Premature Coronary Artery Disease Is More Prevalent in People Who Go to Bed Late

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Abstract

Background: Little is known regarding the impact of quantity and quality of sleep on the incidence of cardiovascular disease. The aim of this study was to investigate the possible independent association of late bedtime and premature coronary artery disease (PCAD).

Methods: Between October 2016 and November 2019, we conducted a cross-sectional population-based study on 30101 participants aged 20–65 years in Khuzestan Comprehensive Health Study (KCHS). Data on major risk factors of cardiovascular disease, habit history, physical activity, and sleep behavior was gathered and participants underwent blood pressure, anthropometric, and serum lipid and glucose profile measurements. PCAD was defined as documented history of developing obstructive coronary artery disease before 45 years in men and before 55 years in women.

Results: Of a total of 30101 participants (64.1% female, mean age: 41.7 ± 11.7 years) included in this study, 1602 (5.3%, 95% confidence interval: 5.1%–5.6%) had PCAD. Late bedtime was reported in 7613 participants (25.3%, 95% confidence interval: 24.9%–25.8%). Age-sex standardized prevalence for PCAD and late bedtime were 3.62 (3.43-3.82) and 27.8 (27.2–28.4), respectively. There was no significant difference (P=0.558) regarding prevalence of PCAD between those with late bedtime (5.5%, 95% CI: 4.9–6.0%) and those with early bedtime (5.3%, 95% CI: 5.0%–5.6%). However, after adjustment for potential confounders, late bedtime was independently associated with PCAD (OR=1.136, 95% CI=1.002–1.288, P=0.046).

Conclusion: In this study, late bedtime was significantly associated with presence of PCAD. Future prospective studies should elucidate the exact role of late bedtime in developing coronary atherosclerosis prematurely.

Keywords: Coronary artery disease, Prevention, Sleep health


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Introduction

Ischemic heart disease is the leading cause of death13 and years of life lost1 world-wide. Although most of the coronary artery disease (CAD) occurs in the elderly, it has been reported that 4–10% of individuals with CAD are younger than 45 years.4 Despite numerous definitions and age cut-offs5–8 for premature coronary artery disease (PCAD), it is clear that developing CAD in younger ages has extra burden on societies because of involving people in their more productive years of life. This problem is more prominent in Middle-Eastern countries and particularly Iran where PCAD is more prevalent than Western countries.9 Hence, identifying the independent predictors of developing CAD at younger ages is of utmost importance to develop evidence-based preventive measures.9,10

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There is evidence that sleep behavior, including sleep duration and bedtime, as an important part of lifestyle has changed in the last decades and it has been reported that people sleep shorter\textsuperscript{11,12} and go to bed later\textsuperscript{13} than before. It has led researchers to investigate the probable effects on sleep behavioral changes of different aspects of health. Studies have demonstrated that sleep duration is associated with obesity, insulin resistance, metabolic syndrome, hyperlipidemia, diabetes mellitus, and also CAD.\textsuperscript{14–18} Furthermore, bedtime, as an indicator for congruence of sleep and circadian rhythm, has a significant relationship with obesity, diabetes mellitus, and insulin resistance in childhood and adulthood.\textsuperscript{19,20–22} However, there is limited data regarding the possible association of bedtime in adults and presence of PCAD. Hence, we aimed to evaluate the relationship between late bedtime and PCAD in a large sample of participant in Khuzestan Comprehensive Health Study (KCHS).

Materials and Methods

Study Population

This study is a subset of the KCHS, which was conducted with the aim of evaluating the health status of the people from the Khuzestan province. The province, with 27 counties and a population of 4,909,285 people, is located in southwestern Iran. KCHS was founded by the National Institute for Medical Research Development (NIMAD) in cooperation with the Digestive Diseases Research Institute (DDRI), Jundishapur Medical University, Iran Blood Transfusion Organization, and Abadan, Dezful and Behbahan Faculties.

Sampling Method

KCHS was performed in the period of October 2016 to November 2019 and the samples were selected using the multi-stage random sampling method. Consequently, 30,101 individuals between 20–65 years of age who were residents of the Khuzestan province for at least one year were enrolled in the study.\textsuperscript{23}

Study Protocol

Those who fulfilled all the inclusion criteria were invited face-to-face by trained staff and those who were unwilling to participate at any stage of the study for any reason, and individuals with mental, psychological or physical disabilities who were not able to complete the questioning process were excluded from the study. After a comprehensive review of the study procedures, each participant signed an informed consent.

Trained nurses performed blood pressure and anthropometric measurements. Height (in centimeters) and weight (in kilograms) were measured. Then, body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in meters squared). Blood pressure was measured with Riester sphygmomanometers, twice on each arm in a standard sitting state. The lower reading on the arm with a higher systolic blood pressure was considered as the participant's blood pressure.

Using self-designed questionnaires, data on demographic characteristics, and past medical history, including history of CAD, traditional risk factors of cardiovascular disease, habit history, and physical activity were collected. Moreover, participants were asked about the time when they go to bed routinely.

After 8–12 hours of overnight fasting, a venous blood sample of 15 milliliters was collected from each participant. Afterward, levels of parameters, including fasting blood sugar (FBS), urea, creatinine (Cr), triglyceride (TG), total cholesterol (Chol), and high-density lipoproteins cholesterol (HDL) were measured in serum samples.\textsuperscript{22}

Definitions

We defined late bedtime as bedtime after 1:00 AM. PCAD was defined as history of acute myocardial infarction (documented in hospital discharge summary) or obstructive CAD diagnosed by coronary angiography or computed tomography coronary angiography before 45 years in men and before 55 years in women.

Statistical Analysis

Mean ± standard deviations were calculated for continuous variables and were compared between two independent groups using Student’s t-test. Categorical variables were compared using the chi-square test or Fisher’s exact test, as appropriate, and were presented as absolute frequencies with percentages. Multivariate logistic regression analysis was used to evaluate the independent predictors of PCAD. Two-tailed \( P \) values were reported with significance defined at \( P \leq 0.05 \).

Results

Of a total of 30,101 participants (64.1% female, mean age: 41.7 ± 11.7 years) included in this study, 1,602 (5.3%, 95% confidence interval: 5.1%–5.6%) had PCAD. Late bedtime was reported in 7613 participants (25.3%, 95% confidence interval: 24.9%–25.8%). The age-sex-standardized prevalence rates for PCAD and late bedtime were 3.62 (3.43–3.82) and 27.8 (27.2–28.4), respectively. Table 1 demonstrates the demographic and clinical characteristics of the study population.

As shown in Table 1, participants who reported to go to bed late were younger and were less likely to have hypertension and positive family history of PCAD than those who reported to go to bed before 1:00 AM. Meanwhile, those who reported to go to bed late were more likely to smoke cigarettes, and have obesity defined as BMI ≥ 30 kg/m\(^2\) than those who reported to go to bed early.

There was no significant difference \( (P = 0.558) \) regarding the prevalence of PCAD between those with late bedtime (5.5%, 95% CI: 4.9%–6.0%) and those with early bedtime (5.3%, 95% CI: 5.0%–5.6%). After adjustment for potential confounders including age, gender, diabetes mellitus, hypertension, cigarette smoking, family history.
of PCAD, physical activity and LDL/HDL ratio, late bedtime was independently associated with PCAD (odds ratio [OR] = 1.136, 95% confidence interval = 1.002–1.288, \( P = 0.046 \). Table 2 shows the independent predictors of PCAD in the study population.

**Discussion**

The main finding of our study was that late bedtime is independently associated with presence of PCAD. Despite numerous studies in children and adolescents evaluating the possible linkage of late bedtime and various aspects of health,\(^24\) there is lack of data regarding adulthood sleep behavior and cardiovascular diseases. To the best of our knowledge, this is the first study to report the independent association of late bedtime and PCAD.

Our findings confirms and expands the previous studies reporting a significant association between late bedtime in childhood and adolescence with major risk factors of CAD including obesity,\(^25\) BMI,\(^20,26\) hypertension,\(^27,28\) reduced insulin sensitivity,\(^15\) and diabetes mellitus.\(^29\) Although late bedtime might predispose the person to CAD via increased risk of abovementioned risk factors, we observed that even after adjustment for all abovementioned risk factors, late bedtime was independently associated with PCAD. This observation signals for other mechanistic pathways for association of late bedtime and PCAD. There is evidence that sleep deprivation and circadian rhythm disruption may lead to oxidative stress in humans.\(^29,30\) Sleep deprivation and restricted sleep times are also associated with increased plasma levels of proinflammatory cytokines including interleukin (IL)-6, IL-1β, and tumor necrosis factor alpha (TNF-α).\(^31-34\) Irwin et al demonstrated that sleep loss induces spontaneous monocytic expression of IL-6 and TNF-α and of signal transducer and activator of transcription (STAT) family proteins, which together map the dynamics of sleep loss on the molecular signaling pathways that regulate inflammatory and other immune responses.\(^35\) Given the pivotal role of oxidative stress and inflammation in initiation and progression of coronary atherosclerosis,\(^2\) it might be concluded that late bedtime contributes to PCAD through induction of inflammation and oxidative stress.

Although multiple studies have been performed on health impacts of late bedtime, there is no agreement regarding the definition of late bedtime and various studies have chosen different times. In contrast with our study, Yan et al\(^22\) and Sasaki et al\(^36\) chose going to bed after 12:00 AM as late bedtime. It seems reasonable to consider bedtime as a continuous variable and invoke receiver operating characteristics curve analysis for choosing an optimal cutoff time as late bedtime. Furthermore, it has been shown that systematic changes in the output of the human circadian pacemaker happen in the aging process\(^37\), so, allocating age-related cut-offs for future studies seems reasonable.

Our study has some limitations that should be mentioned. One of the limitations is that we evaluated sleep behavior through self-reported questionnaires. Studies that evaluated the correlation of objective and subjective sleep duration, have reported a weak\(^20\) to moderate correlation.\(^38-40\) Another limitation is that we did not evaluate some sleep relating factors, such as sleep quality and insomnia which can potentially confound the association of bedtime and PCAD.\(^41\) In this study, 64.1% of

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**Table 1. Demographic and Clinical Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Late Bedtime (n=7613)</th>
<th>Early Bedtime (n=22488)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (y), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–34</td>
<td>3022 (39.8)</td>
<td>6724 (29.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>35–49</td>
<td>2654 (34.9)</td>
<td>8950 (39.8)</td>
<td></td>
</tr>
<tr>
<td>50–65</td>
<td>1922 (25.3)</td>
<td>6814 (30.3)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4824 (63.4%)</td>
<td>14505 (64.5%)</td>
<td>0.073</td>
</tr>
<tr>
<td>TCH/HDL, mean (SD)</td>
<td>3.96 (1.17)</td>
<td>3.93 (1.20)</td>
<td>0.045</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>637 (8.4%)</td>
<td>2015 (9.0%)</td>
<td>0.100</td>
</tr>
<tr>
<td>HTN, n (%)</td>
<td>821 (10.8)</td>
<td>2653 (11.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>BMI (kg/m(^2)), n (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>213 (2.8)</td>
<td>607 (2.7)</td>
<td></td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>2046 (27.3)</td>
<td>6724 (29.9)</td>
<td></td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>2781 (37.1)</td>
<td>8500 (37.8)</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>2457 (32.8)</td>
<td>6657 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>1419 (18.6%)</td>
<td>4752 (21.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>931 (12.2)</td>
<td>2325 (10.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical activity, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mild</td>
<td>2448 (32.2)</td>
<td>6813 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3376 (44.4)</td>
<td>9535 (42.4)</td>
<td></td>
</tr>
<tr>
<td>Intense</td>
<td>1779 (23.4)</td>
<td>6072 (27.0)</td>
<td></td>
</tr>
<tr>
<td>Premature CAD</td>
<td>416 (5.5)</td>
<td>1186 (5.3)</td>
<td>0.558</td>
</tr>
</tbody>
</table>

HTN, Hypertension; BMI, Body mass index; TCH, total cholesterol; HDL, high-density lipoprotein; CAD, coronary artery disease. Continuous variables are presented as mean (SD) or median (25th, 75th percentile). Categorical variables are described as frequency (percentage).

**Table 2. Logistic Regression Analysis for Evaluation of Independent Predictors of Premature Coronary Artery Disease**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>1.07</td>
<td>1.06–1.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.82</td>
<td>0.72–0.94</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.23</td>
<td>1.96–2.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HTN</td>
<td>3.50</td>
<td>3.10–3.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>1.02</td>
<td>1.01–1.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>2.04</td>
<td>1.81–2.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.50</td>
<td>1.27–1.78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical activity</td>
<td>0.055</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1.15</td>
<td>0.99–1.34</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.00</td>
<td>0.87–1.16</td>
<td></td>
</tr>
<tr>
<td>Intense</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>0.87</td>
<td>0.82–0.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bedtime after 1:00 AM</td>
<td>1.13</td>
<td>1.00–1.28</td>
<td>0.046</td>
</tr>
</tbody>
</table>

CI, Confidence interval; HTN, Hypertension; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
the participants were female while according to the latest census in 2016, only 49.3% of residents in the Khuzestan province were female. Although this is a common selection bias in studies with volunteer participation, its probable impact on results should be acknowledged. Finally, due to the cross-sectional design of the study, a causal relationship cannot be inferred. Large-scale prospective cohort studies should elucidate the exact role of sleep behavior on developing CAD prematurely.

In conclusion, our study demonstrated a significant independent association between going to bed after 1:00 AM and PCAD. This finding supports the importance of bedtime in health. Future prospective studies should examine the possible causal relationship of late bedtime and PCAD.

Authors’ Contribution
FKM, HP, ZM, and AAS designed and performed project and drafted the paper. MA, BC, ZK, LD, YP, FA, MN, and SAM contributed to collect data and drafted the paper. MRN, PR, AVF, and SM analyzed data and drafted the paper.

Conflict of Interest Disclosures
The authors declare that there is no conflict of interest.

Ethical Statement
The ethics committee of NIMAD approved the protocol of KCHS at IR.NIMAD.REC.1394.002.

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