specialized settings such as neurological practices. Second, not all sleep disorders (e.g., unspecified sleep disorder) were included in the analyses, which may have impacted the results of this study. Third, the diagnosis of osteoarthritis relied exclusively on ICD-10 codes, while radiographic data would have allowed more detailed analyses. Fourth, no information was available on social and behavioral factors (e.g., shift work, physical activity and alcohol consumption), although these factors may play a confounding role in the association between sleep disorders and osteoarthritis. Fifth, as sleep disorders were diagnosed only once in the majority of patients, the impact of the duration of these conditions on osteoarthritis could not be investigated. Sixth, this was a case-control study, and it was thus not possible to determine causality or temporality with respect to the relationship between sleep disorders and osteoarthritis.

Conclusions

The present case-control study conducted in the United Kingdom identified a positive and significant association between sleep disorders and osteoarthritis. In light of these findings, it is important to improve the diagnosis and the management of sleep disorders to mitigate their potential deleterious effects on osteoarthritis. More research of a longitudinal nature is also warranted to elucidate the exact role played by several chronic conditions in the relationship between sleep disorders and osteoarthritis.

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Table 1

Baseline characteristics of study patients after 1:1 matching

Variable	Patients with osteoarthritis (N = 175,966)	Patients without osteoarthritis (N = 175,966)	P-value
Sex			
Female	61.5	61.5	1.000
Male	38.5	38.5	
Age			
Mean age in years (standard deviation)	64.9 (14.2)	64.9 (14.2)	1.000
≤50 years	15.3	15.3	
51-60 years	22.7	22.7	
61-70 years	24.9	24.9	1.000
71-80 years	22.6	22.6	
>80 years	14.5	14.5	
Mean observation time prior to index date in years (standard deviation)	6.7 (4.9)	6.7 (4.9)	1.000
Comorbidities documented within 12 months prior to index date			
Obesity	10.0	10.0	1.000
Injuries	29.3	29.3	1.000
Other types of arthritis	13.0	13.0	1.000

Data are percentages unless otherwise specified.

Table 2

Association between sleep disorders and osteoarthritis in patients in the United Kingdom

Population	Prevalence in patients with osteoarthritis	Prevalence in patients without osteoarthritis	Odds ratio (95% confidence interval)	P-value
Overall	6.6	5.4	1.25 (1.22-1.29)	<0.001
Sex				
Female	7.3	6.1	1.22 (1.17-1.25)	<0.001
Male	5.6	4.2	1.35 (1.29-1.42)	<0.001
Age				
≤50 years	5.8	3.4	1.76 (1.62-1.92)	<0.001
51-60 years	6.5	4.7	1.41 (1.32-1.49)	<0.001
61-70 years	6.9	5.2	1.34 (1.27-1.42)	<0.001
71-80 years	6.8	6.2	1.11 (1.05-1.18)	<0.001
>80 years	7.1	7.5	0.94 (0.88-1.01)	0.069
Type of sleep disorder				
Nonorganic sleep disorders	2.7	1.8	1.51 (1.44-1.58)	<0.001
Insomnia	3.8	3.6	1.03 (1.00-1.07)	0.081
Hypersomnia	0.1	0.1	1.79 (1.44-2.22)	<0.001
Disorders of the sleep-wake schedule	0.0	0.0	1.28 (0.90-1.82)	0.170
Sleep apnea	0.4	0.1	3.79 (3.20-4.50)	<0.001
Type of osteoarthritis				
Polyosteoarthritis	7.2	5.7	1.28 (1.16-1.42)	<0.001
Hip osteoarthritis	6.7	5.6	1.23 (1.10-1.36)	<0.001
Knee osteoarthritis	5.1	5.2	0.97 (0.86-1.10)	0.613
Other and unspecified osteoarthritis	6.7	5.3	1.27 (1.24-1.32)	<0.001

Figure 1