

Sleep Disturbances, Stress, Obesity and Osteoarthritis

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Abstract

Background: Osteoarthritis, a prevalent health problem with few successful strategies to counter this disabling disorder may be influenced adversely by the interplay of a variety of factors, including obesity, excess stress, and sleep disturbances.

Objective: The present commentary provides an overview of research that specifically focuses on sleep disturbances, obesity, and stress, and their interplay in the context of improving our knowledge base about osteoarthritis and its treatable correlates.

Methods: To examine these issues, data from major electronic data bases and extending from 2014 - 2018 using the key words-stress, sleep, obesity, and osteoarthritis were sought. After reviewing the related abstracts, those English language articles deemed pertinent to the topic of interest were critically reviewed and summarized in narrative form.

Results: A reasonable body of evidence supports the importance of an association between stress, sleep deprivation, injurious physical behaviors, obesity, depression, pain, low life quality, and osteoarthritis, although not necessarily in that order.

Conclusion: Teasing out the differential role of these overlapping factors and heightening individual and public awareness of their linkages appears to have potential merit in efforts to prevent or reduce the degree of osteoarthritis disablement that prevails at both the individual and national level.

Keywords: *Obesity; Osteoarthritis; Pain; Sleep; Sleep Disturbances; Stress*

Background

Sleep, a natural function driven by endogenous 24 hour cyclical circadian rhythms [1] is an increasingly recognized factor of high import in the context of efforts to attain or maintain optimal health and wellbeing across the lifespan [2]. Stress, a widespread health-associated determinant is one factor among many that can seriously impact sleep quality and duration quite markedly, with negative health ramifications [3]. Conversely, sleep disturbances including sleep deprivation, sleep fragmentation, or poor sleep quality that may arise for reasons other than stress, may increase the risk of incurring excess or unremitting levels of stress. At the same time, stress may not only impact weight gain due to its oftentimes negative effects on eating behaviors and emotional eating, but it may increase the risk for sustaining a work, fall, or motor vehicle injury that can lead to osteoarthritis or exacerbate its magnitude, if already present. If this negative series of events cannot be resolved in a timely way, an ensuing cycle of sleep disturbances may conceivably heighten any prevailing stress, as well as the prevailing degree of obesity, and possibly joint loading. Presumably, therefore, although not commonly cited as a primary determinant of osteoarthritis disability, a persistent combination of sleep deprivation, restriction, or fragmentation, along with stress that leads to weight gain, or injury or both, can produce possible irreversible changes in cartilage physiology that fosters a cycle of pain as well as poor life quality and potential mental health declines that continue to interfere with sleep [4].

Indeed, research reveals that the presence of painful osteoarthritis can interfere quite markedly with sleep [5], while producing symptoms of immense fatigue [6] that in turn can foster or perpetuate sleep disturbances [7], along with possible declines in work productivity, physical activity participation, challenges in weight control, or efforts to lose weight, along with the risk of excess emotional, mental, and physical stress. Current research further reveals, inadequate sleep may impair muscle strength [8], a very salient osteoarthritis determinant.

However, a review of the literature reveals very few reports that specifically discuss the role of sleep disturbances in either the context of osteoarthritis or the role of stress in the context of sleep deprivation as this relates to this disabling condition, despite the fact both

sleep and stress are partly governed by co-existing neural mechanisms, and are potentially compounded by the presence of pain as suggested by Petrov, et al. [9] and Mills, *et al* [10]. Moreover, even though Davis [11] reviewed studies that indicated that pain interferes with sleep and, in turn, sleep disturbances increase pain almost 15 years ago, and that almost 60% of those with arthritis do experience night pain, sleep has generally not been addressed as a major treatment concern, target, disease determinant, or outcome variable among the osteoarthritis population with any degree of regularity [10].

Aims

To update the work by Davis [11] and to expand upon this by going beyond the limits of discussing the prevalence of sleep challenges among osteoarthritis sufferers.

Methods

To obtain the desired data and to support the main aim of this report, peer-reviewed articles housed in Scopus, PUBMED, and Web of Science Cumulative Data Bases published over the last five years were specifically sought. Key words included- osteoarthritis, obesity, insomnia, sleep, sleep deprivation, sleep fragmentation, and stress. All articles relevant to the topic in question were carefully reviewed to ascertain their possible value in the present context and articles eliminated were those that did not relate to the specific topics of interest, were non-English manuscripts without an English abstract, or were not readily obtainable. Articles selected were those deemed to support the relevance of conducting future analyses of these issues, and included a number of well cited studies and some attained via a manual search of article citations. These topics include, but are not limited to the concept of 'clocks' and sleep, stress and sleep disturbances, and their individual or collective relationship to obesity or weight gain, injury risk, depression, and widespread pain, all well-established pathogenic or osteoarthritis outcome determinants. However, this report is neither a comprehensive review, nor a systematic review. The sole aim being to examine the body of relevant material and provide a comprehensive overview of a variety of salient research observations related to this topic and to uncover whether there is an unmet need for further research in this realm.

Results

Compared to the numbers of available osteoarthritis related papers, the present search confirmed the continued presence of a highly limited scope of research efforts on this current topic, when using the key words 'osteoarthritis and sleep', whereby Scopus listed 336 articles between January 2014-March 2018; PUBMED - 165; and Web of Science consolidated data base - 583, with many reports that were not on the topic of interest. In addition, a manual search revealed very few additional papers of import were published between 2005-2014. The papers scanned were also very broad in terms of type of report type e.g. review articles versus research articles, research designs of a highly varied nature, e.g. sleep laboratory studies versus animal model studies, highly diverse research questions, substrate or populations examined, as well as the extent of the pathology or prevailing health conditions of subjects in clinical or basic studies. Other variations included but were not limited to different analytic tools, study durations, medication regimens, and the inability to tease out baseline comorbid manifestations from emergent problems. The application of the differential use of sleep as a predictor variable versus an outcome variable made any summative analysis hard to contemplate.

Indeed, it was impossible to synthesize this diverse material, except in a broad way, for example terms used to denote sleep issues alone included the terms, sleep onset, sleep fragmentation, sleep efficiency, total sleep time, sleep quality, sleep-wake schedules, insomnia, sleep problems, sleep disturbances, sleep abnormalities, pain-related sleep disturbances, sleep complaints, sleep disorders, unrefreshing sleep, and others.

The key issues examined and sought in this body of literature were thus those selected a priori and these were then categorized as those describing the impact of sleep in general on wellbeing, stress and sleep, sleep and obesity, osteoarthritis pathology and sleep, and those related specifically to mechanisms of impaired sleep relative to osteoarthritis. Possible future research and clinical directives are also outlined.

Sleep Deprivation, Fragmentation, or Disrupted Sleep

A substantive array of reports supports the importance of an optimal amount of high quality sleep, in order to foster adequate function and optimally adaptive behaviors throughout the day. Conversely, persistent sleep deficiencies can predictably impact one's functional ability, plus one's general coping and cognitive ability, as well as one's overall physiological and mental health status, significantly and adversely. As noted by Engin [12] having an adequate amount of quality sleep each 24 hour period, which is regulated by an intrinsic circadian timing system, specifically helps to coordinate cellular and physiological processes that produce optimal health. However, any presiding desynchronization or uncoupling between these peripheral and central clock components potentially predicts an increased risk for a variety of health issues, such as metabolic disorders.

New research further shows that 'clock genes' expressed in synovial tissues and chondrocytes – are very vulnerable to extrinsic stimuli and their disruption due to sleep disturbances and other factors has been linked to the development of osteoarthritis [13], inflammatory disease factors [14], abnormal chondrocyte metabolic processes [15], and cartilage pathology or joint damage [16], as well as pain [17,18]. In addition, not having enough sleep can also prove highly hazardous to one's health due to its possible negative impact on eating behaviors, weight status, reaction time, cognitive, emotional, and muscular functioning.

Osteoarthritis and Sleep Disturbances

As outlined above, despite the limited number of studies documenting specific sleep problems associated with osteoarthritis [19], the presence of unremitting osteoarthritis pain, and possible mood disturbances that may accompany osteoarthritis, can undoubtedly foster persistent bouts of sleep deprivation and various forms of insomnia [10,21,22]. In addition to perpetuating pain or exacerbating this, excessive fatigue [20] and a low motivation for activity, a poor life quality may readily emerge [21]. At the same time, persistent irritability, depression, and negative eating and exercises practices can raise the risk for obesity, as well as excess osteoarthritis disability [23]. Moreover, pain-evoked interleukin-6 responses [17] associated with inflammation and the onset of negative mood states [24] observed in cases of persistent sleep deficiencies, are likely to exacerbate the progression of any prevailing joint pathology.

Animal studies further reveal that sleep disturbances can result in the expression of angiogenic factors that can disrupt the integrity of a joint as well as producing inevitable irreversible osteoarthritis like changes [23]. Moreover, the inability of patients to achieve normalized continuous sleep patterns post- joint replacement surgery may delay healing and well-being among cases undergoing hip joint replacement surgery [25], who may experience worsened sleep quality after surgery. Inadequate sleep durations can also magnify the extent and intensity of the local pain experience as well as the disease severity that is found among persons with knee osteoarthritis [21,26].

Unfortunately, as discussed at length by Parmalee, *et al.* [27], the presence of chronic osteoarthritis has the potential to increase the risk for incurring sleep disturbances, including disturbances in initiating and maintaining sleep, sleep duration, and continuity. Moreover, if these problems are not resolved, they can predict an increased risk of finding higher rates of depression and disability among persons with high pain levels at follow up with a fair degree of certainty. In support of this idea, Allen, *et al.* [22] found cases with both hip and knee osteoarthritis readily reported experiencing significant sleep problems, independent of any other factor. In the long term, poor sleep, which does affect a sizeable percentage of those with knee or hip osteoarthritis [19], can arguably increase the challenges of managing the disease. In particular, a consistent pattern of poor sleep practices or experiences or both can predictably increase pain severity [19], which in turn, increases the risk for possible worsening of the prevailing pain level, known to increase the severity of the osteoarthritic disease problems [13]. A causative role for persistent disruptions of a person's intrinsic circadian rhythm in the osteoarthritis pain cycle has also been discussed [28].

Consequently, sleep problems may interact in a bidirectional or reciprocal manner to either exacerbate osteoarthritis directly or indirectly by increasing the vulnerability of one or more joints to stress and inflammation, as well as an unrelieved overall feeling of overwhelming stress.

In this regard, Sasaki, *et al.* [21] found nocturnal knee pain that disturbed sleep quality did correlate with the severity of the prevailing patient's knee osteoarthritis, and those with more severe disease had more problems than others with falling asleep and the maintenance of sleep. Jung, *et al.* [29] too found that among cases with hip or knee pain, those with less severe osteoarthritis were able to sleep for longer periods than those with more severe forms of the disease. Dias, *et al.* [30] noted an especially high prevalence of degenerative bone disorders of the temporomandibular joint among women, mean age 46 years, with signs of sleep bruxism, often associated with sleep quality and excess stress.

Taylor, *et al.* [19] found insomnia and obstructive sleep apnea symptoms that were possibly undiagnosed in veterans with osteoarthritis, and consistent with other data, where present, these sleep disturbances were more prevalent in those with higher levels of depression and body mass indices as a whole. Silva, *et al.* [31] too found patients with early knee osteoarthritis associated with obstructive sleep apnea to have higher changes of their peak extensor torque measures, pain, stiffness, and physical function, compared with patients who did not have obstructive sleep apnea. Indeed, Stebbings, *et al.* [32] found cases with osteoarthritis had greater rates of sleeplessness than those with rheumatoid arthritis—often considered a more severe disease. These sleep disturbances were correlated with fatigue, a strong and consistent predictor of nighttime sleep complaints and daytime sleep-related consequences in older adults with comorbid insomnia and osteoarthritis pain [33], the most common reason for preventing continuous sleep [47].

More recent research further extends these observations to show that the disruption of the basic circadian rhythm, which can adversely impact circadian clock processes present in cartilage cells, can either accompany osteoarthritis [46], or result directly in progressive cartilage degeneration that produces osteoarthritis [44]. A link between metabolism, a possible strong osteoarthritis determinant, and circadian rhythm disruption [28] further strengthens the importance of fostering optimal sleep in efforts to prevent or ameliorate the development of osteoarthritis, as does the finding that a misalignment of physical activity cycles with optimal circadian rhythms could increase cartilage susceptibility to injury, a major cause of osteoarthritis [16].

Regardless of whether sleep disruption is caused by osteoarthritis, or can produce osteoarthritic type lesions or both, the high prevalence of abnormal sleep quality in an osteoarthritis patient population [47], along with sleeplessness can undoubtedly impact osteoarthritis intervention attempts no matter how well-founded or efficacious these may be, while augmenting declining function, rather than promoting enhanced functioning [49]. Unfortunately, despite all these apparently highly relevant observations, including those depicted in table 1, this area of possible high clinical relevance has not received much attention, especially in the realm of efforts to intervene upon any of these possible remediable or preventable disease correlates discussed above in well-designed longitudinal studies. Despite more than 15 years of reasonably sound research, this gap between research and practice is potentially a highly costly one in our view given that osteoarthritis remains the leading cause of premature disability and excess morbidity among older populations across the globe.

Authors	Approach	Key findings
Tang, <i>et al.</i> [7]	Conducted a secondary analysis of baseline data from a large longitudinal randomized controlled trial. Multivariate regression analyses were performed to test two sets of predictive models.	There were both similarities and differences in factors predicting nighttime sleep complaints and daytime sleep-related consequences. Individual beliefs/attitudes about sleep and pain were stronger predictors of sleep difficulties than were depression and pain. Fatigue was the strongest and most consistent predictor associated with both nighttime sleep complaints and daytime sleep-related consequences regardless of the scale used to measure these concepts.
Taylor, <i>et al.</i> [19]	300 veterans enrolled in a clinical trial completed the Insomnia Severity Index (ISI) and the Berlin Questionnaire (BQ) at baseline; and proportions of participants with symptoms consistent with insomnia and OSA were calculated, using standard cut-offs for ISI and BQ.	Insomnia and OSA symptoms were very common in the sample, even though a substantial proportion of individuals with symptoms may have been undiagnosed. Characteristics associated with insomnia and OSA symptoms were consistent with prior studies.
Jung, <i>et al.</i> [29]	Investigated the relationship between osteoarthritis and sleep duration using 2010-2012 Korea's National Health and Nutrition Examination Survey data for 11,540 participants. Cases with osteoarthritis were defined as those having knee/hip joint pain and radiographic changes of the knee/hip joints. Sleep time was divide into 4 categories: (1) 0-3 h, (2) 4-5 h, (3) 6-7 h, and (4) ≥ 8 h	Osteoarthritis prevalence was lowest in those participants who had 6-7 h of sleep and progressively increased with shorter sleep durations.
Silva, <i>et al.</i> [31]	Included 60 males, aged 40-70 years, allocated to 4 equal size groups: Control: without OA + OSA; Group with OA, no OSA; Group without OA and with OSA; and Group with OA and OSA. All were examined using knee radiographs, polysomnography, the Western Ontario McMaster Osteoarthritis Index (WOMAC) questionnaire, and a test on an isokinetic dynamometer to evaluate peak isometric knee extensor torque, both concentric and eccentric ($90^\circ/s$ and $180^\circ/s$).	Patients with early knee OA and associated OSA, have higher changes of the peak extensor torque, pain, stiffness, and physical function, compared with patients who did not have OSA.
Salwen, <i>et al.</i> [36]	Conducted a secondary analysis on data from 74 patients with comorbid insomnia and knee osteoarthritis who completed a randomized clinical trial of 8-session multicomponent CBT-I versus an active behavioral desensitization control condition (BD), including a 6-month follow-up assessment. Data collected included-daily diaries of sleep parameters, actigraphy data, and self-report questionnaires administered at specific time points.	Clinically significant pain reductions in response to both treatments were optimally predicted by achieving approximately 6.5 hr sleep duration by mid-treatment. Thus, tailoring interventions to increase total sleep time early in treatment may be an effective strategy to promote long-term pain reductions.
Yeung, <i>et al.</i> [41]	The authors compared sleep macro- and microstructure, and psychometric profiles among 3 broadly age-matched groups of females- patients with fibromyalgia (n = 19); patients with osteoarthritis + sleep disturbance (n = 17); and healthy adults (n = 10).	The levels of alpha-delta sleep were statistically similar in both clinical (fibromyalgia syndrome and osteoarthritis) groups, indicating that it is not a specific abnormality of fibromyalgia syndrome.
Parmalee, <i>et al.</i> [58]	96 African Americans and 128 non-Hispanic whites with physician-diagnosed knee osteoarthritis provided self-reports on their health status, and sleep quality was measured for 3 to 7 nights using wrist-worn accelerometers; pain was self-reported daily over the same period.	These data corroborate previous studies documenting poorer sleep among African Americans vs non-Hispanic Whites of greater night-to-night variability in sleep among the former, as well as a negative association of pain with sleep quality among the latter.
Innes, <i>et al.</i> [68]	A total of 21,982 Appalachian adults age 40 years or older were studied. All completed a comprehensive health survey between 2005 and 2006. Medical history, including physician diagnosis of OA, lifestyle factors, short- and long-term memory loss, sleep quality, and mood were assessed via self-report.	In this large cross-sectional study, OA and related joint pain were strongly associated with perceived memory loss; it was concluded these associations may be partially mediated by sleep and mood disturbances.

Table 1: Sample of several key studies implicating sleep issues in the context of osteoarthritis and showing no truly comparable approach but an overall trend of sleep as a salient osteoarthritis variable.

OA: Osteoarthritis; OSA: Obstructive Sleep Apnea

Discussion and Conclusion

As outlined above, sleep, a crucial state required by all adults for purposes of maximizing functional and cognitive activities of daily living is commonly disturbed in the presence of osteoarthritis. However, although commonly associated with symptoms of disabling osteoarthritis, namely depression, pain, and inflammation [17,35,36], among other factors, sleep problems have received little attention when compared to other realms of osteoarthritis treatment and research endeavors. This is surprising given the considerable impact of sleep deficiencies on motivation for physical activity participation, the onset and perpetuation of hyperalgesic states, poor self-rated health, and the 'spread' of the disease from one joint to additional joints [45]. Moreover, unlike some osteoarthritis determinants, sleep problems appear of key importance in all realms of osteoarthritis prevention, given its link to several primary causes of osteoarthritis such as joint injury, metabolic disturbances, and inflammation, secondary determinants such as 'clock gene' alterations, as well as common osteoarthritis outcomes, such as pain and depression.

Comparable in severity to sleep disturbances found among persons with clinical fibromyalgia syndrome [41], and which has been intensely studied, the fact that the presence of chronic sleep disturbances can predictably interact with or mediate or moderate weight gain and the onset or maintenance of obesity [37,38], an important correlate of chronic osteoarthritis pain, as well as depression, stress and inflammation is less well studied, despite its immense potential utility. Unsurprisingly therefore, weight gain, a possible potent chronic pain and inflammatory mediator, and one factor exacerbating osteoarthritis disability, may perpetuate the stress-sleep disturbance cycle [35] as well as fostering pain in its own right. Excess weight can also be implicated in aggravating osteoarthritis pathology by virtue of the fact that the cellular mechano-environment of the cartilage chondrocyte is also found to regulate the mammary circadian clock [42]. In addition, non-restorative sleep patterns can foster excess fatigue, cognitive dysfunction, and sleepiness [1], exhaustion, poor decision making, depression, behavioral problems, irritability, plus an increased risk of developing arterial disease and unintentional injuries, all well-established osteoarthritis determinants.

Zullig, *et al.* [43] confirmed that measures of comorbidity and activity among cases with osteoarthritis of the hip or knee were affected markedly when sleep problems prevailed. Not only were worse scores in this regard associated with worse mean pain scores, depressive symptoms, fatigue, and insomnia (p values < 0.01), but increasing activity limitations were associated with worse mean scores for function ($p < 0.01$). As well, depression was associated with worse pain ($p = 0.03$), fatigue, and insomnia (p values < 0.01). Persons with knee osteoarthritis have also been shown to have less robust circadian rest/activity rhythms that might contribute to the onset or perpetuation of arthritis symptoms and insomnia [46], increasingly recognized as a major determinant of hyperalgesic states and impaired endogenous pain control mechanisms, and possible excess disability or disease severity [24].

Consequently, even though more research is warranted, there can be little argument that the disability experienced in osteoarthritis is likely to be somewhat linked to the magnitude of sleep quality versus sleep disturbances experienced by the individual, even though this connection continues to constitute a very small to negligible role in efforts to treat common symptoms of the disease such as pain, and inflammation. Indeed, it appears self-evident that simultaneous efforts to foster better sleep patterns, for example by intervening to foster a favorable rather than an unfavorable sleep environment and schedule, medication reviews, better pain control and physical activity schedules, as well as careful attention to nutritional practices, are likely to be of considerable benefit [46]. In particular, careful protection of the joints themselves to reduce the chances of incurring intrinsic mechanically induced genetic modifications of clock genes, and excess pain/trauma may help to reduce the highly negative impact of sleep deprivation attributable to pain and inflammation. Efforts to promote adequate high quality sleep may also foster more optimal health outcomes in general, along with immune system functions, cognitive and problem solving skills, overall behavioral patterns and activity levels that influence osteoarthritis well-being, while minimizing depression, ineffective coping, and overall stress management practices. Cellular functions which are disrupted in osteoarthritis may also improve in response to adequate sleep cycles and duration.

To this end, educating individuals about the importance of sleep health, and related efforts to control stress, salient emotional coping strategies [27], and efficacious joint protection strategies and pain control management [39], along with other evidence-based sleep management strategies are strongly indicated [1]. Moreover, as outlined by Quartenana [17] and Campbell, *et al.* [40], the importance of assessing sleep efficiency or identifying the presence of any insomnia related problem in adults with osteoarthritis at the outset, using validated approaches on a routine basis, along with careful monitoring of the patient's sleep pattern over time, should be especially helpful. Abad, *et al.* [5] also recommend screening for primary sleep disorders in this patient group, and intervening to improve both the osteoarthritic disease process and the associated sleep complaints.

In particular, education about what constitutes a desirable sleep duration, how to minimize pain prior to sleep and encouraging efforts to ensure the environment is conducive to a good night's sleep, plus stressing the important link between adequate sleep, stress management, and weight control is of high potential import. Emphasizing how a lack of quality sleep and/or deficient sleep durations have both independent and summative negative cognitive as well as physiological implications for joint status may be especially helpful for fostering the motivation for maximizing sleep as a key osteoarthritis self-management strategy.

Moreover, the less well publicized fact that stress not only leads to sleep deprivation and indirectly to weight gain, and possible injury that leads to osteoarthritis, but also to excess fatigue—a salient predictor of nighttime sleep complaints and daytime sleep related consequences such as pain, depression, and disability may also be extremely helpful [27,47]. Due to the reciprocal relationship between central and peripheral clock regulatory mechanisms, and the multiple overlapping clinical problems associated with poor sleep hygiene, which may be related to variations in circadian rhythms [52], among other factors, a multi-level and interdisciplinary approach focusing on behavioral, as well as specific pharmacologic targeting of the mammalian clock may prove especially beneficial, among other interventions [36,54-56].

In the interim, sleep problems are clearly a topic of great import and potential clinical relevance to millions of people with osteoarthritis, thus more studies that build on findings from past studies [54,57-65,67,69] and that examine the impact of sleep fragmentation or sleep quality on the development and rate of progression of osteoarthritis at the micro level, as well as how precisely osteoarthritis can lead to insomnia and/or other cognitive problems may be especially helpful for teasing out how to intervene and when to do this optimally to reduce the enormous public health burden of this widespread irreversible disabling health condition [27,40,69].

To this end, it is hoped that Figure 1 conceptualizing some overlapping issues in this realm can provide for an increased discussion concerning the multiple possible therapeutic implications of examining and intervening thoughtfully to alter this negative feedback cycle of compounding and disabling events that can result in more progressive rates and extent of osteoarthritis pathology and suffering and that may greatly reduce life quality in adults with osteoarthritis [20,21].

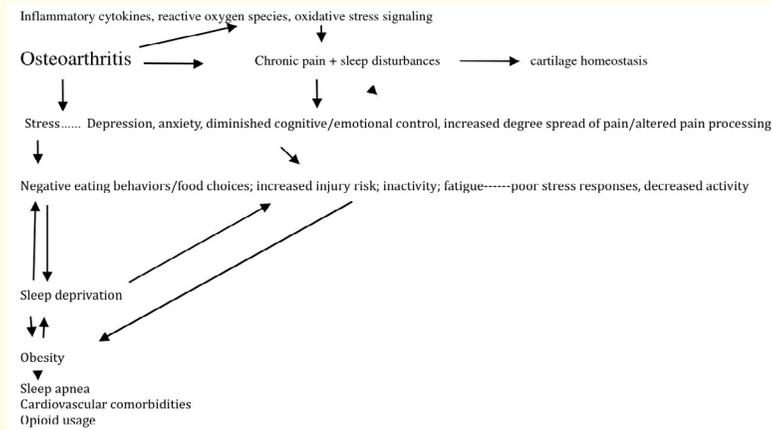


Figure 1: Hypothetical associations between stress, sleep deprivation, osteoarthritis disability, and obesity. Source: [6,10,13,27,49].

In addition, to provide more robust data, it is concluded that the careful exploration of the role of sleep and sleep losses in the context of the pathogenesis of osteoarthritis using subjective as well as advanced technologies, well-defined inclusion criteria, agreed upon definitions of sleep challenges, along with more mainstream standard practices to assess and optimize sleep health will prove of exceptional benefit in attenuating the onset and magnitude of the disability of osteoarthritis that impairs the lives of so many.

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