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Sleep quality and duration are related to microvascular function: The Amsterdam Growth and Health Longitudinal Study

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Abstract

Sleep and sleep disorders are related to cardiovascular disease, and microvascular function is an early cardiovascular disease marker. Therefore, the relationship of sleep (measured in sleep quality and duration) with microvascular function was examined in healthy adults. Sleep quality was assessed with the validated Sleep Wake Experience List (SWEL) questionnaire. Duration of sleep was self-reported in an additional question. Microvascular function was measured using nailfold capillaroscopy. Linear regression analyses were used to examine the relationship between sleep and microvascular function. Potential confounders included physical activity, smoking, blood pressure, body mass index and several biochemical parameters. Analyses were performed in 259 participants (116 men). For women reporting insufficient (<7 hours) sleep duration, microvascular function (post ischemic capillary recruitment) was significantly lower ($b = -11.17$; $p = 0.04$) compared to women reporting sufficient sleep duration.

There was no relationship between sleep quality and microvascular function in females. In males, a trend towards lower capillary recruitment was found in those reporting a combination of poor sleep quality and insufficient duration ($b = -7.54$; $p = 0.09$), compared to those reporting good sleep quality as well as sufficient duration. This study suggests an association between sleep and microvascular function. Which aspects of sleep exactly affect microvascular function, and if indeed the association is different between males and females in other samples, needs further research.

Introduction

Sleep and sleep disorders, such as abnormal sleep duration, poor sleep quality and obstructive sleep apnea syndrome have been shown to relate to cardiovascular- and metabolic diseases, in particular hypertension, insulin resistance and systemic low-grade inflammation[112,249–252].

As a relatively new 'risk factor', there is a lack of insight in the exact mechanisms that relate sleep to cardiometabolic disease. Spiegel et al.[253,254] suggest a stress-related mechanism which causes raised cortisol levels and impaired glucose tolerance. On the other hand, Tochikubo et al.[255] and Bansil et al.[256] suggest a more metabolic syndrome-related mechanism causing, amongst others, increased blood pressure. Finally, several studies[257–259] describe low-grade inflammation with insufficient sleep, which fits both the metabolic and stress-related hypothesis.

The proposed mechanisms may be relevant to various components of the cardiovascular system. A relatively understudied, but important part of the cardiovascular system in this respect is the microvasculature[8]. The microvasculature includes the smallest arteries, arterioles, and capillaries, and is under the influence of, amongst others, the autonomous nervous system, glucose homeostasis and low-grade inflammation. The microvasculature is responsible for exchange of gases, nutrients and disturbed microvascular function contributes to decreased insulin sensitivity and increased peripheral resistance[8]. As a consequence, impaired microvascular function is considered an early phenomenon in the development of cardiovascular disease[260]. Thus, vascular sequellae of deteriorated sleep quality or decreased duration of sleep may be detected in the microvasculature before overt effects on cardiometabolic phenomena (e.g. hypertension and insulin resistance) surface. a change in the vasculature induced by deteriorated sleep quality or decreased duration of sleep may be detected in the microvasculature before overt effects on cardiometabolic phenomena (e.g. hypertension and insulin resistance) surface.

The main aim of the current study was to examine the relationship between sleep quality and sleep duration on the one hand, and microvascular function (as an early markers of cardiovascular damage) on the other, in a group of healthy middle-aged adults.

Methods

Study population

All subjects were participants in the ongoing Amsterdam Growth and Health Longitudinal Study (AGHLS)[26,261]. Briefly, this study started in 1977 with approximately 600 thirteen-year old participants, of whom 344 subjects attended in the most recent round of measurement, when they were 42 years old. The primary goals of the AGHLS initially were to describe the natural development of growth, health, and lifestyle of a group of healthy adolescent boys and girls. Recently, a detailed cohort profile describing the aims, setup, data collection and future plans of the AGHLS was published[26].

All participants gave written informed consent and the study was approved by the medical ethical committee of the VU University Medical Centre.

For the current study, only data from the most recent round of measurement were used. Participants for whom complete data on the sleep questionnaire and valid microvascular measures were available were included. Participants were excluded from the analyses if their hand temperature dropped below 28°C during the microvascular measurements and/or if they were using drugs which affect the cardiovascular system[55]. In total, 259 participants were included in the study (143 females).

Microvascular function

Microvascular function was obtained using nailfold capillary video microscopy of the dorsal skin of the third finger. These measurements were conducted after at least 30 minutes of rest and with a minimum hand temperature of 28°C[55]. Briefly, microvascular measurements include (in duplo) measurements of capillaries at the base of the interphalanx in rest and after four minutes of arterial occlusion (200 mmHg). Baseline capillary density (BCD) was defined as the number of capillaries that were constantly perfused during a 15 second resting state. BCD represents the number of perfused capillaries that are needed for supply and demand of the tissue in rest. After four minutes of arterial occlusion capillary density was assessed during peak reactive hyperemia (PRH). PRH represents a functional measure of capillaries that cause post ischemic hyperemia, and can be regarded as representing a buffer capacity of the microcirculation in case of stress, such as temporal high pressures (supply) or high demands. Microvascular recruitment was calculated by subtracting BCD from capillary density during PRH, to normalize for inter-individual differences[86].

Intra Class Coefficients (ICC) were calculated to test the reproducibility of the microvascular function parameters. Capillary density counts during baseline and after 4 minutes of arterial occlusion were associated with an intra-observer ICC of .97 and .96, and inter-observer ICC's of .86 and .90 respectively, indicating good reproducibility.

Sleep quality and sleep duration

Sleep quality was measured with the Sleep-Wake Experience List (SWEL), a validated questionnaire[69]. The SWEL consists of 15 questions asking about occurrence and severity of six common problems of sleep (i.e. sleep initiation, sleep maintenance, early morning awakening, difficulty waking up, tiredness after waking up and daytime sleepiness) on a 5-point scale ranging from never to always (visualized in Figure 9). For the analyses, questions 1,3,7,8 and 10 were reverse-coded resulting in the interpretation of high scores representing lower sleep quality. Participants were classified as having poor sleep quality if they answered at least one combination of answers to the 15 questions in the upper three (for the occurrence questions) and upper two (for the severity questions) answer Likert-scores. Thus problems must be both reported as 'occurring frequent' and be reported as 'severe'. This classification is according to the manual of the SWEL and also corresponds with a previous study[256].

Information on the average duration of sleep (in hours) was asked in a separate question. Participants with less than seven hours of sleep were classified as having an insufficient amount of sleep[256,258,262].

To allow for comparison with previous research, both classifications described above[256], were combined into one categorical variable: category 1 (45% of the total study population) includes participants with a good quality of sleep and sufficient sleep. Participants in category 2 had a good quality, but insufficient sleep and consists of 22% or the total population. Category 3 includes 22% of the total population which reported poor sleep quality, but with sufficient sleep, and the 11% of participants in category 4 had both poor sleep-quality and insufficient sleep.

Possible confounders

To adjust for possible confounding, both lifestyle- as well as biological variables have been taken into account. Lifestyle variables include physical activity and smoking. Biological variables include blood pressure, triglycerides, HDL-cholesterol, markers of low-grade inflammation and body mass index (BMI). Physical activity was measured with the validated SQUASH questionnaire[263]. In this questionnaire, subjects were asked to fill in the average amount of minutes a week spent on commuting activities, leisure time/sports activities, household activities, and activities at work or school. From this questionnaire, an average total activity in minutes a week was calculated.

Smoking status was gathered using a validated questionnaire and presented as a dichotomous variable (smoking yes/no)[264].

Systolic blood pressure was measured at five minute intervals for 60 minutes in a supine position with an automated device (Dinamap Procare 100, GE healthcare, Germany) and used as a continuous variable in the analyses.

Triglycerides and HDL-cholesterol were measured by enzymatic techniques (Roche Diagnostics GmbH, Mannheim, Germany).

Markers of low grade inflammation include C-Reactive Protein (CRP), InterLeukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) and were measured with electrochemiluminescence detection (Sector Imager 2400, Meso Scale Discovery) using the human vascular injury panel I, human vascular injury panel II, and human pro-inflammatory panel II multi-array plates. Measurements are extensively described elsewhere[265].

BMI (kg/m^2) was calculated from standard weight and height measurements and used as a continuous variable in the analyses.

Statistical analyses

All necessary assumptions for the statistical analyses were checked. Participant characteristics were described by means (standard deviations) in the case of continuous variables and percentages in the case of categorical variables.

Associations between the measures of sleep and microvascular recruitment were assessed by linear regression analyses with microvascular recruitment as the outcome variable. Three sets of analyses were performed; 1) quality of sleep only 2) sleep duration only and 3) the combined quality- and sleep duration categories. For each set of analyses, a crude analysis and an adjusted analysis, was carried out.

All analyses were stratified for males and females55 and were carried out in PASW 19.

Results

Table 21 shows the characteristics of the study population. The median sleep duration for males was 7.9 hours (IQR: 7.4 – 8.4) and 7.6 (6.6 – 8.0) for females.

Participants were excluded because of various reasons; 56 participants were excluded because of technical reasons or logistics, 15 participants used medication that might interfere with microvascular function and an additional 4 participants were dropped from the analyses because they had a too low hand temperature. We analysed these in- and excluded participants by comparing the baseline characteristics shown in Table 21. No clear differences between the two groups appeared (data not shown).

Sleep quality and duration

Table 22 shows the results of the analyses studying the associations regarding quality and duration of sleep and microvascular function. No associations were found between quality of sleep and microvascular function The crude analysis regarding duration of sleep showed a borderline-significant regression coefficient of b = -8.84; p = 0.07 for women. The regression coefficient implies that the difference between short sleepers (<7hrs) and long sleepers (≥7hrs) is 8.84 capillaries/mm^2, where short sleepers have

the lowest capillary recruitment (thus worse microvascular function). This effect became stronger and statistically significant in the fully adjusted model (b = -11.17; p = 0.04). In men, no such associations were apparent.

Sleep quality and -duration combined

Table 23 shows the results of the regression analyses for women and men in the sleep-combination groups. The fully adjusted model shows a significantly (b = -9.02; p = 0.03) lower capillary density for women who have a good quality, but an insufficient duration of sleep compared to subject who reported good quality and sufficient duration of sleep. Although not statistically significant (p=0.09), for men, the fully adjusted model suggests lower capillary density for males reporting poor quality and insufficient duration of sleep compared to males reporting good quality and sufficient duration of sleep.

Table 24 shows an exploratory analysis of the six separate sleep quality domains and their association with microvascular function. For males, 'tiredness after waking up' was statistically significantly associated with lower microvascular recruitment. None of the other relationships show significant associations, but it is important to note that separate components of an integrated questionnaire with overlapping domains have less statistical power than their composite.

Discussion

We found that, in women, insufficient sleep duration was inversely related to microvascular function. For men, this inverse relationship was observed with borderline statistical significance for the combination of poor quality and insufficient duration. Earlier studies examining the relation between sleep duration and cardiovascular disease have shown ambiguous results, particularly with regard to gender differences. Meisinger et al[266] describe a modest association between sleep duration and sleep disturbances and risk of acute coronary events in women, but not in men. Kronholm et al.[267] also described gender differences in the relation between sleep duration and cardiovascular morbidity and mortality in which increased risk in women was found only in short duration compared with mid-range duration sleepers. The gender difference we observed is thus directionally similar to previous studies, with a higher susceptibility in women. It is sometimes suggested that menopause-onset might be a possible explanation for the observed gender differences. The onset of menopause is associated with a decrease in oestrogen-levels, which is in turn associated with elevated concentrations of inflammatory mediators such as IL-6[254] and TNF-α[268], contributing to increased cardiovascular disease risk. This explanation does not, however, apply specifically to an effect of disturbed sleep on cardiovascular risk, let alone to effect modification as suggested by our results. In addition, our

women were pre-menopausal. Finally, a study by Sabanayagam[249] in an elderly population indicated that, compared to sleep duration of 7 hours, there is a positive association of both shorter and longer sleep durations with cardiovascular disease in both men and women. Clearly, the issue of gender differences in the association between sleep and cardiovascular health requires more studies.

Surprisingly, in the present study, biological- and lifestyle covariates did not attenuate the observed relationship between sleep and microvascular function. The adjusted models in table 22 and 23 show essentially identical regression coefficients when adjustments were made. This suggests that sleep quality and sleep duration are associated with microvascular function independent of established cardiovascular risk factors.

Although there is growing evidence supporting an association of sleep with cardiovascular disease[112,249–252] and related conditions, such as diabetes[253,254,] hypertension[255,256,] and low-grade inflammation[257–259,] the current study is the first to relate sleep to microvascular function. Microvascular function may be a central mechanism in both metabolic-[255,256] and stress-related[253,254] pathogenesis of cardiovascular disease.

Our study has some limitations. Sleep quality and duration were self-reported. Although the questionnaire was validated[262], self-reported answers can be associated with information bias. Also, this questionnaire does not provide information on sleep disorders such as snoring or disturbed breathing. Furthermore a cut-off point of <7 hours for insufficient duration of sleep is used in other studies[256], but is still arbitrary. Due to the lack of diversity in reported hours of sleep in the currently used study population, duration of sleep was only used as a binary variable (e.g. short versus long) Additional analyses in the sample of long-sleepers (>9hrs) only showed no significant effects of sleep duration on microvascular function. Also, differences in microvascular function when comparing mid-range(7-9hrs) and short-sleepers (<7hrs) were not apparent. (data not shown). However, we cannot rule out graded effects, which may be particularly relevant within long-sleepers, since long sleeping has been linked to cardiovascular risk in numerous studies.

Finally, the AGHLS has previously been shown to be a healthy cohort, in which severe microvascular dysfunction or extreme behaviors are absent[55]. Using the relatively healthy population of the AGHLS may therefore miss effects that can be observed in more heterogeneous populations. It should be noted, however, that a difference in 7-9 capillaries is a clinically relevant difference[1].

In conclusion, the current study shows a significantly lower capillary density for women with insufficient hours of sleep compared to females with sufficient sleep duration. For males, good quality of sleep together with insufficient duration was associated with lower capillary density.

These results could be relevant for intervention or prevention strategies of cardiovascular diseases. Microvascular function, which is known as early marker of cardiovascular disease is related to sleep but what aspects exactly affect microvascular function is still not clear. Also, the mechanisms behind the observed gender differences, needs further research.

Perspective

Both quality and duration of sleep are associated with microvascular function in men. In women, insufficient sleep alone was associated with microvascular function. Even though microvascular function is an early marker of cardiovascular disease, no associations are found for body fatness and microvascular function in the AGHLS study population[261]. The effect of decreased sleep quality or duration can be revealed more early. Sleep may affect cardiovascular disease, starting with microvascular dysfunction.

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