

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

4  
5 Ekavi N. Georgousopoulou<sup>1,2</sup>, Nathan M. D’Cunha<sup>2</sup>, Duane D. Mellor<sup>2,4</sup>, Stefanos  
6 Tyrovolas<sup>1,3</sup>, Nenad Naumovski<sup>2</sup>, Alexandra Foscolou<sup>1</sup>, Vassiliki Bountziouka<sup>1</sup>, Efthimios  
7 Gotsis<sup>1</sup>, George Metallinos<sup>1</sup>, Dimitra Tyrovola<sup>1</sup>, Suzanne Piscopo<sup>5</sup>, Giuseppe  
8 Valacchi<sup>6,7</sup>, Nikos Tsakountakis<sup>8</sup>, Akis Zeimbekis<sup>9</sup>, Josep-Antoni Tur<sup>10</sup>, Antonia-Leda  
9 Matalas<sup>1</sup>, Evangelos Polychronopoulos<sup>1</sup>, Christos Lionis<sup>8</sup>, Labros Sidossis<sup>1,11</sup>, Demosthenes  
10 B. Panagiotakos<sup>1,2,11</sup>; MEDIS study group

11 <sup>1</sup>Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio  
12 University, Athens, Greece; <sup>2</sup>Faculty of Health, University of Canberra, Canberra, Australia;  
13 <sup>3</sup>Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, CIBERSAM, Universitat de  
14 Barcelona, Barcelona, Spain; <sup>4</sup>School of Life Science, Coventry University, Coventry, UK;  
15 <sup>5</sup>University of Malta, Nutrition, Family and Consumer Studies Office, Msida, Republic of  
16 Malta; <sup>6</sup>Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy;  
17 <sup>7</sup>Plants for Human Health Institute, Animal Science Department, NC State University,  
18 Kannapolis, U.S.A.; <sup>8</sup>Clinic of Social and Family Medicine, School of Medicine, University  
19 of Crete, Heraklion, Greece; <sup>9</sup>Health Center of Kalloni, General Hospital of Mitilini, Mitilini,  
20 Greece; <sup>10</sup>Research Group on Community Nutrition and Oxidative Stress, Universitat de les  
21 Illes Balears & CIBERobn, E-07122 Palma de Mallorca, Spain; <sup>11</sup>Department of Kinesiology  
22 and Health, Rutgers University, New Jersey, USA.

23 **Running title:** Sleep quantity and Metabolic Syndrome features

24 **Funding:** The study has been funded by the Hellenic Heart Foundation, the Graduate  
25 program of the Department of Nutrition and Dietetics, Harokopio University in Athens,  
26 Greece and the Rutgers, The State University of New Jersey, USA. Stefano Tyrovolas’ work  
27 was funded through a scholarship from the Foundation for Education and European Culture  
28 (IPEP). Josep A. Tur was funded by grants PI14/00636, CIBERobn CB12/03/30038, and  
29 CAIB/EU 35/2001

30 **Corresponding author:**

31 Prof Demosthenes B Panagiotakos

32 Harokopio University, 176 71 Athens, Greece

33 Tel. +30 210-9549332

34 Email: [dbpanag@hua.gr](mailto:dbpanag@hua.gr)

1 **ABSTRACT**

2 **Background:** Metabolic Syndrome (MetS) as a combination of features has been known to  
3 significantly increase Cardiovascular Disease (CVD) risk, whilst MetS presence is linked to  
4 lifestyle parameters including physical activity and dietary habits; recently, the potential  
5 impact of sleeping habits has also become an issue under consideration. The aim of this study  
6 was to investigate the role of sleep quantity in several MetS components. **Methods:** *Design:*  
7 Cross-sectional observational study. *Setting:* 26 Mediterranean islands and the rural Mani  
8 region (Peloponnesus) of Greece. *Participants:* during 2005-2017, 3130 older (aged 65-100  
9 years) Mediterranean residents were voluntarily enrolled. *Measurements:* Dietary habits  
10 (including MedDietScore assessment), physical activity status, socio-demographic  
11 characteristics, lifestyle parameters (sleeping and smoking habits) and clinical profile aspects  
12 including Metabolic Syndrome (MetS) components (i.e., waist circumference, systolic and  
13 diastolic blood pressure, fasting glucose, triglycerides, LDL and HDL-cholesterol) were  
14 derived through standard procedures. **Results:** The number of daily hours of sleep was  
15 independently associated with greater waist circumference (b coefficient per 1 hour=0.91,  
16 95% Confidence Interval (CI); 0.34, 1.49), higher LDL-cholesterol levels (b per 1 hour=3.84,  
17 95%CI; 0.63, 7.05) and lower diastolic blood pressure levels (b per 1 hour=-0.98, 95%CI; -  
18 1.57, -0.39) after adjusting for participants' age, gender, body mass index, daily walking  
19 time, level of adherence to Mediterranean diet and smoking status. No association was  
20 revealed between hours of sleep per day and fasting glucose, triglycerides, HDL-cholesterol  
21 and systolic blood pressure. **Conclusions:** Increased hours of sleep is an indicator of  
22 metabolic disorders among elderly individuals, and further research is needed to identify the  
23 paths through which sleep quantity is linked to MetS features in different age-groups.

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

1 **INTRODUCTION**

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

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

1 cholesterol pathways associated with increased CVD risk at both the transcriptome level and  
2 in the circulating lipid profile (13, 14). This implies that the effect of sleep deprivation  
3 impacts on the component factors of MetS, and as such merits investigation.

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

14

## 15 **MATERIALS AND METHODS**

### 16 *Methodology*

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

### 21 *The Study's sample*

22 Between 2005-2017, a random population-based, multistage sampling method (i.e., age  
23 group, 3 levels (65 - 75, 75 - 85, 85+) and 2 sex levels) was used to voluntarily enrol older  
24 men and women people from 26 Mediterranean islands: including Malta Republic (n=250),

1 Sardinia (n=60) and Sicily (n=50), Mallorca and Menorca (n=111), Republic of Cyprus  
2 (n=300), Gökçeada (n=55) in Turkey, and the Greek islands of Lesbos (n=142), Samothraki  
3 (n=100), Cephalonia (n=115), Crete (n=131), Corfu (n=149), Limnos (n=150), Ikaria (n=76),  
4 Syros (n=151), Naxos (n=145), Zakynthos (n=103), Salamina (n=147), Kassos (n=52),  
5 Rhodes and Karpathos (n=149), Tinos (n=129), Ai-Stratis (n=30), Spetses (n=92), Aegina  
6 (n=59), Paros (n=90) as well as the rural region of East Mani (n=295, 157 men aged 75±7  
7 years and 138 women aged 74±7 years) (a Greek peninsula, which is in the southeast,  
8 continental area of Europe, with a total population of 13,005 people (census 2011), which has  
9 morphological and cultural specificities, which are not common across in the rest of Greece.  
10 Individuals who resided in assisted-living centres, had a clinical history of cardiovascular  
11 disease (CVD) or cancer, or had left the island for a considerable period of time during their  
12 life (i.e., >5 years) were excluded from participating in the study; these criteria were applied  
13 because the study aimed to assess lifestyle patterns that were not a response of individuals  
14 modifying how they live due to existing chronic health care conditions or by environmental  
15 factors, other than their living milieu. The participation rate varied according to the region,  
16 from 75% to 89%. Thus, information from 3130 individuals, 1,574 men, aged 75±8 years and  
17 1,556 women, aged 74±7 years, were analyzed.

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

## 21 ***Bioethics***

22 The study followed the ethical considerations provided by the World Medical Association  
23 (52<sup>nd</sup> WMA General Assembly, Edinburgh, Scotland; October 2000). The Institutional Ethics  
24 Board of Harokopio University approved the study design (16/19-12-2006), as well as the

1 regional offices of the participated Institutions. Participants were informed about the aims  
2 and procedures of the study and gave their consent prior to being interviewed.

### 3 *Evaluation of clinical characteristics*

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

### 26 *Evaluation of lifestyle and socio-demographic characteristics*

27 Sleep was assessed estimating the amount of sleeping hours on a typical day while  
28 interviewing the participants using the self-reported Wake After Sleep Onset (WASO). The  
29 frequency and the hours of sleeping during the day, as well as the wake-up and going-to-sleep  
30 time were also recorded according to individuals self-reporting. Dietary habits were assessed  
31 through a semi-quantitative, validated and reproducible food-frequency questionnaire (20).  
32 Trained dietitians estimated the mean daily energy intake and the mean percentage of total  
33 energy derived from dietary carbohydrates. To evaluate the level of adherence to the  
34 Mediterreanean diet, the MedDietScore (possible range 0-55) was used (21). Higher values for

1 this diet score being indicative of greater adherence to the Mediterranean diet. Participants  
2 were also encouraged to report the duration of following their dietary pattern (i.e., the number  
3 of years this pattern had been in place). Basic socio-demographic characteristics such as age,  
4 sex, as well as lifestyle characteristics, such as smoking habits and physical activity status,  
5 were also recorded. Current smokers were defined as smokers at the time of the interview,  
6 whereas former smokers were defined as those who previously smoked, but had not done so  
7 for a year or more. Current and former smokers were defined as had ‘*ever smokers*’. The  
8 remaining participants were assigned as occasional or non-smokers. **Physical activity was**  
9 **evaluated in MET-minutes per week, using the shortened, translated and validated into**  
10 **Greek, version of the self-reported International Physical Activity Questionnaire (IPAQ) (22,**  
11 **23). Frequency (times per week), duration (minutes per session) and intensity of physical**  
12 **activity during sports, occupation, and leisure activities were assessed. Participants were**  
13 **instructed to report only episodes of activity lasting at least 10 minutes since this is the**  
14 **minimum required to achieve health benefits. Physically active individuals were defined**  
15 **those who reported at least 3 MET-min. Daily walking time was calculated by using the**  
16 **IPAQ question about walking (times per week and average time spent).**

17 Further details about the MEDIS study have extensively been published elsewhere  
18 (24, 25).

### 19 ***Statistical analysis***

20 Continuous variables are expressed as mean  $\pm$  standard deviation for variables following  
21 assessing for normal distribution, or median (inter-quartile range) for variables not following  
22 a normal distribution. Normality was tested using P-P plots. Differences in continuous  
23 variables between males and females were evaluated with the Student’s t-test for normally  
24 distributed parameters and the Mann-Whitney test for non-parametric variables. Correlations

1 between continuous variables were tested using Pearson's  $r$  when both variables were  
2 normally distributed or Spearman's  $\rho$  when at least one of them did not have a normal  
3 distribution. Nominal variables are presented as frequencies and relative frequencies (%).  
4 Pearson's Chi-square test was used to assess the association between two nominal variables.  
5 Linear regression models were used to evaluate the association between sleep duration, other  
6 participants' characteristics (i.e., age, sex, BMI, physical activity, MedDietScore, smoking  
7 habits) and levels of the MetS components (fasting glucose levels, waist circumference,  
8 systolic and diastolic arterial blood pressure, triglycerides, LDL and HDL levels).  
9 Logarithmic transformation was used for the dependent variable that did not have a normal  
10 distribution (triglycerides and HDL-c). Results are expressed as  $b$  coefficients and the 95%  
11 confidence intervals. Type I error was predefined at 0.05. Statistical analysis was carried out  
12 in IBM SPSS version 23.0 (Armonk, NY: IBM Corp.).

13

## 14 **RESULTS**

15 Mean sleep duration time was  $8.30 \pm 1.76$  h per day, and specifically  $8.30 \pm 1.75$  h for  
16 men and  $8.20 \pm 1.77$  h for women ( $p=0.52$ ). **Moreover, sleep duration did not differ between**  
17 **retired and non-retired individuals ( $p=0.244$ ), with the latter consisting 20.9% of the total**  
18 **sample.** Sleep duration was positively associated with waist circumference (Pearson's  $r=0.12$ ,  
19  $p=0.01$ ) and LDL-c (Pearson's  $r=0.23$ ,  $p=0.001$ ) and inversely associated with diastolic  
20 arterial blood pressure (Pearson's  $r=-0.15$ ,  $p=0.002$ ). No association was observed between  
21 sleep and fasting glucose levels ( $p=0.20$ ), systolic arterial blood pressure ( $p=0.59$ ), fasting  
22 triglycerides ( $p=0.44$ ) and HDL-c ( $p=0.47$ ). MetS prevalence according to IDF criteria was  
23 65.3% and did not differ between genders ( $p=0.49$ ).

24 Mean BMI was  $28.3 \pm 4.67$   $\text{kg/m}^2$ , while the level of adherence to Mediterranean diet  
25 was  $32.5 \pm 4.99$  out of 55 (or 59% of ideal adherence), as calculated via the MedDietScore.



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

7 [Table 1]

8 As presented in *Table 1*, females had higher BMI than males ( $28.9\pm 5.10$  kg/m<sup>2</sup> vs.  
9  $27.8\pm 4.12$  kg/m<sup>2</sup> respectively,  $p<0.001$ ), but their smoking prevalence was fivefold lower  
10 compared to men (5.2% vs. 26.1% respectively,  $p<0.001$ ). No differences were revealed for  
11 their level of adherence to Mediterranean diet ( $p=0.88$ ), daily walking time ( $p=0.24$ ) nor their  
12 daily hours of sleep ( $p=0.53$ ). As expected, females had lower waist circumference than men  
13 ( $100\pm 15.1$  cm vs.  $102\pm 12.3$  cm respectively,  $p=0.001$ ), higher HDL-c levels (55 (46,63)  
14 mg/dL vs. 46 (40,54) mg/dL, respectively,  $p<0.001$ ) and lower LDL-c levels ( $129\pm 22.6$   
15 mg/dL vs.  $123\pm 39.3$  mg/dL, respectively,  $p=0.026$ ). Interestingly, no differences were  
16 detected for triglycerides' levels ( $p=0.55$ ), fasting glucose levels ( $p=0.72$ ), systolic ( $p=0.86$ )  
17 and diastolic ( $p=0.46$ ) arterial blood pressure levels.

18 Characteristics of the participants according to their MetS status are presented in  
19 *Table 2*. As expected, subjects with MetS had higher waist circumference than MetS-free  
20 subjects ( $107\pm 10.4$  cm vs.  $96.8\pm 12.5$  cm respectively,  $p<0.001$ ), lower HDL-c levels (49  
21 (42,58) mg/dL vs. 56 (49,62) mg/dL, respectively,  $p<0.001$ ), higher LDL-c levels ( $130\pm 40.2$   
22 mg/dL vs.  $115\pm 44.1$  mg/dL, respectively,  $p=0.003$ ), higher BMI ( $30.8\pm 4.37$  kg/m<sup>2</sup> vs.  
23  $28.2\pm 3.81$  kg/m<sup>2</sup> respectively,  $p<0.001$ ), higher fasting glucose levels ( $126\pm 36.9$  mg/dL vs.  
24  $101\pm 36.1$  mg/dL, respectively,  $p<0.001$ ), higher triglycerides' levels (132 (102,177) mg/dL  
25 vs. 100 (86,119) mg/dL, respectively,  $p<0.001$ ), higher systolic ( $138\pm 15.4$  mmHg vs.

1 123±14.2 mmHg, respectively,  $p<0.001$ ) and diastolic arterial blood pressure levels  
2 (79.5±9.62 mmHg vs. 74.9±9.96 mmHg, respectively,  $p<0.001$ ), as well as less daily walking  
3 time (60 (30,120) minutes/day vs. 120 (30,240) minutes/day respectively,  $p<0.001$ ).  
4 Interestingly, no differences were detected for gender ( $p=0.49$ ), age ( $p=0.50$ ), daily hours of  
5 sleep ( $p=0.42$ ), smoking status ( $p=0.76$ ), nor their level of adherence to Mediterranean diet  
6 ( $p=0.53$ ). No significant interaction between gender and sleep duration was detected when  
7 MetS presence is regarded.

8 [Table 2]

9 *Table 3 and Figure 1 present the multivariable linear regression models that were*  
10 *implemented with the MetS individual component factors (waist circumference, fasting*  
11 *glucose levels, LDL-c and HDL-c levels, triglycerides levels, systolic and diastolic arterial*  
12 *blood pressure) as dependent variables. Total daily hours of sleep was independently*  
13 *associated with greater waist circumference in the age and gender adjusted model (b per 1*  
14 *hour=0.70, 95%CI; 0.07, 1.32) which remained significant and became stronger after*  
15 *adjusting for lifestyle factors such as smoking, daily walking, MedDietScore and BMI (b per*  
16 *1 hour=0.91, 95%CI; 0.34, 1.49). When LDL-c levels are regarded, the daily hours of*  
17 *sleeping was a significant independent variable in the age and gender adjusted model (b per 1*  
18 *hour=5.14, 95%CI; 2.10, 8.19), whilst in the final model it remained significant, but the*  
19 *effect size decreased (b per 1 hour=3.84, 95%CI; 0.63, 7.05). Total daily hours of sleep were*  
20 *independently and equally associated with lower diastolic blood pressure levels in the age*  
21 *and gender adjusted model (b per 1 hour=-0.92, 95%CI; -1.49, -0.34) and the multi-adjusted*  
22 *model (b per 1 hour=-0.98, 95%CI; -1.57, -0.39). No associations were revealed between*  
23 *hours of sleep per day and fasting glucose, triglycerides, and systolic arterial blood pressure*  
24 *levels in any of the the multivariable models.*

25 [Table 3]

1 [Figure 1]

2 **DISCUSSION**

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

18 Over the last decade, there has been a growth in research describing the impact of  
19 short sleep duration (10, 26-28), yet few have attempted to elucidate the risks associated with  
20 over-sleeping. In studies inclusive of all adults, longer sleep duration may be protective of  
21 MetS (29, 30). However, this is believed to be the first study examining the association  
22 between the individual component features of MetS and sleep quantity in a relatively healthy  
23 elderly cohort. In the Mediterranean area, MetS is estimated to affect 20-25% of individuals  
24 (31), with prevalence as high as 46.8% using NCEP-ATPIII criteria (32). These data  
25 highlight the need to understand the optimal sleep range to promote positive health and well-

1 being relative to the components of MetS in an aging population and the need for sleep  
2 duration to be assessed in the clinical setting. Furthermore, this needs to be incorporated as  
3 part of a holistic preventative lifestyle approach, considering social factors alongside physical  
4 activity, diet and mental wellbeing (7).

5         The association of waist circumference to CVD and diabetes risk factors has been  
6 well described (33). In this cohort, the association of an increased waist circumference for  
7 each hour of sleep was demonstrated independent of other CVD risk factors such as age,  
8 gender, BMI and lifestyle characteristics. These findings highlight that an increased waist  
9 circumference and the presence of visceral adiposity could indicate the presence of insulin  
10 resistance and chronic low-grade inflammation. The production of adipocytokines from the  
11 central adipose tissue is implicated in atherogenic dyslipidemia such as high serum  
12 triglycerides and low HDL-c (34), however, this was not associated with sleep duration in  
13 this cohort. In research using participants with obstructive sleep apnea, each hour of  
14 additional sleep was associated with a seven percent increase in interleukin-6 (IL-6) and an  
15 eight percent increase in C-reactive protein (CRP) (35). The Women's Health Study (36)  
16 found both IL-6 and CRP to be associated with increased waist circumference, BMI, and  
17 waist-to-hip ratio. Other adipocytokines including leptin, resistin, tumor necrosis factor  $\alpha$  and  
18 angiotensin II have also been related to insulin resistance and visceral fat accumulation (37).  
19 The role of a genetic predisposition towards obesity, waist circumference and BMI has been  
20 observed in a UK cohort, which suggested this effect was moderated by sleep amongst other  
21 lifestyle characteristics (38). This study found short and long sleep duration to compound the  
22 influence of a genetic predisposition towards obesity. Collectively, these findings indicate a  
23 need for a focus on the reversing central adiposity which is associated inflammation. This  
24 research supports the view that clinician should consider sleep management alongside other

1 lifestyle advice such as diet and physical activity in the treatment and prevention of MetS and  
2 CVD risk.

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

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

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

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

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

### 19 *Strengths and Limitations*

20 It is important to note that this is a cross-sectional survey and therefore lacks the ability to  
21 infer causal relationships. The measurements have been performed once and may be prone to  
22 measurement and reporting errors. However this methodology is commonly used in this field  
23 and this study used validated instruments and suitably qualified and trained staff, making the  
24 results comparable to other studies. The sleeping habits have been assessed only regarding  
25 quantity and not quality or patterns (e.g., daytime nap duration), which could be equally

1 important, this was employed as the measuring method is easier to implement and could be  
2 implemented in routine clinical practice. Furthermore, sleep duration was self-reported and  
3 not objectively measured (e.g., via polysomnography); however, in an outpatient  
4 environment, sleep data will also be self-reported and thus this information can be of  
5 practical importance. Moreover, the data on sleep were not obtained separately for weekends  
6 and weekdays, although it is common among elderly to adopt the same pattern every day, this  
7 could increase the robustness of the data. The use of individual component factors rather than  
8 a global assessment of MetS could also be viewed as a limitation, as well as the high MetS  
9 prevalence in the study sample, which is common among elderly though. However, with the  
10 different classifications of MetS and the inclusion of raised markers or treatment it was felt  
11 that in this analysis considering each feature in isolation would provide a clearer view of  
12 CVD risk. Additionally, without considering the separate features it would not be possible to  
13 elucidate the differing effects of sleep quantity on the component features.

#### 14 *Conclusions*

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

24

25

1 **ACKNOWLEDGMENTS**

2 We are, particularly, grateful to the men and women from the islands of Malta, Sardinia,  
3 Sicily, Mallorca, Menorca, Cyprus, Gökçeada, Lesvos, Samothraki, Crete, Corfu, Lemnos,  
4 Zakynthos, Cephalonia, Naxos, Syros, Ikaria, Salamina, Kassos, Rhodes, Karpathos, Tinos,  
5 Ai-Stratis, Spetses, Aegina, Paros and the rural area of Mani, who participated in this  
6 research. The MEDIS study group is: M. Tornaritis, A. Polystipiotti, M. Economou, (field  
7 investigators from Cyprus), A. Zeimbekis, K. Gelastopoulou, I. Vlachou (field investigator  
8 from Lesvos), I. Tsiligianni, M. Antonopoulou, N. Tsakountakis, K. Makri (field  
9 investigators from Crete), E. Niforatos, V. Alpentzou, M. Voutsadaki, M. Galiatsatos (field  
10 investigators from Cephalonia), K. Voutsas, E. Lioliou, M. Miheli (field investigator from  
11 Corfu), S. Tyrovolas, G. Pounis, A. Katsarou, E. Papavenetiou, E. Apostolidou, G.  
12 Papavassiliou, P. Stravopodis (field investigators from Zakynthos), E. Turloukis, V.  
13 Bountziouka, A. Aggelopoulou, K. Kaldaridou, E. Qira, (field investigators from Syros and  
14 Naxos), D. Tyrovolas (field investigator from Kassos), I. Protopappa (field investigator from  
15 Ikaria), C. Prekas, O. Blaserou, K.D. Balafouti (field investigators from Salamina), S.  
16 Ioakeimidi (field investigators from Rhodes and Karpathos), A. Foscolou (field investigator  
17 from Tinos), A. Foscolou, T. Paka, P. Drepanidis (field investigators from Gökçeada), A.  
18 Mariolis, E. Petropoulou, A. Kalogerakou, K. Kalogerakou (field investigators from Mani),  
19 S. Piscopo (field investigators from Malta), J.A. Tur (field investigators from Mallorca and  
20 Menorca), G. Valacchi, B. Nanou (field investigators from Sardinia and Sicily), E. Votsi  
21 (field investigator from Ai-Stratis), A. Foscolou, K. Katsana, P. Drepanidis, S. Iosifidis (field  
22 investigators from Spetses), A. Foscolou, K. Gouvas, G. Soulis, K. Katsana (field  
23 investigators from Aegina), A. Foscolou, K. Gouvas, K. Katsas, P. Kaloudi, E. Papachristou,  
24 K. Stamouli (field investigators from Paros) for their substantial assistance in the enrolment  
25 of the participants. **Conflict of interest:** None to declare



1

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

| Characteristics                                   | All          | Males<br>( $n=1574$ ) | Females<br>( $n=1556$ ) | <i>p</i> |
|---|--------------|-----------------------|-------------------------|----------|
| 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 <sup>2</sup> )              | 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     |

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

5

1

**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%) | <i>P</i> |
|--------------------------------------|---------------|-----------------|----------|
| 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 <sup>2</sup> ) | 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   |

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

5

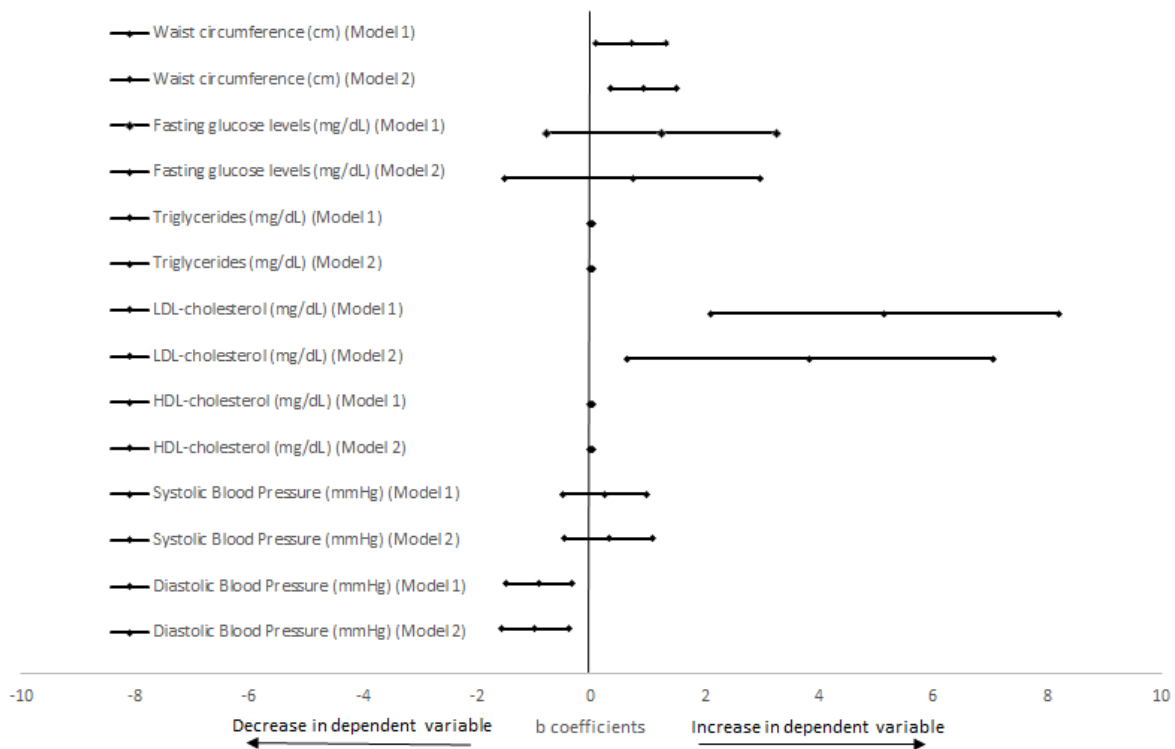
6

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

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

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



3  
 4 Increase means positive association with sleep hours, whereas, decrease means negative  
 5 association between sleep hours and features of MetS.

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

10

1 **References**

- 2 1. National Cholesterol Education Program. Third Report of the National Cholesterol  
3 Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High  
4 Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*.  
5 2002;106(25):3143-421.
- 6 2. Kastorini C-M, Panagiotakos DB, Chrysohoou C, Georgousopoulou E, Pitaraki E,  
7 Puddu PE, et al. Metabolic syndrome, adherence to the Mediterranean diet and 10-year  
8 cardiovascular disease incidence: The ATTICA study. *Atherosclerosis*. 2016;246:87-93.
- 9 3. Federation ID. IDF Consensus Worldwide Definition of the Metabolic Syndrome  
10 [cited 2017]. Available from: [https://www.idf.org/e-library/consensus-statements/60-](https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome)  
11 [idfconsensus-worldwide-definitionof-the-metabolic-syndrome](https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome).
- 12 4. Reaven GM. The metabolic syndrome: is this diagnosis necessary? *The American*  
13 *journal of clinical nutrition*. 2006;83(6):1237-47.
- 14 5. Salas-Salvado J, Guasch-Ferre M, Lee CH, Estruch R, Clish CB, Ros E. Protective  
15 Effects of the Mediterranean Diet on Type 2 Diabetes and Metabolic Syndrome. *The Journal*  
16 *of nutrition*. 2016.
- 17 6. Tambalis KD, Panagiotakos DB, Georgousopoulou EN, Mellor DD, Chrysohoou C,  
18 Kouli G-M, et al. Impact of physical activity category on incidence of cardiovascular disease:  
19 Results from the 10-year follow-up of the ATTICA Study (2002–2012). *Preventive*  
20 *Medicine*. 2016;93:27-32.
- 21 7. Georgousopoulou EN, Mellor DD, Naumovski N, Polychronopoulos E, Tyrovolas S,  
22 Piscopo S, et al. Mediterranean lifestyle and cardiovascular disease prevention.  
23 *Cardiovascular Diagnosis and Therapy*. 2017;7(Suppl 1):S39-S47.
- 24 8. Georgousopoulou EN, Naumovski N, Mellor DD, Tyrovolas S, Piscopo S, Valacchi  
25 G, et al. Association between siesta (daytime sleep), dietary patterns and the presence of  
26 metabolic syndrome in elderly living in Mediterranean area (MEDIS study): The moderating  
27 effect of gender. *The journal of nutrition, health & aging*. 2016.
- 28 9. Sperry SD, Scully ID, Gramzow RH, Jorgensen RS. Sleep Duration and Waist  
29 Circumference in Adults: A Meta-Analysis. *Sleep*. 2015;38(8):1269-76.
- 30 10. Xi B, He D, Zhang M, Xue J, Zhou D. Short sleep duration predicts risk of metabolic  
31 syndrome: A systematic review and meta-analysis. *Sleep Medicine Reviews*. 2014;18(4):293-  
32 7.
- 33 11. Fernandez-Mendoza J, He F, LaGrotte C, Vgontzas AN, Liao D, Bixler EO. Impact of  
34 the Metabolic Syndrome on Mortality is Modified by Objective Short Sleep Duration. *Journal*  
35 *of the American Heart Association*. 2017;6(5).
- 36 12. González-Ortiz M, Martínez-Abundis E. Impact of Sleep Deprivation on Insulin  
37 Secretion, Insulin Sensitivity, and Other Hormonal Regulations. *Metabolic Syndrome and*  
38 *Related Disorders*. 2005;3(1):3-7.
- 39 13. Aho V, Ollila HM, Kronholm E, Bondia-Pons I, Soinen P, Kangas AJ, et al.  
40 Prolonged sleep restriction induces changes in pathways involved in cholesterol metabolism  
41 and inflammatory responses. *Scientific reports*. 2016;6:24828.
- 42 14. Maloberti A, Giannattasio C, Dozio D, Betelli M, Villa P, Nava S, et al. **Metabolic**  
43 **syndrome in human immunodeficiency virus-positive subjects: prevalence, phenotype, and**  
44 **related alterations in arterial structure and function.** *Metab Syndr Relat Disord*.  
45 2013;11(6):403-11.
- 46 15. Panagiotakos DB, Georgousopoulou EN, Pitsavos C, Chrysohoou C, Skoumas I,  
47 Pitaraki E, et al. Exploring the path of Mediterranean diet on 10-year incidence of  
48 cardiovascular disease: the ATTICA study (2002-2012). *Nutrition, metabolism, and*  
49 *cardiovascular diseases : NMCD*. 2015;25(3):327-35.

- 1 16. Salas-Salvadó J, Bulló M, Babio N, Martínez-González MÁ, Ibarrola-Jurado N,  
2 Basora J, et al. Reduction in the Incidence of Type 2 Diabetes With the Mediterranean Diet.  
3 *Diabetes Care*. 2010;34(1):14.
- 4 17. Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, et al. A  
5 randomised controlled trial of dietary improvement for adults with major depression (the  
6 'SMILES' trial). *BMC Medicine*. 2017;15(1):23.
- 7 18. Lourida I, Soni M, Thompson-Coon J, Purandare N, Lang IA, Ukoumunne OC, et al.  
8 Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review.  
9 *Epidemiology*. 2013;24(4):479-89.
- 10 19. Yannakoulia M, Anastasiou CA, Karfopoulou E, Pehlivanidis A, Panagiotakos DB,  
11 Vgontzas A. Sleep quality is associated with weight loss maintenance status: the MedWeight  
12 study. *Sleep Medicine*. 2017;34:242-5.
- 13 20. Tyrovolas S, Pounis G, Bountziouka V, Polychronopoulos E, Panagiotakos DB.  
14 Repeatability and validation of a short, semi-quantitative food frequency questionnaire  
15 designed for older adults living in Mediterranean areas: the MEDIS-FFQ. *Journal of nutrition*  
16 *for the elderly*. 2010;29(3):311-24.
- 17 21. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet  
18 score and its relation to clinical and biological markers of cardiovascular disease risk.  
19 *Nutrition, metabolism, and cardiovascular diseases : NMCD*. 2006;16(8):559-68.
- 20 22. Papatheanasiou G, Georgoudis G, Papandreou M, Spyropoulos P, Georgakopoulos D,  
21 Kalfakakou V, et al. Reliability measures of the short International Physical Activity  
22 Questionnaire (IPAQ) in Greek young adults. *Hellenic journal of cardiology : HJC =*  
23 *Hellenike kardiologike epitheorese*. 2009;50(4):283-94.
- 24 23. Craig CL, Marshall AL, Sjoström M, Bauman AE, Booth ML, Ainsworth BE, et al.  
25 *International physical activity questionnaire: 12-country reliability and validity. Medicine and*  
26 *science in sports and exercise*. 2003;35(8):1381-95.
- 27 24. Tyrovolas S, Haro JM, Mariolis A, Piscopo S, Valacchi G, Tsakountakis N, et al.  
28 Successful aging, dietary habits and health status of elderly individuals: a k-dimensional  
29 approach within the multi-national MEDIS study. *Experimental gerontology*. 2014;60:57-63.
- 30 25. Tyrovolas S, Zeimbekis A, Bountziouka V, Voutsas K, Pounis G, Papoutsou S, et al.  
31 Factors Associated with the Prevalence of Diabetes Mellitus Among Elderly Men and  
32 Women Living in Mediterranean Islands: The MEDIS Study. *The review of diabetic studies :*  
33 *RDS*. 2009;6(1):54-63.
- 34 26. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG,  
35 et al. Short Sleep Duration as a Risk Factor for Hypertension. *Hypertension*. 2006;47(5):833.
- 36 27. Hall MH, Muldoon MF, Jennings JR, Buysse DJ, Flory JD, Manuck SB. Self-  
37 Reported Sleep Duration is Associated with the Metabolic Syndrome in Midlife Adults.  
38 *Sleep*. 2008;31(5):635-43.
- 39 28. Koren D, Dumin M, Gozal D. Role of sleep quality in the metabolic syndrome.  
40 *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. 2016;9:281-310.
- 41 29. Najafian J, Toghianifar N, Mohammadifard N, Nouri F. Association between sleep  
42 duration and metabolic syndrome in a population-based study: Isfahan Healthy Heart  
43 Program. *Journal of research in medical sciences : the official journal of Isfahan University*  
44 *of Medical Sciences*. 2011;16(6):801-6.
- 45 30. Sabanayagam C, Zhang R, Shankar A. Markers of Sleep-Disordered Breathing and  
46 Metabolic Syndrome in a Multiethnic Sample of US Adults: Results from the National Health  
47 and Nutrition Examination Survey 2005-2008. *Cardiology research and practice*.  
48 2012;2012:630802.

- 1 31. Anagnostis P. Metabolic syndrome in the Mediterranean region: Current status. *Indian*  
2 *Journal of Endocrinology and Metabolism*. 2012;16(1):72-80.
- 3 32. De Luis DA, Lopez Mongil R, Gonzalez Sagrado M, Lopez Trigo JA, Mora PF,  
4 Castrodeza Sanz J. Prevalence of metabolic syndrome with International Diabetes Federation  
5 Criteria and ATP III Program in patients 65 years of age or older. *J Nutr Health Aging*.  
6 2010;14(5):400-4.
- 7 33. Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity,  
8 diabetes, and vascular diseases. *European heart journal*. 2008;29(24):2959-71.
- 9 34. Huang PL. A comprehensive definition for metabolic syndrome. *Disease Models &*  
10 *Mechanisms*. 2009;2(5-6):231-7.
- 11 35. Patel SR, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R, et al. Sleep Duration  
12 and Biomarkers of Inflammation. *Sleep*. 2009;32(2):200-4.
- 13 36. Rexrode KM, Pradhan A, Manson JE, Buring JE, Ridker PM. Relationship of total  
14 and abdominal adiposity with CRP and IL-6 in women. *Annals of Epidemiology*.13(10):674-  
15 82.
- 16 37. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and  
17 controversies. *BMC Medicine*. 2011;9(1):48.
- 18 38. Celis-Morales C, Lyall DM, Guo Y, Steell L, Llanas D, Ward J, et al. Sleep  
19 characteristics modify the association of genetic predisposition with obesity and  
20 anthropometric measurements in 119,679 UK Biobank participants. *The American journal of*  
21 *clinical nutrition*. 2017.
- 22 39. Weinbrenner T, Schröder H, Escuriol V, Fito M, Elosua R, Vila J, et al. Circulating  
23 oxidized LDL is associated with increased waist circumference independent of body mass  
24 index in men and women. *The American journal of clinical nutrition*. 2006;83(1):30-5.
- 25 40. Viscogliosi G, Cipriani E, Liguori ML, Marigliano B, Saliola M, Ettorre E, et al.  
26 Mediterranean Dietary Pattern Adherence: Associations with Prediabetes, Metabolic  
27 Syndrome, and Related Microinflammation. *Metabolic Syndrome and Related Disorders*.  
28 2013;11(3):210-6.
- 29 41. Khan CT, Woodward SH. Calibrating actigraphy to improve sleep efficiency  
30 estimates. *Journal of sleep research*. 2017.
- 31 42. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice?  
32 *The American journal of clinical nutrition*. 2006;83(6):1248-51.
- 33 43. Bassi N, Karagodin I, Wang S, Vassallo P, Priyanath A, Massaro E, et al. Lifestyle  
34 Modification for Metabolic Syndrome: A Systematic Review. *The American Journal of*  
35 *Medicine*. 2014;127(12):1242.e1-.e10.

36