The association between sleeping time and metabolic syndrome features among older adults living in Mediterranean region. The MEDIS study.

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THE ASSOCIATION BETWEEN SLEEPING TIME AND METABOLIC SYNDROME FEATURES, AMONG OLDER ADULTS LIVING IN MEDITERRANEAN REGION: THE MEDIS STUDY.

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ABSTRACT

Background: Metabolic Syndrome (MetS) as a combination of features has been known to significantly increase Cardiovascular Disease (CVD) risk, whilst MetS presence is linked to lifestyle parameters including physical activity and dietary habits; recently, the potential impact of sleeping habits has also become an issue under consideration. The aim of this study was to investigate the role of sleep quantity in several MetS components**. Methods:** *Design:* Cross-sectional observational study. *Setting:* 26 Mediterranean islands and the rural Mani region (Peloponnesus) of Greece. *Participants:* during 2005-2017, 3130 older (aged 65-100 years) Mediterranean residents were voluntarily enrolled. *Measurements:* Dietary habits (including MedDietScore assessment), physical activity status, socio-demographic characteristics, lifestyle parameters (sleeping and smoking habits) and clinical profile aspects including Metabolic Syndrome (MetS) components (i.e., waist circumference, systolic and diastolic blood pressure, fasting glucose, triglycerides, LDL and HDL-cholesterol) were derived through standard procedures. **Results**: The number of daily hours of sleep was independently associated with greater waist circumference (b coefficient per 1 hour=0.91, 95% Confidence Interval (CI); 0.34, 1.49), higher LDL-cholesterol levels (b per 1 hour=3.84, 95%CI; 0.63, 7.05) and lower diastolic blood pressure levels (b per 1 hour=-0.98, 95%CI; -1.57, -0.39) after adjusting for participants' age, gender, body mass index, daily walking time, level of adherence to Mediterranean diet and smoking status. No association was revealed between hours of sleep per day and fasting glucose, triglycerides, HDL-cholesterol and systolic blood pressure. **Conclusions:** Increased hours of sleep is an indicator of metabolic disorders among elderly inviduals, and further research is needed to identify the paths through which sleep quantity is linked to MetS features in different age-groups.

Keywords: Metabolic Syndrome components; Sleep; Elderly; Lifestyle; MEDIS; Mediterranean-type diet

INTRODUCTION

The metabolic syndrome (MetS) has been defined as "*multiple, interrelated factors that raise cardiovascular disease (CVD) risk*" (1, 2, 3). The classic definition includes presence of several metabolic risk factors, such as insulin resistance, central obesity, dyslipidemia and elevated blood pressure levels, with recent research expanding these to include chronic stress, inflammation processes, and epigenetic interactions (2). This has brought into question clinical value of confirming a diagnosis of MetS to identify individuals at risk of CVD, as it may exclude people with increased risk that do not present with the minimum of three or more risk factors (4). Thus, suggesting that identifying and managing risk associated with the individual isolated characteristics of MetS could be of equal if not greater clinical importance than diagnosing MetS (5).

The role of lifestyle factors particularly those beyond diet (5) and physical activity (6) in relation to CVD risk and MetS is an area of increasing interest. This includes associations between social interaction, depression and risk of CVD (7) and have included investigations which found associations between sleeping pattern including daytime sleeping and MetS risk (8). Increasing evidence of the potential role of sleep in MetS components has recently emerged in the literature, meta-analysis in 2015 of 21 studies found a robust and consistent negative association between insufficient sleep and waist circumference (9). This aligns with a separate review, which found an increased risk for MetS in short, but not in longer duration sleepers (10). However, the mechanism of how sleep duration may influence MetS risk is unclear. Moreover, elevated blood pressure and glucose dysregulation has been proposed as a primary driver behind the excess in mortality risk in short-duration sleepers (11). The impact of sleep deprivation on the endocrine system is complex and include decreased insulin sensitivity, and dysregulation of hormonal pathways including cortisol, leptin and insulin-like-growth factor-1 (12). Furthermore, sleep deprivation modifies inflammatory and cholesterol pathways associated with increased CVD risk at both the transcriptome level and in the circulating lipid profile (13, 14). This implies that the effect of sleep deprivation impacts on the component factors of MetS, and as such merits investigation.

Despite understanding the impact of lack of sleep on metabolic risk, little is known regarding the association of sleep quantity on MetS features, ESPECIALLY in older adult population. Moreover, older people residing in the Mediterranean region have attracted considerable scientific and public interest, surrounding their lifestyle and dietary factors, as potentially preventative and curative for several health conditions (15-19). Recently, the MEDIS group has shown that sleeping during the day (siesta) is positively associated with odds of hypertension (7). To our knowledge, no study has investigated the relationship between the quantity of sleep and the individual component factors of MetS in elderly individuals. Thus, the aim of the present work was to evaluate the associations between sleep quantity and MetS features' in elderly individuals from the Mediterranean region.

MATERIALS AND METHODS

Methodology

The Mediterranean Islands (MEDIS) study is an ongoing, large-scale, multinational epidemiological project, which is exploring the association between lifestyle habits, psycho-social characteristics, and living environment, on cardiometabolic factors, among older people (>65 years), residing in the Mediterranean area.

The Study's sample

Between 2005-2017, a random population-based, multistage sampling method (i.e., age group, 3 levels (65 - 75, 75 - 85, 85+) and 2 sex levels) was used to voluntarily enrol older men and women people from 26 Mediterranean islands: including Malta Republic (n=250), Sardinia (n=60) and Sicily (n=50), Mallorca and Menorca (n=111), Republic of Cyprus (n=300), Gökçeada (n=55) in Turkey, and the Greek islands of Lesvos (n=142), Samothraki (n=100), Cephalonia (n=115), Crete (n=131), Corfu (n=149), Limnos (n=150), Ikaria (n=76), Syros (n=151), Naxos (n=145), Zakynthos (n=103), Salamina (n=147), Kassos (n=52), Rhodes and Karpathos (n=149), Tinos (n=129), Ai-Stratis (n=30), Spetses (n=92), Aegina (n=59), Paros (n=90) as well as the rural region of East Mani (n=295, 157 men aged 75±7 years and 138 women aged 74±7 years) (a Greek peninsula, which is in the southeast, continental area of Europe, with a total population of 13,005 people (census 2011), which has morphological and cultural specificities, which are not common across in the rest of Greece. Individuals who resided in assisted-living centres, had a clinical history of cardiovascular disease (CVD) or cancer, or had left the island for a considerable period of time during their life (i.e., >5 years) were excluded from participating in the study; these criteria were applied because the study aimed to assess lifestyle patterns that were not a response of individuals modifying how they live due to existing chronic health care conditions or by environmental factors, other than their living milieu. The participation rate varied according to the region, from 75% to 89%. Thus, information from 3130 individuals, 1,574 men, aged 75±8 years and 1,556 women, aged 74±7 years, were analyzed.

A multidisciplinary group of health scientists (physicians, dietitians, public health nutritionists, and nurses) with experience in field investigation collected all the required information using a quantitative questionnaire and standard procedures.

Bioethics

The study followed the ethical considerations provided by the World Medical Association (52^{nd} WMA General Assembly, Edinburgh, Scotland; October 2000). The Institutional Ethics Board of Harokopio University approved the study design (16/19-12-2006), as well as the regional offices of the participated Institutions. Participants were informed about the aims and procedures of the study and gave their consent prior to being interviewed.

Evaluation of clinical characteristics

All of the measurements taken in the different study centers were standardized, and the questionnaires were translated into all of the cohorts' languages following the World Health Organization (WHO) translation guidelines for tools assessment (www.who.int/substance_abuse/research_tools/translation/en/). Height and weight were measured using standard procedures to attain body mass index (BMI) scores (kg/m^2). Waist circumference (cm) was measured at the midpoint between the 12th rib and the iliac crest. Fasting blood lipids levels (HDL-c, LDL-c and triglycerides) and fasting glucose levels were also recorded. Blood pressure was either self-reported or, in most islands measured by trained physicians or nurses with participants in a sitting position and calm and the average of three measurements was calculated. The IDF Epidemiology Task Force group definition of MetS was used to identify individuals with MetS (3).

Evaluation of lifestyle and socio-demographic characteristics

Sleep was assessed estimating the amount of sleeping hours on a typical day while interviewing the participants using the self-reported Wake After Sleep Onset (WASO). The frequency and the hours of sleeping during the day, as well as the wake-up and going-to-sleep time were also recorded according to individuals self-reporting. Dietary habits were assessed through a semi-quantitative, validated and reproducible food-frequency questionnaire (20). Trained dietitians estimated the mean daily energy intake and the mean percentage of total energy derived from dietary carbohydrates. To evaluate the level of adherence to the Mediterrenean diet, the MedDietScore (possible range 0-55) was used (21). Higher values for this diet score being indicative of greater adherence to the Mediterranean diet. Participants were also encouraged to report the duration of following their dietary pattern (i.e., the number of years this pattern had been in place). Basic socio-demographic characteristics such as age, sex, as well as lifestyle characteristics, such as smoking habits and physical activity status, were also recorded. Current smokers were defined as smokers at the time of the interview, whereas former smokers were defined as those who previously smoked, but had not done so for a year or more. Current and former smokers were defined as had '*ever smokers*'. The remaining participants were assigned as occasional or non-smokers. Physical activity was evaluated in MET-minutes per week, using the shortened, translated and validated into Greek, version of the self-reported International Physical Activity Questionnaire (IPAQ) (22, 23). Frequency (times per week), duration (minutes per session) and intensity of physical activity during sports, occupation, and leisure activities were assessed. Participants were instructed to report only episodes of activity lasting at least 10 minutes since this is the minimum required to achieve health benefits. Physically active individuals were defined those who reported at least 3 MET-min. Daily walking time was calculated by using the IPAQ question about walking (times per week and average time spent).

Further details about the MEDIS study have extensively been published elsewhere (24, 25).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation for variables following assessing for normal distribution, or median (inter-quartile range) for variables not following a normal distribution. Normality was tested using P-P plots. Differences in continuous variables between males and females were evaluated with the Student's t-test for normally distributed parameters and the Mann-Whitney test for non-parametric variables. Correlations between continuous variables were tested using Pearson's r when both variables were normally distributed or Spearman's rho when at least one of them did not have a normal distribution. Nominal variables are presented as frequencies and relative frequencies (%). Pearson's Chi-square test was used to assess the association between two nominal variables. Linear regression models were used to evaluate the association between sleed duration, other participants' characteristics (i.e., age, sex, BMI, physical activity, MedDietScore, smoking habits) and levels of the MetS components (fasting glucose levels, waist circumference, systolic and diastolic arterial blood pressure, triglycerides, LDL and HDL levels). Logarithmic transformation was used for the dependent variable that did not have a normal distribution (triglycerides and HDL-c). Results are expressed as b coefficients and the 95% confidence intervals. Type I error was predefined at 0.05. Statistical analysis was carried out in IBM SPSS version 23.0 (Armonk, NY: IBM Corp.).

RESULTS

Mean sleep duration time was 8.30±1.76 h per day, and specifically 8.30±1.75 h for men and 8.20±1.77 h for women ($p=0.52$). Moreover, sleep duration did not differ between retired and non-retired individuals ($p=0.244$), with the latter consisting 20.9% of the total sample. Sleep duration was positively associated with waist circumference (Pearson's $r=0.12$, $p=0.01$) and LDL-c (Pearson's $r=0.23$, $p=0.001$) and inversely associated with diastolic arterial blood pressure (Pearson's $r=-0.15$, $p=0.002$). No association was observed between sleep and fasting glucose levels ($p=0.20$), systolic arterial blood pressure ($p=0.59$), fasting triglycerides ($p=0.44$) and HDL-c ($p=0.47$). MetS prevalence according to IDF criteria was 65.3% and did not differ between genders ($p=0.49$).

Mean BMI was 28.3±4.67 kg/m^2, while the level of adherence to Mediterranean diet was 32.5±4.99 out of 55 (or 59% of ideal adherence), as calculated via the MedDietScore.

Regarding the MetS individual components, mean waist circumference 101±14.0 cm, mean fasting glucose 116±39.5 mg/dL and mean LDL-c 126±41.3 mg/dL with median HDL-c 50 mg/dL and median triglyceride levels 119 mg/dL. Participants' mean systolic and diastolic arterial blood pressures were 135±21.9 mmHg, and 77.6±13.0 mmHg respectively. Descriptive characteristics of the study sample, divided into two groups with respect to their gender, are summarized in *Table 1*.

[Table 1]

As presented in *Table 1*, females had higher BMI than males (28.9±5.10 kg/m^2 vs. 27.8±4.12 kg/m^2 respectively, $p<0.001$), but their smoking prevalence was fivefold lower compared to men (5.2% vs. 26.1% respectively, $p<0.001$). No differences were revealed for their level of adherence to Mediterranean diet ($p=0.88$), daily walking time ($p=0.24$) nor their daily hours of sleep ($p=0.53$). As expected, females had lower waist circumference than men (100±15.1 cm vs. 102±12.3 cm respectively, $p=0.001$), higher HDL-c levels (55 (46,63) mg/dL vs. 46 (40,54) mg/dL, respectively, $p<0.001$) and lower LDL-c levels (129±22.6 mg/dL vs. 123±39.3 mg/dL, respectively, $p=0.026$). Interestingly, no differences were detected for triglycerides' levels ($p=0.55$), fasting glucose levels ($p=0.72$), systolic ($p=0.86$) and diastolic ($p=0.46$) arterial blood pressure levels.

Characteristics of the participants according to their MetS status are presented in *Table 2*. As expected, subjects with MetS had higher waist circumference than MetS-free subjects (107±10.4 cm vs. 96.8±12.5 cm respectively, $p<0.001$), lower HDL-c levels (49 (42,58) mg/dL vs. 56 (49,62) mg/dL, respectively, $p<0.001$), higher LDL-c levels (130±40.2 mg/dL vs. 115±44.1 mg/dL, respectively, $p=0.003$), higher BMI (30.8±4.37 kg/m^2 vs. 28.2±3.81 kg/m^2 respectively, $p<0.001$), higher fasting glucose levels (126±36.9 mg/dL vs. 101±36.1 mg/dL, respectively, $p<0.001$), higher triglycerides' levels (132 (102,177) mg/dL vs. 100 (86,119) mg/dL, respectively, $p<0.001$), higher systolic (138±15.4 mmHg vs.

123±14.2 mmHg, respectively, $p<0.001$) and diastolic arterial blood pressure levels (79.5±9.62 mmHg vs. 74.9±9.96 mmHg, respectively, $p<0.001$), as well as less daily walking time (60 (30,120) minutes/day vs. 120 (30,240) minutes/day respectively, $p<0.001$). Interestingly, no differences were detected for gender ($p=0.49$), age ($p=0.50$), daily hours of sleep ($p=0.42$), smoking status ($p=0.76$), nor their level of adherence to Mediterranean diet ($p=0.53$). No significant interaction between gender and sleep duration was detected when MetS presence is regarded.

[Table 2]

Table 3 and *Figure 1* present the multivariable linear regression models that were implemented with the MetS individual component factors (waist circumference, fasting glucose levels, LDL-c and HDL-c levels, triglycerides levels, systolic and diastolic arterial blood pressure) as dependent variables. Total daily hours of sleep was independently associated with greater waist circumference in the age and gender adjusted model (b per 1 hour=0.70, 95%CI; 0.07, 1.32) which remained significant and became stronger after adjusting for lifestyle factors such as smoking, daily walking, MedDietScore and BMI (b per 1 hour=0.91, 95%CI; 0.34, 1.49). When LDL-c levels are regarded, the daily hours of sleeping was a significant independent variable in the age and gender adjusted model (b per 1 hour=5.14, 95%CI; 2.10, 8.19), whilst in the final model it remained significant, but the effect size decreased (b per 1 hour=3.84, 95%CI; 0.63, 7.05). Total daily hours of sleep were independently and equally associated with lower diastolic blood pressure levels in the age and gender adjusted model (b per 1 hour=-0.92, 95%CI; -1.49, -0.34) and the multi-adjusted model (b per 1 hour=-0.98, 95%CI; -1.57, -0.39). No associations were revealed between hours of sleep per day and fasting glucose, triglycerides, and systolic arterial blood pressure levels in any of the the multivariable models.

[Table 3]

[Figure 1]

DISCUSSION

This analysis has demonstrated that self-reported sleep duration can have variable effects on the individual component factors used in the diagnosis of MetS in a relatively healthy elderly cohort residing in the Mediterranean area. Using a component analysis of sleep quantity, individuals with greater duration of total sleep are more likely to have a higher waist circumference and LDL-c. More specifically, for every hour increase in total sleep waist circumference is expected to rise per 1 cm and LDL-cholesterol per approximately 4 mg/dL, even when important confounders were considered. From a clinical point of view, these findings could provide the clinicians an important lifestyle parameter to assess for elderly individuals. On the other hand, increased total sleep hours were found to be associated with slight decrease in diastolic blood pressure, but not of clinical importance. Interestingly, no associations were observed between sleep duration with respect to fasting glucose, triglycerides, HDL-c levels and systolic blood pressure. This is suggestive of a mixed effect of sleep quantity on features of MetS, with four of the seven features not being influenced by sleep duration and this can explain the lack of association between hours of sleep and the MetS as an entity.

Over the last decade, there has been a growth in research describing the impact of short sleep duration (10, 26-28), yet few have attempted to elucidate the risks associated with over-sleeping. In studies inclusive of all adults, longer sleep duration may be protective of MetS (29, 30). However, this is believed to be the first study examining the association between the individual component features of MetS and sleep quantity in a relatively healthy elderly cohort. In the Mediterranean area, MetS is estimated to affect 20-25% of individuals (31), with prevalence as high as 46.8% using NCEP-ATPIII criteria (32). These data highlight the need to understand the optimal sleep range to promote positive health and wellbeing relative to the components of MetS in an aging population and the need for sleep duration to be assessed in the clinical setting. Furthermore, this needs to be incorporated as part of a holistic preventative lifestyle approach, considering social factors alongside physical activity, diet and mental wellbeing (7).

The association of waist circumference to CVD and diabetes risk factors has been well described (33). In this cohort, the association of an increased waist circumference for each hour of sleep was demonstrated independent of other CVD risk factors such as age, gender, BMI and lifestyle characteristics. These findings highlight that an increased waist circumference and the presence of visceral adiposity could indicate the presence of insulin resistance and chronic low-grade inflammation. The production of adipocytokines from the central adipose tissue is implicated in atherogenic dyslipidemia such as high serum triglycerides and low HDL-c (34), however, this was not associated with sleep duration in this cohort. In research using participants with obstructive sleep apnea, each hour of additional sleep was associated with a seven percent increase in interleukin-6 (IL-6) and an eight percent increase in C-reactive protein (CRP) (35). The Women's Health Study (36) found both IL-6 and CRP to be associated with increased waist circumference, BMI, and waist-to-hip ratio. Other adipocytokines including leptin, resistin, tumor necrosis factor α and angiotensin II have also been related to insulin resistance and visceral fat accumulation (37).

The role of a genetic predisposition towards obesity, waist circumference and BMI has been observed in a UK cohort, which suggested this effect was moderated by sleep amongst other lifestyle characteristics (38). This study found short and long sleep duration to compound the influence of a genetic predisposition towards obesity. Collectively, these findings indicate a need for a focus on the reversing central adiposity which is associated inflammation. This research supports the view that clinician should consider sleep management alongside other lifestyle advice such as diet and physical activity in the treatment and prevention of MetS and CVD risk.

The link between MetS and CVD risk in older adults of the Mediterranean region has been previously reported, with an increase in the likelihood of CVD by 83% in individuals from Athens, Greece (2). Elevated triglycerides and LDL-c, as along with lower levels of HDL-c, are associated with CVD risk, although the presented model only found an association between sleep duration per hour and increased LDL-c. Previously, high waist circumference has been demonstrated to be associated with elevated oxidized LDL-c independent of BMI in healthy older adults from Spain (39). This again suggests that low-grade chronic inflammation may induce oxidative stress through the release of adipocytokines. While optimal sleep increases the ability to process moderate oxidative stress, this data may be explained by diminishing returns in the presence of higher than optimal sleep quantity.

While these findings suggest that extra sleep may have detrimental effects in this cohort, it also poses the question as to why individuals with these risk factors may be sleeping more. This analysis include a relatively healthy cohort, evident by adherence to an MD diet and 60 minutes (median) of daily walking time. Adherence to an MD has been inversely associated with the risk of MetS, impaired fasting glucose, and insulin resistance (40). It is plausible that a reverse cause-effect may be occurring with individuals living with symptoms of MetS sleeping more, possibly including during the day (7). This highlights the need for greater identification of sleep habits and behaviors in clinical practice due to the potential moderating effect on MetS symptoms, preferably with more objective methods such as polysomnography that could also assess sleep quality (41).

Questions remain as to whether MetS should be treated on an individual basis or whether the emphasis on a full lifestyle intervention is suitable to reduce disease risk (42).

Reaven suggested that the clustering of components of the MetS occur only in insulin resistant individuals and that focus on diagnosing MetS is unnecessary (4). Others contend that the identification of markers for MetS is crucial to treating the complex interaction between each component (37). The results from this healthy cohort, support the contention that each component, such as LDL-c, has individual importance, however it the lifestyle variable of sleep quantity that appeared to moderate these component features differently, suggesting that individual components of MetS need to be considered separately, even if treatment is holistic. While the model presented is relative to sleep quantity, it did account for other lifestyle factors. However, it cannot be ignored that broad lifestyle recommendations can improve MetS symptoms and CVD risk (7, 21, 43) and along with an adjunctive benefit that may be derived by sleep quantification in the clinical setting.

Future research should aim to identify the reasons underlying the relationship between sleep quantity and the biochemical pathways impacting LDL-c and reduced diastolic blood pressure. Furthermore, the link between insulin resistance and over-sleeping requires further investigation to be able to make evidence recommendations based on the optimal sleeping time. As the current middle-aged population progresses ages, future research will also need to consider the impact of increased nocturnal light and electronic device exposure and interactions between circadian entrainment and MetS.

Strengths and Limitations

It is important to note that this is a cross-sectional survey and therefore lacks the ability to infer causal relationships. The measurements have been performed once and may be prone to measurement and reporting errors. However this methodology is commonly used in this field and this study used validated instruments and suitably qualified and trained staff, making the results comparable to other studies. The sleeping habits have been assessed only regarding quantity and not quality or patterns (e.g., daytime nap duration), which could be equally important, this was employed as the measuring method is easier to implement and could be implemented in routine clinical practice. Furthermore, sleep duration was self-reported and not objectively measured (e.g., via polysomnography); however, in an outpatient environment, sleep data will also be self-reported and thus this information can be of practical importance. Moreover, the data on sleep were not obtained separately for weekends and weekdays, although it is common among elderly to adopt the same pattern every day, this could increase the robustness of the data. The use of individual component factors rather than a global assessment of MetS could also be viewed as a limitation, as well as the high MetS prevalence in the study sample, which is common among elderly though. However, with the different classifications of MetS and the inclusion of raised markers or treatment it was felt that in this analysis considering each feature in isolation would provide a clearer view of CVD risk. Additionally, without considering the separate features it would not be possible to elucidate the differing effects of sleep quantity on the component features.

Conclusions

Increasing sleep duration has a variable effect on component features of Met S in an elderly population, with changes to waist circumference and LDL-c potentially increasing risk and reductions in diastolic blood pressure reducing risk, but may increase risk of other conditions. Sleep duration appears to influence markers of metabolic health in apparently healthy older adults; however, more work is required in order to elucidate mechanisms and how aging influences the role of sleep duration on health. It is logical that clinicians as part of lifestyle assessment, including quantifying sleep in subjects with existing MetS risk factors should become an integral part of clinical practice; especially taking into account that MetS is a CVD risk factor of great significance.

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Table 1. Lifestyle, psychosocial and clinical characteristics of the MEDIS study participants (*n* = 3130) in respect to their gender.

Characteristics	All	Males (*n=1574*)	Females (*n=1556*)	*p*
Age (years)	74.2±7.34	74.8±7.49	73.6±7.14	<0.001
Daily sleep (hours)	8.30±1.76	8.30±1.75	8.20±1.77	0.53
Body Mass Index (kg/m^2)	28.3±4.67	27.8±4.12	28.9±5.10	<0.001
Smoking (current), yes (%)	15.6	26.1	5.2	<0.001
MedDietScore (0-55)	32.5±4.99	32.5±4.98	32.5±5.00	0.88
Daily Walking time (minutes)*	60 (30,120)	60 (30,120)	60 (25,120)	0.24
Waist circumference (cm)	101±14.0	102±12.3	100±15.1	0.001
Fasting glucose levels (mg/dL)	116±39.5	116±37.7	115±41.2	0.72
Diabetes mellitus, yes (%)	22.3	22.8	21.8	0.571
Diabetes treatment (disk and/or insulin), yes (%)	13.38	14.2	12.6	0.283
Triglycerides (mg/dL)*	119 (92,160)	119 (95,160)	118 (91,156)	0.55
LDL-cholesterol (mg/dL)	126±41.3	123±39.3	129±22.6	0.03
HDL-cholesterol (mg/dL)*	50 (43,60)	46 (40,54)	55 (46,63)	<0.001
Hyperlipidemia, yes (%)	47.7	40.8	54.9	<0.001
Hyperlipidemic treatment, yes (%)	30.3	35.3	25.5	<0.001
Systolic Blood Pressure (mmHg)	135±21.9	135±19.8	134±23.6	0.86
Diastolic Blood Pressure (mmHg)	77.6±13.0	77.8±12.0	77.3±14.0	0.46
Hypertension, yes (%)	62.3	55.7	68.9	0.012
Hypertension treatment, yes (%)	54.6	47.4	62.1	0.02

*values are presented as median (25th, 75th percentiles). P-values derived from Student's t-test or non-parametric Mann-Whitney test (*) for non-continuous variables and chi-squared test for nominal variables

Table 2. Lifestyle, psychosocial and clinical characteristics of the MEDIS study participants (*n* = 3130) in respect to their Metabolic Syndrome (MetS) status.

Characteristics	**MetS** *(65.3%)*	**No MetS** *(34.7%)*	***P***
Age (years)	74.3±6.62	74.8±7.36	0.50
Gender, male (%)	29.6	33.3	0.49
Daily sleep (hours)	7.91±1.82	7.59±1.56	0.42
Body Mass Index (kg/m^2)	30.8±4.37	28.2±3.81	<0.001
Smoking (current), yes (%)	8.5	7.5	0.76
MedDietScore (0-55)	33.0±5.16	32.5±6.57	0.53
Daily Walking time (minutes)*	60 (30,120)	120 (30,240)	0.03
Waist circumference (cm)	107±10.4	96.8±12.5	<0.001
Fasting glucose levels (mg/dL)	126±36.9	101±36.1	<0.001
Triglycerides (mg/dL)*	132 (102,177)	100 (86,119)	<0.001
LDL-cholesterol (mg/dL)	130±40.2	115±44.1	0.003
HDL-cholesterol (mg/dL)*	49 (42,58)	56 (49,62)	<0.001
Systolic Blood Pressure (mmHg)	138±15.4	123±14.2	<0.001
Diastolic Blood Pressure (mmHg)	79.5±9.62	74.9±9.96	<0.001

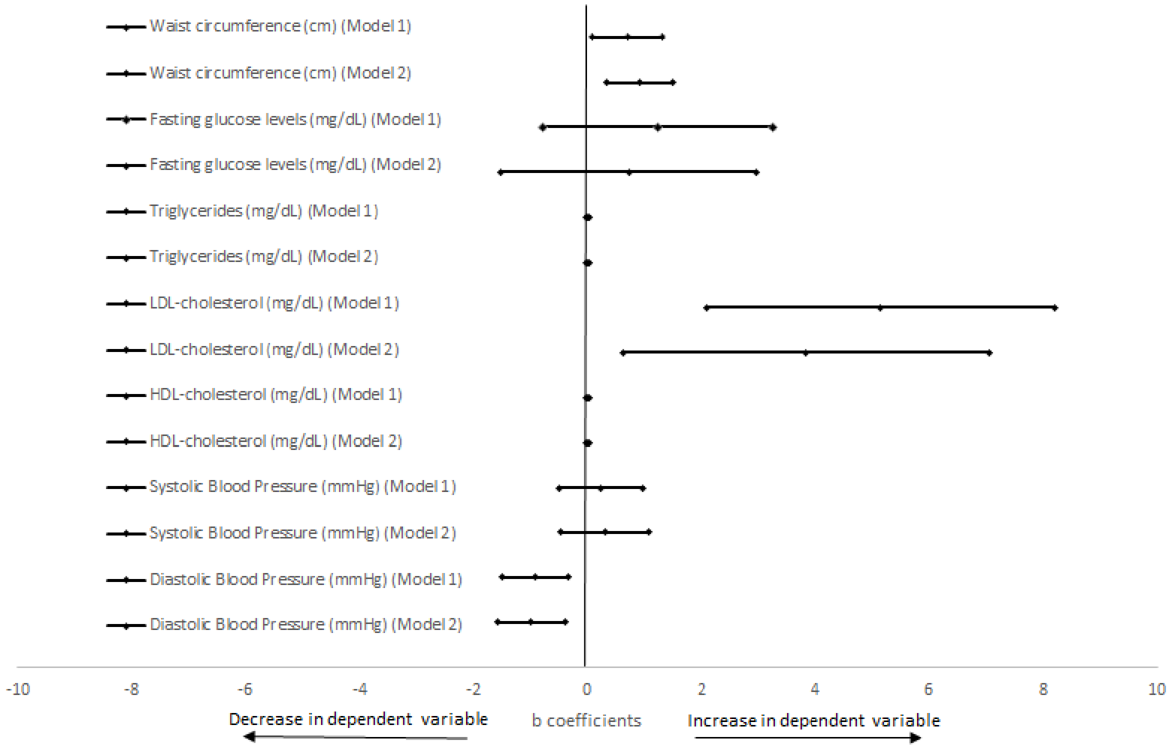
*values are presented as median (25^{th}, 75^{th} percentiles). P-values derived from Student's t-test or non-parametric Mann-Whitney test (*) for non-continuous variables and chi-squared test for nominal variables

Table 3. Multivariable linear logistic regression model for the role of hours of total sleep in Metabolic Syndrome components (*n* = 3130).

Dependent Variable	b coefficient (per 1 hour)	Standard error	95% Confidence Interval	*p*
Waist circumference (cm) *(Model 1)*	0.70	0.32	(0.07,1.32)	0.03
Waist circumference (cm) *(Model 2)*	0.91	0.29	(0.34,1.49)	0.002
Fasting glucose levels (mg/dL) (*Model 1)*	1.23	1.03	(-0.79,3.25)	0.23
Fasting glucose levels (mg/dL) (*Model 2)*	0.73	1.13	(-1.51,2.96)	0.52
Triglycerides (mg/dL)* *(Model 1)*	0.001	0.01	(-0.03,0.03)	0.95
Triglycerides (mg/dL)* *(Model 2)*	0.006	0.02	(-0.02,0.04)	0.69
LDL-cholesterol (mg/dL) *(Model 1)*	5.14	1.54	(2.10,8.19)	0.001
LDL-cholesterol (mg/dL) *(Model 2)*	3.84	1.62	(0.63,7.05)	0.02
HDL-cholesterol (mg/dL)* *(Model 1)*	-0.001	0.01	(-0.02,0.02)	0.92
HDL-cholesterol (mg/dL)* *(Model 2)*	-0.005	0.01	(-0.03,0.02)	0.67
Systolic Blood Pressure (mmHg) *(Model 1)*	0.24	0.38	(-0.50,0.98)	0.52
Systolic Blood Pressure (mmHg) *(Model 2)*	0.32	0.39	(-0.46,1.09)	0.42
Diastolic Blood Pressure (mmHg) *(Model 1)*	-0.92	0.29	(-1.49,-0.34)	0.002
Diastolic Blood Pressure (mmHg) *(Model 2)*	-0.98	0.30	(-1.57,-0.39)	0.001

LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein. Model 1: All models have been adjusted for age and gender. Model 2: All models have been adjusted for age, gender, Body Mass Index, Daily walking, MedDietScore, and smoking status. *indicates that logarithmic transformation has been used to normalize the dependent variable

Figure 1. Multivariable linear logistic regression model coefficients for the role of hours of total sleep in Metabolic Syndrome components (n = 3130).



Increase means positive association with sleep hours, whereas, decrase means negative association between sleep hours and features of MetS.

LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein. Model 1: All models have been adjusted for age and gender. Model 2: All models have been adjusted for age, gender, Body Mass Index, Daily walking, MedDietScore, and smoking status. Logarithmic transformation has been used to normalize the dependent variables HDL-cholesterol and Triglycerides levels.

References

1. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421.
2. Kastorini C-M, Panagiotakos DB, Chrysohoou C, Georgousopoulou E, Pitaraki E, Puddu PE, et al. Metabolic syndrome, adherence to the Mediterranean diet and 10-year cardiovascular disease incidence: The ATTICA study. Atherosclerosis. 2016;246:87-93.
3. Federation ID. IDF Consensus Worldwide Definition of the Metabolic Syndrome [cited 2017]. Available from: https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome.
4. Reaven GM. The metabolic syndrome: is this diagnosis necessary? The American journal of clinical nutrition. 2006;83(6):1237-47.
5. Salas-Salvado J, Guasch-Ferre M, Lee CH, Estruch R, Clish CB, Ros E. Protective Effects of the Mediterranean Diet on Type 2 Diabetes and Metabolic Syndrome. The Journal of nutrition. 2016.
6. Tambalis KD, Panagiotakos DB, Georgousopoulou EN, Mellor DD, Chrysohoou C, Kouli G-M, et al. Impact of physical activity category on incidence of cardiovascular disease: Results from the 10-year follow-up of the ATTICA Study (2002–2012). Preventive Medicine. 2016;93:27-32.
7. Georgousopoulou EN, Mellor DD, Naumovski N, Polychronopoulos E, Tyrovolas S, Piscopo S, et al. Mediterranean lifestyle and cardiovascular disease prevention. Cardiovascular Diagnosis and Therapy. 2017;7(Suppl 1):S39-S47.
8. Georgousopoulou EN, Naumovski N, Mellor DD, Tyrovolas S, Piscopo S, Valacchi G, et al. Association between siesta (daytime sleep), dietary patterns and the presence of metabolic syndrome in elderly living in Mediterranean area (MEDIS study): The moderating effect of gender. The journal of nutrition, health & aging. 2016.
9. Sperry SD, Scully ID, Gramzow RH, Jorgensen RS. Sleep Duration and Waist Circumference in Adults: A Meta-Analysis. Sleep. 2015;38(8):1269-76.
10. Xi B, He D, Zhang M, Xue J, Zhou D. Short sleep duration predicts risk of metabolic syndrome: A systematic review and meta-analysis. Sleep Medicine Reviews. 2014;18(4):293-7.
11. Fernandez-Mendoza J, He F, LaGrotte C, Vgontzas AN, Liao D, Bixler EO. Impact of the Metabolic Syndrome on Mortality is Modified by Objective Short Sleep Duration. Journal of the American Heart Association. 2017;6(5).
12. González-Ortiz M, Martínez-Abundis E. Impact of Sleep Deprivation on Insulin Secretion, Insulin Sensitivity, and Other Hormonal Regulations. Metabolic Syndrome and Related Disorders. 2005;3(1):3-7.
13. Aho V, Ollila HM, Kronholm E, Bondia-Pons I, Soininen P, Kangas AJ, et al. Prolonged sleep restriction induces changes in pathways involved in cholesterol metabolism and inflammatory responses. Scientific reports. 2016;6:24828.
14. Maloberti A, Giannattasio C, Dozio D, Betelli M, Villa P, Nava S, et al. Metabolic syndrome in human immunodeficiency virus-positive subjects: prevalence, phenotype, and related alterations in arterial structure and function. Metab Syndr Relat Disord. 2013;11(6):403-11.
15. Panagiotakos DB, Georgousopoulou EN, Pitsavos C, Chrysohoou C, Skoumas I, Pitaraki E, et al. Exploring the path of Mediterranean diet on 10-year incidence of cardiovascular disease: the ATTICA study (2002-2012). Nutrition, metabolism, and cardiovascular diseases : NMCD. 2015;25(3):327-35.

16. Salas-Salvadó J, Bulló M, Babio N, Martínez-González MÁ, Ibarrola-Jurado N, Basora J, et al. Reduction in the Incidence of Type 2 Diabetes With the Mediterranean Diet. Diabetes Care. 2010;34(1):14.
17. Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). BMC Medicine. 2017;15(1):23.
18. Lourida I, Soni M, Thompson-Coon J, Purandare N, Lang IA, Ukoumunne OC, et al. Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review. Epidemiology. 2013;24(4):479-89.
19. Yannakoulia M, Anastasiou CA, Karfopoulou E, Pehlivanidis A, Panagiotakos DB, Vgontzas A. Sleep quality is associated with weight loss maintenance status: the MedWeight study. Sleep Medicine. 2017;34:242-5.
20. Tyrovolas S, Pounis G, Bountziouka V, Polychronopoulos E, Panagiotakos DB. Repeatability and validation of a short, semi-quantitative food frequency questionnaire designed for older adults living in Mediterranean areas: the MEDIS-FFQ. Journal of nutrition for the elderly. 2010;29(3):311-24.
21. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2006;16(8):559-68.
22. Papathanasiou G, Georgoudis G, Papandreou M, Spyropoulos P, Georgakopoulos D, Kalfakakou V, et al. Reliability measures of the short International Physical Activity Questionnaire (IPAQ) in Greek young adults. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese. 2009;50(4):283-94.
23. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Medicine and science in sports and exercise. 2003;35(8):1381-95.
24. Tyrovolas S, Haro JM, Mariolis A, Piscopo S, Valacchi G, Tsakountakis N, et al. Successful aging, dietary habits and health status of elderly individuals: a k-dimensional approach within the multi-national MEDIS study. Experimental gerontology. 2014;60:57-63.
25. Tyrovolas S, Zeimbekis A, Bountziouka V, Voutsa K, Pounis G, Papoutsou S, et al. Factors Associated with the Prevalence of Diabetes Mellitus Among Elderly Men and Women Living in Mediterranean Islands: The MEDIS Study. The review of diabetic studies : RDS. 2009;6(1):54-63.
26. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, et al. Short Sleep Duration as a Risk Factor for Hypertension. Hypertension. 2006;47(5):833.
27. Hall MH, Muldoon MF, Jennings JR, Buysse DJ, Flory JD, Manuck SB. Self-Reported Sleep Duration is Associated with the Metabolic Syndrome in Midlife Adults. Sleep. 2008;31(5):635-43.
28. Koren D, Dumin M, Gozal D. Role of sleep quality in the metabolic syndrome. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2016;9:281-310.
29. Najafian J, Toghianifar N, Mohammadifard N, Nouri F. Association between sleep duration and metabolic syndrome in a population-based study: Isfahan Healthy Heart Program. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2011;16(6):801-6.
30. Sabanayagam C, Zhang R, Shankar A. Markers of Sleep-Disordered Breathing and Metabolic Syndrome in a Multiethnic Sample of US Adults: Results from the National Health and Nutrition Examination Survey 2005-2008. Cardiology research and practice. 2012;2012:630802.

31. Anagnostis P. Metabolic syndrome in the Mediterranean region: Current status. Indian Journal of Endocrinology and Metabolism. 2012;16(1):72-80.
32. De Luis DA, Lopez Mongil R, Gonzalez Sagrado M, Lopez Trigo JA, Mora PF, Castrodeza Sanz J. Prevalence of metabolic syndrome with International Diabetes Federation Criteria and ATP III Program in patients 65 years of age or older. J Nutr Health Aging. 2010;14(5):400-4.
33. Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. European heart journal. 2008;29(24):2959-71.
34. Huang PL. A comprehensive definition for metabolic syndrome. Disease Models & Mechanisms. 2009;2(5-6):231-7.
35. Patel SR, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R, et al. Sleep Duration and Biomarkers of Inflammation. Sleep. 2009;32(2):200-4.
36. Rexrode KM, Pradhan A, Manson JE, Buring JE, Ridker PM. Relationship of total and abdominal adiposity with CRP and IL-6 in women. Annals of Epidemiology.13(10):674-82.
37. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Medicine. 2011;9(1):48.
38. Celis-Morales C, Lyall DM, Guo Y, Steell L, Llanas D, Ward J, et al. Sleep characteristics modify the association of genetic predisposition with obesity and anthropometric measurements in 119,679 UK Biobank participants. The American journal of clinical nutrition. 2017.
39. Weinbrenner T, Schröder H, Escurriol V, Fito M, Elosua R, Vila J, et al. Circulating oxidized LDL is associated with increased waist circumference independent of body mass index in men and women. The American journal of clinical nutrition. 2006;83(1):30-5.
40. Viscogliosi G, Cipriani E, Liguori ML, Marigliano B, Saliola M, Ettorre E, et al. Mediterranean Dietary Pattern Adherence: Associations with Prediabetes, Metabolic Syndrome, and Related Microinflammation. Metabolic Syndrome and Related Disorders. 2013;11(3):210-6.
41. Khan CT, Woodward SH. Calibrating actigraphy to improve sleep efficiency estimates. Journal of sleep research. 2017.
42. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice? The American journal of clinical nutrition. 2006;83(6):1248-51.
43. Bassi N, Karagodin I, Wang S, Vassallo P, Priyanath A, Massaro E, et al. Lifestyle Modification for Metabolic Syndrome: A Systematic Review. The American Journal of Medicine. 2014;127(12):1242.e1-.e10.