Title

Cross-sectional and longitudinal relationships between rest-activity rhythms and circulating inflammatory markers in older men: the osteoporotic fractures in men sleep study

Authors

Xiao, Q
Evans, D
Redline, S
et al.

Publication Date

2019-12-01

DOI

10.1016/j.sleep.2019.11.1178

Peer reviewed

Sleep-Wake Research (ISWF) and Department of Neurology, Medical University of Vienna, Spitalgasse 23, 1090, Vienna, Austria; [7] *School of Kinesiology, University of British Columbia, Vancouver, Canada;* [8] *Zentrum für Angewandte Prävention®, Blasewitzer Str. 41; D-01307, Dresden, Germany;* [9] *Sozialpädiatrisches Zentrum Landshut; am Kinderkrankenhaus St. Marien gGmbH; Grillparzerstraße 9; 84036 Landshut; Barbara.Schneider@st-marien-la.de, Landshut, Germany;* [10] *Center of Sleep Medicine, UOSD of Neurophysiopathology and Disorders of Movement, AOU G Martino, Department of Clinical and Experimental Medicine, University of Messina, Via Consolare Valeria 1, 98123, Messina, Italy;* [11] *Lyon Neuroscience Research Center, INSERM U1028-CNRS UMR5292, University Claude Bernard Lyon 1, Centre Hospitalier Le Vinatier Bâtiment 452, 95 Boulevard Pinel, 69675 Bron, Lyon, France;* [12] *Sozialpaediatrisches Zentrum, Meppen, Germany;* [13] *Department of Paediatrics, University of British Columbia, 2329 West Mall, V6T 1Z4, Vancouver, Canada;* [14] *Division of Sleep Medicine, Vanderbilt University School of Medicine, Medical Center North A-0118, 1161 21st Ave South, Nashville, United States*

Introduction: Restlessness as a phenotypical behavioral characteristic is present in many diagnoses. In context with iron deficiency syndromes such as restless sleep disorder, RLS, and ADHD, *restlessness examinations* necessitate an inclusive holistic viewpoint, which consider e.g., sensory processing dysfunctions, (dis)comfort and pain in an environmental context. Novel digital technologies allow cost-effective big data collections, for disentangling restlessness from various perspectives. For instance, to capture *restlessness* and *circadian rhythm* related changes over the day specifically and become a 'learning system', we are utilizing digital tools, which include standardized questionnaires and structured behavioral observations allowing home-data-collection. With this abstract, we are presenting the framework for developing this registry (https://sleepnetwork.org/rls-vs-gp).

Materials and methods: **(A)** Research Ethics: In addition to the study protocol and data analysis plan, create the research ethics framework for managing the registry: documentation of data transfer agreements, consenting procedure, and approved procedures at all sites.**(B)** Data collection: Review tools for their user-friendliness, which allow customized data collection, utilization of validated questionnaires, and the capture of standardized behavioral observations.

Results: **(A)** *Research Ethics* requires in addition to data transfer agreements, explicit consent for sharing data between institutions; further all participating institutions need to share their protocols, consent forms and valid local ethics approvals. **(B)** *Data collection:* In 2018 & 2019, students of the Vancouver Summer Sleep School reviewed: **(1)** A free web-app with a mobile interface (Sleep/Wake-Behaviours-App, SWAPP), a commercial mobile app with web-based design feature (Ethica, Toronto), and a traditional free university-file-sharing-service (BCCHR SHARE). SWOT analysis favored due to its convenience and mobile-friendliness the commercial mobile app (which also allowed to customize design). However, maintenance related financial challenges suggested to review available free survey platforms with similar functionality (Qualtrics and REDCap). SWOT analysis favored Qualtrics, which allows greater customization and visual appeal. **(2)** The Sleep Disturbance Scale for Children (SDSC; Bruni 1996), ADHD Rating Scale IV (DuPaul 1998) and the structured behavioral observation concepts (Suggested Clinical Immobilization Test, SCIT; Suggested Immobilization Test; SIT) were transferred into Qualtrics (https://sleepnetwork.org/rls-vs-gp). For improving user-friendliness at home data collection, we customized navigation by: (i) creating three story-telling guides; (ii) using 'piped text' to have questions address the participant by name; (iii) developing a 'highlightable' storyline that precedes each set of questions and allows to review internal consistency; (iv) branching pathways depending on question responses using display logic.

Conclusions: Research has shown that categorical diagnoses of RLS and ADHD do not embrace the enormous abundance of their phenotypic expressions. New strategies for observational phenotyping utilizing standardized validated questionnaires and the exploration of patient reported behaviors (e.g., video technology) are necessary to expand the spectrum of "restlessness phenotypes". Networks and registries allow for shared harmonized data collection across multiple centers. The use of new digital web-based technologies can support this, as they are highly appealing because of their accessibility, convenience and customizability.

Acknowledgements: BCCHR for providing Qualitrics and the RLS vs. GP Study Group for directing the data collection concept.

Aging and Developmental Issues

CROSS-SECTIONAL AND LONGITUDINAL RELATIONSHIPS BETWEEN REST-ACTIVITY RHYTHMS AND CIRCULATING INFLAMMATORY MARKERS IN OLDER MEN: THE OSTEOPOROTIC FRACTURES IN MEN SLEEP STUDY

Q. Xiao [1], D. Evans [2], S. Redline [3], N. Lane [4], S. Ancoli-Israel [5], K. Stone [6]. [1] *University of Iowa, Iowa City, United States;* [2] *California Pacific Medical Center Research Institute, San Francisco, United States;* [3] *Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Boston, United States;* [4] *University of California at Davis School of Medicine, Sacramento, United States;* [5] *University of California San Diego, La Jolla, United States;* [6] *California Pacific Medical Center, San Francisco, United States*

Introduction: A growing body of literature has linked sleep disturbances, lower levels of physical activity and prolonged sedentary behaviors with inflammatory diseases and higher levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6). However most studies only focused on either nighttime sleep or activities during waking hours, and few have examined the overall patterns of 24-hour rest-activity rhythms in relation to inflammation. Moreover, most previous studies are cross-sectional, and more longitudinal analyses are needed to clarify the temporal relationships between rest-activity patterns and inflammation. To address these limitations of previous studies, we studied both the cross-sectional and prospective associations between rest-activity rhythms and circulating inflammatory markers in the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study.

Materials and methods: We used wrist-worn actigraphy to measure rest-activity rhythms over ~5 days at baseline (2003-2005, mean age 76 years). We applied an extended cosine model to calculate amplitude (peak-to-nadir difference in activity), acrophase (time of peak activity), mesor (minimum+1/2 amplitude, a measure of mean of activity), and pseudo-F statistic of goodness-of-fit (a measure of the strength of rhythmicity). We measured multiple inflammatory markers (CRP, interferon gamma (INFg), IL-1, IL-6, Tumor necrosis factor alpha (TNFa), and Tumor Necrosis Factor Soluble Receptor II (TNF sRII)) from fasting blood at baseline and at a follow-up visit (follow-up time: 3.5 ± 0.5 years). We also calculated an inflammation index by counting the number of markers in the highest quartile for each individual, and defined index score>2 as elevated inflammation. We used multiple regression to examine the associations between baseline rest-activity rhythm parameters and inflammatory markers at baseline (N=2,538), and changes in markers between baseline and follow up (N=985).

Results: In cross-sectional analysis, a lower amplitude at baseline is associated with a higher inflammation index. Participants with the lowest quartile of amplitude are 65% more likely to have elevated inflammation than those with the highest quartile (Odds ratio (95% Confidence interval): 1.65 (1.22, 2.24)). In prospective analysis, we found that when compared to normal acrophase (12:30-16:30), an earlier acrophase is associated with a two-fold increase in the risk of developing elevated inflammation among those who did not have elevated inflammation at baseline (2.08 (1.02, 4.23)). No individual inflammatory markers are associated with rest-activity rhythms in either cross-sectional or prospective analysis.

Conclusions: We found a cross-sectional relationship between a lower amplitude of rest-activity rhythms and higher inflammation in older men. In addition, an early acrophase predicted a higher risk of developing elevated inflammation over an average of four years of follow up.

Acknowledgements: The MrOS Study is supported by National Institutes of Health funding (U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128). The MrOS Sleep Study is supported under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847,

R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839.

Other

UNFAVOURABLE SLEEP CHARACTERISTICS AND ADIPOSITY IN CHILDREN: DOES PARENTAL WEIGHT STATUS MAKE A DIFFERENCE?

L. Xiu [1], M. Hagströmer [2], L. Bergqvist-Norén [1], C. Marcus [1], M. Ekstedt [3,4]. [1] *Division of Paediatrics, Department of Clinical Science, Intervention and Technology, Sweden;* [2] *Department of Neurobiology, Care, Sciences and Society, Sweden;* [3] *Department of Learning, Informatics, Management and Ethics, Medical Management Centre, Karolinska Institutet, Stockholm, Sweden;* [4] *Faculty of Health and Life Sciences, Linnaeus University, Kalmar, Sweden*

Introduction: The role of sleep as an obesity-related behavior has attracted a lot attention over the last decade. An association between short sleep and incidence of obesity in children has been indicated by several reviews. Delayed and irregular sleep schedules probably also contribute to unhealthy weight gain in children. However, the current evidence heavily relies on subjective report. Moreover, children born to parents with obesity are at higher risk of developing adiposity. Less is known about the association between sleep and adiposity when taking the context of family obesity risk into consideration, which is essential for better understanding of how sleep is involved in familial vulnerability for adiposity development. Therefore, in this study, we examined the sleep development in children at different obesity risks, as well as explored the associations of serial unfavorable sleep characteristics with adiposity and whether the associations differed by family obesity risks.
Materials and methods: This is a sub study of the Early Stockholm Obesity Prevention Project, which is a randomized controlled obesity prevention targeting preschoolers with parents with overweight or obesity. Totally, 238 children were recruited to the project when they were eight months old and followed-up until six years old. Among them, 107 children without intervention were included in this analysis, with 64 with overweight and/or obese parents (high-obesity-risk) and 43 with normal weight parents (low-obesity-risk). Child sleep was measured annually using a wrist-worn accelerometer since two years old. Five unfavorable sleep characteristics were defined using published thresholds at each age respectively, including late sleep onset, prolonged sleep latency, short sleep, low sleep efficiency and irregular sleep onset. At each age, score was 1 for the occurrence of the respective unfavorable characteristic and 0 for not occurrence. Therefore, for each unfavorable characteristic, the total score was 0 to 5 across ages, where 0 indicated never having this characteristic and 5 indicated the maximal experience of this characteristic.
Results: There was no difference in either sleep measures or unfavorable sleep characteristics among children at different obesity risks across ages. After adjusting for other confounders, the late sleep score was positively associated with higher body mass index (BMI) z-score (0.15, 95% confidence interval (CI) 0.04-0.26) and greater waist circumference (0.61, 95% CI 0.23-0.98). The short sleep score was also positively associated higher BMI z-score (0.16, 95% CI 0.02-0.30). No association of other unfavorable sleep characteristics with adiposity can be detected. When taking family obesity risks into consideration, we found that compared to children at low obesity risk and without habitual late sleep (total scores < 3), those at high obesity risk and with habitual late sleep (total scores ≥ 3) had more increase in both BMI z-score (0.15, 95% CI 0.04-0.26) and waist circumference (0.61, 95% CI 0.23-0.98).
Conclusions: Late sleep and short sleep were associated with greater weight gain from aged 2 to 6 years. Although the sleep development was similar in children at different obesity risks, children with obese parents and having habitual late sleep were at higher risk of adiposity.

Sleep Breathing Disorders

ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA AND LIPID METABOLISM DURING REM AND NREM SLEEP

H. Xu [1,2], J. Guan [1,2], S. Yin [1,2]. [1] *Shanghai Jiao Tong University Affiliated Sixth People's Hospital, China;* [2] *Shanghai Key Laboratory of Sleep Disordered Breathing, Shanghai, China*

Introduction: Obstructive sleep apnea (OSA) is thought to be associated with dyslipidemia. However, differences concerning dyslipidemia during rapid eye movement (REM) and non-REM (NREM) sleep have yet to be determined. This study was designed to explore the association between lipid profiles and OSA during REM or NREM sleep.
Materials and methods: This is a clinical cohort. A total of 2,619 participants with at least 30 min of REM sleep were included. Sleep variables and fasting lipid profiles [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein (apo)A-I, apoB, apoE, and lipoprotein(a) (Lp(a))] were obtained from each subject. Apnea-hypopnea indices (AHIs) in REM and NREM sleep (AHIREM and AHINREM, respectively) were recorded. Linear regression analysis was used to assess the associations of AHIREM and AHINREM with lipid profiles.
Results: When stratified by the AHI_{REM} severity of OSA, all demographics, clinical variables, and sleep parameters differed between the groups except for apoA-I. In fully adjusted multivariate linear regression models, AHI_{REM} was independently associated with increasing levels of TG, HDL-C, and apoE ($p = 0.04$, $p = 0.01$ and $p = 0.01$, respectively). AHI_{NREM} was independently associated with increasing levels of TC, TG, LDL and apoB, and lower level of HDL-C (all $p < 0.05$). In sensitivity analyses by only exploring associations in patients who had an $AHI_{NREM} < 5$ or $AHI_{REM} < 5$ times per hour in separate regression models, AHI_{REM} was not associated with all lipid profile in almost all adjusted models (all $p > 0.05$), while AHI_{NREM} was associated with elevated TC, LDL-C, and apoB ($p = 0.03$, $p = 0.01$ and $p = 0.01$, respectively).
Conclusions: AHINREM was independently associated with the greatest alterations in serum lipids, including TC, LDL-C, and apoB.
Acknowledgements: The authors acknowledge the help of all staffs who works at Department of Otolaryngology Head and Neck Surgery & Center of Sleep Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital. They helped us a lot in sample collection.

Sleep Breathing Disorders

STRUCTURAL RISK FACTORS FOR OBSTRUCTIVE SLEEP APNEA AT DIFFERENT LEVELS OF OBESITY

L. Xu [1,2], D. Mazzotti [2], B. Keenan [2], A. Wiemken [2], B. Staley [2], B. Benedikstdottir [3], S. Juliusson [4], A. Pack [2], T. Gislason [3,5], R. Schwab [2]. [1] *Department of Respiratory Medicine, Peking University People's Hospital, Beijing, China;* [2] *Department of Medicine and Center for Sleep and Circadian Neurobiology, University of Pennsylvania, Philadelphia, United States;* [3] *Faculty of Medicine, School of Health Sciences, University of Iceland, Iceland;* [4] *ENT Department, Iceland;* [5] *Department of Sleep, The National University Hospital of Iceland, Reykjavik, Iceland*

Introduction: Obesity is known as the most important risk factor for obstructive sleep apnea (OSA). However, how obesity interact with soft tissue volume and craniofacial structures in patients with OSA is not clear. This study aimed to evaluate the relationship between upper airway anatomic structures and overall obesity level based on body mass index (BMI) in adult patients with OSA.
Materials and methods: 576 OSA patients (mean age 53.9±10.4 years, 80.7% male) with oxygen desaturation index (ODI) $\geq$ 10 events/h were included in this study from the Iceland Sleep Apnea Cohort. Airway size, soft tissue volumes, craniofacial dimensions and the ratio between soft tissue volume and inside-mandibular volume (IMV) were quantified using three-dimensional magnetic resonance imaging (MRI). Using unadjusted and adjusted linear regression, we compared upper airway anatomy among three clinically-relevant BMI groupings: < 30 kg/m^2(N=178), 30-35 kg/m^2 (N=212), $\geq$35 kg/m^2 (N=186). The linear association between upper airway anatomy structures and continuous BMI were also accessed. Multivariable regression model was performed to identify the most associated anatomy structures with continuous BMI.
Results: As expected, ODI increased as BMI increased (28.23±12.63, 35.57±17.89, 38.85±20.87 events/hours in patients with BMI$<$ 30, 30-35, $\geq$35kg/m^2 respectively, p$<$ 0.0001). When adjusting for age, gender and ODI, no difference was observed in upper airway volumes, average and minimal airway area among BMI groups. Patients with BMI$\geq$35 kg/m^2 had larger all of soft tissue volumes except for the soft palate. Conversely,