International PhD Program in Neuroscience
XXXII Cycle

Diet and mental health: association between dietary patterns and sleep quality

PhD Thesis

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ACKNOWLEDGEMENTS

I would like to express my special appreciation and thanks to my advisor Professor Fabio Galvano for the continuous assistance during my PhD programme and related research, his advises and valuable suggestions.

I would like to thank my family and my beloved ones for supporting and encouraging me throughout this experience.

LIST OF ABBREVIATIONS

5-HT (5-Hydroxytryptamine)

AA (Arachidonic Acid)

ACTH (Adrenocorticotropic Hormone)

BDNF (Brain-Derived Neurotrophic Factor)

CKK (Cholecystokinin)

CRF (Corticotropin-Releasing Factor)

CRP (C-Reactive Protein)

DALYs (Disability-Adjusted Life-Years)

DHA (Docosahexaenoic Acid)

EECs (Enteroendocrine Cells)

ECCs (Enterochromaffins Cells)

EPA (Eicosapentaenoic Acid)

GABA (Gamma-Aminobutyric Acid)

HPA (Hypothalamic-Pituitary-Adrenal)

LPS (Lipopolysaccharide)

MAP-kinase (Mitogen-Activated Protein kinase)

NF-κB (Nuclear Factor Kappa-light-chain-enhancer of activated B cells)

PGE2 (Prostaglandin E2)

PI3-kinase (Phosphatidylinositol 3-kinase)

PUFA (Polyunsaturated Fatty Acids)

SCFAs (Short-Chain Fatty Acids)

YLDs (Years Lived with Disability)

ABSTRACT

Mental health diseases represent a major public health threat due to their impact on general population, the scarce timely diagnosis, and the growing trends highly influenced by the modern society and current unhealthy lifestyles. Sleep disorders may appear in an early phase of mental diseases and they do not just represent a symptom but they are often connected from a pathophysiological point of view. A recent field of psychiatry, so-called "nutrition psychiatry" focuses on finding the relation between dietary factors, eating habits, and mental diseases; several studies have been conducted on cognitive and depressive disorders, but data on sleep quality is scarce. The aim of this project was to test whether an association between dietary pattern and sleep quality could be observed in a cohort of southern Italian individuals. Data from nearly 2000 adults living in Sicily have been collected. A food frequency questionnaire and validated instruments were used to assess the adherence to the Mediterranean diet and an index evaluating the inflammatory potential of the diet. Sleep quality was tested through the Pittsburg sleep quality index. Multivariate logistic regressions were performed to determine the association between exposure and outcome. The studies showed that a total of 1314 individuals (67.9% of the cohort) reported adequate sleep quality: for each point increase of the Mediterranean diet score, individuals were 10% more likely to have adequate sleep quality. In contrast, for each one standard deviation increment of the inflammatory

score of the diet, individuals were 27% less likely to have adequate sleep quality. Adherence to the Mediterranean diet showed stronger association also with specific sleep quality domains investigated (i.e., sleep duration, latency, efficiency, and day dysfunction) while no findings were found for the inflammatory score besides sleep latency. In conclusions, dietary factors, with particular regard to foods and compounds rich in antioxidants, are associated with sleep quality. Future studies are needed to better understand the potential mechanisms underlining such associations.

GENERAL INTRODUCTION

Over the last decade, mental health diseases have represented the major contributors to years of life lost due to disability in developed countries while alarming trends have been registered also in developing ones [1]. Recent reports estimated that the global population living with depression is estimated to be 322 million people and that anxiety disorders affects more than 260 million people (4.4% and 3.6% of the global population, respectively) [2]. Mental disorders have been accounted for 14% of worldwide Years Lived with Disability (YLD), with depressive disorders leading to a global total of over 50 million YLD and anxiety disorders to 24.6 million YLD in 2015 [3]. Furthermore, it is noteworthy that depression and anxiety are often associated, if not prodromic, to some of the other mental conditions and related to other non-communicable diseases, such as cardiovascular disease and cancer [4]. Together with the aforementioned disorders, sleep quantity and quality, sleep patterns, and more in general sleep-related features have been of interest as emerging conditions not only to an end unto themselves, but again as potentially related to other health conditions [5]. Recognizing early symptoms of mental disorders, identifying potential risk factors and intervening to modify chronic exposure to them is of paramount importance to prevent the development of serious conditions fated to have a growing impact on the general population and future generations.

A growing body of literature has focused the attention on potential risk factors for mental disorders, involving (paleo)anthropology and studies on human evolution and biology together with culture and environment [6]. On one side, we are witnesses of a fast evolution of human society, rise in technological advances, global industrialization and urbanization of the environment occurred over the last 50 years; on the other side, very little genetic variations have occurred since last thousands of years, leading to a potential evolutionary mismatch between our ancestral genome and the current environmental exposure [6]. The modern world led to the rise of non-communicable chronic diseases due to important changes in lifestyle factors, including, among others, adoption of unhealthy dietary patterns and sleeping habits [7]. Diet per se has been estimated to be the most important risk factor for non-commutable diseases in the modern era [8]: it has been calculated that dietary factors are responsible for 10.9 million deaths and 255 million DALYs (disability-adjusted life-years) [8]. The modern era is characterized by a "nutrition transition" process characterized by a global shift from traditional dietary patterns toward so-called "Westernized" diets, rich in processed energy-dense food, refined sugars, trans-fatty acids, animal protein and excessive sodium, and scarce consumption of plant-derived foods, accompanied by over nutrition and less engagement in physical activities [6]. There is a large number of studies comprehensively assessing the relation between diet and human health, showing not only an impact on cardio-metabolic diseases and certain cancers, but also a potential role in affecting mental health disorders risk [9]. The urban environment may also lead to disruption of circadian cycle due to continuous exposure to stimuli such as 24-h day light, acoustic pollution, busy working schedule, and societal challenges, which may play a role in anxiety and mood disorders, depression and sleep disorders [10]. There is convincing evidence that sleep quantity and quality affect human health: inadequate sleep duration and quality has been associated with increased risk of cancer [11], cardiovascular outcomes [12], diabetes [13] and all-cause mortality [14]. Moreover, long-term changes in sleep quality and architecture have been related to cognitive impairment, including dementias and Alzheimer's disease [15].

The interrelation between sleep and diet has been hypothesized about 30 years ago: habitual sleep duration has been generally associated with higher calorie intake and either absolute or relative intake of nutrients or foods [16]. When considering dietary patterns, individuals sleeping less hours had a diet of lower quality based on Healthy Eating Index scores [17]. Among the potential mechanisms proposed to explain the impact of sleep on dietary intake, extended hours of wakefulness may increase the chances of eating occasions (i.e., unhealthy snacking) [18], alter the time of intake (i.e., late evening or night feeding) [19], while physiologically sleep deprivation has been demonstrated to affect appetite- (i.e., leptin and ghrelin) and metabolic-related (i.e., cortisol, insulin sensitivity and growth hormones) hormonal homeostasis [18,20,21]. These hypotheses would also provide the rationale explaining the relation between sleep duration and higher obesity rates [22]. Besides its influence on metabolic disorders through increased risk of obesity, some recent research focused on the role of sleep toward diet quality, showing a general association between short sleep duration and lower diet quality as well as irregular eating behaviors [18]. A more intriguing hypothesis includes the possibility of an opposite relation between diet and sleep features (quantity/quality). Several mechanisms have been associated with the sleep-wake cycle, including (i) neuroendocrine regulation through neurotransmitters, such as serotonin (5-hydroxytryptamine, 5-HT), gamma-aminobutyric acid (GABA), orexin, melanin-concentrating hormone, acetylcholine, galanin, noradrenaline, and histamine, and (ii) neuroinflammatory processes that alter the normal functionality of the brain and increase the risk of brain disorders. Consequently, nutritional and dietary aspects that influence or modulate the aforementioned mechanisms may have downstream effects on sleep. The aim of this project was too test whether there was an association between dietary pattern and sleep quality in a cohort of southern Italian individuals.

Godos J, Ferri R, Caraci F, Cosentino FII, Castellano S, Galvano F, Grosso G. Adherence to the Mediterranean Diet is Associated with Better Sleep Quality in Italian Adults. Nutrients. 2019 Apr 28;11(5). pii: E976. doi: 10.3390/nu11050976

CHAPTER 1

Adherence to the Mediterranean Diet is Associated with Better Sleep Quality in Italian Adults

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Received: 20 February 2019; Accepted: 25 April 2019; Published: 18 April 2019

Abstract: Background: Sleep quality has been associated with human health and diseases, including cognitive decline and dementia; however major determinants of sleep disorders are largely unknown. The aim of this study was to evaluate the association between sleep quality and adherence to the Mediterranean dietary pattern in a sample of Italian adults. Methods: A total of 1936 individuals were recruited in the urban area of Catania during 2014–2015 through random sampling. A food frequency questionnaire and validated instruments were used to assess the adherence to the Mediterranean diet and sleep quality (Pittsburg sleep quality index). Multivariate logistic regressions were performed to determine the association between exposure and outcome. Results: A total of 1314 individuals (67.9% of the cohort) reported adequate sleep quality: for each point increase of the Mediterranean diet score, individuals were 10% more likely to have adequate sleep quality. In an additional analysis stratifying the sample by weight status, the association between sleep quality and high adherence to the Mediterranean diet was observed only among normal/overweight individuals but not in obese participants. Conclusions: high adherence to a Mediterranean diet is associated with better sleep quality either toward direct effect on health or indirect effects through improvement of weight status.

Keywords: Mediterranean diet; sleep quality; cognitive decline; dementia; weight status; mental health; obesity; cohort; Italy

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1. Introduction

Epidemiological evidence suggests that sleeping habits might be related to human health, including cardio-metabolic and mental health outcomes [1,2]. Most of existing evidence focuses on sleep duration, suggesting that lack of sleep may exert negative effects on a variety of systems [3]. The mechanisms mediating the relation between sleep and health status are not entirely clear, but are likely to be multifactorial, involving hormonal disruption, metabolic impairment, and inflammatory processes [4,5].

Although short term sleep deprivation is associated to decrements in the psychomotor vigilance task, the most consistent finding animal studies showed that chronic unhealthy sleeping behaviors may impact central nervous system structural plasticity in different ways, including reduction of spine density and attenuation of synaptic efficacy in the hippocampus [6]. Long-term changes in sleep quality and architecture have been related to cognitive impairment; while the incidence of sleep disorders may increase with normal aging, further impairment of sleep-dependent memory consolidation has been observed in relation with neurodegenerative diseases, including dementias and Alzheimer's disease [7]. It is not clear whether sleep disturbances occur with higher rate in individuals having cognitive impairment or dementia, or they may also represent an independent risk factor for such pathological conditions. However, sleep disorders and cognitive decline seem to be somehow connected at the pathophysiological level [8]. Therefore, it is potentially important to identify determinants of sleep disorders in middle-aged and older adults as a strategy to prevent cognitive decline and dementia.

Among the many factors studied, diet has been the focus of recent attention due to the potential relation with both sleep quality and its related health outcomes [9]. The Mediterranean dietary pattern has gained popularity over recent decades due to its palatable taste and a strong evidence of benefits for health [10]. Despite a single definition of Mediterranean diet cannot be achieved, it refers to the traditional diet of Southern Italian people explored in the 60s by Ancel Keys, characterized by certain peculiarities including high consumption of plant-based foods (such as fruit, vegetable, legumes and nuts), preference for whole-grain cereals, fish (whenever available) and dairy products instead of other sources of refined carbohydrates and animal proteins, respectively; other characteristics were the daily consumption of olive oil and moderate intake of alcohol (mostly red wine) during meals [11]. A combination of these features has been further investigated in several studies, leading to the development of a number of adherence scores ideally optimized for type of population (i.e., geographical localization), diet parameters availability (i.e., completeness of dietary questionnaires), and generalizability of results (i.e., use of comparable scores) [12]. High adherence to the Mediterranean diet has been associated with a number of cardio-metabolic health outcomes [13,14], including lower risk of cardiovascular-related disorders [15,16], diabetes [17], metabolic syndromes [18,19], and non-alcoholic fatty liver disease [20,21]. These beneficial effects are ascribed to various mechanisms, mostly involving a high content in antioxidants and healthy dietary fats, which in turn may improve insulin sensitivity, reduce vascular inflammation and improve endothelial dysfunction [22]. Lately, a large body of literature has also shown that adherence to a Mediterranean dietary pattern may exert benefits also toward mental health and neurological outcomes, including stroke, cognitive impairment, depression, and dementia [23–28]. Recent evidence shows a relation between adherence to the Mediterranean diet and sleep duration and quality in adults [29–31], but only few studies have been performed and more research is warranted to better investigate such a relation. The aim of this study was to evaluate the association between sleep quality and adherence to the Mediterranean dietary pattern in a sample of Italian adults.

2. Materials and Methods

2.1. Study Population

The Mediterranean healthy Eating, Aging, and Lifestyles (MEAL) study is cross-sectional study aimed to explore the relation between nutritional and lifestyle behaviors characterizing individuals living in the Mediterranean area. The detailed study protocol with the rationale, design, and methods has been described in detail elsewhere [32]. Briefly, the cohort consisted of a random sample of men and women (age 18+ years) registered in the records of local general practitioners in the urban area of Catania, one of the largest cities in the east coast of Sicily, southern Italy, during 2014–2015. The sampling technique included stratification by municipality area, age, and sex of inhabitants, and randomization into subgroups, with randomly selected general practitioners being the sampling units, and individuals registered to them comprising the final sample units. Pregnant women were not considered in this study. Participants randomly selected for recruitment were stratified by sex and 10-year age groups. The theoretical sample size was set at 1500 individuals to provide a specific relative precision of 5% (Type I error, 0.05; Type II error, 0.10), taking into account an anticipated 70% participation rate. Out of 2405 individuals invited, the final sample size was 2044 participants (response rate of 85%). All the study procedures were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. Participants provided written informed consent and the study protocol was approved by the ethics committee of the referent health authority.

2.2. Data Collection

Data regarding demographic (i.e., age, sex, educational and occupational level) and lifestyle characteristics (i.e., physical activity, smoking and drinking habits) were collected. Educational level was categorized as: (i) low (primary/secondary), (ii) medium (high school), and (iii) high (university). Occupational level was classified as: (i) unemployed, (ii) low (unskilled workers), (iii) medium (partially skilled workers), and (iv) high (skilled workers). Physical activity level was assessed using International Physical Activity Questionnaires (IPAQs) [33], which are comprised a set of questionnaires (5 domains) on time spent being physically active in the last 7 days that allow categorization of physical activity as: (i) low, (ii) moderate, and (iii) high. Smoking status was classified as: (i) non-smoker, (ii) ex-smoker, and (iii) current smoker. Alcohol consumption was categorized as (i) none, (ii) moderate drinker (0.1-12 g/d) and (iii) regular drinker (>12 g/d). Anthropometric measurements were performed according to standardized methods [34]. Height was measured to the nearest 0.5 cm without shoes, with the back square against the wall tape, eyes looking straight ahead, with a right-angle triangle resting on the scalp and against the wall. Body mass index (BMI) was calculated, and patients were categorized as under/normal weight (BMI <25 kg/m^2), overweight (BMI 25 to 29.9 kg/m^2), and obese (BMI ≥30 kg/m^2) [35].

2.3. Dietary Assessment

Dietary data was collected using long and short food frequency questionnaires (FFQs), developed and previously validated for the Sicilian population [36,37]. The FFQs consisted of 110 food and drink items representative of the diet during the previous 6 months. Participants of the study were asked how often, on average, they had consumed foods and drinks included in the FFQ, with nine responses ranging from "never" to "4–5 times per day". Intake of food items characterized by seasonality referred to consumption during the period in which the food was available and then adjusted by its proportional intake over one year. After exclusion of 107 entries with unreliable intakes (<1000 or >6000 kcal/d, controlled case by case and validated due to missing food items or unreliable answers), a total of 1936 individuals were included in the analyses for the present study.

2.4. Adherence to the Mediterranean Diet

Mediterranean diet adherence was assessed using the score developed by Sofi et al. [15]. Briefly, a scoring system (the MEDI-LITE score) was built based on existing literature weighting all the median (or mean) values for the sample size of each study population and then calculating a mean value of all the weighted medians; hence, two standard deviations were used to determine three different categories of consumption for each food group. For food groups, typical of the Mediterranean diet (fruit, vegetables, cereals, legumes and fish), two points were given to the highest category of consumption, one point for the middle category and zero points for the lowest category of intake. Contrariwise, for food groups not typical of the Mediterranean diet (meat and meat-based products, dairy products), two points were given for the lowest category, one point for the middle category and zero points for the highest category of consumption. Regarding alcohol, categories related to the alcohol unit (one alcohol unit = 12 g of alcohol) were used by giving two points to the middle category (1–2 alcohol units/d), one point to the lowest category (>1 alcohol unit/d) and zero points to the highest category of consumption (>2 alcohol units/d). The final score comprised nine food categories (including olive oil) with a score ranging from zero points (lowest adherence) to 18 points (highest adherence).

2.5. Sleep Quality

The Pittsburg sleep quality index (PSQI) [38] was used to assess participants' sleep quality and disturbances in the past six month. It consists of 19 items which are rated on a four-point scale (0–3) and grouped into seven components (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction). The item scores in each component were summed and converted to component scores ranging from 0 (better) to 3 (worse) based on guidelines. Total PSQI scores were calculated as the summation of seven component scores ranging from zero to 21, where higher score indicates worse condition. A total global PSQI score of <5 is indicative of adequate sleep quality.

2.6. Statistical Analysis

Categorical variables are presented as frequencies of occurrence and percentages differences between groups were tested using a Chi-squared test. First, the difference between distribution of background variables by sleep quality (adequate vs. inadequate) was tested. Second, differences in distribution of sleep-related characteristics between groups of individuals divided into quartiles of Mediterranean diet adherence score (Q1 had the lowest adherence, Q4 had the highest adherence) was tested. The relation between adherence to the Mediterranean diet and sleep-related outcomes was tested through multivariate logistic regression analysis adjusted for baseline characteristics (age, sex, marital, educational and occupational status, smoking and alcohol drinking habits, and physical activity level) comparing individuals grouped into quartiles or estimating the association by 1-point increase of the Mediterranean diet adherence score. A sensitivity analysis excluding, one at a time, each individual component of the Mediterranean diet adherence score was performed. Finally, a subgroup analysis by weight status categorization (normal/overweight and obese individuals) has been performed to test stability of results. All reported *p* values were based on two-sided tests and compared to a significance level of 5%. SPSS 17 (SPSS Inc., Chicago, IL, USA) software was used for all the statistical analysis.

3. Results

A total of 1314 individuals (67.9% of the sample) reported an overall adequate sleep quality according to the PSQI score. The distribution of the baseline characteristics of the study participants by sleep quality revealed that there were no significant differences between groups with the exception of occupational level, as there was a significantly higher proportion of individuals with adequate quality of sleep in the highest category than in the lower. However, the distribution was not linear, and a high proportion of individuals with adequate quality of sleep were present also in the lowest category (Table 1).

Table 1. Baseline characteristics of the study participants by sleep quality. *n* indicates the number of individuals that satisfy each condition within the total sample; % indicates the percentages of individuals that satisfy each condition within the total sample.

	Sleep quality		
	Inadequate (*n* = 622)	**Adequate (*n* = 1314)**	***p-value***
Sex, *n* (%)			0.052
Men	278 (44.7)	526 (40.0)	
Women	344 (55.3)	788 (60.0)	
Age groups, *n* (%)			0.161
<30	124 (19.9)	226 (17.2)	
30-49	218 (35.0)	485 (36.9)	
50-69	209 (33.6)	416 (31.7)	
≥70	71 (11.4)	187 (14.2)	
Educational status, *n* (%)			0.119
Low	224 (36.0)	473 (36.0)	
Medium	248 (39.9)	472 (35.9)	
High	150 (24.1)	369 (28.1)	
Occupational status, *n* (%)			0.011
Unemployed	131 (24.8)	330 (29.2)	
Low	84 (15.9)	181 (16.1)	
Medium	167 (31.6)	273 (24.2)	
High	146 (27.7)	345 (30.5)	
Smoking status, *n* (%)			0.595
Never smoker	375 (60.3)	820 (62.4)	
Former smoker	89 (14.3)	187 (14.2)	
Current smoker	158 (25.4)	307 (23.4)	
Physical activity level, *n* (%)			0.169
Low	93 (16.6)	236 (20.2)	
Moderate	291 (52.0)	565 (48.4)	
High	176 (31.4)	367 (31.4)	
Health status, *n* (%)			
Hypertension	292 (46.9)	684 (52.1)	0.036
Type-2 diabetes	45 (7.2)	101 (7.7)	0.725
Dyslipidemias	118 (19.0)	238 (18.1)	0.649
Cardiovascular disease	57 (9.3)	97 (7.6)	0.198
Cancer	19 (3.1)	59 (4.5)	0.134
Weight status, *n* (%)			0.372
Normal	267 (47.6)	584 (47.2)	
Overweight	205 (36.5)	425 (34.4)	
Obese	89 (15.9)	228 (18.4)	

The relation between specific indicators of sleep quality of the study participants by quartiles of the Mediterranean diet adherence score are reported in Table 2. Among participants more adherent to the dietary pattern (the highest quartile, Q4) there was a higher proportion of individuals with overall better sleep quality compared to the less adherent (the lowest quartile, Q1; 72.4% vs. 58.9%; P <0.001); among specific domains of the PSQI, significantly lower occurrences of shorter sleep durations, longer sleep latency, day dysfunction due to sleepiness, very low sleep efficiency and self-reported sleep quality occurred among participants in the highest quartile of the Mediterranean diet adherence score.

Table 2. Overall sleep quality and sleep-related characteristics of the study participants by quartiles of Mediterranean diet adherence score. *n* indicates the number of individuals that satisfy each condition within the total sample; % indicates the percentages of individuals that satisfy each condition within the total sample.

	Mediterranean diet adherence score*				
	Q1	**Q2**	**Q3**	**Q4**	***p-value***
Overall sleep quality, *n* (%)					<0.001
Adequate	272 (58.9)	403 (68.0)	440 (72.6)	199 (72.4)	
Inadequate	190 (41.1)	190 (32.0)	166 (27.4)	76 (27.6)	
Sleep duration, *n* (%)					<0.001
>7 h	246 (53.2)	371 (62.6)	376 (62.0)	171 (62.2)	
6-7 h	111 (24.0)	130 (21.9)	137 (22.6)	57 (20.7)	
5-6 h	65 (14.1)	58 (9.8)	74 (12.2)	33 (12.0)	
<5 h	40 (8.7)	34 (5.7)	19 (3.1)	14 (5.1)	
Sleep disturbance, *n* (%)					0.311
None	53 (11.5)	54 (9.1)	74 (12.2)	35 (12.7)	
Low	335 (72.5)	444 (74.9)	451 (74.4)	207 (75.3)	
Medium	74 (16.0)	95 (16.0)	81 (13.4)	33 (12.0)	
High	0	0	0	0	
Sleep latency, *n* (%)					0.003
Very short	172 (37.2)	253 (42.7)	298 (49.2)	135 (49.1)	
Short	153 (33.1)	210 (35.4)	181 (29.9)	85 (30.9)	
Medium	101 (21.9)	94 (15.9)	97 (16.0)	41 (14.9)	
Long	36 (7.8)	36 (6.1)	30 (5.0)	14 (5.1)	
Day dysfunction, *n* (%)					<0.001
None	296 (64.1)	433 (73.0)	440 (72.6)	201 (73.1)	
Low	75 (16.2)	91 (15.3)	93 (15.3)	30 (10.9)	
Medium	35 (7.6)	28 (4.7)	27 (4.5)	23 (8.4)	
High	56 (12.1)	41 (6.9)	46 (7.6)	21 (7.6)	
Sleep efficiency, *n* (%)					<0.001
High	296 (64.1)	433 (73.0)	440 (72.6)	201 (73.1)	
Medium	75 (16.2)	91 (15.3)	93 (15.3)	30 (10.9)	
Low	35 (7.6)	28 (4.7)	27 (4.5)	23 (8.4)	
Very low	56 (12.1)	41 (6.9)	46 (7.6)	21 (7.6)	
Self-rated sleep quality, *n* (%)					0.043
Very low	14 (3.0)	29 (4.9)	15 (2.5)	13 (4.7)	
Low	17 (3.7)	15 (2.5)	15 (2.5)	0 (0)	
Medium	17 (3.7)	26 (4.4)	20 (3.3)	11 (4.0)	
High	414 (89.6)	523 (88.2)	556 (91.7)	251 (91.3)	
Need medication to sleep, *n* (%)	48 (10.4)	70 (11.8)	50 (8.3)	24 (8.7)	0.187

*Groups represent individuals divided into quartiles.

Among the whole sample, a higher adherence to the Mediterranean diet was associated with a higher likelihood of adequate overall sleep quality (highest vs. lowest quartile, OR = 1.82, 95% CI: 1.32, 2.52; Table 3). However, among the specific indicators of sleep quality, only sleep latency was significantly associated with higher adherence to the dietary pattern, while no day dysfunction due to sleepiness was associated with the third quartile of the Mediterranean diet adherence score, but not with the highest. When considering the relation with 1-point increase of the Mediterranean diet adherence score, the multivariate regression analysis revealed that individuals were 10% more likely to have an overall adequate sleep quality, while among individual components of the PSQI score, 1-point increase of the dietary adherence score was significantly associated with having adequate sleep duration, latency, and efficiency (Table 3).

Table 3. Association between overall and individual domains of sleep quality and adherence and quartiles of the Mediterranean diet adherence score. Odds ratios indicate the probability that a subject was an adequate sleeper to the probability that the subject was not, between subjects included in each quartile, compared to those included in the lowest.

	Mediterranean diet adherence score				
	Q1	**Q2**	**Q3**	**Q4**	**1-point increment**
	OR (95% CI)*				
Adequate sleep quality	1	1.48 (1.15, 1.90)§	1.85 (1.43, 2.39)§	1.82 (1.32, 2.52)§	1.10 (1.05, 1.16)§
Sleep duration	1	1.39 (1.04, 1.86)§	1.29 (0.97, 1.71)	1.35 (0.94, 1.92)	1.07 (1.02, 1.12)§
Sleep disturbance	1	0.81 (0.51, 1.30)	1.26 (0.82, 1.95)	1.31 (0.77, 2.21)	1.04 (0.97, 1.12)
Sleep latency	1	1.12 (0.84, 1.50)	1.64 (1.23, 2.17)§	1.52 (1.07, 2.16)	1.07 (1.02, 1.12)§
Day dysfunction	1	1.12 (0.85, 1.49)	1.42 (1.07, 1.88)#	1.25 (0.88, 1.77)	1.04 (1.00, 1.09)#
Sleep efficiency	1	1.36 (1.00, 1.84)#	1.33 (0.98, 1.80)	1.40 (0.95, 2.05)	1.06 (1.01, 1.12)#
Need medication to sleep	1	0.67 (0.42, 1.07)	1.34 (0.80, 2.25)	1.05 (0.57, 1.93)	1.03 (0.95, 1.11)
Self-rated sleep quality	1	1.04 (0.73, 1.48)	1.16 (0.83, 1.64)	1.30 (0.86, 1.98)	1.04 (0.98, 1.09)

*adjusted for age (continuous), sex (male/female), BMI (<25 kg/m^2, 25-30 kg/m^2, >30 kg/m^2), physical activity (low/medium/high), educational status (low/medium/high), occupational status (unemployed/low/medium/high), smoking status (current/former/never), alcohol consumption (no/moderate/regular), health status (presence of hypertension, type-2 diabetes, dyslipidaemias, cardiovascular disease, cancer), and total energy intake. # indicates $p < 0.05$. § indicates $p < 0.001$.

An alternative analysis by excluding one at the time each individual component of the Mediterranean diet adherence score was performed in order to test whether any of these could explain alone the association of the score (Table 4). The results show that the association was robust, as the association with overall sleep quality was significant in all alternative scores; moreover, exclusion of no individual component, besides olive oil, showed significant association with the aforementioned aspects of sleep quality, including sleep duration, latency, and efficacy, suggesting that olive oil may play an independent role in sleep quality.

Table 4. Association between overall and individual domains of sleep quality and alternative Mediterranean diet adherence scores with exclusion of each individual component one at the time. Odds ratios indicate the probability that a subject was an adequate sleeper to the probability that the subject was not, between subjects included in each 1-point score, compared to those having 1 unit lower.

	Mediterranean diet adherence score, 1-point increment recalculated excluding:								
	Fruit	**Vegetable**	**Legume**	**Dairy**	**Whole-grain**	**Fish**	**Meat**	**Olive oil**	**Alcohol**
	OR (95% CI)*								
Overall sleep quality	1.12 (1.06, 1.18)§	1.11 (1.06, 1.17)§	1.10 (1.05, 1.17)§	1.13 (1.07, 1.19)§	1.09 (1.04, 1.15)#	1.11 (1.06, 1.17)§	1.10 (1.05, 1.15)§	1.09 (1.03, 1.14)#	1.10 (1.05, 1.15)§
Sleep duration	1.08 (1.02, 1.14)#	1.07 (1.02, 1.12)#	1.08 (1.03, 1.14)#	1.08 (1.03, 1.14)#	1.06 (1.01, 1.11)#	1.07 (1.02, 1.13)#	1.07 (1.02, 1.13)#	1.04 (0.99, 1.09)	1.06 (1.01, 1.11)#
Sleep disturbance	1.03 (0.95, 1.11)	1.03 (0.95, 1.11)	1.06 (0.98, 1.15)	1.07 (0.99, 1.16)	1.05 (0.97, 1.13)	1.06 (0.98, 1.14)	1.03 (0.96, 1.11)	1.03 (0.96, 1.11)	1.04 (0.97, 1.12)
Sleep latency	1.08 (1.03, 1.14)#	1.09 (1.03, 1.14)#	1.07 (1.02, 1.13)#	1.07 (1.02, 1.12)#	1.06 (1.01, 1.11)#	1.08 (1.03, 1.14)#	1.08 (1.03, 1.13)#	1.06 (1.01, 1.11)#	1.07 (1.02, 1.12)#
Day dysfunction	1.04 (0.99, 1.09)	1.04 (0.99, 1.10)	1.04 (0.99, 1.10)	1.06 (1.01, 1.11)#	1.05 (1.00, 1.10)#	1.05 (1.00, 1.10)#	1.05 (1.00, 1.10)#	1.04 (0.99, 1.09)	1.04 (0.99, 1.09)
Sleep efficiency	1.06 (1.00, 1.12)#	1.07 (1.01, 1.12)#	1.06 (1.01, 1.12)#	1.09 (1.03, 1.15)#	1.06 (1.01, 1.11)#	1.06 (1.01, 1.12)#	1.06 (1.01, 1.12)#	1.05 (1.00, 1.11)#	1.07 (1.02, 1.12)#
Need medication to sleep	1.04 (0.96, 1.14)	1.03 (0.95, 1.12)	1.03 (0.94, 1.12)	1.02 (0.94, 1.10)	1.03 (0.96, 1.12)	1.04 (0.96, 1.13)	1.04 (0.96, 1.12)	1.02 (0.94, 1.10)	1.02 (0.95, 1.10)
Self-rated sleep quality	1.03 (0.96, 1.09)	1.04 (0.98, 1.10)	1.04 (0.98, 1.11)	1.04 (0.98, 1.11)	1.05 (0.99, 1.11)	1.04 (0.98, 1.10)	1.04 (0.98, 1.10)	1.03 (0.97, 1.10)	1.04 (0.98, 1.10)

*adjusted for age (continuous), sex (male/female), BMI (<25 kg/m^2, 25-30 kg/m^2, >30 kg/m^2), physical activity (low/medium/high), educational status (low/medium/high), occupational status (unemployed/low/medium/high), smoking status (current/former/never), alcohol consumption (no/moderate/regular), health status (presence of hypertension, type-2 diabetes, dyslipidaemias, cardiovascular disease, cancer), and total energy intake. # indicates $p < 0.05$. § indicates $p < 0.001$.

Table 5 summarizes the results of a supplementary analysis, in which the associations of all endpoints were tested separately according to body weight status of study participants, leading to some differences: Specifically, the association between adequate sleep quality and higher adherence to the Mediterranean diet was observed only among normal/overweight individuals (highest vs. lowest quartile, OR = 2.30, 95% CI: 1.49, 3.54; 1-point increase, OR = 1.10, 95% CI: 1.04, 1.16), while this was not found in obese participants. Among the specific indicators of sleep quality, only sleep latency was associated with the diet score in the former group, but not in the latter (Table 5).

Table 5. Association between overall and individual domains of sleep quality and adherence and quartiles of the Mediterranean diet adherence score by weight status. Odds ratios indicate the probability that a subject was an adequate sleeper to the probability that the subject was not, between subjects included in each 1-point score, compared to those having 1 unit lower.

	Mediterranean diet adherence score				
	Q1	**Q2**	**Q3**	**Q4**	**1-point increment**
	OR (95% CI)*				
Normal/overweight					
Overall sleep quality	1	1.22 (0.87, 1.71)	1.79 (1.27, 2.54)§	2.30 (1.49, 3.54)§	1.10 (1.04, 1.16)§
Sleep duration	1	1.32 (0.94, 1.83)	1.29 (0.92, 1.79)	1.32 (0.89, 1.97)	1.06 (1.01, 1.12)#
Sleep disturbance	1	0.82 (0.47, 1.40)	1.28 (0.77, 2.13)	1.22 (0.67, 2.22)	1.03 (0.95, 1.12)
Sleep latency	1	1.08 (0.77, 1.51)	1.96 (1.40, 2.74)§	1.62 (1.09, 2.41)§	1.09 (1.03, 1.15)#
Day dysfunction	1	1.26 (0.91, 1.74)	1.51 (1.09, 2.10)§	1.27 (0.86, 1.88)	1.03 (0.97, 1.08)
Sleep efficiency	1	1.32 (0.92, 1.88)	1.29 (0.90, 1.84)	1.48 (0.96, 2.28)	1.04 (0.99, 1.10)
Need medication to sleep	1	0.62 (0.37, 1.04)	1.24 (0.69, 2.23)	0.97 (0.50, 1.89)	1.01 (0.92, 1.10)
Self-rated sleep quality	1	0.97 (0.65, 1.46)	1.27 (0.85, 1.89)	1.31 (0.82, 2.08)	1.04 (0.98, 1.11)
Obese					
Overall sleep quality	1	0.91 (0.39, 2.15)	1.11 (0.49, 2.50)	1.12 (0.33, 3.79)	1.12 (0.95, 1.32)
Sleep duration	1	1.67 (0.75, 3.73)	1.58 (0.75, 3.36)	2.68 (0.80, 8.96)	1.09 (0.94, 1.26)
Sleep disturbance	1	1.38 (0.42, 4.54)	1.71 (0.59, 4.92)	3.41 (0.81, 14.36)	1.20 (0.98, 1.49)
Sleep latency	1	1.08 (0.49, 2.36)	0.69 (0.33, 1.43)	0.65 (0.21, 2.01)	0.89 (0.77, 1.03)
Day dysfunction	1	0.69 (0.32, 1.49)	1.06 (0.52, 2.19)	1.22 (0.39, 3.79)	1.07 (0.93, 1.23)
Sleep efficiency	1	1.91 (0.81, 4.50)	1.32 (0.61, 2.87)	1.46 (0.44, 4.81)	1.13 (0.97, 1.33)
Need medication to sleep	1	0.48 (0.09, 2.40)	1.36 (0.24, 7.59)	1.57 (0.40, 5.92)	1.21 (0.87, 1.69)
Self-rated sleep quality	1	1.28 (0.54, 3.00)	0.87 (0.38, 1.97)	0.92 (0.25, 3.30)	0.95 (0.81, 1.11)

*adjusted for age (continuous), sex (male/female), BMI (<25 kg/m^2, 25-30 kg/m^2, >30 kg/m^2), physical activity (low/medium/high), educational status (low/medium/high), occupational status (unemployed/low/medium/high), smoking status (current/former/never), alcohol consumption (no/moderate/regular), health status (presence of hypertension, type-2 diabetes, dyslipidaemia, cardiovascular disease, cancer), and total energy intake. # indicates $p < 0.05$. § indicates $p < 0.001$.

4. Discussion

In the present study, a relation between sleep quality and adherence to the Mediterranean dietary pattern has been reported in a cohort of Southern Italian adults. Among the main domains investigated, only sleep latency resulted in being independently associated with higher adherence to this dietary pattern, suggesting that the overall sleep quality rather than specific aspects are associated with a healthier diet. Considering the impact of sleep-related habits toward adverse health outcomes, it is crucial to investigate and identify potential dietary determinants of sleep quality.

To our knowledge, only two studies previously investigated the association between adherence to the Mediterranean diet and sleep parameters in adults [29,30]. One study was conducted on about 1500 older adults living in Spain followed up for 2.8 years and monitored for their sleep duration and indicators of poor sleep quality. The authors found that individuals more adherent to the Mediterranean dietary pattern had a lower risk of a variation (increase or decrease) in sleep duration of more than 2 hours and were also at lower risk of poor sleep quality [29]. Another study investigated the relation between adherence to the Mediterranean diet and specific aspects of sleeping, such as insomnia symptoms, finding a positive effect with adherence to a Mediterranean dietary pattern [30]. Some studies investigated the association between sleep duration and overall diet quality [39,40], while others also explored the relation between sleep patterns and eating behaviors, such as unbalanced food variety, irregular meal times, snacking between meals, eating out, and other potentially unhealthy eating habits [41,42]. Concerning our specific findings on sleep latency, intervention studies suggest a causal association between higher fat and carbohydrate intake close to bedtime and high sleep latency [43], thus confirming our results. In general, a consistent relation between dietary behaviors, nutrition quality, and sleep-related habits has been reported in most of the aforementioned studies. However, the direction of the association is debatable, whether better dietary habits might lead to better sleeping patterns or the other way around. In fact, experimental studies demonstrated both ways of association: on one side, it has been demonstrated that a high-quality diet improved sleep duration; on the other, it has been shown that sleep deprivation may increase appetite for high-calorie foods [44].

The Mediterranean dietary pattern may assure an adequate nutritional profile, including high consumption of fruit, vegetable, fish, whole-grains, olive oil, and limited amounts of meat, dairy and alcohol [45]. Previous reports from the cohort investigated in this study showed a significant inverse relation between higher adherence to the Mediterranean diet and likelihood of being obese [46], hypertensive [47] or suffer from dyslipidemia [48]. However, no individual component of the Mediterranean diet has been shown to be responsible alone for such associations, while some evidence on consumption of certain classes of polyphenols (such as flavonoids, phenolic acids and phytoestrogens) may explain, at least in part, these previous findings [49,50]. Similar considerations have been drafted while examining the association between higher adherence to the Mediterranean diet and mental health, which in turn might be associated with improved sleep patterns [51,52]. Richness of the Mediterranean diet in bioactive compounds with beneficial effects, such as antioxidant or anti-inflammatory properties, may exert neuroprotection and reduce oxidative damage and cerebral ischemia [53]. In fact, impaired antioxidant defense responses, such as increased rate of oxidative processes in several organs, including heart, liver and brain, have been reported during sleep deprivation while increased neuro-inflammation has been postulated to contribute to poor sleep quality [54,55]. Further evidence also shows that sleep duration and quality may be mediated by C-reactive protein (CRP), γ-glutamyl transferase (GGT), carotenoids, uric acid, and some vitamins, including vitamin C and D [56,57]. The high content of the Mediterranean diet in polyunsaturated fatty acids (PUFA) and phytochemicals, such as polyphenols, have been demonstrated to have an impact on inflammatory biomarkers [58]. Cohort studies have shown an inverse association between dietary PUFA [59,60] and polyphenols with better mental health (i.e., depressive symptoms, cognitive impairment, etc.) [61–63]. A variety of neuroprotective activities have been described, including anti-amyloidogenic efficacy, neuroprotection via modulation of neural mediators, and modulation of different signaling pathways [64,65]. Moreover, environmental stimuli (including exercise, but also sleep and dietary patterns) have been linked to hippocampal neurogenesis, a phenomenon occurring also in human adults, that seems to be linked to a number of pathological conditions, including stress, anxiety and depression, and cognitive impairment [66]. The resulting benefits of high adherence to the Mediterranean diet on sleep, cognition, mood, and Alzheimer's disease may, thus, also depend on the enhancement of structural and functional brain plasticity mediated by components of this dietary pattern, such as PUFA and polyphenols [67,68].

In addition to the aforementioned potential mechanisms, in this study we also hypothesized that the association between adherence to the Mediterranean diet and sleep quality might somehow mediate the effects of obesity on sleep quality; this relation has been reported in previous papers [69], but rarely investigated in light of dietary factors associated with weight status. In a sub-analysis of the present study we found that adherence to the Mediterranean diet was significant in normal and overweight individuals, but was not evident in the obese. Prospective cohort studies showed evidence of a causal relation between short sleep duration and occurrence of obesity at later age [70]. The most studied mechanism relating sleep and body weight regards the balance between leptin and ghrelin, two hormones involved in food intake and energy balance which have been demonstrated to be altered following sleep disturbances [71]. Leptin is an adipocyte-derived hormone that suppresses hunger and stimulates energy expenditure while ghrelin is stomach-derived peptide that stimulates appetite and fat production. Some studies showed that short sleep and sleep deprivation may decrease circulating leptin and increase ghrelin levels [72], despite findings not being univocal [73,74]. Among other hormones potentially involved in the relation between sleep quality and body weight, some studies showed that sleep disturbances may increase morning cortisol levels, inhibit insulin sensitivity and growth hormone secretion [75,76]. The relation between poor sleep and obesity has been widely demonstrated, and also the other way around, where excess body weight may favor the occurrence of sleep apnea, which in turn causes scarce sleep quality [77]. Most important, recent evidence shows that obstructive sleep apnea may have an impact on the structure and function of blood vessels, adversely affecting cognition in addition to culminating in mortality and morbidity [78]. Hypoxia, hypertension, hypo-perfusion, endothelial dysfunction, inflammation, and oxidative stress noted in obstructive sleep apnea patients also occur in Alzheimer's disease patients, suggesting a pathological commonality that may relate both conditions [79]. In this context, higher adherence to a Mediterranean dietary pattern has been proven to provide advantages on metabolic profiles and long-term weight status maintenance [80,81]. Also in this regard, Mediterranean dietary polyphenols have been hypothesized to potentially play a role in weight management through a number of mechanisms, including activation of β-oxidation; a prebiotic effect for gut microbiota; induction of satiety; stimulation of energy expenditure by inducing thermogenesis in brown adipose tissue; modulation of adipose tissue inhibiting adipocyte differentiation; promotion of adipocyte apoptosis and increasing lipolysis [82,83]. Thus, it may be possible that the association between adherence to the Mediterranean diet and sleep quality retrieved in our study may, in fact, be mediated by a better weight status. This hypothesis will need further exploration in future studies.

The findings of this study should be considered in light of some limitations. First, the real direction of the associations retrieved cannot be identified through cross-section studies and reverse causation should be taken into account as potential explanation of the results presented. It is noteworthy to emphasize that even with a prospective study design, the possibility that sleep and dietary patterns are part of an overall healthier or unhealthier lifestyle pattern cannot be ruled out, and that only further research into mechanistic and experimental studies would clarify the nature of the association. Second, the use of self-reported FFQs and sleep quality tools may be affected by recall and social desirability biases. However, the tools used in this study are well-established instruments to investigate the research question proposed and methods are comparable to the existing literature. Third, given the variety of Mediterranean adherence scores used in the literature, results may not be directly comparable with studies using other instruments. However, the adherence score used in the present study is based on the summary of scientific literature providing evidence of association between the Mediterranean diet and health outcomes, suggesting the robustness of the instrument. Forth, despite controlling for occupational status, we were unable to test the role of financial allowance in the study participants, which might play a role in adherence to the Mediterranean diet and could be further investigated. Moreover, within the same category of occupational status we had no data for jobs that possibly required night shifts or had characteristics that might have influenced sleeping patterns. However, assuming a random distribution for such types of jobs (meaning not associated with adherence to the Mediterranean diet), this potential bias should be non-differential among exposure groups.

5. Conclusions

In conclusion, high adherence to a Mediterranean dietary pattern is associated with better sleep quality, either toward a direct effect on health or indirect effects through improvement of weight status. Further research should explore whether investigating sleep quality within the context of adherence to the Mediterranean diet might be part of an overall healthier lifestyle pattern, and should investigate the topic with a prospective and longitudinal study design. Future experimental studies are needed to test the impact of sleep quality on health and dietary intake allowing to investigate on causality and mechanisms. Finally, the potential mediating effect of weight status on the relation between Mediterranean diet and sleep quality requires further investigation.

Author Contributions: J.G. conceived the study, performed the analysis, interpreted the data and wrote the manuscript. R.F. and F.C. contributed to the drafting of the manuscript and provided expertise for the interpretation of

the results and clinical aspects. F.I.I.C. and S.C. critically revised the manuscript and provided expertise in clinical aspects. G.G. and F.G. provided the data and reviewed the draft, equally contributing to the paper. All authors read and approved the final version of manuscript.

Funding: This study was partially supported by a fund from the Italian Ministry of Health “Ricerca Corrente” (RC n. 2751594) (Drs. Ferri, Caraci and Cosentino).

Acknowledgments: J.G. is a PhD student in the International PhD Program in Neuroscience at the University of Catania.

Conflicts of Interest: The authors declare no conflict of interest.

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Godos J, Ferri R, Caraci F, Cosentino FII, Castellano S, Shivappa N, Hebert JR, Galvano F, Grosso G. Dietary Inflammatory Index and Sleep Quality in Southern Italian Adults. Nutrients. 2019 Jun 13;11(6). pii: E1324. doi: 10.3390/nu11061324.

CHAPTER 2

Dietary Inflammatory Index and Sleep Quality in Southern Italian Adults

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Received: 28 April 2019; Accepted: 8 June 2019; Published: 13 June 2019

Abstract: Background: Current evidence supports the central role of a subclinical, low-grade inflammation in a number of chronic illnesses and mental disorders; however, studies on sleep quality are scarce. The aim of this study was to test the association between the inflammatory potential of the diet and sleep quality in a cohort of Italian adults. Methods: A cross-sectional analysis of baseline data of the Mediterranean healthy Eating, Aging, and Lifestyle (MEAL) study was conducted on 1936 individuals recruited in the urban area of Catania during 2014–2015 through random sampling. A food frequency questionnaire and other validated instruments were used to calculate the dietary inflammatory index (DII®) and assess sleep quality (Pittsburg sleep quality index). Multivariable logistic regression analyses were performed to determine the association between exposure and outcome. Results: Individuals in the highest quartile of the DII were less likely to have adequate sleep quality (odds ratio (*OR*) = 0.49, 95% CI: 0.31, 0.78). Among individual domains of sleep quality, an association with the highest exposure category was found only for sleep latency (*OR* = 0.60, 95% CI: 0.39, 0.93). Conclusions: The inflammatory potential of the diet appears to be associated with sleep quality in adults. Interventions to improve diet quality might consider including a dietary component that aims to lower chronic systemic inflammation to prevent cognitive decline and improve sleep quality.

Keywords: sleep quality; cognitive decline; dementia; mental health; cohort; Italy; dietary inflammatory index; diet; inflammation; dietary patterns

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1. Introduction

Inflammation represents an important physiological defense mechanism that protects the human body from external insults. As long as the inflammatory response is properly regulated—in response to real insults and counteracted by negative feedback mechanisms—it remains an essential mechanism for the maintenance of body homeostasis [1]. However, current evidence supports the central role of a subclinical, low-grade systemic inflammation in a number of chronic illnesses [2]. Elevated circulating levels of markers of inflammation, including C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha, and interleukin (IL)-1 and IL-6, may lead to inflammation of the central nervous system, which has a role in the progression of chronic neurodegenerative disease [3]. Consequently, there is a growing body of research investigating whether such markers prompted by inflammation might also contribute to their pathogenesis [4]. Pathological alterations in sleeping behaviors and inflammatory disease states have common origins that involve an increased number of inflammatory cytokines [5]. Metabolic and immunological consequences of sleep deprivation seem to lead to antioxidant imbalance, including perturbations in catalase and glutathione peroxidase levels, as well as indexes of glutathione recycling activities, which are decreased after sleep deprivation, while recovery sleep normalizes antioxidant content and enhances enzymatic antioxidant activities [6]. A similar relation to circulating levels of inflammatory biomarkers has also been observed with affective and cognitive disorders [7]. Several biomarkers of inflammation and antioxidants, such as CRP, γ-glutamyl transferase (GGT), carotenoids, uric acid, vitamin C, and vitamin D, have been associated with sleep quality parameters and duration [8,9].

Inflammation has been hypothesized to be a link that mediates diet and chronic diseases [10]. There is consistent evidence suggesting that "Western-like" dietary patterns, characterized by high intake of processed, refined foods, tend to be positively associated with biomarkers of inflammation, predominantly CRP, while vegetable- and fruit-based or "healthy" patterns tend to be inversely associated [11]. Evidence on the relation between diet and low-grade inflammation has been further strengthened following comprehensive analyses of intervention trials showing that a healthy dietary pattern was associated with significant reductions in CRP [12]. Among the various investigated dietary patterns, the Mediterranean diet has been associated with lower concentrations of inflammatory biomarkers (including CRP and IL-6) [13].

The Dietary Inflammatory Index (DII®) is a literature-derived score that has been developed to evaluate the inflammatory potential of the diet and link diet to inflammation. It takes into account six inflammatory markers (i.e., CRP, IL-1beta, IL-4, IL-6, IL-10, and TNF-alpha) [14]. The DII has proven to be of value for its association with health status in the general population [15–17]. Along with 18 other construct validations that use circulating inflammatory biomarkers, it has been tested for validity in a population living in the Mediterranean area [18]. Recent studies showed a potential association between adherence to a Mediterranean diet and parameters of sleep quality [19-21]. However, no study focusing on the relationship between the DII and sleep has been published (though one study in Korea [22] did consider sleep when assessing the relationship between the DII and cognitive decline in older adults). Thus, the aim of this study was to test the association between DII scores and sleep quality in a cohort of Italian adults.

2. Materials and Methods

2.1. Study Population

The Mediterranean healthy Eating, Aging, and Lifestyles (MEAL) study is an observational study designed to explore the relation between nutritional and lifestyle behaviors that characterizes individuals living in the Mediterranean area. The results of a cross-sectional analysis of baseline data are presented in this manuscript. The details of the study protocol, with the rationale, design, and methods, have been described elsewhere [23]. Briefly, the cohort consisted of a random sample of 2044 men and women (age 18+ years) recruited in the urban area of Catania, one of the largest cities of the eastern cost of Sicily, southern Italy, during 2014–2015. All study procedures were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. Participants provided written informed consent, and the study protocol was approved by the ethics committee of the referent health authority.

2.2. Data Collection

Data regarding demographic (i.e., age, sex, educational level, and occupational level) and lifestyle characteristics (i.e., physical activity, smoking habits, and drinking habits) were collected. Educational level was categorized as: (i) low (primary/secondary), (ii) medium (high school), and (iii) high (university). Occupational level was classified as: (i) unemployed, (ii) low (unskilled workers), (iii) medium (partially skilled workers), and (iv) high (skilled workers). Physical activity level was assessed using the International Physical Activity Questionnaires (IPAQ) [24], which comprised a set of questionnaires (five domains) on time spent being physically active in the last 7 days that allow us to categorize physical activity as: (i) low, (ii) moderate, and (iii) high. Smoking status was classified as: (i) non-smoker, (ii) ex-smoker, and (iii) current smoker. Alcohol consumption was categorized as (i) none, (ii) moderate drinker (0.1–12 g/day), and (iii) regular drinker (>12 g/day). Anthropometric measurements were performed according to standardized methods [25]. Height of the participant, without shoes with the back square against the wall tape, eyes looking straight ahead, with a right-angle triangle resting on the scalp and against the wall, was measured by a health professional to the nearest 0.5 cm. Body mass index (BMI) was calculated from measured height and weight, and patients were categorized as under/normal weight (BMI <25 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2) [26].

2.3. Dietary Assessment

Dietary data were collected using a validated food frequency questionnaire (FFQ) consisting of 100 food and drink items representative of the diet during the last 6 months [27,28]. Participants were asked how often, on average, they had consumed foods and drinks included in the FFQ, with nine responses ranging from "never" to "4–5 times per day". Intake of food items characterized by seasonality referred to consumption during the period in which the food was available and then adjusted by its proportional intake over one year. After excluding data on 107 participants with unreliable dietary intakes (<1000 or >6000 kcal/d), data from a total of 1936 individuals were included in the analyses for the present study. Following the identification of the food intake, the energy content as well as the micro-nutrient intake was obtained using standard food composition tables of the Italian Research Center for Foods and Nutrition [29]. The process of the estimation of polyphenol intakes has been previously described in detail [30]. Briefly, data on the polyphenol content in foods were retrieved from the Phenol-Explorer database (www.phenol-explorer.eu) [31], using the most recent version of the database containing data on the effects of cooking and food processing on polyphenol contents in order to apply polyphenol-specific retention factors [32]. Micro-nutrient, macro-nutrient, and polyphenol intake were adjusted for total energy intake (kcal/day) using the residual method [33]. Finally, a Mediterranean diet adherence score was calculated based on a previously published methodology [34] using literature-derived weighted median servings of foods characterizing this dietary pattern (including olive oil, fruit, vegetables, cereals, legumes, fish, and moderate alcohol intake indicating higher adherence and meat and meat-based products, dairy products, and no/excessive alcohol consumption indicating lower adherence; the final score comprised nine food categories with a score ranging from 0 points (lowest adherence) to 18 points (highest adherence) [35].

2.4. DII Score

A complete description of the process of developing the DII has been published elsewhere [14,36]. Briefly, the dietary data of the sample were first linked to the world database that provided a robust estimate of a mean and SD for each parameter [14]. This was achieved by subtracting the "standard global mean" from the intake reported via the FFQ and dividing this value by the standard deviation (SD) to obtain "z" scores. To minimize the effect of "right skewing", these "z" scores were then converted to a centered proportion. The centered proportion for each food parameter for each individual was then multiplied by the respective food parameter effect score (inflammatory potential for each food parameter), which was derived from a literature review, to obtain a food-parameter-specific DII score for an individual. All of the food-parameter–specific DII scores were then summed to create the overall DII score for each participant in the study [14]. Finally, energy-adjusted DII (E-DII) scores were calculated using the density method, wherein all food parameters were converted to per 1000 kcal of nutrients and the same procedure was used to relate individual exposure data to the global energy-adjusted database. The DII was based on a total of 33 food parameters (energy, carbohydrate, protein, total fat, alcohol, fiber, cholesterol, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, omega 3, omega 6, vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, folic acid, iron, magnesium, zinc, selenium, anthocyanidins, flavan3ols, flavones, flavonols, flavonones, isoflavones, garlic, tea, and onion) that were available for the MEAL cohort. The E-DII score was based on 32 food parameters (all of the previous, except for energy).

2.5. Sleep Quality

The Pittsburgh sleep quality index (PSQI) [37] was used to assess participants' sleep quality and disturbances in the past six months. It consists of 19 items that are rated on a four-point scale (0–3) and grouped into seven components (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction). The item scores in each component were summed and converted to component scores ranging from 0 (better) to 3 (worse) based on guidelines. Total PSQI score was calculated as the summation of seven component scores ranging from 0 to 21, where a higher score indicates worse sleep. A score of <5 on total global PSQI score is indicative of adequate sleep quality.

2.6. Statistical Analysis

Categorical variables are presented as frequencies of occurrence and percentages, and continuous variables are presented as the mean and standard deviation (SD); differences between groups were tested using a Chi-squared test or a Student's *t*-test, respectively. The DII was analyzed both as a categorical (quartiles) or a continuous (1 SD increment) variable. The relation between the DII and sleep-related outcomes was tested using a simple univariable (unadjusted) and multivariable logistic regression analysis adjusted for baseline characteristics (age, sex, marital, educational, and occupational status, smoking and alcohol drinking habits, and physical activity level) comparing individuals grouped into quartiles or estimating the association by a 1 SD increment of the DII. Because previous studies suggested a potential role of the Mediterranean diet in sleep quality [19,20] as well as a previous analysis in the cohort [21], we also tested whether the association between DII and sleep quality was independent of adherence to this dietary pattern by performing an additional model that further adjusted for the Mediterranean diet adherence score. All reported *P* values were based on two-sided tests and compared to a significance level of 5%. The SPSS® 17

(SPSS Inc., Chicago, IL, USA) software was used for all of the statistical analyses.

3. Results

The distribution of background variables by quartiles of DII is shown in Table 1. There were no clear trends in the distribution of age, sex, weight, or health status across DII quartiles. However, a higher proportion of individuals in lower occupational status categories were found in the lower quartiles of DII, while those with medium–high status had significantly higher DII scores. Moreover, there was a higher proportion of regular alcohol drinkers in the lower quartiles of DII, while none–moderate drinkers had higher DII scores (Table 1).

Table 1. Baseline characteristics of the study sample according to Dietary Inflammatory Index (DII) quartiles.

	DII quartiles				*p*-value
	Q1	**Q2**	**Q3**	**Q4**	
Age groups, *n* (%)					<0.001
<30	95 (19.4)	85 (16.7)	81 (16.1)	89 (20.5)	
30–49	184 (37.6)	169 (33.1)	196 (39.0)	154 (35.4)	
50–69	160 (32.7)	190 (37.3)	166 (33.1)	109 (25.1)	
≥70	50 (10.2)	66 (12.9)	59 (11.8)	83 (19.1)	
Men, *n* (%)	174 (35.4)	235 (46.1)	214 (43.1)	181 (41.4)	0.006
Weight status, *n* (%)					0.01
BMI <25	240 (52.5)	197 (41.9)	202 (44.2)	212 (51.2)	
BMI 25–30	151 (33.0)	179 (38.1)	170 (37.2)	130 (31.4)	
BMI >30	66 (14.4)	94 (20.0)	85 (18.6)	72 (17.4)	
Smoking status, *n* (%)					0.93
Current	120 (24.4)	121 (23.7)	112 (22.5)	112 (25.6)	
Former	67 (13.6)	78 (15.3)	71 (14.3)	60 (13.7)	
Never	305 (62.0)	311 (61.0)	314 (63.2)	265 (60.6)	
Educational level, *n* (%)					0.26
Low	186 (37.8)	189 (37.1)	161 (32.4)	161 (36.8)	
Medium	189 (38.4)	190 (37.3)	192 (38.6)	149 (34.1)	
High	117 (23.8)	131 (25.7)	144 (29.0)	127 (29.1)	
Occupational level, *n* (%)					0.001
Unemployed	145 (34.8)	98 (22.4)	132 (30.8)	86 (22.9)	
Low	70 (16.8)	81 (18.5)	61 (14.3)	54 (14.4)	
Medium	94 (22.5)	127 (29.1)	108 (25.2)	111 (29.5)	
High	108 (25.9)	131 (30.0)	127 (29.7)	125 (33.2)	
Physical activity level, *n* (%)					0.15
Low	92 (21.1)	75 (17.0)	86 (19.1)	76 (18.9)	
Medium	206 (47.2)	209 (47.5)	223 (49.6)	218 (54.2)	
High	138 (31.7)	156 (35.5)	141 (31.3)	108 (26.9)	
Alcohol consumption, *n* (%)					<0.001
None	88 (17.9)	91 (17.8)	107 (21.5)	88 (20.1)	
Moderate (0.1–12 g/day)	252 (51.2)	312 (61.2)	332 (66.8)	310 (70.9)	
Regular (>12 g/day)	152 (30.9)	107 (21.0)	58 (11.7)	39 (8.9)	
Health status, *n* (%)					
Hypertension	220 (44.7)	279 (54.7)	254 (51.1)	223 (51.0)	0.02
Diabetes	34 (6.9)	49 (9.6)	44 (8.9)	19 (4.3)	0.01
Dyslipidemias	101 (20.5)	99 (19.4)	80 (16.1)	76 (17.4)	0.27
Cardiovascular disease	42 (8.7)	34 (7.0)	43 (8.8)	35 (8.1)	0.70
Cancer	24 (4.9)	16 (3.1)	15 (3.0)	23 (5.3)	0.17

The frequency of adequate overall sleep quality and its individual domains across quartiles of DII are shown in Table 2. A lower proportion of participants with adequate sleep quality was found among higher quartiles of DII. Among individual domains, a significantly higher rate of sleep disturbance and low self-rated sleep quality was found among participants with higher DII scores (Table 2).

Table 2. Overall sleep quality and sleep-related characteristics of the study participants by quartiles of Dietary Inflammatory Index (DII).

	DII quartiles				
	Q1	**Q2**	**Q3**	**Q4**	***p*-value**
Adequate sleep quality, *n* (%)	357 (72.6)	339 (66.5)	340 (68.4)	278 (63.6)	0.03
Sleep duration, *n* (%)					0.71
>7 h	296 (60.2)	316 (62.0)	292 (58.8)	260 (59.5)	
6–7 h	121 (24.6)	108 (21.2)	106 (21.3)	100 (22.9)	
5–6 h	49 (10.0)	58 (11.4)	71 (14.3)	52 (11.9)	
<5 h	26 (5.3)	28 (5.5)	28 (5.6)	25 (5.7)	
Sleep disturbance, *n* (%)					0.04
None	70 (14.2)	53 (10.4)	57 (11.5)	36 (8.2)	
Low	366 (74.4)	373 (73.1)	368 (74.0)	330 (75.5)	
Medium	56 (11.4)	84 (16.5)	72 (14.5)	71 (16.2)	
High	0	0	0	0	
Sleep latency, *n* (%)					0.17
Very short	227 (46.1)	240 (47.1)	221 (44.5)	170 (38.9)	
Short	157 (31.9)	152 (29.8)	173 (34.8)	147 (33.6)	
Medium	83 (16.9)	85 (16.7)	79 (15.9)	86 (19.7)	
Long	25 (5.1)	33 (6.5)	24 (4.8)	34 (7.8)	
Day dysfunction due to sleepiness, *n* (%)					0.30
None	300 (61.0)	273 (53.5)	273 (54.9)	234 (53.5)	

Low	163 (33.1)	196 (38.4)	181 (36.4)	159 (36.4)	
Medium	27 (5.5)	39 (7.6)	41 (8.2)	42 (9.6)	
High	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.5)	
Sleep efficiency, *n* (%)					0.27
High	360 (73.2)	365 (71.6)	342 (68.8)	303 (69.3)	
Medium	64 (13.0)	75 (14.7)	82 (16.5)	68 (15.6)	
Low	27 (5.5)	32 (6.3)	21 (4.2)	33 (7.6)	
Very low	41 (8.3)	38 (7.5)	52 (10.5)	33 (7.6)	
Self-rated sleep quality, *n* (%)					<0.05
Very low	16 (3.3)	16 (3.1)	13 (2.6)	21 (4.8)	
Low	57 (11.6)	91 (17.8)	70 (14.1)	61 (14.0)	
Medium	301 (61.2)	286 (56.1)	307 (61.8)	276 (63.2)	
High	118 (24.0)	117 (22.9)	107 (21.5)	79 (18.1)	
Need of medication to sleep, *n* (%)					0.44
Not during the past month	453 (92.1)	453 (88.8)	447 (89.9)	391 (89.5)	
Less than once a week	16 (3.3)	23 (4.5)	20 (4.0)	15 (3.4)	
Once or twice a week	5 (1.0)	13 (2.5)	16 (3.2)	13 (3.0)	
Three or more times a week	18 (3.7)	21 (4.1)	14 (2.8)	18 (4.1)	

Table 3 provides a direct comparison of mean DII scores between individuals with adequate/inadequate sleep quality features. Overall, the results reflected the previous findings, with average DII scores higher among individuals with inadequate sleep quality, self-rated sleep quality, and, in addition, long sleep latency and efficiency (Table 3).

Table 3. Mean scores (and standard deviation) of Dietary Inflammatory Index (DII) by outcome.

	DII, mean (SD)	***p*-value**
Sleep quality		<0.001
Inadequate	−0.67 (2.09)	
Adequate	−1.05 (2.10)	
Sleep duration		0.16
Inadequate	−0.85 (2.09)	
Adequate	−0.98 (2.10)	
Sleep disturbance		0.006
Inadequate	−0.88 (2.11)	
Adequate	−1.30 (1.96)	
Sleep latency		0.01
Inadequate	−0.82 (2.10)	
Adequate	−1.06 (2.10)	
Day dysfunction		0.09
Inadequate	−0.84 (2.08)	
Adequate	−1.00 (2.11)	
Sleep efficiency		0.01
Inadequate	−0.74 (2.06)	
Adequate	−1.00 (2.11)	
Need of medication to sleep		0.14
Inadequate	−0.72 (1.95)	
Adequate	−0.95 (2.11)	
Self-rated sleep quality		0.006
Inadequate	−0.86 (2.12)	
Adequate	−1.18 (2.00)	

The association of overall sleep quality and its individual domains with the DII is shown in Table 4. Individuals in the highest quartile of DII were less likely to have adequate sleep quality (odds ratio (*OR*) = 0.49, 95% CI: 0.31, 0.78); the association remained significant also when considering a 1-SD increment of the score (*OR* = 0.73, 95% CI: 0.61, 0.88). Among individual domains of sleep quality, an association with the highest exposure category was found only for sleep latency (*OR* = 0.60, 95% CI: 0.39, 0.93), while the linear association with a 1-SD increment of the score was significant for sleep duration (*OR* = 0.79, 95% CI: 0.66, 0.93; Table 4).

Table 4. Association between overall and individual domains of sleep quality † by quartiles of the DII.

	DII, *OR* (95% CI)				1-SD increment
	Q1	**Q2**	**Q3**	**Q4**	
Adequate sleep quality					
Model 1 ‡	1	0.67 (0.51, 0.88)	0.65 (0.49, 0.86)	0.57 (0.43, 0.75)	0.83 (0.75, 0.92)
Model 2 §	1	0.76 (0.54, 1.07)	0.79 (0.56, 1.11)	0.67 (0.47, 0.95)	0.86 (0.76, 0.97)
Model 3 ¶	1	0.67 (0.47, 0.96)	0.65 (0.44, 0.96)	0.49 (0.31, 0.78)	0.73 (0.61, 0.88)
Sleep duration					
Model 1 ‡	1	1.02 (0.79, 1.31)	0.84 (0.65, 1.08)	0.89 (0.68, 1.15)	0.93 (0.85, 1.03)
Model 2 §	1	1.19 (0.86, 1.64)	1.00 (0.73, 1.37)	1.00 (0.72, 1.38)	0.95 (0.85, 1.07)
Model 3 ¶	1	1.04 (0.75, 1.46)	0.77 (0.53, 1.12)	0.67 (0.43, 1.04)	0.79 (0.66, 0.93)
Sleep disturbance					
Model 1 ‡	1	0.66 (0.45, 0.96)	0.73 (0.50, 1.06)	0.52 (0.34, 0.80)	0.81 (0.69, 0.94)
Model 2 §	1	0.73 (0.46, 1.16)	0.76 (0.48, 1.20)	0.56 (0.34, 0.93)	0.82 (0.69, 0.98)
Model 3 ¶	1	0.73 (0.45, 1.19)	0.79 (0.46, 1.35)	0.62 (0.31, 1.21)	0.84 (0.65, 1.09)
Sleep latency					
Model 1 ‡	1	0.95 (0.74, 1.22)	0.83 (0.65, 1.07)	0.69 (0.53, 0.90)	0.89 (0.81, 0.97)
Model 2 §	1	1.00 (0.73, 1.36)	0.87 (0.64, 1.19)	0.73 (0.53, 1.01)	0.90 (0.80, 1.01)
Model 3 ¶	1	0.93 (0.67, 1.28)	0.77 (0.54, 1.10)	0.60 (0.39, 0.93)	0.85 (0.72, 1.00)
Day dysfunction					
Model 1 ‡	1	0.70 (0.55, 0.90)	0.73 (0.57, 0.94)	0.70 (0.54, 0.91)	0.92 (0.84, 1.01)
Model 2 §	1	0.67 (0.49, 0.92)	0.75 (0.54, 1.02)	0.66 (0.48, 0.91)	0.90 (0.80, 1.01)
Model 3 ¶	1	0.67 (0.48,	0.76 (0.53,	0.68 (0.44,	0.94 (0.79,

		0.94)	1.10)	1.06)	1.11)
Sleep efficiency					
Model 1 ‡	1	0.85 (0.64, 1.12)	0.68 (0.52, 0.90)	0.74 (0.55, 0.99)	0.88 (0.79, 0.97)
Model 2 §	1	0.91 (0.64, 1.29)	0.79 (0.56, 1.12)	0.87 (0.61, 1.23)	0.91 (0.80, 1.04)
Model 3 ¶	1	0.88 (0.61, 1.27)	0.75 (0.50, 1.11)	0.78 (0.48, 1.25)	0.85 (0.71, 1.02)
Need of medication to sleep					
Model 1 ‡	1	0.63 (0.41, 0.98)	0.67 (0.43, 1.05)	0.67 (0.43, 1.06)	0.89 (0.76, 1.04)
Model 2 §	1	0.72 (0.42, 1.24)	0.84 (0.48, 1.45)	0.92 (0.52, 1.63)	0.99 (0.81, 1.21)
Model 3 ¶	1	0.67 (0.38, 1.17)	0.76 (0.40, 1.44)	0.79 (0.37, 1.69)	0.92 (0.69, 1.22)
Self-rated sleep quality					
Model 1 ‡	1	0.92 (0.69, 1.22)	0.78 (0.58, 1.05)	0.65 (0.47, 0.89)	0.85 (0.76, 0.96)
Model 2 §	1	1.10 (0.76, 1.58)	0.99 (0.69, 1.44)	0.75 (0.50, 1.11)	0.90 (0.78, 1.03)
Model 3 ¶	1	1.18 (0.81, 1.72)	1.15 (0.75, 1.77)	0.97 (0.58, 1.64)	1.01 (0.83, 1.23)

† Higher scores indicate worse quality. ‡ Model 1 is unadjusted for any covariate. § Model 2 is adjusted for age (continuous), sex (male/female), body mass index (BMI, <25 kg/m2, 25–30 kg/m2, >30 kg/m2), physical activity (low/medium/high), educational status (low/medium/high), occupational status (unemployed/low/medium/high), smoking status (current/former/never), alcohol consumption (no/moderate/regular), health status (presence of hypertension, type-2 diabetes, dyslipidemias, cardiovascular disease, cancer), and total energy intake. ¶ Model 3 adjusted as in Model 2 + adherence to Mediterranean diet.

4. Discussion

In the present study, the relation between DII and sleep quality was investigated in a cohort of Italian adults. Individuals with higher DII scores were found to be significantly less likely to have adequate sleep quality. Among the various individual components of the sleep quality score, the strongest association was found for sleep latency. Interestingly, after adjusting for adherence to the Mediterranean diet, the association between DII and sleep became even stronger, suggesting that if both the DII and the Mediterranean diet act through a similar mechanism of action related to inflammation, the DII is a stronger predictor for the inflammatory potential of the diet. To our knowledge, this is the first study to focus on the relation between the inflammatory potential of diet and sleep quality parameters.

Existing studies on the role of nutrition in sleep quality by a mediating effect of inflammatory biomarkers are scarce. A study conducted on about 1500 community-dwelling middle-aged men reported that an inverse association between plant-sourced dietary pattern (characterized by beta-carotene, vitamin A, lutein, and zeaxanthin) and CRP was stronger in participants with severe sleep apnoea [38]. In a study exploring the association of sleep with metabolic pathways and metabolites, researchers have found that several metabolites that have previously been linked to inflammation and oxidative stress, including erythrulose (advanced glycation end-product) (positive association) and several γ-glutamyl pathway metabolites, including 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF, fatty acid, dicarboxylate), isovalerate (valine, leucine, and isoleucine and fatty acid metabolism), and inflammation associated complement component 3 peptide (HWESASXX) (inverse association) were associated with sleep parameters (i.e., duration) [39]. Data on about 2000 individuals from the National Health and Nutrition Examination Survey (NHANES) revealed that both healthy eating and adequate sleep were the two health behavior pairs associated with lower levels of inflammation [40]. More in-depth studies conducted on the same cohort showed that adequate sleep quality was associated with optimal inflammation, oxidative stress, and antioxidant level, while selected sleep quality–cardio–metabolic health relationships were moderately mediated by C-reactive protein (CPR) and vitamins A and C; additionally, in women only, the indirect effects were moderate-to-large for CRP, GGT, carotenoids, uric acid, and vitamin C [8]. Specifically, moderate-to-large indirect mediation by GGT, carotenoids, uric acid, and vitamin D was found for sleep duration to waist circumference and systolic blood pressure relationships, whereas vitamin C was a moderate mediator of the sleep duration to diastolic blood pressure relationship [9]. These results suggest that inflammation may be a key mediating effect between sleep-related disorders and other conditions known to be related to a subclinical, low-grade inflammatory status. Chronic alteration of sleep quality has been related to mental health impairment and increased risk of cognitive disorders, including stress, depression, dementia, and Alzheimer's disease [41]. Diet has been studied over the last few decades for its potential role in affecting mental health. A number of comprehensive reviews of the literature have been performed to investigate the role of diet in affective and cognitive disorders that may be related to sleep impairment. A meta-analysis showed that a high-quality diet, regardless of type (i.e., healthy/prudent or

Mediterranean) together with a relatively low dietary inflammatory index was associated with a lower risk of depressive symptoms [42]. Similarly, another meta-analysis investigating a posteriori derived dietary patterns showed that a diet characterized by a high intakes of fruit, vegetables, whole grain, fish, olive oil, low-fat dairy, and antioxidants and low intakes of animal-derived foods was apparently associated with a decreased risk of depression; in contrast, a dietary pattern characterized by a high consumption of red and/or processed meat, refined grains, sweets, high-fat dairy products, butter, potatoes, and high-fat gravy, and low intakes of fruits and vegetables was associated with an increased risk of depression [43]. There also is evidence that a pro-inflammatory diet, as indicated by a higher DII score, may be associated with an increased risk of having depressive symptoms [44]. Regarding cognitive disorders, a systematic review exploring their relation with various dietary patterns showed that the Mediterranean diet had the strongest evidence supporting protection against cognitive decline among older adults. However, studies on the Dietary Approach to Stop Hypertension (DASH) diet, the Mediterranean-DASH diet, the Intervention for Neurodegenerative Delay (MIND) diet, the anti-inflammatory diet and the healthy diet recommended by guidelines via the dietary index, and prudent healthy diets generated via statistical approaches also provided promising results [45]. Moreover, previous studies specifically investigating the inflammatory potential of the diet showed that pro-inflammatory dietary patterns (also identified by higher DII scores) were associated with higher concentrations of inflammatory markers and accelerated cognitive decline at older ages [46,47].

The mechanisms through which diet may influence mental health features include effects on inflammation and oxidative stress, as well as a direct effect through the gut–brain axis. The relation between the DII and mental health may depend, at least in part, on the underlying potential effect of specific foods and compounds on influencing inflammatory pathways. In fact, several dietary factors have been hypothesized to play a role in systemic inflammation [48]. Plant-derived foods are important sources of antioxidants, including vitamins and polyphenols, which have been shown to contribute to inflammatory response and may exert neuroprotective effects and reduce oxidative damage [49]. Healthy fats, such as mono- and certain poly-unsaturated fatty acids, have been shown to play a significant role in neuroinflammation leading to a lower risk of affective disorders and could improve inflammation-associated depressive symptoms [50]. In contrast, food sources of refined carbohydrates may negatively affect dietary glycemic load and index, which have been associated with an acute inflammatory response [51]. Similarly, consumption of meat products has been associated with production of inflammation-provoking antibodies and an increase in pro-inflammatory response [52].

Besides its direct metabolic effects and immunologic responses related to nutritional factors, diet is known to influence the gut microbiota, which may play a role in chronic and low-grade activation of the inflammatory system's spread from peripheral tissue to the brain [53]. In fact, there is a large body of experimental and clinical studies suggesting a mechanistic link between gut-derived inflammatory response and neurodegeneration, potentially contributing to the pathogenesis of affective and cognitive disorders [54]. This inflammatory status could be triggered by changes in the gut microbiota's composition and dysbiosis due to dietary habits, i.e., consumption of pro-inflammatory diets, high in fat and sugar, in contrast to high fiber and whole grains, which would lead to an anti-inflammatory response [55,56]. The mechanisms involved in the process have yet to be fully elucidated, but they may include the modulation of plasma levels of lipopolysaccharide, and the inflammasome, type I interferon, and NF-KB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathways [57].

The present study has some limitations that should be kept in mind when considering its results. First, the cross-sectional design does not allow for considering temporality in judging whether a causal relation exists; rather, it provides evidence of an association with no clear cause–effect identification. Thus, reverse-causation should be taken into account; namely, we are not able to determine whether the inflammatory potential of the diet affects sleep quality or sleep features lead to unhealthy dietary habits. Second, the structured assessment methods that were used to assess dietary habits, such as the FFQ, are known to be associated with recall bias [58,59]. However, no ideal method to collect dietary data exists and the FFQ is widely used in nutritional epidemiology.

5. Conclusions

In conclusion, these findings confirm our original hypothesis that the inflammatory potential of the diet is associated with sleep quality in adults. Future studies with prospective designs with the potential to provide stronger data for causal inference should be designed and implemented. Interventions to improve diet quality might consider including a dietary component that aims to lower chronic systemic inflammation to prevent cognitive decline and improve sleep quality.

Author Contributions: J.G. conceived the study, performed the analysis, interpreted the data, and wrote the manuscript. R.F. and F.C. contributed to the drafting of the manuscript and provided expertise for the interpretation of the results and clinical aspects. F.I.I.C. and S.C. critically revised the manuscript and provided expertise in clinical aspects. N.S. and J.R.H. provided insights on the methodology, performed analysis, and reviewed the draft. G.G. and F.G. provided the data and reviewed the draft, equally contributing to the paper. All authors read and approved the final version of manuscript.

Funding: This study was partially supported by a fund from the Italian Ministry of Health “Ricerca Corrente” (RC n. 2751594) (Drs. Ferri, Caraci, and Cosentino).

Acknowledgments: J.G. is a PhD student in the International PhD Program in Neuroscience at the University of Catania.

Conflicts of Interest: The authors declare no conflicts of interest.

Disclosure: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

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GENERAL DISCUSSION

Role of nutritional components on the brain: micro- and macro-nutrients

Based on the specialist function, various types of cells may have different requirements in terms of nutrients. Taking into account the blood-brain barrier filtering the absorption of molecules and compounds, several nutritional compounds play a role in brain health.

Among macronutrients, a large body of evidence has been provided for the role of omega-3 fatty acids for brain health: docosahexaenoic acid (DHA) represents one of the most important structural components of neuron membranes responsible for their stability and transmission of serotonin, norepinephrine and dopamine; eicosapentaenoic acid (EPA) is capable of modulating both metabolic and immune process, which may reduce pro-inflammatory cytokines, such as arachidonic acid (AA, an n-6 PUFA) level on cell membrane and prostaglandin E2 (PGE2) synthesis [23]. Dietary omega-3 have been suggested to influence brain health through several potential mechanisms, including the neuroendocrine modulation of the serotoninergic and dopaminergic transmission and anti-inflammatory action [24].

Protein and amino acid intake can positively influence sleep quality and duration participating to elaborate neurotransmitters and neuromodulators [25]. Among the most studied, tryptophan (an essential plant-derived amino acid) is of major interest because acts as an upstream precursor to bioactive metabolites related to sleep, including serotonin and melatonin [26]. Glycine, a non-essential amino acid, may exert a positive action toward sleep quality by reducing the core body temperature exerting excitatory and inhibitory role on neurotransmission via N-methyl-D-aspartate type glutamate receptors and glycine receptors, respectively [27]. L-ornithine, another non-essential, non-protein amino acid, may play a direct role in the central nervous system relieving stress and improving sleep and fatigue symptoms through reducing stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis accompanied by reduction in the serum corticosterone concentration and attenuating the stress response mediated by the GABA receptor [28].

Carbohydrates are needed as glucose is the main source of energy in the brain, while depressive and other mood disturbances may lead to an excessive consumption ("carbohydrate craving") due to enhancement in brain serotonin synthesis [29]. Some studies pointed out that different type of carbohydrates may play different role specifically toward sleep quality: in fact, high-glycemic index carbohydrates stimulate glucose entry into the blood and facilitates a greater insulin response, which mediates the uptake of large neutral amino acid into muscle, but not tryptophan that is largely bound to plasma albumin, leading ultimately to higher availability for serotonin synthesis [30]. However, excessive chronic consumption of added simple sugars have been shown to be associated with cognitive impairments, especially worsened hippocampal memory function; this relation might be mediated by increased hippocampal inflammation, which is especially pronounced in the high sugar/low fat condition [31]. In contrast, complex carbohydrates not digestible by human enzymes and broken down by the intestinal flora leading to production of short chain fatty acids (SCFAs) as a by-product of their fermentation; SCFAs (including acetate, propionate, and butyrate) have shown anti-inflammatory effects that can be transmitted also to the brain via pathways involving direct central nervous system signaling (see paragraph *Gut-Brain axis*) and the immune system activation (see paragraph *Inflammation*) [32].

Among micronutrients, vitamins B-group may modulate cognitive performance, preserve memory during aging, improve cerebral and cognitive functions in the elderly; vitamin D may be involved in the prevention of neurodegenerative disorders; alpha-tocopherol (a vitamin E component) is involved in nervous membranes protection [33]. Among minerals, manganese, zinc and copper participate in enzymatic mechanisms protecting against oxidative stress; iron play a role for oxygenation, energy production, and neurotransmitters and myelin synthesis in the cerebral parenchyma; and calcium, potassium and magnesium modulate sleep through proper functioning of ion channels [34].

Feeding time, circadian rhythm and hormonal homeostasis

The circadian cycle regulates and coordinates many biological processes, such as the sleep-wake cycle, hormone secretion, glucose homeostasis and thermogenesis. The periodicity of behavioural and metabolic processes is determined by circadian rhythms that are 24-hour cycles [35]. Several environmental and lifestyle factors have been proven to be stimuli for the circadian cycle, including hormones, physical activity, nutrients and their patterns, feeding and fasting state, sleep-wake state and temperature [36]. As the effect of circadian rhythm on metabolic processes and energy balance is bidirectional, any detrimental effects of the stimuli may cause energy imbalance and thus lead to higher risk of age-related diseases.

The fasting-refeeding physiology bases on the 24-hour cycle capacity to acquire food when it is available and to store and utilize these resources during the rest of the day without compromising fitness and vitality [37]. According to recent evidence, the fasting period is believed to serve as a time for repair and renewal of the organism, as the theory of the physiology of fasting states that certain biochemical processes are triggered once stored resources are being utilized and not during the feeding period [19]. One of the possible mechanisms underlying the relationship between circadian rhythm, sleep and metabolism is adiponectin, a hormone involved in glucose metabolism. As it appears, the relationship between adiponectin and the circadian system is bidirectional and its expression has been proven to be circadian periodic [38]. Adiponectin levels increase significantly in response to intermittent fasting, and higher levels of adiponectin has been inversely associated with risk of cardiovascular diseases [38]; interestingly, recent data suggest that sleep restriction may decrease levels of adiponectin in healthy individuals and thus contribute to the risk of cardiovascular diseases [39]. Much of the attention has been also payed to the Brain-Derived Neurotrophic Factor (BDNF), which is a fundamental neurotrophin regulating brain functions as neurotransmitter modulator, modulating neuronal survival and growth, and participating in neuronal plasticity [40]. Additionally, it has been show to exert evident role in glucose and energy metabolism since receptors for both BDNF and insulin are coupled to PI3-kinase/Akt and MAP kinase intracellular signaling pathways [40]. Experimental studies have determined that intermittent fasting increases BDNF expression in several regions of the brain, and BDNF at least in part mediates intermittent fasting-induced neurogenesis, synaptic plasticity and neuronal resistance to injury and disease. It may also mediate behavioural and metabolic responses to fasting including regulation of appetite, peripheral glucose metabolism and autonomic control of the cardiovascular and gastrointestinal systems [41]. A decreased serum levels of BDNF has been associated with insomnia and sleep deprivation [42], and it has been demonstrated that subjects suffering from current symptoms of insomnia exhibited significantly decreased serum BDNF levels compared with sleep-healthy controls [40]. Finally, significant fluctuations of gut microbiota during the day-night shift may result in time-of-day-specific taxonomic configurations related not only to rhythmic food intake and dietary structure but also to the biological clock, suggesting an interaction between microorganisms and circadian genes as well as emotion and physiological stress [43].

Gut-Brain axis

In healthy adults, the composition of the intestinal microbiota is generally stable over time, with the bacterial phyla Firmicutes (including *Lactobacillus*, *Clostridium*, and *Enterococcus* genus) and Bacteroidetes (i.e., *Bacteroides* genus) representing the majority of the intestinal flora [44], while facultative anaerobes (*E. coli*), pro-inflammatory *Ruminococcus*, or nonbacterial microbes leading to pathogenic conditions when excessively represented [45]. The diversity and stability of the microbiota are important indices for the overall health of an individual [46]. Moreover, type, quality, and origin of food shape the gut microbiota profile and affect its composition and function [47]. Higher intake of fiber [48], pre- and probiotics [49] have been shown to modulate the gut microbiota. Healthy dietary patterns, such as the Mediterranean diets and other plant-rich diets have been related to increased diversity of the microbiota [50]. Albeit rather preliminary, some studies have shown a possible correlation between gut microbiota composition (i.e., a modification in the *Firmicutes*/*Bacteroidetes*/*Clostridium* ratio) and depressive state and chronic stress, which may be connected to sleep as well [51].

Current research is emphasizing on the interexchange of signals influenced by the gut microbiota that are detected and transduced in information from the gut to the nervous system involving neural, endocrine, and inflammatory mechanisms [52]. Gut microbiota has been shown to directly affect neurotransmitter metabolism with implications for enteric and central nervous system function through production of molecules, such as SCFAs, secondary bile acids, and tryptophan metabolites [53]. The signal can be propagated by interaction with enteroendocrine cells (EECs) and enterochromaffins cells (ECCs), which are able to induce central responses (i.e., by controlling serotonin release) via long-distance neural signaling by vagal or afferent nerve fibers that extend into intestinal villi [54]. The intestinal flora plays a role in gut peptides modulation, which in turn are part of the complex pathway characterizing the gut-brain axis [55]. The neuropeptide Y, which is among the most abundant peptide in the brain (including the nucleus of the solitary tract, hypothalamus, and amygdala) and highly regulated by peripheral signaling, is able to regulate the release of GABA [56]. Another mechanism may rely on glucagon-like peptide-1, an incretin hormone, which is involved in the modulation of the HPA axis and overall response to stress as well as playing a role in lowering postprandial blood glucose via augmentation of glucose-dependent insulin release and inhibition of glucagon secretion [57]. Cholecystokinin (CKK), a peptide able to control gastric emptying, gallbladder contraction, pancreatic enzyme release, and suppression of appetite, while at central nervous system level it has been demonstrated to play a role on anxiety-like behavior through the activation of the CCK2 receptors in limbic regions [58]. Serum ghrelin, which is known for its adipogenic effects and for playing a role in response to stress (I.e., triggering motivation for rewards), has been shown to be associated with modification of certain gut bacteria strains, such as negatively correlated with the commensal *Bifidobacterium* and *Lactobacillus* strains, and directly with *Bacteroides*/*Prevotella* species [59]. Corticotropin-releasing factor (CRF) plays a key role in response to stress mediating the neural control of adrenocorticotropic hormone (ACTH) release from pituitary corticotrophs, which in turn regulate acutely cortisol secretion but may lead to the development of stress-related disorders (i.e., anxiety and depression) when exposed to chronic stress [60]. The CRF system also influence some functions within the gastrointestinal system, including gut motility and permeability [61]. Interestingly, animal studies showed that increased CRF may be associated with alteration in the intestinal microbial community (i.e., reduction in Lactobacillus), as well as an opposite relation, such as alteration of the CRF signaling (i.e., CRF-mediated activation of the HPA axis) following changes in the gut microbiota [62].

Among indirect mechanisms, altered intestinal flora ("*dysbiosis*") may lead to increased permeability of the intestinal mucosa ("*leaky gut*"); as a result, bacterial components, such as lipopolysaccharides (LPS) from the bacterial cell wall, bind on circulating macrophages and monocytes, which in turn stimulate an inflammatory response with rise in circulating pro-inflammatory cytokines [63]. SCFAs may exert anti-inflammatory action by binding to G-protein receptors found in multiple cells, including nerve fibers, EECs, glial cells in the brain, and adipocytes, which suppress a neuroinflammatory response, i.e., against the LPS inflammatory responses in microglia [64]. Moreover, there is evidence of a direct anti-inflammatory action through promotion of microglial activation [65]. Furthermore, gut neurotransmitters, such as serotonin, has been shown to exert both pro-inflammatory and anti-inflammatory functions, thus playing a role in the modulation of immune and inflammatory responses [66].

Inflammation and oxidative stress

Low-grade inflammation, characterized by the presence of pro-inflammatory cytokines in the blood stream while occurring no clinical symptoms, and oxidative stress parameters and antioxidant capacity have been reported to potentially play a role in several non-communicable diseases, including mental disorders [67]. Concerning sleep, there is a growing body of research investigating the possible cross-talk between pathological alterations in sleep patterns and inflammation-related diseases that involve increased inflammatory cytokines release [68]. Cytokines are soluble intercellular signaling molecules that are involved in in the pathophysiology of several mental disorders (i.e., anxiety and depression) through affecting neurotransmitter synthesis, release and reuptake [69].

Up to date, several mechanisms that underline sleep-inflammation cross-talk have been hypothesized, implicating dysregulation of inflammatory balance, partially caused by the activation microglia in central nervous system [70], in alterations in neurotransmitters, intracellular signaling, gene transcription, reduced synaptic plasticity and hippocampal neurogenesis, and epigenetic changes that in turn can contribute to short-term and long-lasting imbalances of neuronal function and behavior [71]. Recent research demonstrated that there is a bidirectional link between sleep and inflammation and oxidative stress. It has been showed that sleep disturbances and extreme long sleep duration may be associated with higher levels of CRP and IL-6, while short sleep duration only with IL-6 [72]. It has been demonstrated that individuals with sleep disorders are prone to increased oxidative damage and impaired antioxidant defense, and that the magnitude of changes is associated with severeness of disorders [73]. Healthy and unhealthy dietary patterns have been shown to affect inflammatory biomarkers, which in turn may have an effect on neuroinflammation. In fact, several dietary factors have been hypothesized to influence systemic inflammation, mainly through pro- or anti-inflammatory cytokine release and regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway [74]. Plant-based foods are key sources of antioxidant vitamins and polyphenols, which have been shown to exert neuroprotective effects through regulation of inflammatory and oxidative response damage [75]. Similarly, healthy fats, such as mono and certain poly-unsaturated fatty acids, like omega-3, exert anti-inflammatory effects improving cognitive functions [76]. On the contrary, processed foods and highly caloric foods have been shown to pro-inflammatory cytokine release and therefore worsen inflammatory state. In example, food sources of refined carbohydrates may negatively affect dietary glycemic index and load, which in turn may induce acute inflammatory response [77]. Similarly, consumption of processed meat products, has been associated with production of biomarkers of inflammation [78].

CONCLUSIONS

There is currently insufficient evidence available to conclude whether it is possible to modulate sleep quality through interventions on dietary habits nor on individual components of the diet. However, the findings are promising and an association between dietary factors and sleep quality has been demonstrated. It is important to better understand the potential mechanisms relating nutrition with brain health that may lead to increased sleep quality. Future research should provide evidence from large cohort studies to individualize potential candidates among dietary patterns, individual foods or molecules, as well as time-related eating habits, while clinical intervention studies could confirm the retrieved associations. Studies conducted in the laboratory setting could focus on mechanisms. Finally, interventions on the gut microbiota may be a useful tool to explore the role of the gut–brain axis in sleep quality and disorders.

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