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Original Article

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Original Article

Cross-sectional associations of objectively-measured sleep characteristics with obesity and type 2 diabetes in the PREDIMED-Plus trial

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Abstract

Study Objectives: To examine independent and combined associations of sleep duration and sleep variability with body composition, obesity and type 2 diabetes (T2D) in elders at high cardiovascular risk.

Methods: Cross-sectional analysis of 1986 community-dwelling elders with overweight/obesity and metabolic syndrome from PREDIMED-Plus trial. Associations of accelerometry-derived sleep duration and sleep variability with body mass index (BMI), waist circumference (WC) and body composition were assessed fitting multivariable-adjusted linear regression models. Prevalence ratios (PR) and 95% confidence intervals (CI) for obesity and T2D were obtained using multivariable-adjusted Cox regression with constant time. "Bad sleepers" (age-specific non-recommended sleep duration plus sleep variability above the median) and "good sleepers" (age-specific recommended sleep duration plus sleep variability below the median) were characterized by combining sleep duration and sleep variability, and their associations with these outcomes were examined.

Results: One hour/night increment in sleep duration was inversely associated with BMI (β −0.38 kg/m^2 [95% CI −0.54, −0.23]), WC (β −0.86 cm [95% CI −1.25, −0.47]), obesity (PR 0.96 [95% CI 0.93, 0.98]), T2D (PR 0.93 [95% CI 0.88, 0.98]) and other DXA-derived adiposity-related measurements (android fat and trunk fat, all $p < .05$). Each 1-hour increment in sleep variability was positively associated with T2D (PR 1.14 [95% CI 1.01, 1.28]). Compared with "good sleepers," "bad sleepers" were positively associated with obesity (PR 1.12 [95% CI 1.01, 1.24]) and T2D (PR 1.62 [95% CI 1.28, 2.06]).

Conclusions: This study revealed cross-sectional associations of sleep duration with adiposity parameters and obesity. Sleep duration and sleep variability were associated with T2D. Considering simultaneously sleep duration and sleep variability could have additional value, particularly for T2D, as they may act synergistically.

Statement of Significance

The present work, conducted in elders with obesity and metabolic syndrome within the PREDIMED-Plus trial, agrees on previous literature in that nocturnal sleep duration is relevant for both adiposity, obesity and type 2 diabetes (T2D). Furthermore, it adds on novel knowledge about relevant associations between night-to-night sleep variability and T2D in this age group. Future research should prospectively confirm these observations in this and other population groups.

Key Words: sleep duration; night-to-night sleep variability; accelerometry; adiposity; obesity; type 2 diabetes; body composition

Introduction

The increasing prevalence rates of obesity and related metabolic disorders parallel an epidemic of sleep disturbances, which results from the curtailment in habitual sleep duration and poor sleep quality [1]. Several lines of evidence from experimental [2, 3] and epidemiological studies in middle-aged [4–9] and older adults [9–11] have consistently revealed positive associations between short sleep duration and body mass index (BMI) or other adiposity measurements—including waist circumference (WC) and total fat mass [6, 8–11]—as well as with poor glucose control and type 2 diabetes (T2D) risk [5, 7]. While most of this evidence is of cross-sectional nature [5–9, 11, 12] and based on self-report sleep measures [7–10, 13], those few studies assessing these associations prospectively [6, 10, 13] or using accelerometry [6, 11] have shown similar results.

Besides sleep duration, disruptions of sleep-wake patterns have also been linked to obesity and metabolic dysregulation [14]. In fact, in experimental studies, sleep-wake cycle disturbances have proven to induce obesity-driving effects, such as increases in the preference for calorie-dense foods, reductions in energy expenditure and adverse effects on appetite-related hormones [15]. High night-to-night variability in sleep duration reflects such disruptions in sleep-wake patterns and a number of epidemiological studies among young and older adults have reported positive associations between high sleep variability and adiposity parameters [11, 16, 17]. Furthermore, poor glucose control has been related to high sleep variability in children [18]. In spite of this limited evidence, no study has yet evaluated the association between sleep variability and T2D in other age groups. Moreover, the associations of sleep duration in relation to adiposity parameters, obesity and T2D remain unexplored in elderly adults with overweight/obesity and metabolic syndrome, a population susceptible to metabolic and age-related sleep disturbances [19]. From a public health perspective, these associations are of great importance, since identification of sleep characteristics that are strongly related to an increased risk of obesity and T2D could facilitate the development of public health advice specifically targeted at the improvement of sleep habits and subsequent management of the aforementioned conditions in this vulnerable group.

Taking the above into account, the present study aimed to cross-sectionally examine independent associations of objectively measured sleep duration and sleep variability with adiposity parameters, obesity, and T2D in an elderly Mediterranean population at high cardiovascular risk. Since sleep duration and sleep variability may not only affect metabolic health in an independent manner, but also may act synergistically, joint associations of sleep duration and sleep variability with the aforementioned study outcomes were also assessed.

Subjects and Methods

Study design and population

This is a cross-sectional analysis of baseline data from the PREDIMED-Plus trial, a 6-year lifestyle intervention study aiming at evaluating a lifestyle strategy for the prevention of cardiovascular morbimortality on 6874 senior adults (the protocol is available at http://predimedplus.com/ and the trial was

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registered at the International Standard Randomized Controlled Trial http://www.isrctn.com/ISRCTN89898870).

Eligible participants were community-dwelling adults (aged 55–75 in men; 60–75 in women) with BMI ≥ 27 and <40 kg/m^2, and meeting ≥3 metabolic syndrome individual components [20]. Study participants involved in the present analyses were included as detailed in the flow-chart (Supplementary Figure S1). Briefly, out of the 6874 participants recruited from a total of 23 centers of the PREDIMED-Plus trial, accelerometry data at baseline was available in a subsample of participants (n = 1993) to whom accelerometry was randomly offered. Participants with incomplete accelerometry-derived sleep data were excluded (n = 7), resulting in an effective sample size of 1986. Additionally, total dual-energy X-ray absorptiometry (DXA) scans were performed in 7 out of the 23 recruiting centers. Therefore, only a subsample of the participants with accelerometry-derived sleep data also underwent DXA scans, and the sample size for those analysis involving DXA-derived body composition parameters was 649. Data for DXA-derived visceral adipose tissue (VAT) mass was available in 4 of the 7 recruiting centers with access to CoreScan software. Thus, the analyses involving VAT in the present study included n = 288 participants. Study protocol and procedures were approved following the ethical standards of the Declaration of Helsinki by the Institutional Review Boards of the recruiting centers. All participants provided written informed consent.

Sleep and physical activity assessment by accelerometry

A wrist-worn triaxial accelerometer (GENEActiv, ActivInsights Ltd, Kimbolton, United Kingdom) was used to monitor daily activities and sleep patterns. Participants were asked to wear the accelerometer on their nondominant wrist nonstop during the evaluation, which was established for 8 consecutive 24-hour days. However, the total amount of monitored days varied according to the day of the clinical visit and the day the monitor was returned. The data used for the analysis in this study was extracted between the first and the last sleep period and included only if the monitor had been worn for ≥16 hours per day, and have a minimum of 2 valid days. The accelerometer data was recorded at 40 Hz with a ±8 g dynamic range, and acceleration data was expressed relative to gravity (g) units (1 g = 9.81 m/second^2). Raw data files were managed on servers at the University of Málaga and processed with R-package (R Core Team, Vienna, Austria) using the open-source R-package GGIR, version 1.2–5 (cran.r-project.org/web/packages/GGIR/index.html). This open source code has been validated in relation to self-calibrated functions [21]. The method of sleep detection has been previously validated in individuals with at least one valid night and it has been published elsewhere [22]. Briefly, by visualizing the arm angle, night sleep and daytime napping were characterized as a period marked by a low frequency of changes in arm angle. After the detection of the onset of the night, the average nocturnal sleep duration, and intra-individual between-night standard deviation of the sleep duration was calculated. Sleep duration was defined as the time between sleep onset to wake, excluding the time spent awake in between these two time-points. To use as a covariate, the time spent in moderate to vigorous physical activity (MVPA) in bouts of 10 minutes or more was calculated as described previously [23] and further categorized according to compliance of the WHO recommendations for MVPA set in ≥150 minutes/week [24].

Adiposity parameters and glucose-related indices

Weight (kg) divided by height (meters) squared was used to calculate BMI. WC (cm) was measured with anthropometric tape following the PREDIMED-Plus operations protocol. Obesity was defined as BMI ≥30 kg/m^2. DXA scans (DXA, Lunar iDXA and DXA Lunar Prodigy Primo, GEHealthcare, United Kingdom) were performed by trained radiology technicians to ascertain body composition. For the present study, total fat, android and gynoid fat, VAT, trunk fat and lean mass (all expressed in kg) were included. VAT (kg) was obtained using the GE CoreScan software. Android fat was divided by gynoid fat to calculate android-to-gynoid ratio.

Fasting plasma glucose (mg/dl) and glycated hemoglobin (HbA1c, %) were determined using standard enzymatic methods. T2D was defined as previous clinical diagnosis of diabetes, or HbA1c ≥6.5% or use of antidiabetic medication at baseline or fasting plasma glucose >126 mg/dl in both the screening visit and baseline visit.

Other covariates

Self-reported age, sex, education, marital and employment status, smoking habits, depression, sleep apnea and use of sedatives were recorded based on structured interviews. Participants completed a 17-item questionnaire to evaluate the adherence to an energy-restricted Mediterranean diet (MedDiet). Total daily intake (g/day) of alcohol, carbohydrate, fat, protein and sugar were calculated using a semi-quantitative food frequency questionnaire [25]. Blood pressure was measured in triplicate with a semiautomatic oscillometer (Omron HEM-705CP, Netherlands) and high blood pressure was defined as systolic and/or diastolic blood pressure ≥130/85 mmHg or using antihypertensive drugs.

Statistics

Baseline characteristics were examined for the total study population and across five categories of night sleep duration (<6 hours, 6 to <7 hours, 7 to <8 hours, 8 to <9 hours, and ≥9 hours). One-way ANOVA and Chi-square tests were used, as appropriate, to examine between-categories differences.

Linear regression models were fitted to examine the associations of 1 hour/day increment in sleep duration and sleep variability with BMI, WC, DXA-derived body composition measurements, fasting plasma glucose, and HbA1c. Since obesity and T2D were highly prevalent (all of them >10%), Cox regression models with constant time of follow-up set at t = 1 (given the cross-sectional design) and robust variance estimates rather than logistic regression [26, 27] were employed to assess prevalence ratios (PR) for obesity and T2D. A number of models were examined. For all outcomes, model 1 was adjusted for sex and age (continuous). Model 2 was further adjusted for smoking habits (current smoker, past smoker, never smoked), education level (primary education, secondary education, academic/graduate), marital status (single/divorced, married and widower) and employment status (working, nonworking, retired), sedative medication (yes/no), current or previous depression (yes/no), adherence to an energy-restricted MedDiet (score from 0 to

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17-items, continuous), alcohol consumption (g/day, continuous and adding a quadratic term), compliance to MVPA recommendations set in ≥150 minutes/week (yes/no), daytime napping (minutes/day) and recruiting center. Beside these covariates, model 2 in each outcome was specifically adjusted for factors that may affect these associations. Model 2 for BMI, WC, and body composition parameters was further adjusted for T2D (yes/no). Model 2 for fasting plasma glucose was further adjusted for WC (continuous). Model 2 for HbA1c was further adjusted for WC (continuous) and anti-diabetic medication (yes/no). Model 2 for obesity was further adjusted for T2D and high blood pressure (yes/no). Model 2 for T2D was further adjusted for obesity and high blood pressure (yes/no). For all outcomes, model 3 included variables in model 2 plus current or previous sleep apnea (yes/no). A fourth model was fitted by including variables from model 3 plus sleep variability in case of evaluating sleep duration as exposure, or sleep duration in case of evaluating sleep variability as exposure, in order to account for possible influence of one another in their associations with the study outcomes. We used multiple imputation methods using the Stata "MI" module (the number of imputation was set to 20) to replace the missing values of HbA1c in 178 participants. Time spent in daytime napping was log-transformed to approximate normality.

Joint analyses relied on the combination of categories of sleep duration with categories of sleep variability, in relation to all study outcomes. Based on these categories, a total of six joint categories were created: (1) category 1 ("good sleepers") included those participants following their age-specific recommended sleep duration (7–9 hours/night sleep for individuals with <65 years and 7–8 hours/night for individuals with ≥65 years) plus low sleep variability (<median sleep *SD*) (*n* = 400), (2) category 2 included participants with sleep duration that may be appropriate according to their age, plus low sleep variability (*n* = 489); (3) category 3 included participants with non-recommended sleep duration plus low sleep variability (*n* = 96); (4) category 4 included participants following their age-specific recommended sleep duration plus high sleep variability (*n* = 385); (5) category 5 included participants with sleep duration that may be appropriate according to their age, plus high variability (*n* = 469); and (6) category 6 ("bad sleepers") for participants with non-recommended sleep duration (<6 hours/night sleep for individuals with <65 years and <5 hours/night for individuals with ≥65 years or ≥9 hours/night) plus high sleep variability (≥median sleep *SD*) (*n* = 147).

A more detailed description of how categories and groups were built is provided in Supplementary Information 2. For joint analyses, all categories were compared with category 1 "good sleepers" (reference) against the study outcomes. In order to address whether the magnitude of association revealed by the joint analyses on obesity and T2D was different to that from sleep duration and sleep variability separately, we tested fully-adjusted Cox regression models using categories of short sleep (<6 hours/nocturnal sleep duration) versus recommended sleep (≥7–9 hours/nocturnal sleep duration [reference]), as well as for categories of high sleep variability versus low sleep variability (reference).

To account for multiple-testing, Benjamini-Hochberg false discovery rate (FDR) procedure [28] was applied and statistical significance was defined as FDR < 0.05. Effect modification by sex, age (<65 years, ≥65 years) and T2D on the associations between sleep variables (sleep duration and sleep variability) on each study outcome were tested using the likelihood ratio test between the fully adjusted model and the same model adding the interaction product-term.

The robustness of the findings was tested by performing a number of sensitivity analyses: (1) excluding those participants sleeping ≥9 hours per night (*n* = 38), and (2) excluding those participants with previous/current comorbidities, such as neurodegenerative disorders (*n* = 3), previous/current depression (*n* = 420), previous non-atherosclerotic cardiovascular disease (thrombosis, *n* = 30 and cardiopathy, *n* = 43), previous nephropathy (*n* = 123) and previous cancer (*n* =143), and (3) excluding those participants with <5 nights of valid accelerometry-derived sleep data (*n* = 127).

Values are presented as means and 95% confidence intervals (CI), unless otherwise indicated. All analyses were cross-sectional and were conducted using Stata (14.0, StataCorp, TX) and statistical significance was set as <.05.

Results

Baseline characteristics for the entire population and by categories of nocturnal sleep duration are displayed in Table 1, and summarized according to categories of sleep variability in Supplementary Table S1. The mean age of participants was 65.0 years and the mean nocturnal sleep duration and sleep variability were 6.9 ± 1.1 hours and 0.89 ± 0.4 hours, respectively. The mean BMI in the population was 32.6 ± 3.4 kg/m^2. According to categories of sleep duration, those participants in the categories of shorter nocturnal sleep duration (<6 hours and 6 to <7 hours) were more likely to be young, men and current smokers. They were also more likely to have central obesity indices, consume more alcohol, have higher fat intake and adhere less to an energy-restricted MedDiet, along with having higher education and being currently employed (Table 1). Participants involved in the analysis concerning DXA measures (with or without VAT data available) did not differ from those with accelerometry-derived sleep data only, nor from the rest of the participants enrolled in the PREDIMED-Plus trial in terms of age, sex, BMI, and prevalence of obesity and T2D ($p > .05$ for all comparisons). No significant differences in these characteristics were also observed between participants with accelerometry data and the rest of the participants enrolled in the PREDIMED-Plus trial.

In multivariable regression analyses, 1 hour/night increment in sleep duration was inversely and significantly associated with BMI, WC, some of the DXA-derived adiposity measurements (android fat and trunk fat) (Table 2 and Supplementary Table S2). Each 1 hour increment in sleep variability was not significantly associated with any of the continuous outcomes (Table 3 and Supplementary Table S2). Concerning HbA1c, these associations remained nonsignificant after excluding those participants using anti-diabetic medication (*n* = 479) (data not shown). Figure 1 shows the multivariable-PR (95% CI) of obesity and T2D per each 1 hour/night increment in sleep duration and sleep variability, in fully adjusted models. Associations are fully displayed in Supplementary Table S3. A 1 hour/night increment of sleep duration was associated with a 4% and 7% lower prevalence of obesity and T2D, respectively. Additionally, incrementing 1 hour sleep variability was associated with significantly higher

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Table 1. Baseline characteristics of the study population from PREDIMED-Plus trial across categories of nocturnal sleep duration

	Categories of nocturnal sleep duration (hours)						
	Total *N* = 1986	<6 hours *n* = 339	6 to <7 hours *n* = 662	7 to <8 hours *n* = 700	8 to <9 hours *n* = 247	≥9 hours *n* = 38	*P*-value
Sleep parameters							
Nocturnal sleep duration, hours	6.9 ± 1.1	5.3 ± 0.7	6.5 ± 0.3	7.4 ± 0.3	8.4 ± 0.2	9.3 ± 0.3	<.001
Night sleep variability, hours	0.89 ± 0.4	1.0 ± 0.6	0.88 ± 0.4	0.87 ± 0.4	0.83 ± 0.3	0.86 ± 0.3	<.001
Daytime napping duration, minutes	84.6 ± 41.3	71.5 ± 43.7	73.4 ± 41.3	85.6 ± 45.5	117.5 ± 51.0	166.1 ± 67.2	<.001
Age, years	65.0 ± 4.9	64.1 ± 5.0	64.6 ± 5.2	65.2 ± 4.8	66.3 ± 4.4	67.9 ± 3.7	<.001
Men, *n* (%)	1058 (53)	254 (75)	373 (56)	326 (46)	93 (37)	12 (32)	<.001
BMI, kg/m^2	32.6 ± 3.4	33.1 ± 3.4	32.5 ± 3.5	32.4 ± 3.4	32.6 ± 3.3	32.4 ± 3.24	.023
Waist circumference, cm	107.1 ± 9.3	109.9 ± 9.5	107.4 ± 8.9	106.2 ± 9.3	105.2 ± 9.4	106.3 ± 9.2	<.001
General obesity[a], *n* (%)	1467 (74)	275 (81)	479 (72)	500 (71)	186 (75)	27 (71)	.013
Abdominal obesity[b], *n* (%)	1834 (92)	307 (91)	615 (93)	650 (93)	226 (92)	36 (95)	.621
Type 2 diabetes, *n* (%)	668 (36)	133 (39)	238 (36)	230 (33)	69 (28)	21 (55)	.002
Hypertriglyceridemia, *n* (%)	838 (42)	138 (41)	264 (40)	297 (42)	119 (48)	20 (53)	.131
High blood pressure, *n* (%)	1860 (93)	320 (94)	613 (93)	657 (94)	234 (95)	36 (95)	.705
Hyperglycemia, *n* (%)	1367 (69)	249 (73)	462 (69)	475 (68)	154 (62)	27 (71)	.064
Low HDL-c, *n* (%)	907 (46)	148 (44)	307 (46)	316 (45)	118 (48)	18 (47)	.855
Sleep apnea, *n* (%)	251 (13)	53 (15)	77 (12)	94 (13)	24 (10)	3 (8)	.168
Depression, *n* (%)	420 (21)	63 (18)	115 (17)	161 (23)	69 (28)	12 (32)	.001
Fasting plasma glucose, mg/dl	113.7 ± 29.1	116.5 ± 31.7	113.7 ± 28.0	113.1 ± 28.8	110.0 ± 26.6	125.5 ± 38.0	.007
HbA1c, %	6.1 ± 0.8	6.2 ± 0.9	6.1 ± 0.8	6.1 ± 0.7	6.0 ± 0.7	6.5 ± 0.9	.005
Anti-diabetic medication, *n* (%)	479 (24)	88 (26)	160 (24)	164 (23)	50 (20)	17 (45)	.020
Sedative treatment, *n* (%)	475 (24)	59 (17)	121 (18)	188 (27)	93 (37)	14 (37)	<.001
Smoking, *n* (%)							
Never	857 (43)	100 (29)	276 (42)	329 (47)	129 (52)	23 (61)	<.001
Former	894 (45)	186 (55)	308 (46)	303 (43)	87 (35)	10 (26)	
Current	235 (12)	53 (16)	78 (12)	68 (10)	31 (13)	5 (13)	
Alcohol intake, g/day	11.4 ± 15.4	14.6 ± 16.8	12.1 ± 16.6	10.7 ± 14.1	7.9 ± 12.8	8.5 ± 12.5	<.001
Carbohydrate intake, g/day	249.0 ± 80.4	255.3 ± 81.4	249.7 ± 82.6	245.8 ± 75.9	250.3 ± 84.3	230.4 ± 84.3	.260
Fat intake, g/day	103.9 ± 31.7	108.3 ± 34.6	105.2 ± 31.2	102.6 ± 30.6	99.9 ± 31.6	92.8 ± 25.3	.002
Protein intake, g/day	97.8 ± 24.5	98.8 ± 25.6	99.0 ± 24.4	97.3 ± 24.3	96.1 ± 23.0	90.7 ± 28.1	.142
Sugar intake, g/day	7.3 ± 12.9	8.5 ± 13.8	6.7 ± 12.9	7.5 ± 12.7	7.3 ± 13.4	4.4 ± 8.7	.186
Adherence to energy-restricted MedDiet (score from 0 to 17 item)	8.6 ± 2.7	8.3 ± 2.7	8.7 ± 2.7	8.6 ± 2.7	8.7 ± 2.7	9.7 ± 2.9	.008
Compliance of MVPA recommendations[c], *n* (%)	371 (19)	53 (16)	140 (21)	141 (20)	33 (13)	4 (11)	.018
Education status, *n* (%)							
Primary education	1010 (51)	155 (46)	306 (46)	369 (53)	153 (62)	27 (71)	<.001
Secondary education	537 (27)	88 (26)	192 (29)	195 (28)	56 (22)	6 (16)	
Academic/graduate	439 (22)	96 (28)	164 (25)	136 (19)	38 (16)	5 (13)	
Employment status, *n* (%)							
Working	425 (21)	103 (30)	161 (24)	131 (19)	29 (12)	1 (2)	<.001
Non-working	472 (24)	62 (18)	147 (23)	182 (26)	71 (29)	10 (26)	
Retired	1089 (55)	174 (52)	354 (53)	387 (55)	147 (59)	27 (72)	
Marital status, *n* (%)							
Single/divorced	291 (15)	56 (17)	103 (15)	100 (14)	24 (10)	8 (21)	.017
Married	1482 (74)	250 (74)	507 (77)	514 (73)	186 (75)	25 (66)	
Widower	213 (11)	33 (10)	52 (8)	86 (12)	37 (15)	5 (13)	
Body composition	*n* = 649	*n* = 105	*n* = 209	*n* = 249	*n* = 72	*n* = 14	
Total fat, kg	34.3 ± 7.3	34.4 ± 6.8	38.0 ± 7.7	34.6 ± 6.9	34.1 ± 7.1	35.0 ± 8.9	.937
Android fat, kg	3.7 ± 0.9	3.9 ± 0.9	3.7 ± 1.0	3.7 ± 0.8	3.6 ± 1.0	3.6 ± 0.8	.313
Gynoid fat, kg	5.0 ± 1.4	4.9 ± 1.4	5.0 ± 1.5	5.1 ± 1.4	5.0 ± 1.2	5.2 ± 1.5	.706
Android-gynoid fat ratio, kg	0.8 ± 0.2	0.83 ± 0.21	0.76 ± 0.19	0.76 ± 0.19	0.74 ± 0.18	0.73 ± 0.25	.008
VAT[d], kg	2.3 ± 0.8	2.4 ± 0.9	2.4 ± 0.9	2.1 ± 0.8	2.2 ± 0.8	2.3 ± 0.2	.088
Trunk fat mass, kg	20.3 ± 4.3	20.7 ± 3.9	20.1 ± 4.7	20.3 ± 4.0	19.8 ± 4.6	19.6 ± 4.5	.619
Lean mass, kg	47.8 ± 9.7	50.4 ± 9.0	48.3 ± 9.7	46.9 ± 9.7	46.4 ± 9.4	43.2 ± 7.7	.004

Data is presented as mean ± *SD* unless otherwise indicated. HDL-c, high-density lipoprotein cholesterol. P-value for differences between categories of nocturnal sleep duration was calculated by chi-square or one-way ANOVA for categorical and continuous variables, respectively.

[a]General obesity defined as BMI ≥30 kg/m^2.

[b]Abdominal obesity defined as waist circumference ≥102 cm in men and ≥88 cm in women.

[c]Recommendations for MVPA set on ≥150 minutes/week for elderly persons, based on accelerometry-derived 10-minute bout MVPA.

[d]VAT was determined in a subsample of participants undergoing body composition, the participants included were 288 in total and according to categories of sleep duration, as follows: 52 at the category of <6 hours; 93 at the category between 6 and <7 hours; 109 at the category of 7 to <8 hours, 31 at the category of 8 to <9 hours, and 3 at the ≥9 hours.

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Table 2. Multivariable-adjusted β-coefficients (95% CI) per increment of 1 hour accelerometer-derived nocturnal sleep duration in relation to anthropometry and DXA-derived parameters, fasting plasma glucose and HbA1c

Outcomes	*n*	Sleep duration (hours)	*P*-value	Adjusted *P*-value*	Sleep duration (hours)[a]	*P*-value	Adjusted *P*-value*
Anthropometry and glucose parameters							
BMI, kg/m^2	1986	−0.37 (−0.52, −0.22)	<.001	.005	−0.38 (−0.54, −0.23)	<.001	.005
WC, cm	1986	−0.82 (−1.20, −0.43)	<.001	.005	−0.86 (−1.25, −0.47)	<.001	.005
Fasting plasma glucose, mg/dl	1986	−0.74 (−2.04, 0.55)	.262	.262	−0.60 (−1.92, 0.71)	.369	.369
HbA1c, %	1986	−0.04 (−0.07, −0.01)	.026	.057	−0.03 (−0.06, 0.001)	.056	.108
DXA-derived parameters							
Total fat, kg	649	−0.54 (−1.08, 0.09)	.054	.089	−0.49 (1.05, 0.05)	.077	.121
Android fat, kg	649	−0.10 (−0.17, −0.03)	.007	.025	−0.09 (−0.17, −0.02)	.009	.033
Gynoid fat, kg	649	−0.07 (−0.17, 0.02)	.140	.171	−0.06 (−0.16, 0.03)	.184	.224
Android-Gynoid ratio	649	−0.010 (−0.023, 0.003)	.118	.162	−0.011 (−0.024, 0.002)	.105	.144
VAT, kg	288	−0.08 (−0.17, 0.002)	.057	.089	−0.08 (−0.17, 0.003)	.059	.108
Trunk fat mass, kg	649	−0.43 (−0.77, −0.09)	.012	.033	−0.42 (−0.76, −0.08)	.016	.044
Lean mass, kg	649	−0.25 (−0.65, 0.14)	.207	.227	−0.23 (−0.63, 0.16)	.252	.277

Linear regression models for sleep duration and the presented continuous outcome. Model adjusted for sex, age (years), marital status (single/divorced, married and widower), employment (working, nonworking, retired), education (primary education, secondary education, academic/graduate), smoking habit (current smoker, past smoker, never smoked), sedative treatment (yes/no), sleep apnea (yes/no), type 2 diabetes (yes/no), depression (yes/no), 17-score energy-restricted Mediterranean diet, alcohol intake (g/day, continuous and adding a quadratic term), compliance to MVPA recommendations set in ≥150 minutes/week (yes/no), time spent in sustained inactivity bouts ("daytime napping", minutes/day, log10 transformed) and intervention center. Model of fasting plasma glucose was additionally adjusted for waist circumference. Model for HbA1c was additionally adjusted for waist circumference and anti-diabetic treatment (yes/no). *P*-value from linear regression for sleep duration and night-to-night sleep variability and the presented outcomes.
[a]Model additionally adjusted for sleep variability (continuous).
*Adjusted *P*-value for multiple-testing using Benjamin-Hochberg procedure considering FDR < 0.05 as significant.

Table 3. Multivariable-adjusted β-coefficients (95% CI) per increment of 1 hour accelerometer-derived night-to-night sleep variability in relation to anthropometry and DXA-derived parameters, fasting plasma glucose, and HbA1c

Outcomes	*n*	Sleep variability (hours)	*P*-value	Adjusted *P*-value*	Sleep variability (hours)[a]	*P*-value	Adjusted *P*-value*
Anthropometry and glucose parameters							
BMI, kg/m^2	1986	0.01 (−0.36, 0.33)	.935	.935	−0.16 (−0.51, 0.19)	.377	.460
WC, cm	1986	−0.35 (−1.23, 0.54)	.440	.537	−0.67 (−1.56, 0.22)	.141	.387
Fasting plasma glucose, mg/dl	1986	2.11 (−0.84, 5.05)	.161	.431	1.88 (−1.11, 4.86)	.218	.434
HbA1c, %	1986	0.07 (0.02, 0.14)	.045	.355	0.06 (−0.01, 0.13)	.097	.387
DXA-derived parameters							
Total fat, kg	649	1.39 (−0.14, 2.93)	.075	.355	1.26 (−0.27, 2.80)	.107	.387
Android fat, kg	649	0.12 (−0.08, 0.32)	.246	.451	0.09 (−0.11, 0.30)	.359	.460
Gynoid fat, kg	649	0.23 (−0.04, 0.51)	.097	.355	0.22 (−0.06, 0.49)	.126	.387
Android-Gynoid ratio	649	−0.010 (−0.046, 0.027)	.606	.666	−0.012 (−0.049, 0.024)	.506	.506
VAT, kg	288	0.41 (−0.23, 0.40)	.287	.451	0.14 (−0.12, 0.39)	.299	.460
Trunk fat mass, kg	649	0.47 (−0.48, 1.43)	.328	.451	0.36 (−0.58, 1.32)	.452	.497
Lean mass, kg	649	0.73 (−0.38, 1.85)	.196	.431	0.67 (−0.44, 1.79)	.237	.434

Linear regression models for night-to-night sleep variability and the presented continuous outcomes. Model adjusted for sex, age (years), marital status (single/divorced, married and widower), employment (working, nonworking, retired), education (primary education, secondary education, academic/graduate), smoking habit (current smoker, past smoker, never smoked), sedative treatment (yes/no), sleep apnea (yes/no), type 2 diabetes (yes/no), depression (yes/no), 17-score energy-restricted Mediterranean diet, alcohol intake (g/day, continuous and adding a quadratic term), compliance to MVPA recommendations set in ≥150 minutes/week (yes/no), time spent in sustained inactivity bouts ("daytime napping", minutes/day, log10 transformed) and intervention center. Model of fasting plasma glucose was additionally adjusted for waist circumference. Model for HbA1c was additionally adjusted for waist circumference and anti-diabetic treatment (yes/no). *P*-value from linear regression for sleep duration and night-to-night sleep variability and the presented outcomes.
[a]Model additionally adjusted for sleep duration (continuous).
*Adjusted *p*-value for multiple-testing using Benjamin-Hochberg procedure considering FDR < 0.05 as significant.

T2D prevalence, even after adjusting for sleep duration. No significant association was found between sleep variability and obesity prevalence. The associations of sleep duration and sleep variability with obesity and T2D remained unchanged in magnitude and strength when analyses where conducted removing the covariates T2D, obesity and high blood pressure from the fully adjusted model.

Being characterized as "bad sleeper" was positively associated with BMI, fasting plasma glucose and HbA1c (Table 4), as well as with higher obesity and T2D prevalence (Figure 2, a and b, respectively) as compared to "good sleepers." Participants with non-recommended sleep duration plus low sleep variability (category 3) were also significantly associated with high obesity prevalence (Figure 2a). Participants with sleep duration that may

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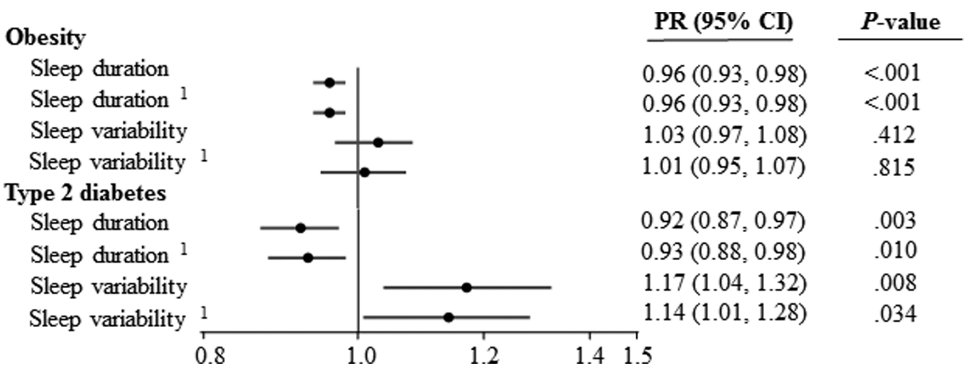

Figure 1. Multivariable-Prevalence Ratio (95% CI) for obesity and type 2 diabetes per increment of 1 hour in nocturnal sleep duration and night-to-night sleep variability. Model adjusted for sex, age (years), marital status (single/divorced, married and widower), employment (working, nonworking, retired), education (primary education, secondary education, academic/graduate), smoking habit (current smoker, past smoker, never smoked), high blood pressure (yes/no), sedative treatment (yes/no), sleep apnea (yes/no), depression (yes/no), 17-score energy-restricted Mediterranean diet, alcohol intake (g/day, continuous and adding a quadratic term), compliance to MVPA recommendations set in ≥150 minutes/week (yes/no), time spent in sustained inactivity bouts ("daytime napping," minutes/day, log10 transformed) and intervention center. Additionally, the model for obesity was adjusted for type 2 diabetes (yes/no) and high blood pressure (yes/no), whereas the model for type 2 diabetes was adjusted for obesity and high blood pressure (yes/no). [1]Model additionally adjusted for sleep variability in case of sleep duration or sleep duration in case of sleep variability.

Table 4. Multivariable-adjusted β-coefficients (95% CI) for anthropometry and DXA-derived parameters, fasting plasma glucose, and HbA1c in bad sleepers[a] vs. good sleepers[b]

Outcomes	Good sleepers (*n* = 400)	Bad sleepers (*n* = 147)	P-value	Adjusted P-value*
Anthropometry and glucose parameters				
BMI, kg/m^2	Ref.	0.87 (0.22, 1.51)	.008	.029
WC, cm	Ref.	1.47 (−0.18, 3.13)	.081	.222
Fasting plasma glucose, mg/dl	Ref.	7.89 (2.38, 13.40)	.005	.027
HbA1c, %	Ref.	0.37 (0.21, 0.52)	<.001	.011
DXA-derived parameters				
Total fat, kg	Ref.	1.36 (−0.94, 3.66)	.246	.338
Android fat, kg	Ref.	0.23 (−0.06, 0.54)	.130	.256
Gynoid fat, kg	Ref.	0.50 (−0.36, 0.46)	.813	.813
Android-Gynoid ratio	Ref.	0.04 (−0.01, 0.09)	.140	.256
VAT, kg	Ref.	0.17 (−0.19, 0.53)	.354	.432
Trunk fat mass, kg	Ref.	0.88 (−0.54, 2.31)	.222	.338
Lean mass, kg	Ref.	0.41 (−1.25, 2.07)	.625	.687

Ref., reference category. Linear regression models for "bad sleepers" vs. "good sleepers" (Ref.) and the presented continuous outcomes. Model adjusted for sex, age (years), marital status (single/divorced, married and widower), employment (working, nonworking, retired), education (primary education, secondary education, academic/graduate), smoking habit (current smoker, past smoker, never smoked), sedative treatment (yes/no), sleep apnea (yes/no), type 2 diabetes (yes/no), depression (yes/no), 17-score energy-restricted Mediterranean diet, alcohol intake (g/day, continuous and adding a quadratic term), compliance to MVPA recommendations set in ≥150 minutes/week (yes/no), time spent in sustained inactivity bouts ("daytime napping", minutes/day, log10 transformed) and intervention center. P-value from linear regression for category of "bad sleepers" vs. "good sleepers" (Ref.) and the presented outcomes.

[a]Bad sleepers: non-recommended sleep duration (<6 hours/night sleep for individuals with <65 years and <5 hours/night for individuals with ≥65 years or ≥9 hours/night) plus high sleep variability (≥median sleep *SD*).

[b]Good sleepers: recommended sleep duration (7–9 hours/night sleep for individuals with <65 years and 7–8 hours/night for individuals with ≥65 years) plus low sleep variability (<median sleep *SD*).

*Adjusted *p*-value for multiple-testing using Benjamin-Hochberg procedure considering FDR < 0.05 as significant.

be appropriate according to their age-specific plus high variability (category 5) were positively associated with T2D (Figure 2b). No significant associations were found in relation to WC and DXA-derived parameters (Table 4). Participants in the category of short sleep duration had significantly higher obesity and T2D prevalence than those in the category of longer sleep duration [PR 1.15 (1.07, 1.24) p < .001 and PR 1.30 (1.09, 1.55) p = .004, respectively]. Similarly, participants in the category of high sleep variability had higher T2D prevalence [PR 1.24 (1.10, 1.39) p = .001], but not obesity prevalence [PR 1.03 (0.98, 1.08) p = .244], as compared with those in the category of low sleep variability.

No significant interactions with sex, age or T2D were found (p > .05 for all interactions). Results from sensitivity analysis on adiposity parameters and T2D were consistent with those of the primary analysis in relation to sleep duration and variability after excluding those participants sleeping ≥9 hours/night (n = 38) (Supplementary Table S4), or participants with <5 nights of valid accelerometry data (n = 127) (Supplementary Table S5). Results were also similar when removing those participants with previous/current history of neurodegenerative disorders, depression, non-atherosclerotic cardiovascular disease, nephropathy or cancer (data not shown).

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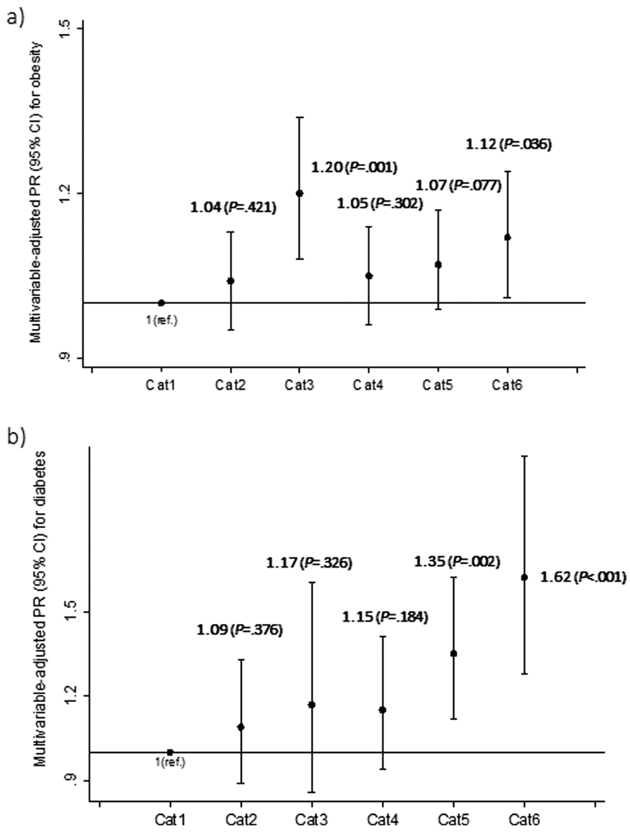

Figure 2. Multivariable-adjusted PR for obesity (a) and type 2 diabetes (b) in joint categories of sleep duration and sleep variability. Cat, category. Category 1 ("good sleepers") included those participants following their age-specific recommended sleep duration (7–9 hours/night sleep for individuals with <65 years and 7–8 hours/night for individuals with ≥65 years) plus low sleep variability (<median sleep *SD*) (*n* = 400). Category 2 included participants with sleep duration that may be appropriate according to their age-specific plus low sleep variability (*n* = 489). Category 3 included participants with non-recommended sleep duration plus low sleep variability (*n* = 96). Category 4 included participants following their age-specific recommended sleep duration plus high sleep variability (*n* = 385). Category 5 included participants with sleep duration that may be appropriate according to their age-specific plus high variability (*n* = 469). Category 6 ("bad sleepers") for participants with non-recommended sleep duration (<6 hours/night sleep for individuals with <65 years and <5 hours/night for individuals with ≥65 years or ≥9 hours/night) plus high sleep variability (≥median sleep *SD*) (*n* = 147).

Discussion

The main findings of the present study suggest that one hourly increase in nocturnal sleep duration was inversely associated with adiposity-related anthropometric and DXA-derived body composition parameters, as well as with a 4% and 7% lower prevalence of obesity and T2D, respectively. Contrary, each hourly increase in sleep variability was directly associated with a 14% higher T2D prevalence. When considering their combined effects, "bad sleepers" were positively associated with BMI, fasting plasma glucose, HbA1c, and with a 12% and 62% higher prevalence of obesity and T2D prevalence, respectively.

A number of previous studies have observed inverse associations between nocturnal sleep duration and adiposity-related parameters using both self-reported [8, 10, 12, 29–32] and accelerometry-derived sleep data [11]. For instance, two large population cohorts (NHANES [8] and KNHANES [12, 29]) of middle-aged and elder adults, showed that shorter sleep duration was consistently associated with larger BMI, WC, DXA-derived fat mass and obesity.

The inverse association between sleep duration and T2D prevalence observed in the Mediterranean population evaluated in our study is in line with findings from previous cross-sectional [5, 7, 32] and large prospective studies including middle-aged and older adults in other populations, such as the Nurses' Health Study [13] and EPIC-Norfolk study [33]. Interestingly, the magnitude of association between sleep duration and T2D appeared to be greater than that observed with obesity. This may be partially explained by the high prevalence of obesity in our study population, which could contribute to a decrease in the sensitivity to detect these associations.

Several mechanisms have been suggested to explain the aforementioned observations. Short sleep duration may be accompanied by increased opportunities to eat during the day, as well as by enhanced hedonic perception of highly palatable foods [34]. Accordingly, in our study short sleepers had higher fat intake and lower score for the adherence to a healthy dietary pattern (MedDiet). Short sleep duration may also reduce time devoted to physical activity and its intensity as a result of increased feelings of tiredness, hence perpetuating a positive energy balance and contributing to weight gain and poor glucose control [34]. Admittedly, the cross-sectional design of our study precludes conclusions on the potential causality of these associations.

Current evidence on sleep variability and adiposity parameters in middle-aged and old adults remains scarce and inconsistent. Previous studies showing direct associations between night-to-night sleep variability and obesity in old adults [17] were conducted using self-reported sleep data. However, evidence from other studies using accelerometry-derived sleep variability [11, 35], such as that from Ogilvie et al. [11], support our findings in relation to the lack of significant associations with BMI, WC and total body fat when sleep duration was included in the statistical models. Notably, in our study the magnitude of these associations was similar regardless of including sleep duration as a covariate.

Furthermore, we observed that high sleep variability was independently and positively associated with the prevalence of T2D, suggesting a plausible impact of sleep variability on glucose control in elders with metabolic disturbances. To the best of our knowledge, no previous study has ever evaluated sleep variability in relation to T2D in older populations. Nevertheless, earlier studies evaluating these associations have mostly focused on children [18] and adolescents [36] showing direct associations between high sleep variability or disturbed sleep architecture and alterations in glucose metabolism. Potential mechanisms underlying these observations involve several disruptions at the level of the central nervous system, including impaired cortisol rhythm promoting insulin resistance, as well as in peripheral tissues, such as liver alterations of glucose metabolism or pancreatic beta-cell secretion driven by a pro-inflammatory and pro-oxidative status [37].

As far as we know, this is the first study examining associations between combined sleep duration and sleep variability with obesity and T2D. According to our findings, the magnitude of the associations with T2D increased when sleep duration and sleep variability were combined. We found that participants in the categories of short sleep duration and high sleep variability

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had 30% and 24% higher T2D prevalence, respectively whereas in joint analysis (category of “bad sleepers” vs. “good sleepers”) this prevalence raised up to a 62%.

Interestingly, from the results obtained in the joint analyses, it seems that sleep duration, particularly non-recommended sleep duration, has an important contribution on obesity prevalence and the magnitude of association, regardless of low or high sleep variability. In spite of this, the magnitude of association is slightly attenuated when high sleep variability is considered in the joint analyses. Furthermore, the magnitude of the associations with T2D increased when non-recommended sleep duration and high sleep variability were combined, highlighting the importance of considering both sleep characteristics due to their potential synergistic effects on metabolic health. Nevertheless, these results need to be further confirmed in longitudinal analyses.

A number of limitations in the present study should be acknowledged. First, the cross-sectional design does not allow to make any causal inference of the observed associations, and therefore reverse causation cannot be excluded. Admittedly, the cross-sectional observations derived from the present study are limited in their potential clinically relevance, yet they add on understanding to current knowledge in relation to sleep characteristics, adiposity, and T2D. Second, the high prevalence of abdominal obesity (92%) in our study did not allow us to assess its associations with sleep characteristics. In addition, since some of the outcomes in our study were part of the inclusion criteria, the observed associations may have been affected. Third, although the prevalence of sleep apnea was reported in our study, information regarding treatment approaches was not available. Fourth, residual confounding may remain despite adjusting for several potential confounders. Fifth, we acknowledge potential selection bias from including those participants with available data on accelerometry and DXA for the present analyses. Nevertheless, in a series of analyses conducted, we have observed no significant differences between participants with DXA measures (with or without VAT data available) and/or accelerometry data, and the rest of the participants from the PREDIMED-Plus trial in main characteristic variables. Finally, participants were elder Mediterranean adults at high cardiovascular risk, thus results cannot be extrapolated to other study populations. Our study has also several strengths including the use of accelerometry, a reliable method to assess sleep data compared to other subjective tools [38], and the inclusion of DXA-derived body composition parameters in addition to other classical adiposity parameters like BMI or WC.

Conclusions

The findings reported in our study add on new evidence in relation to sleep characteristics, obesity, and T2D, which may be particularly relevant for the development of public health strategies in the management of these conditions among elders at high cardiovascular risk. In this population, we found that sleep duration was important for both obesity and T2D prevalence. Sleep variability, however, was more relevant for T2D. Further studies are required to prospectively confirm our findings and elucidate other possible mechanisms underlying these observations.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Conflict of interest statement. None declared.

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