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The effects of Time Restricted Feeding on mental health and cognitive status

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PhD Thesis

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LIST OF ABBREVIATIONS

5-HT (5-Hydroxytryptamine)
ACTH (Adrenocorticotropic Hormone)
AD (Alzheimer's disease)
ADF (Alternate-day fasting)
BDNF (Brain-Derived Neurotrophic Factor)
CK1 (Casein kinase 1)
CKK (Cholecystokinin)
CRF (Corticotropin-Releasing Factor)
CRP (C-Reactive Protein)
DALYs (Disability-Adjusted Life-Years)
DHA (Docosahexaenoic Acid)
ECCs (Enterochromaffins Cells)
EECs (Enteroendocrine Cells)
EPA (Eicosapentaenoic Acid)
ERKs 1-2 (extracellular signal regulated kinases 1 e 2)
FTW (Feeding Time Window)
GABA (Gamma-Aminobutyric Acid)
HD (Huntington's disease)
HPA (Hypothalamic-Pituitary-Adrenal)
IF (Intermittent Fasting)
LC3A (Autophagy marker Light Chain 3)
LPS (Lipopolysaccharide)
MAP-kinase (Mitogen-Activated Protein kinase)
NF-κB (Nuclear Factor Kappa-light-chain-enhancer of activated B cells)
NO (Nitric Oxide)
PD (Parkinson's disease)
PGC1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha)
PGC1α (Peroxisome proliferator-activated receptor γ coactivator 1α)
PGE2 (Prostaglandin E2)
PI3-kinase (Phosphatidylinositol 3-kinase)
ROS (reactive oxygen species)
SIRT1 (Sirtuin 1)
TNFα (Tumor necrosis factor α)
TRE (Time Restricted Eating)

TRF (Time Restricted Feeding)
WDF (Whole-day fasting)
YLDs (Years Lived with Disability)

ABSTRACT

In the last decades society has undergone a profound change and it is estimated that life expectancy at birth in Europe has risen by more than 10 years from 1960 to 2010. However, this high increase in life expectancy was not adequately balanced by an improvement in the quality of life. In fact, higher life expectancy led also to an increase in the prevalence of chronic diseases related to aging, such as cognitive impairment, dementia and Alzheimer's disease. Moreover, it is estimated that the global population suffering from depression is about 300 million people and that anxiety disorders affect more than 260 million people worldwide. Equally alarming is the increase in sleep disturbances which is a disorder itself and can be a risk factor for the onset of other mental illnesses.

It is challenging to find the only trigger behind the onset of mental illness because there are largely multifactorial etiologies, involving complex interactions between genetic and environmental factors. Among environmental factors, lifestyle and nutrition seem to play a role of primary importance. Many studies have indicated that high adherence to western-like diets characterized by high calorie and ultra-refined foods intake often accompanied by underactivity increases the risk of depression and anxiety. Conversely, recent scientific evidence demonstrated the beneficial effect of omega-3 rich fish and plant based dietary patterns toward mental health. Not only the specific foods or dietary patterns can have an effect; also intermittent fasting has emerged as an innovative strategy to prevent and treat mental health disease, sleep disturbances and cognitive impairment but the data available are still scarce. Among all types of intermittent fasting regimens, time restricted feeding (TRF) protocol appears to be the most promising because it allows to induce benefits of a total fasting without reducing global calories and nutrients intake and just modulating temporal feeding\fasting window during the day.

The aim of this project was to investigate the association between time feeding period and mental and cognitive health in a cohort of southern Italian individuals. Data from nearly 2000 adults living in Sicily have been collected. A validated food frequency questionnaire was used to assess food and nutrient intake; time of usual meal was asked to calculate the window of time between daily meals. Cognitive health was evaluated using the Short Portable Mental Status Questionnaire. Mental health outcomes included perceived stress, depressive

symptoms, and sleep quality assessed through validated instruments. Multivariate logistic regressions were performed to determine the association between exposure and outcome.

The studies showed that individuals having a feeding time window of 10 hours (FTW-10) or less were less likely to have impaired cognitive health; the association was significant also for those individuals having breakfast. No association was found between FTW-10 and overall mental health in the whole sample, despite individuals older than 70 years old undergoing a FTW-10 were less likely to have mental health distress than others with no restricted time feeding.

In conclusions, having a shorter feeding time window might exert a beneficial effect toward brain mechanisms, both related to mental and cognitive health. However, results are not univocal and future studies are needed to better understand the potential mechanisms underlying such associations.

GENERAL INTRODUCTION

In the last decades, society has undergone a profound change due to better health care and hygiene practices, greater food availability, improved medical treatments and reduced child mortality.

All these changes have led to an increase in life expectancy. It is estimated that life expectancy at birth in Europe has risen by more than 10 years from 1960 to 2010 and it is thought that the new generations can already aim to live one hundred years (García Candil et al. 2019). However, the higher life expectancy led also to an increase in the prevalence of chronic conditions related to aging such as cognitive impairment, dementia and Alzheimer's Disease. In fact, this dramatic increase in life expectancy was not adequately balanced by an increase in the quality of life both for the elderly and for the general population. It is estimated that the global population suffering from depression is about 300 million people and that anxiety disorders affect more than 260 million people (4.4% and 3.6% of the global population, respectively) (Friedrich 2017). Mental disorders account 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 (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators 2018). Equally alarming is the increase in sleep disturbances which is a disorder itself and can be a risk factor for the onset of other mental illness (Friedrich 2017).

It is challenging to find a single trigger behind the onset of mental illness because there it is dependent on multifactorial etiologies, involving complex interactions between genetic and environmental factors (Uher & Zwicker 2017). Among environmental factors, lifestyle and nutrition seem to play a role of primary importance, as a transition from adherence to traditional plant-based dietary patterns (i.e. Mediterranean diet) to western-like dietary patterns accompanied by reduced physical activity has been observed. Many studies have indicated that higher adherence to western diet characterized by high calorie density foods (refined grains, sugar, cooking oils, corn syrup, and processed foods) increases the risk of depression and anxiety (Jacka et al. 2010) (Sánchez-Villegas et al. 2011; Sánchez-Villegas et al. 2012; Psaltopoulou et al. 2013; Lai et al. 2014).

Conversely, recent scientific evidence demonstrated the beneficial effect of omega 3 rich fish and plant based foods as fruits, vegetables, whole grains and legumes on mental health (Sánchez-Villegas et al. 2009; Akbaraly et al. 2009; Godos et al. 2020).

Not only the specific foods or dietary patterns can have an effect; also Intermittent Fasting (IF) has emerged as an innovative strategy to prevent and treat mental health disease, sleep disorders and cognitive impairment (Michalsen et al. 2003; Varady & Hellerstein 2007; Longo & Mattson 2014; Almeneessier & BaHammam 2018).

The term Intermittent fasting is a general concept because in the scientific literature there are numerous protocols of fasting regimens depending on the intensity of food\drink restriction, the frequency or the duration of fasting time (Tinsley & La Bounty 2015). Among all types of intermittent fasting regimens, Time Restricted Feeding (TRF) protocol appears to be the most promising and interesting in the field of neurosciences because it allows to induce benefits of a total fasting without reducing global calories and nutrients intake through modulating temporal feeding\fasting window during the day (Hatori et al. 2012).

The concept of TRF arose within the context of circadian rhythms. According to Longo and Mattson (Longo & Mattson 2014), TRF modifies brain neurochemistry and neuronal network activity in ways that optimize brain function and peripheral energy metabolism. In this scenario the recently increased focus on the role of diet and dietary patterns on mental health has given birth to a new and fascinating field of psychiatry called "nutrition psychiatry", which focuses on finding the relation between dietary factors, eating habits and mental disorders (Logan & Jacka 2014). *Figure 1* summarizes the complex interrelationship between nutrition, sleep disorders and cognition.

Unfortunately to date, most of the studies have been conducted in laboratory settings and studies on humans, even though observational, are limited.

This project aims to provide an overview of the main effects of intermittent fasting, especially of time restricted feeding regimens, on mental health and cognitive function in a cohort of adults living in the Mediterranean area.

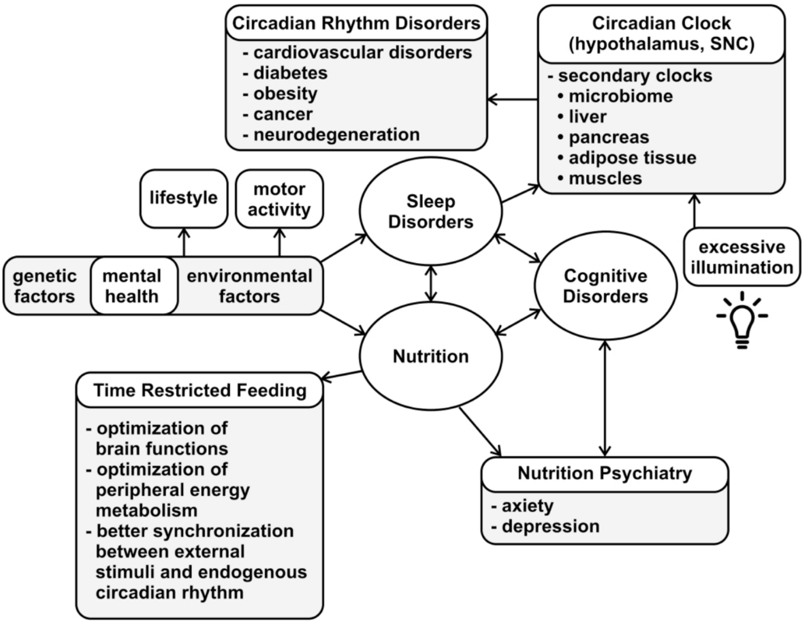

Figure 1. Schematic summary of the complex interrelationship between nutrition, sleep disorders and cognition.

CHAPTER 1

Association between Time Restricted Feeding and cognitive status in older italian adults

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ABSTRACT

Background
Due to the increased life expectancy, the prevalence of aging-related health conditions, such as cognitive impairment, dementia and Alzheimer's disease is increasing. Among the modifiable risk factors, dietary factors have proved to be of primary importance in preserving and improving mental health and cognitive status in older adults, possibly through the modulation of adult neurogenesis, neuronal plasticity and brain signaling. Feeding/fasting timing manipulation has emerged as an innovative strategy to counteract and treat cognitive decline. The aim of this study was to investigate the association between the timing of the feeding period and cognitive status in a cross-sectional cohort of adults living in the Mediterranean area.

Methods
Demographic and dietary characteristics of 883 adults living in Southern Italy (Sicily) were analyzed. Food frequency questionnaires were used to calculate the time window between the first and the last meal of an average day. Participants

with an eating time window duration of more than 10 h were then identified, as well as those with eating time restricted to less than 10 h (TRF).

Results

After adjusting for potential confounding factors, individuals adherent to TRF were less likely to have cognitive impairment, compared to those with no eating time restrictions [odds ratio (OR) = 0.28; 95% confidence intervals (CI): 0.07–0.90]; a similar association was found for individuals having breakfast (OR = 0.37, 95% CI: 0.16–0.89), but not for those having dinner.

Conclusions

The results of this study reveal that time restricted eating may be positively associated with cognitive status, and thus exert plausible effects on brain health

Keywords: time restricted feeding; intermittent fasting; chrononutrition; cognitive; brain diseases; brain; aging; risk factor; cohort; Mediterranean diet

Introduction

Due to the increased life expectancy, aging-related health conditions are becoming a relevant socio-economic burden for all populations worldwide [1]. In fact, in recent years a significant rise in the prevalence of neurodegenerative diseases, including a progressive global deterioration of cognitive abilities in multiple domains, such as learning, memory, orientation, language, comprehension and judgment has been observed in older adults [2]. To date, there is no effective pharmacological treatment capable of curing dementia [3]; thus, it is important to prevent or delay the onset of cognitive deterioration.

Despite the fact that the causes of neurological diseases are multifactorial, there is a growing body of evidence showing that modifiable risk factors, such as nutrition and lifestyle, play an important role in the prevention of neurodegenerative diseases [4]. Among modifiable risk factors, dietary factors have been identified as playing a potential role in preserving and possibly improving mental health and cognitive status in older adults [5]. Recent scientific evidence demonstrated the beneficial effect of plant-based foods and beverages, rich in polyphenols [6], toward cognitive health, including fruits and vegetables [7]), nuts, whole grains and legumes [8,9,10], and coffee [11]. However, not only plant-based foods and/or manipulation of macronutrient intake have an effect; in fact nutritional interventions that consist of reducing global calories or increasing the fasting window between two meals have often been reported to improve healthspan and lifespan in a variety of organisms in laboratory settings, with increasing evidence that they are effective in humans [12]. However, only recently some studies have been published on intermittent fasting (IF) and outcomes related to cognitive status, although results are unequivocal [13,14].

Time-restricted feeding (TRF) is a form of IF in which all nutrient intake occurs within a few hours (usually ≤12 h) everyday, without any attempt to alter nutrient quality or calories. The concept of TRF arose within the context of circadian rhythms, which are daily circa 24-h rhythms in physiology, metabolism and behavior sustained under constant light or dark conditions [15]. TRF has been hypothesized to modify brain neurochemistry and neuronal network activity in ways that optimize brain function and peripheral energy metabolism [16,17]. Indeed, favorable effects of IF toward insulin metabolism, regulation of autophagy and neuro-inflammation, modulation of the expression of brain derived neurotrophic factor (BDNF) and regulation of behavior have been previously demonstrated; and importantly, all of the foregoing may affect neurogenesis and neuroplasticity [18]. However, most of the studies have been conducted in laboratory settings and studies on humans, even though observational, are lacking [19]. The aim of this study was to investigate the association between time feeding period and cognitive status in a cohort of adults living in the Mediterranean area.

Methods

2.1. Study Population

The MEAL study is an observational study aiming to investigate the association between nutritional and lifestyle habits characterizing the classical Mediterranean area and non-communicable diseases. The baseline data comprised a sample of 2044 men and women aged 18 or more years old randomly selected and enrolled between 2014 and 2015 in the main districts of the city of Catania, southern Italy. Details of the study protocol are published elsewhere [20]. Briefly, data collection was performed through the registered records of local general practitioners 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%). Given the outcome investigated has a major impact at older ages, the analysis for the present study was restricted to individuals of age of 50 years old or older (n = 916). Aims of the study were introduced to all participants and informed written consent was obtained. The study protocol has been reviewed and approved by the concerning ethical committee and all the study procedures were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

2.2. Data Collection

Face-to-face assisted personal interviews were conducted and electronic data collection was performed using tablet computers. All participants were provided with a paper copy of the questionnaire to visualize the response options. Nonetheless, final answers were registered directly by the interviewer. The demographic data including gender, age at recruitment, highest educational degree achieved, occupation (specifies the character of the most important employment during the year before the investigation) or last occupation before retirement, and marital status were collected. Occupational status was categorized as (i) unemployed, (ii) low (unskilled workers), (iii) medium (partially skilled workers), and (iv) high (skilled workers). Educational status was categorized as (i) low (primary/secondary), (ii) medium (high school), and (iii) high (university). The International Physical Activity Questionnaire (IPAQ) was used to assess physical activity [21], it included a set of questionnaires (five domains) investigating the time spent being physically active in the last 7 days. According to the IPAQ guidelines, physical activity level was categorized as (i) low, (ii) moderate, and (iii) high. Smoking status was categorized as (i) non-smoker, (ii) ex-smoker, and (iii) current smoker, while alcohol consumption was categorized as (i) none, (ii) moderate drinker (0.1–12 g/d) and (iii) regular drinker (>12 g/d). Data regarding health status including information about anthropometric measurements assessed through standard methods and previous or current cardiometabolic diseases and cancer were also collected [22].

2.3. Dietary Assessment

In order to assess the dietary intake, two food frequency questionnaires (FFQ, a long and a short version) previously tested for validity and reliability for the Sicilian population were administered [23,24]. The determination of the food intake, the energy content as well as the macro- and micro-nutrients intake were obtained through comparison with food composition tables of the Italian Research Center for Foods and Nutrition (Available online: https://www.crea.gov.it/-/tabella-di-composizione-degli-alimenti accessed on 17 July 2020). Intake of seasonal foods referred to consumption during the period in which the food was available and then adjusted by its proportional intake in one year. FFQs with unreliable intakes (<1000 or >6000 kcal/d) were excluded from the analyses (n = 22) leaving a total of 883 individuals included in the analysis.

2.4. Time Feeding

Participants were asked whether and what time, on average, they consumed their daily meals over the last 6 months (including breakfast, snacks, lunch and dinner). Consequently, the window of time between the first and the last meal of an average day was calculated; participants were finally categorized in those having an eating time window duration of more than 10 h and those with time restricted feeding less than 10 h (TRF).

2.5. Cognitive Evaluation

Cognitive status was evaluated using the Short Portable Mental Status Questionnaire (SPMSQ) [25], designed to measure cognitive impairment in both general and hospital population [26] also applied to the Italian population [27]. This 10-item tool was administered by the clinician in the office or in a hospital. The pre-defined categories for interpretation of the screening tool were (i) intact, less than 3 errors; (ii) mild, 3 to 4 errors; (iii) moderate, 5 to 7 errors, and (iv) severe, 8 or more errors. For this study, we considered more than 2 errors as a cut off point for impaired cognitive status.

2.6. Statistical Analysis

We analyzed the baseline cross-sectional data from this cohort. Exposure variables were eating time window (TRF vs. no eating time restriction), having breakfast and having dinner (vs. skipping). Categorical variables are presented as frequencies of occurrence and percentages; differences between groups were tested with Chi-squared test. Continuous variables are presented as means and standard deviations (SDs); differences between groups were tested with Student's t-test or Mann-Whitney U-test for normally and not-normally distributed variables, respectively. The relation between exposure variables and cognitive status 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). 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 calculations.

Results

Background characteristics of the study population according to feeding time window duration and meal habits are presented in Table 1. Among those having TRF there were less individuals with low educational and occupational status, more former smokers, less overweight, obesity, type-2 diabetes, hypertension, dyslipidemia and CVD (Table 1). Also regarding breakfast and dinner there were some differences among groups: for instance, among those having breakfast there were more older women, lower educational and occupational status, more never smokers, hypertensive, dyslipidemic and previous CVD; regarding dinner, there was a significant different distribution of occupational status categories despite with no clear trends (Table 1).

Table 1. Background characteristics of the study population according to eating time window duration 8TRF vs no restriction), breakfast (yes vs. no), and dinner (yes vs.no)

	TRF			Breakfast			Dinner		
	Yes (*n* = 98)	No (*n* = 785)	*p*-Value	Yes (*n* = 702)	No (*n* = 181)	*p*-Value	Yes (*n* = 859)	No (*n* = 24)	*p*-Value
Sex, *n* (%)			0.226			<0.001			0.499
Men	48 (49)	334 (42.5)		281 (40)	101 (55.8)		370 (43.1)	12 (50)	
Women	50 (51)	451 (57.5)		421 (60)	80 (44.2)		489 (56.9)	12 (50)	
Age, mean (SD)	65.2 (9.4)	65.1 (9.6)	0.057	65.5 (9)	62.8 (9.6)	0.001	65 (9.6)	61.5 (7.9)	0.080
Educational status, *n* (%)			0.008			0.001			0.480
Low	38 (38.8)	413 (52.6)		380 (54.1)	71 (39.2)		441 (51.3)	10 (41.7)	
Medium	45 (45.9)	240 (30.6)		210 (29.9)	75 (41.4)		277 (32.2)	8 (33.3)	
High	15 (15.3)	132 (16.8)		112 (16)	35 (19.3)		141 (16.4)	6 (25)	
Occupational status, *n* (%)			0.001			<0.001			0.022
Unemployed	9 (9.9)	194 (28.4)		184 (29.8)	19 (12.3)		199 (26.6)	4 (16.7)	
Low	25 (27.5)	110 (16.1)		93 (15)	42 (27.1)		126 (16.8)	9 (37.5)	
Medium	30 (33)	204 (29.9)		187 (30.3)	47 (30.3)		231 (30.8)	3 (12.5)	
High	27 (29.7)	174 (25.5)		154 (24.9)	47 (30.3)		193 (25.8)	8 (33.3)	
Smoking status, *n* (%)			<0.001			<0.001			0.815
Never smoker	37 (37.8)	460 (58.6)		419 (59.7)	78 (43.1)		485 (56.5)	12 (50)	
Former smoker	43 (43.9)	144 (18.3)		126 (17.9)	61 (33.7)		181 (21.1)	6 (25)	
Current smoker	18 (18.4)	181 (23.1)		157 (22.4)	42 (23.2)		193 (22.5)	6 (25)	
Physical activity level, *n* (%)			0.659			0.142			0.183
Low	23 (25)	173 (26.3)		161 (27.5)	35 (21.5)		193 (26.6)	3 (12.5)	
Moderate	43 (46.7)	327 (49.8)		290 (49.5)	80 (49.1)		354 (48.8)	16 (66.7)	
High	26 (28.3)	157 (23.9)		135 (23)	48 (29.4)		178 (24.6)	5 (20.8)	
BMI categories, *n* (%)			<0.001			0.286			0.203
Normal	44 (62)	256 (33.7)		253 (37.3)	47 (30.7)		292 (35.9)	8 (44.4)	
Overweight	27 (38)	312 (41.1)		273 (40.3)	66 (43.1)		330 (40.6)	9 (50)	
Obese	0 (0)	192 (25.3)		152 (22.4)	40 (26.1)		191 (23.5)	1 (5.6)	
Health status, *n* (%)									
Type-2 diabetes	9 (9.2)	135 (17.2)	0.043	120 (17.1)	24 (13.3)	0.213	143 (16.6)	1 (4.2)	0.103
Hypertension	61 (62.2)	599 (76.3)	0.003	536 (76.4)	124 (68.5)	0.030	646 (75.2)	14 (58.3)	0.061
Dyslipidemias	13 (13.3)	289 (36.8)	<0.001	273 (38.9)	29 (16)	<0.001	297 (34.6)	5 (20.8)	0.162
CVD	8 (8.3)	128 (16.9)	0.031	128 (18.9)	8 (4.6)	<0.001	135 (16.3)	1 (4.2)	0.110
Cancer	8 (8.2)	66 (8.4)	0.934	62 (8.8)	12 (6.6)	0.340	70 (8.1)	4 (16.7)	0.137

Nutrients and food group consumption across TRF, breakfast and dinner eaters are shown in Table 2. Individuals having TRF consumed more fibre, vitamin C, vitamin E, fruit, legumes, less potassium, less meat (total and red), and dairy products (Table 2); those having breakfast had lower intake of vitamin C and vitamin E while consumed more total meat, nuts and dairy products and less legumes; finally, those having dinner had lower energy intake, carbohydrate intake, fibre, PUFA, vitamin C, vitamin E, sodium, and higher intake of vitamin D and fish (Table 2).

Table 2. Mean (and standard deviation) of micro-, macro-nutrients and major food groups intake according to feeding time window duration (time feeding restricted to 10 vs. no restriction), breakfast (yes vs. no), and dinner (yes vs. no).

	TRF			Breakfast			Dinner		
	Yes (*n* = 98)	No (*n* = 785)	*p*-Value	Yes (*n* = 702)	No (*n* = 181)	*p*-Value	Yes (*n* = 859)	No (*n* = 24)	*p*-Value
	Mean (SD)			Mean (SD)			Mean (SD)		
Energy intake (kcal/d)	2110.8 (759.6)	2039.8 (637.1)	0.310	2034.4 (631.6)	2099.5 (724.4)	0.231	2040 (639.9)	2320 (967.3)	0.038
Energy intake (kJ/d)	8606.97 (3161.637)	8257.8 (2614.5)	0.224	8230.6 (2585.3)	8552.3 (3017.9)	0.150	8262.1 (2626.6)	9530 (4078.4)	0.022
Macronutrients									
Carbohydrates (g/d)	299 (108.9)	314.6 (117)	0.186	297.8 (107.2)	312.2 (119.2)	0.116	299.4 (108.5)	348 (146.5)	0.032
Fiber (g/d)	35.6 (14.5)	32.3 (13.7)	0.027	32.3 (13.9)	34.2 (13.5)	0.098	32.6 (13.8)	38.2 (14.3)	0.049
Protein (g/d)	84.4 (29.5)	84.8 (28.6)	0.900	84.8 (29)	84.7 (27.9)	0.981	84.6 (28.6)	89.4 (32.7)	0.422
Fat (g/d)	60.5 (30.9)	59.2 (20.6)	0.595	59.3 (20.3)	59.8 (27.4)	0.791	59.3 (21.3)	65.6 (40)	0.165
Cholesterol (mg/d)	174.3 (91.8)	190.1 (85.9)	0.089	190.4 (87.2)	180.7 (84.8)	0.179	188.7 (86.8)	177.2 (86.9)	0.522
SFA	22.9 (12.1)	23.6 (9.1)	0.541	23.7 (8.9)	23.1 (11.5)	0.520	23.5 (9.2)	26 (17.7)	0.207
MUFA	26 (13.1)	25.2 (8)	0.358	25.2 (8)	25.7 (11.3)	0.485	25.2 (8.6)	27.8 (15.3)	0.169
PUFA g	11.4 (5.7)	10.9 (4.2)	0.345	11 (4.3)	11.2 (5)	0.209	7.3 (6.5)	10.7 (14.1)	0.015
Total Omega-3	1.69 (0.83)	1.76 (0.85)	0.480	1.8 (0.9)	1.7 (0.8)	0.325	1.76 (0.85)	1.48 (0.44)	0.107
Micronutrients									
Vitamin A (Retinol)	897.92 (379)	867.3 (428.8)	0.500	872.5 (427.2)	863.8 (410.2)	0.806	869 (425)	929 (368.7)	0.494
Vitamin C (mg/d)	203.4 (118.6)	153,9 (92.4)	<0.001	154 (94.2)	180.5 (104.2)	0.001	158.4 (96.9)	198.3 (88.9)	0.047
Vitamin E (mg/d)	9.8 (4.4)	8.5 (3)	<0.001	8.5 (3)	9.2 (3.9)	0.013	8.6 (3.2)	10 (4.5)	0.039
Vitamin B12	5.6 (4.2)	6.2 (4.3)	0.206	6.3 (4.5)	5.8 (3.5)	0.157	6.2 (4.4)	5 (2.1)	0.211
Vitamin D	5.6 (6.3)	5.6 (5.4)	0.963	5.7 (5.6)	5.5 (5.1)	0.677	5.7 (5.6)	3.5 (1)	0.050
Sodium (mg/d)	2699.9 (1248.9)	2767.8 (1065.3)	0.560	2744.5 (1016.7)	2821.9 (1324.9)	0.393	2743.7 (1070.5)	3354 (1468.8)	0.007
Potassium (mg/d)	3649.8 (1331.8)	3987.3 (1456.4)	0.020	3651.4 (1345.9)	3826.7 (1358.3)	0.119	3673.6 (1344.3)	4212.6 (1458.5)	0.053
Food groups									
Cereals (total, g/d)	222 (129.5)	228,2 (132.1)	0.662	226.2 (129.5)	232.7 (140.4)	0.556	226.4 (131)	268.2 (151.4)	0.125
Vegetables (g/d)	264.7 (118.5)	261 (148)	0.526	258.1 (140.4)	274 (161.2)	0.190	260.6 (145.9)	288.5 (105.9)	0.353
Fruit (g/d)	482.2 (337.1)	398.52 (313)	0.014	401.77 (322.4)	431.2 (293.1)	0.265	405.3 (316.7)	497.6 (310.3)	0.159
Legumes (g/d)	46.1 (40.6)	36.5 (35.3)	0.013	36.4 (36)	42.3 (35.7)	0.047	37.5 (36.1)	40.6 (34.2)	0.677
Nuts (total, g/d)	14.8 (19.2)	21.3 (33.1)	0.057	22 (34.6)	15.3 (17.7)	0.011	20.8 (32.1)	17 (23.2)	0.564
Fish (g/d)	66.5 (70.2)	65.3 (61.5)	0.861	65.6 (63.7)	65 (58.1)	0.909	66.2 (63.2)	39.5 (14.9)	0.039
Meat (total, g/d)	57.4 (31.6)	70.5 (39.9)	0.002	70.7 (41.1)	63 (30.9)	0.018	69.2 (39.6)	66 (30.4)	0.698
Red meat (g/d)	27.4 (19.6)	33.84 (24.7)	0.023	33.7 (27.3)	31.1 (21.1)	0.248	33.1 (26.3)	33 (20.8)	0.974
Processed Meat (g/d)	13.8 (22.4)	13.4 (16)	0.85	13.5 (16.5)	13.7 (18.3)	0.878	13.3 (16.8)	20.1 (19.4)	0.052
Dairy products (g/d)	157.9 (176.3)	194.8 (171.4)	0.046	202.1 (175.4)	146.7 (152.2)	<0.001	191 (171.2)	196.8 (212.3)	0.862
Alcohol (total, g/d)	8.79 (11.3)	8.23 (12.8)	0.681	8 (12.6)	9.4 (13.1)	0.187	8.2 (12.6)	11.2 (16.2)	0.253
Coffee (mL/d)	57.1 (38.8)	60.4 (44.1)	0.484	59.1 (44.1)	63.7 (41.6)	0.207	60 (43.8)	61.5 (36)	0.870
Tea (mL/d)	70.3 (128.19	57.6 (122.2)	0.337	60 (127.5)	54.9 (102.9)	0.615	59.2 (123.3)	52.1 (107.2)	0.785
Olive oil (mL/d)	7.6 (3.1)	7.2 (3.1)	0.267	7.2 (3.2)	7.5 (3.1)	0.313	7.3 (3.2)	6.8 (3.2)	0.435

A total of 82 individuals had impaired cognitive status: most of them resulted having mild impairment, while four participants reported moderate impairment. Cognitive impaired individuals were older, with higher proportion less physically active, and had higher rates of hypertension (Supplementary Table S1). Table 3 reports the associations between the exposure variables and cognitive status. The multivariate model shows that individuals having TRF were less likely to have cognitive impairment compared to those with no eating time restrictions [odds ratio (OR) = 0.28; 95% confidence intervals (CI): 0.07–0.90)]; a similar association was found for those individuals having breakfast (OR = 0.37, 95% CI: 0.16–0.89), but no for dinner (Table 3).

Table 3. Association between feeding time window duration (time feeding restricted to 10 vs. no restriction), breakfast (yes vs. no), dinner (yes vs. no), and cognitive status in the study sample.

	Cognitive Impairment, OR (95% CI)					
	TRF	*p*-Value	Breakfast	*p*-Value	Dinner	*p*-Value
Model 1	0.39 (0.14–1.10)	0.077	0.45 (0.22–0.94)	0.034	0.59 (0.17–2.1)	0.238
Model 2	0.42 (0.15–1.20)	0.105	0.51 (0.25–1.10)	0.078	0.46 (0.13–1.66)	0.418
Model 3	0.28 (0.07–0.90)	0.049	0.37 (0.16–0.89)	0.025	0.48 (0.13–1.85)	0.289

Model 1 is unadjusted. Model 2 includes adjustment for age and sex. Model 3 includes adjustment for variables as model 2 + educational and occupational level, smoking status, physical activity level, BMI categories, and type-2 diabetes, hypertension, dyslipidemia, previous history of CVD and cancer.

Discussion

In the present cross-sectional study, the relation between TRF and cognitive status was investigated in a cohort of Italian adults. Individuals who practiced TRF were less likely to screen positive for impaired cognitive status, and among those practicing TRF only those who did not skip breakfast were less likely to screen positive for impaired cognitive status. Interestingly, the results of TRF in humans seem to depend on the time of day of the eating window and not only related to fasting duration per se [28,29,30,31,32]. In fact, studies showed that restricting food intake starting from the middle of the day (skipping dinner) reduced body fat, fasting glucose, insulin resistance, hyperlipidemia and inflammation [29,30]. Conversely, restricting the entire food daily intake to the late afternoon (skipping breakfast) either produced mostly null results or worsened cardiometabolic health [28,31,32]. The circadian system may explain these dichotomous time-of-day effects. Circadian rhythms are self-sustained ~24 h oscillations in physiology, metabolism and behavior induced by coordinated transcriptional–translational feedback loops involving clock genes such as CLOCK, BMAL1 CRY1/2 and PER1/2 which in turn cause oscillations in a numerous of downstream targets. Jamshed and colleagues [33] investigated the effects of early TRF (skipping dinner) on gene expression, circulating hormones and cardiometabolic risk on eleven overweight adults. After only 4 days of early TRF they found changes in the expression of 6 circadian clock genes and upregulation of both SIRT1 and LC3A that have a role in autophagy. Autophagy has been shown to play a determinant role in protecting against multiple chronic disorders such as diabetes, heart disease, cancer, and neurodegenerative diseases, by recycling used and damaged proteins and organelles.

To our knowledge, our study is the first to focus on the relation between TRF and cognitive status in humans. Unfortunately, our current understanding regarding IF on cognitive status and neurodegenerative diseases is mainly inferred from in vitro or animal studies because human studies are lacking. There are very few interventional studies exploring the effects of TRF on humans and they mainly concern metabolic aspects such as weight reduction and/or insulin resistance. Sutton and colleagues [34] found that a 5-week of 8-h early time restricted feeding improved insulin levels, insulin sensitivity, b cell responsiveness, blood pressure, and oxidative stress levels in men with prediabetes even though food intake was matched to the control arm and no weight loss occurred. Similarly, another study conducted during orthodox religious fasting reported that time restricted eating might be associated with better metabolic and glycemic profile [35,36]. Maintaining adequate blood pressure prevents cerebral microhemorrhages which contribute to cognitive impairment, geriatric psychiatric syndromes, and gait disorders [37]. These findings are also relevant because metabolic syndrome is another major risk factor for a variety of neurological diseases [38].

Fasting per se may counteract aging which is the most recognized risk factor for cognitive impairment, dementia and neurological disease [16]. In fact, aging is associated with many morpho-functional changes that can affect behaviour,

cognition and susceptibility to neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) [39]. Over the years the most relevant changes occur in the hippocampus and in the prefrontal cortex which are crucial for spatial and working memory [40,41]. It has been demonstrated that the deterioration of these two structures is widely responsible for the decline seen in cognitive functions during aging [42]. Aging is characterized by a deterioration in the extent of dendritic branching both in apical and basilar dendrites in the hippocampus and in the superficial cortical layer of the prefrontal cortex [43] leading to reduction in cognitive function [44]. Moreover, aged neurons show an increased density of calcium channels that leads to an alteration of after-hyperpolarization (AHP) potential. In fact after depolarization, neurons utilize potassium channels to repolarize but when AHP is increased, neurons need to reset longer to resting potential [45]. This coincides with a reduction in levels of BDNF which correlates with age-related cognitive deficits [46]. Many studies have shown that Intermittent fasting may enhance synaptic plasticity, neurogenesis and neuroprotection especially by an increase in BDNF [47,48]. BDNF has an effect also in neural precursor cells (NPC) which reside in the dentate gyrus of the hippocampus in which they are relevant for the formation of new neurons that integrate into the hippocampal circuitry and play roles in spatial pattern separation, a fundamental domain of learning and memory [49,50,51].
Another physiological mechanism during aging is the progressive loss of synapses in some regions of the human brain that leads to worsened communication between neurons and is associated with increased inflammation and oxidative stress [52]. Findings in rodents suggest that IF enhances neuronal resilience to excitotoxic stress, preventing learning deficit [53] due to hippocampal cell death and stimulating neurogenesis [49,54]. The consequent increased expression of synaptic proteins regulating calcium homeostasis [55] attenuates the typical decline in motor coordination and spatial learning typically observed in old rats.

IF may exert also neuroprotective effects by an improved mitochondrial respiratory activity [56] due to an upregulation of PGC1α which contributes to mitochondrial biogenesis and detoxification [57]. The upregulation of PGC1α modulates also the expression of nitric oxide (NO) which has antioxidant and protective properties in the endothelium and may preserve the brain microvasculature [58,59]. Interestingly a TRF protocol was also reported to diminish ROS production, improve endothelial function [60] and reduce levels of pro-inflammatory cytokines as TNFα, IL-1β and IL-6 [54]. In neurodegenerative diseases, these changes related to aging occur at a much faster rate and it has been hypothesized that intermittent fasting could also have a beneficial effect on their treatment. Compared to ad libitum-fed controls, mice and rats on an IF diet exhibit less neuronal dysfunction, degeneration and fewer clinical symptoms in models of AD, PD and Huntington's disease (HD) [16]. In a different in vivo study carried out by Chaix et al. [61], there were 17 serum metabolites that were higher in TRF than ad libitum feeding group, including anserine and carnosine, which have shown therapeutic potential against the oxidative stress observed in pathologies characterized by cognitive dysfunctions [62,63]. Differently from caloric restriction, IF could prevent cognitive decline in a triple transgenic AD mouse model by acting on mitochondrial dysfunction and oxidative imbalance without reductions in β-amyloid protein and phospho-tau levels [64]. Moreover, it has recently been demonstrated that TRF protocol improves sleep, motor coordination and autonomic nervous system function in mouse models of Huntington's disease [65,66].

Current evidence, even though limited and conflicting [67,68] has associated TRF with changes in human gut microbiota. In particular, Zeb et al. demonstrated that TRF may modulate microbial composition and increase its relative abundance, thereby influencing the host metabolism and nutritional status [68]. Consequently, gut microbiome imbalance has been associated with numerous inflammatory, immune and nervous system-related diseases through a communication pathway called microbiome-brain axis [69], also influencing brain development and function [70].

This study has a major strength to be the first reporting an association between TRF and cognitive status, suggesting this hypothesis to be further tested in future studies. However, albeit among the first reported in the scientific literature, the findings of this study should be considered in light of some limitations. First, the cross-sectional nature of the study cannot allow us to draft conclusions on the association between TRF and cognitive status. However, this type of study is important to be performed in order to provide preliminary results of potential interest in spite of clinical intervention trials; in fact, it is crucial to have preliminary data before setting up intervention trials strongly affecting the eating habits of older individuals at risk of cognitive impairment and altered cognitive function (lack of compliance). Another limitation of our study includes the possibility of residual confounding due to the characteristics of individuals having TRF, as they demonstrated to be potentially more health conscious with higher socio-educational level and, thus, at lower risk of age-related disorders. Despite the fact that we adjusted for all these potential confounding factors, we cannot rule out the possibility of existence of related unmeasured confounders. Finally, despite statistically significant, we found wide CIs for the association between TRF and cognitive status: although the direction of the association is significant, the strength of these findings should be confirmed in future studies with larger sample, more cases and more individuals exposed to the variable of interest.

Conclusions

In conclusion, restricting the daily time feeding window is associated with reduced odds of impaired cognitive status especially when it is obtained through restricting food intake starting from the middle of the day in alignment with circadian rhythms. Therefore, large sample interventional human studies in which cognitive status, regional brain volumes, neural network activity, and biochemical analyses of cerebrospinal fluid are needed to clarify the impact of TRF on mental health.

Author Contributions

Conceptualization, W.C., J.G., G.G., F.G.; methodology W.C., J.G., G.G., F.G.; formal analysis, W.C., J.G., G.G., F.G.; writing—original draft preparation, W.C., J.G., S.C., G.C., R.F., F.C., G.G., F.G.; writing—review and editing, W.C., J.G., S.C., G.C., R.F., F.C., G.G., F.G.; supervision, R.F., F.C., G.G., F.G. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University of Catania (protocol code 802/23 December 2014).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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CHAPTER 2

Association between time restricted feeding and mental health in Italian adults

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ABSTRACT

Background

In recent years, mental disorders have represented a relevant public health problem due to their deleterious effect on quality of life, the scarce timely diagnosis, and the growing trends highly influenced by modern society and current unhealthy lifestyles. Not only the specific foods or dietary patterns have been hypothesized to play a role on mental health; also, temporal regulation of feeding\fasting has emerged as an innovative strategy to prevent and treat mental health disease. The aim of this project was to investigate the association between time restricted feeding (TRF) and mental health outcomes including perceived stress, depressive symptoms, and sleep quality assessed in a cohort of southern Italian adults.

Methods

Demographic and dietary characteristics of 2,044 adults living in southern Italy were analyzed. Food frequency questionnaires were used to calculate dietary intakes; participants were also asked what time, on average, they consumed their meals to calculate the eating window of time and identify those eating within 10 hours or less (TRF). Logistic regression analyses were performed to test the association between mental health outcomes.

Results
After adjusting for potential confounding factors, no associations were found between TRF and mental health outcomes; however, when performing the analyses by age groups, individuals older than 70 years having a feeding time window of 10 hours were less likely to have signs of mental health distress [odds ratio (OR) = 0.14, 95% confidence interval (CI): 0.03-0.60]. No further associations were found for specific mental health outcomes explored separately.

Conclusions
Restricting the daily time feeding window is associated with lower signs of mental health distress in individuals older than 70 years. Albeit preliminary, these findings on elderly individuals require further investigation using prospective design and an amended approach to control for fasting.

Keywords: time restricted feeding; intermittent fasting; chrononutrition; mental health; brain diseases; brain; aging; risk factor; cohort; Mediterranean

Introduction

In recent years, mental disorders have represented a relevant public health problem due to their deleterious effect on quality of life, the scarce timely diagnosis, and the growing trends highly influenced by modern society and current unhealthy lifestyles. In fact, it is estimated that the global population suffering from depression is about 300 million people and that anxiety disorders affect more than 260 million people worldwide (4.4% and 3.6% of the global population, respectively) [1]. Mental disorders account 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 [2]. Equally alarming is the increase in sleep disturbances, which is a disorder itself, and can be a risk factor for the onset of any other mental illness [1].

There are many reasons why mental health diseases are on the rise in both developed and developing countries. The modern lifestyle characterized by a busy working schedule, prolonged illumination, societal challenges, sedentary behaviors and urban pollution play a relevant role in the onset of anxiety, mood disorders, depression, cognitive, and sleep disorders [3]. This lifestyle leads to a chronic disruption of circadian rhythms, which may explain the association between mental health and other metabolic diseases, such as obesity, diabetes, cardiovascular and neurodegenerative disease [4]. In this scenario, also diet plays a role of primary importance, as pointed out by a newly developed discipline called "nutrition psychiatry" that focuses on finding the relation between dietary factors, eating habits, and mental diseases [5]. On this matter, several studies have indicated that a habitual western diet characterized by high calorie density foods (i.e., refined grains, sugar, cooking oils, corn syrup, and processed foods) increase the risk for depression and anxiety [6–10]. Conversely, recent scientific evidence demonstrated the beneficial effect of omega-3 rich fish and plant-based foods as fruits, vegetables, whole grains and legumes toward mental health [11–13].

However, not only plant-based foods and\or manipulation of macronutrient intake have an effect; in fact nutritional interventions that consist of reducing global calories or increasing the fasting window between two meals have often been reported to improve sleep and mental health [14–16] in a variety of organisms in laboratory settings, with increasing evidence that they are effective in humans [17]. Time restricted feeding (TRF) is a form of intermittent fasting (IF) in which all nutrient intake occurs within a few hours (usually ≤12h) everyday, without any attempt to alter nutrient quality or calories. The concept of TRF arose within the context of circadian rhythms, which are daily circa 24-hour rhythms in physiology, metabolism and behavior sustained under constant light or dark conditions [18]. TRF has been hypothesized to modify brain neurochemistry and neuronal network activity in ways that optimize brain function and peripheral energy metabolism [19].

However, most of the studies have been conducted in laboratory settings and studies on humans, even though observational, are scarce. The aim of this study was to investigate the association between time feeding period and mental health outcomes in a cohort of adults living in the Mediterranean area.

Methods

2.1 Study population

The MEAL study is an observational study aiming to investigate the association between nutritional and lifestyle habits characterizing the traditional Mediterranean area and non-communicable diseases. The baseline data comprised a sample of 2,044 men and women aged 18 or more years old. Details of the study protocol are published elsewhere [20]. Briefly, individuals were randomly selected in the main districts of the city of Catania, southern Italy. The enrolment and data collection was performed between 2014 and 2015 through the registered records of local general practitioners 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 2,405 individuals invited, the final sample size was 2,044 participants (response rate of 85%). All participants were informed about the aims of the study and provided a written informed consent. All the study procedures were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. The study protocol has been reviewed and approved by the concerning ethical committee.

2.2 Data collection

An electronic data collection was performed by face-to-face assisted personal interview, using tablet computers. In order to visualize the response options, participants were provided with a paper copy of the questionnaire. However, final answers were registered directly by the interviewer. The demographic data included gender, age at recruitment, highest educational degree achieved, occupation (specifies the character of the most important employment during the year before the investigation) or last occupation before retirement, and marital status. Occupational status was categorized as (i) unemployed, (ii) low (unskilled workers), (iii) medium (partially skilled workers), and (iv) high (skilled workers). Educational status was categorized as (i) low (primary/secondary), (ii) medium (high school), and (iii) high (university). Physical activity was evaluated with the International Physical Activity Questionnaires (IPAQ) [21], which included a set of questionnaires (5 domains) investigating the time spent being physically active in the last 7 days. Based on the IPAQ guidelines, final score allowed to categorize physical activity level as (i) low, (ii) moderate, and (iii) high. Smoking status was categorized as (i) non-smoker, (ii) ex-smoker, and (iii) current smoker, while alcohol consumption was categorized as (i) none, (ii) moderate drinker (0.1-12 g/d) and (iii) regular drinker (>12 g/d). Health status included information about anthropometric measurements assessed through standard methods and previous or current cardiometabolic diseases and cancer [22].

2.3 Dietary assessment

The dietary assessment was performed by the administration of two food frequency questionnaires (FFQ, a long and a short version) that have been previously tested for validity and reliability for the Sicilian population [23,24]. The identification of the food intake, the energy content as well as the macro- and micro-nutrients intake were obtained through comparison with food composition tables of the Italian Research Center for Foods and Nutrition (Available online: https://www.crea.gov.it/-/tabella-di-composizione-degli-alimenti accessed on 17 July 2020). Intake of seasonal foods referred to consumption during the period in which the food was available and then adjusted by its proportional intake in one year. After excluding FFQs with unreliable intakes (<1,000 or >6,000 kcal/d) or lacking information (n = 107), a total of 1,937 individuals were included in the analysis.

2.4 Eating time

Participants were asked whether and what time, on average, they consumed their daily meals over the last 6 months (including breakfast, snacks, lunch and dinner). Consequently, the window of time between the first and the last meal of an average day was calculated; participants were finally categorized in those having an eating time window duration of more than 10 hours and those with eating time restricted to less than 10 hours.

2.5 Mental health status

Mental distress was considered as having any (one or more) of the following: low sleep quality, high perceived stress, and depressive symptoms. These mental health outcomes were defined as follow:

The Pittsburgh sleep quality index (PSQI) [25] 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.

To evaluate stress symptoms, previously validated the Perceived Stress Scale (PSS) was used [26]. Briefly, PSS is a 14-item questionnaire used to measure perceived stress, i.e., how individuals perceive situations as stressful. Each question has answer options ranging from zero to four (0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = always). The scale total is the sum of the scores of these 14 items and the scores can range from zero (minimum) to 56 (maximum). The sex-specific median value was considered as cut-off point to define high or low perceived stress.

The 10-item Center for the Epidemiological Studies of Depression Short Form (CES-D-10) was used as a screening tool for depressive symptoms [27]. Briefly, CES-D-10 is a 10-item questionnaire widely used to screen for depressive symptoms in the general population. CES-D-10 is assessing depressive symptoms in the past week; total scores can range from 0 to 30. Higher scores suggest greater severity of symptoms, a score ≥ 16 indicated was considered as a case with depressive symptoms. After excluding the individuals who did not complete CES-D-10, a total sample of 1,572 was included in the final analysis.

2.6 Statistical analysis

Categorical variables are presented as frequencies of occurrence and percentages; differences between groups were tested with Chi-squared test. Continuous variables are presented as means and standard deviations (SDs); differences between groups were tested with Student's t-test or Mann-Whitney U-test for normally and not-normally distributed variables, respectively. Differences in background characteristics and nutrient intake by mental health status were investigated. The association between the eating time window (TRF vs. no time restriction) and mental health outcomes was tested through logistic regression analyses included a unadjusted, a sex- and age- adjusted, and a multivariate adjusted model for baseline characteristics (age, sex, marital, educational and occupational status, smoking and alcohol drinking habits, and physical activity level). The analyses were also performed by stratifying by age groups. 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 calculations.

Results

A total of 976 individuals (62% of the entire sample) reported having signs of mental distress. The distribution of the background characteristics of the study population according to mental health status is presented in Table 1. No differences were found for age, sex, educational and occupational status, smoking status and BMI groups (Table 1). However, individuals with signs of mental health distress had lower physical activity level and were unmarried; moreover, there was a lower proportion of individuals with hypertension among those with mental health distress.

Table 1. Background characteristics of the study population according to mental health status (n = 1,572).

	Mental health status		
	No distress (n = 596)	Signs of distress (n = 976)	P-value
Sex, n (%)			0.257
Men	261 (43.8)	399 (40.9)	
Women	335 (56.2)	577 (59.1)	
Age, mean (SD)	47.9 (17.6)	45.9 (17.5)	0.056
Educational status, n (%)			0.487
Low	164 (27.5)	293 (30)	
Medium	254 (42.6)	390 (40)	
High	178 (29.9)	293 (30)	
Occupational status, n (%)			0.164
Unemployed	120 (24)	227 (28.5)	
Low	82 (16.4)	124 (15.6)	
Medium	115 (23)	195 (24.5)	
High	183 (36.6)	251 (31.5)	
Smoking status, n (%)			0.766
Never smoker	384 (64.4)	626 (64.1)	
Former smoker	141 (23.7)	243 (24.9)	
Current smoker	71 (11.9)	107 (11)	
Physical activity level, n (%)			0.007
Low	87 (14.6)	190 (19.5)	
Moderate	281 (47.3)	493 (50.6)	
High	226 (38)	291 (29.9)	
BMI categories, n (%)			0.065
Normal	252 (44.8)	448 (50.3)	
Overweight	219 (38.9)	295 (33.1)	
Obese	92 (16.3)	173 (16.5)	
Health status, n (%)			
Type-2 diabetes	32 (5.4)	61 (6.3)	0.473
Hypertension	309 (51.8)	456 (46.7)	0.049
Dislipidemias	88 (14.8)	165 (16.9)	0.262
Marital status			0.001
Unmarried	227 (38.1)	439 (45)	
Married	369 (61.9)	537 (55)	

Dietary variables by mental health status are presented in Table 2. Individuals who reported having signs of mental health distress reported eating more total fats (including saturated and mono-unsaturared fatty acids), higher intake of all fats, higher intake of vitamin A, vitamin D, and vitamin E, and higher intake of sodium; less intake of cereals and more vegetables, processed meat, and nuts.

Table 2. Mean (and standard deviation) of micro-, macro-nutrients and major food groups intake according to mental health status.

	Mental status		
	No distress (n = 596)	Signs of distress (n = 976)	*P-value*
	Mean (SD)		
Energy intake (kcal/d)	2031.1 (764.8)	2120.2 (896.3)	0.044
Energy intake (kJ/d)	8285,8 (3188)	8616.4 (3727.2)	0.072
Macronutrients			
Carbohydrates (g/d)	304.5 (130.5)	305.6 (129.7)	0.874
Fiber (g/d)	33.8 (20.7)	33.7 (18.7)	0.907
Protein (g/d)	85.4 (36.8)	89.1 (42.7)	0.078
Fat (g/d)	56.8 (21.6)	63.9 (33)	<0.001
Cholesterol (mg/d)	178.7 (92.7)	198.1 (127.3)	0.001
SFA %	22 (9)	24.9 (13.1)	<0.001
MUFA %	24.2 (8.6)	26.8 (12.9)	<0.001
PUFA %	10.7 (4.8)	11.7 (6.9)	0.002
Total Omega-3 g	1.6 (0.7)	1.7 (0.9)	0.048
Micronutrients			
Vitamin A (Retinol)	861.4 (453.2)	921.5 (514.4)	0.019
Vitamin C (mg/d)	174.5 (132.2)	171.1 (122.9)	0.607
Vitamin E (mg/d)	8.7 (3.6)	9.3 (4.7)	0.012
Vitamin B12	6.9 (7.8)	7 (6.9)	0.363
Vitamin D	4.9 (4.3)	5.8 (8)	0.011
Sodium (mg/d)	2925 (1071)	3067.1 (1312.1)	0.026
Potassium (mg/d)	3814.1 (2014.6)	3946 (2000.3)	0.206
Food groups			
Cereals (total, g/d)	228.1 (138.4)	210.8 (129.7)	0.013
Vegetables (g/d)	265 (190.6)	286.1 (198.8)	0.038
Fruit (g/d)	423.4 (369.5)	419 (374.2)	0.823
Legumes (g/d)	42.7 (64.8)	38.8 (47.5)	0.173
Nuts (total, g/d)	19.3 (29.8)	24.8 (56.2)	0.026
Fish (g/d)	61.4 (77.1)	69.1 (93.9)	0.095
Meat (total, g/d)	66 (34)	69.5 (38.2)	0.073
Red meat (g/d)	34.3 (25.2)	33.2 (23.7)	0.380
Processed Meat (g/d)	15.7 (15.1)	20.1 (25.2)	<0.001
Dairy products (g/d)	200 (190.2)	207 (179.3)	0.462
Alcohol (total, g/d)	6.7 (9.5)	7.6 (12.2)	0.119
Coffee (ml/d)	57 (43.5)	54 (42.5)	0.185
Tea (ml/d)	68.4 (138.3)	83.6 (167.9)	0.068
Olive oil (ml/d)	6.7 (2.9)	6.9 (3.1)	0.336

Out of the entire sample, 169 individuals (10.7%) reported having an eating time window equal or less than 10 hours. Table 3 describes the association between TRF compared to no eating time restrictions, and mental health distress. While the less adjusted models showed an inverse association between TRF and signs of mental distress, after adjusting for potential confounding factors, no associations were found; however, when performing the analyses by age groups, older adults and elderly having a feeding time window of 10 hours or less were less likely to have signs of mental health distress [odds ratio (OR) = 0.50, 95% confidence interval (CI): 0.28-0.87 and OR = 0.14, 95% CI: 0.03-0.65, respectively] compared to those having no feeding time restriction (Table 3). Regarding other specific mental health outcomes, individuals reporting TRF in the full cohort were less likely to have high perceived stress (OR = 0.48, 95% CI: 0.26-0.86) while older adults showed being less likely to have both high perceived stress and depressive symptoms (OR = 0.51, 95% CI: 0.25-1.00 and OR = 0.50, 95% CI: 0.26-0.96, respectively; Table 3). No associations were specifically found with sleep quality (Table 3).

Table 3. Association between feeding time window duration (10-hour restricted feeding vs. no time restricted feeding) and mental health distress and its individual components.

	OR (95% CI)		
	Full cohort	older adults (>50 y)	elderly (>70 y)
Signs of mental distress			
Model 1	0.65 (0.45-0.95)	0.49 (0.30-0.78)	0.30 (0.11-0.85)
Model 2	0.67 (0.46-0.98)	0.50 (0.31-0.81)	0.30 (0.10-0.84)
Model 3	0.66 (0.43-1.03)	0.50 (0.28-0.87)	0.14 (0.03-0.65)
Low sleep quality			
Model 1	0.83 (0.55-1.25)	0.67 (0.39-1.15)	0.56 (0.18-1.72)
Model 2	0.87 (0.57-1.32)	0.67 (0.39-1.15)	0.58 (0.19-1.78)
Model 3	0.90 (0.56-1.43)	0.69 (0.37-1.29)	0.42 (0.08-2.36)
High perceived stress			
Model 1	0.48 (0.30-0.77)	0.53 (0.29-0.95)	0.92 (0.30-2.84)
Model 2	0.47 (0.29-0.76)	0.54 (0.30-0.97)	0.93 (0.30-2.90)
Model 3	0.48 (0.26-0.86)	0.51 (0.25-1.00)	0.55 (0.11-2.74)
Depressive symptoms			
Model 1	0.74 (0.49-1.13)	0.56 (0.32-0.97)	0.73 (0.24-2.25)
Model 2	0.76 (0.50-1.16)	0.59 (0.34-1.00)	0.72 (0.23-2.24)
Model 3	0.77 (0.46-1.27)	0.50 (0.26-0.96)	0.25 (0.04-1.41)

Model 1 is unadjusted.
Model 2 is adjusted for age and sex.
Model 3 is adjusted for variables as model 2 + total energy intake, educational and occupational level, smoking status, physical activity level, BMI categories, and health status

Discussion

In the present study, the relation between TRF and mental health status was investigated in a cohort of Italian adults. No associations were found between eating time window and mental health outcomes except for elderly individuals: in fact, patients older than 70 years having an eating time window of 10 hours or less were less likely to have signs of mental health distress. To our knowledge, this is the first study to focus on the relation between TRF and mental health status in humans.

Although fasting may be promising in neurosciences, existing studies are mainly conducted in vitro while clinical trials have usually investigated cardio-metabolic outcomes [28]. According to recent hypotheses, fasting may counteract aging processes, which are the most recognized risk factor for cognitive impairment, dementia and neurological disease [19]. The link between fasting and mental health effects appears to be primarily ketone bodies [29]: even a short-term daily fasting can modestly increase circulating ketones. Especially beta-hydroxybutyrate induces in turn the transcription of brain-derived neurotrophic factor (BDNF) a fundamental neurotrophin that plays critical roles in neurotransmission, neuronal survival growth and plasticity [30]. Diminished BDNF signaling is found in neurodegenerative disorders and interventions that increase BDNF levels or activate receptor tropomyosin-related kinase B (TrkB) have been shown to ameliorate clinical symptoms in mouse models of neurodegenerative diseases, stroke and depression [31,32]. Additionally, it seems that BDNF has a synergistic effect with serotonin on mood and depression [33]. In fact, serotonin may improve mood and protect neurons against degeneration by activating receptors coupled to cyclic AMP production and stimulation of BDNF production [34]. BDNF, in turn, can enhance the survival and growth of serotonergic neurons [35].

A decreased serum level of BDNF has been associated with insomnia and sleep deprivation, and it has been demonstrated that subjects suffering from current symptoms of insomnia and depression exhibited significantly lower serum BDNF levels [36,37]. However, the effects of TRF on sleep quality are controversial. Observational studies conducted on Muslims during Ramadan have found a reduction in REM sleep time [38]. Probably, the reduction in REM sleep could be related to the consumption of a traditional large late meal before going to rest that leads to an increase in nocturnal body temperature which can disturb sleep [39]. Although expanding the fasting time window during the day seems to be beneficial, shifting food intake to the darkest hours can partially reverse circadian rhythms. Eating in misalignment with circadian clocks worsens several cardiometabolic endpoints, particularly glucose tolerance [40–42]. Adiponectin is a hormone involved in glucose metabolism that has been proven to be circadian periodic [43] and may have an effect on sleep. Recent data have shown that sleep restriction may decrease levels of adiponectin in healthy individuals [44] but intermittent fasting can raise the levels of this hormone [43]. Finally, lower adiponectin levels have been associated with anxiety and stress-related affective disorders [45], suggesting an important effect of adiponectin toward mental health.

Even our gut bacteria seem to follow circadian oscillations and recent evidence have identified the intestinal microbiota as a key player in the responses to stress, anxiety, depression and cognition through what is called the gut-brain axis [5].
Recent studies [46,47] suggest that TRF determines healthy gut microbiota through an increase in bacteria diversity especially of Lactobacillaceae, Prevotellaceae, and Bacteroidaceae families. Preliminary studies have shown a possible correlation between gut microbiota composition (i.e., a modification in the Firmicutes/Bacteroidetes/Clostridium ratio) and depressive state and response to chronic stress [48]. Having a reduced diversity of bacteria determines an increased permeability of the intestinal mucosa ("leaky gut") and an increase in the inflammatory state through the secretion of cytokines especially (TNF-a, IL-1, IL-6). In a rat model of sepsis, intermittent fasting counteracts mental deficits preventing both LPS-induced elevation of IL-6, IL-1α ,IL-1β and TNF-α levels, and the LPS-induced reduction of BDNF levels in the hippocampus. IF stimulates also the secretion of IL-10 that is able to counteract NF-κB pro-inflammatory signaling and may inhibit the development of chronic neurodegenerative diseases [49].

Regarding specific nutrients and food groups, we did not find clear trends in line with the available scientific literature. In fact, while some dietary elements denoting a healthy diet, such as sodium, total fat, and processed meat were less consumed in individuals with better health, other factors, such as vitamin E and vegetables, were more consumed in those having worse. It may be possible that such individual elements alone were not enough to exert an effect on mental health status or that other factors, including the feeding time window duration, might play a stronger role or, at least, more clinically evident over a chronic habitual exposure.

Albeit among the first of its kind, the findings of this study should be considered in light of some limitations. First, the cross-sectional nature of the study does not permit to define a causal relationship, rather the association. Second, the structured assessment methods that were used to assess dietary habits, such as the FFQ, are known to be associated with recall bias. Third, we can only rely on average habits, but daily fluctuations of feeding.

Conclusions

In conclusion, restricting the daily time feeding window is associated with lower signs of mental health distress in individuals older than 70 years. No associations were found between feeding time window and any other single mental health outcomes (sleep quality, perceived stress, depressive symptoms). These findings require further investigation, with studies better designed, more controlled, and with a prospective approach.

Author Contributions

Conceptualization, W.C., J.G., G.G., F.G.; methodology W.C., J.G., G.G., F.G.; formal analysis, W.C., J.G., G.G., F.G.; writing—original draft preparation, W.C., J.G., S.C., G.C., R.F., F.C., G.G., F.G.; writing—review and editing, W.C., J.G., S.C., G.C., R.F., F.C., G.G., F.G.; supervision, R.F., F.C., G.G., F.G. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University of Catania (protocol code 802/23 December 2014).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Conflicts of Interest
The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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GENERAL DISCUSSION

Intermittent fasting

In recent years, a great attention has been paid by the scientific community to fasting and exploration of its possible effects toward human health.
Although to date intermittent fasting protocols represent an innovation in the field of dietetics, it must be considered that fasting has been practiced since the dawn of humankind, when it was imposed by limited access to food (Crittenden & Schnorr 2017). Humans have been hunter-gatherers for two million years and thus they often ate intermittently depending upon food availability. Evidence of our origins are those mechanisms that are conserved among mammals to counteract fasting, including organs for the uptake and storage of rapidly mobilizable glucose (liver glycogen stores), longer-lasting energy substrates, such as fatty acids in adipose tissue, or alternative fuel for the brain as ketone bodies. After the agricultural revolution (about ∼10,000 years ago) our ancestors changed their habits by eating more and more frequently (Paoli et al. 2019).
In western culture the habit of three or more meals every day has become consolidated and as a result, people in the Western World are constantly in the postprandial state (Lopez-Miranda & Marin 2010) often induced by nutrient-poor but highly calorie dense foods, while it is well known that the human body evolved to endure periods of fasting/starvation and thus accumulates easily excess calories in the form of adipose tissue (Mattson et al. 2017).
Considering the above, fasting seems to be an "old" new strategy to improve health or prevent diseases especially as it confers benefits on cell metabolism beyond calorie restriction (Hatori et al. 2012).
In general, Intermittent Fasting is commonly defined as the total abstinence of energy-containing foods and beverages for a period ranging from 12-36 hours. The majority of intermittent fasting protocols in the scientific literature can be grouped into one of three categories: whole-day fasting, alternate day fasting and time-restricted feeding (Tinsley & La Bounty 2015). Each form of intermittent fasting utilizes different periods of feeding and fasting. *Whole-day fasting* (WDF) is the simplest form of intermittent fasting as it typically consists of 1 to 2 non-consecutives days of complete fasting per week plus *ad libitum* eating on the other days. *Alternate-day fasting* (ADF) is characterized by an alternation between *ad libitum* feeding days and fasting days. *Time-restricted feeding* (TRF)

also usually called *Time Restricted Eating* (TRE) when it refers to humans, consists of daily fasting periods lasting 12–20 hours alternating with a daily four-to-twelve hour "feeding window". It is important to note that fasting means the complete abstinence from caloric intake, but some intermittent fasting programs allow small amounts of food consumption (up to approximately 25% of daily caloric requirements) during fasting days, meaning they are actually utilizing a "*modified fasting protocol*".

Effects of fasting on brain, cognitive and mental health

Recent studies (Manzanero et al. 2014; Kim et al. 2015; Mattson et al. 2018) have shown that Intermittent Fasting can have a significant effect on the brain neuroplasticity, neurogenesis, bioenergetics and resistance of the nervous system to injury and disease.
According to Mattson et al. (Mattson et al. 2018), the beneficial effects of a periodic fasting derive mainly from the switch of cellular fuel which occurs in absence of food with consequent cellular and molecular adaptations of neural networks.
After at least 12 hours of fasting, blood glucose levels and hepatic glycogen stores drop so the body is forced to find an alternative energy source to glucose for the brain and produces ketone bodies. Ketones (acetoacetate, beta-hydroxybutyrate and acetone), constitute an efficient source of energy and possibly enhance neuron bioenergetics and cognitive performance (Veech et al. 2001; Murray et al. 2016). The use of fasting or ketogenic diets has always aroused interest in neuroscience especially from the discoveries of the role of ketone bodies on seizure's control in children with refractory epilepsy (Martin et al. 2016). To date there are some promising studies investigating the effects of exogenous administration of ketone esters for the treatment of neurological disorders (Camberos-Luna & Massieu 2020).
Ketone bodies are more than just an energy source for neurons; the increased beta-hydroxybutyrate levels in hippocampal and cortical neurons induce the transcription of brain-derived neurotrophic factor (BDNF) (Shimazu et al. 2013). BDNF is a member of the neurotrophin family of proteins that plays critical roles in the development, maintenance and plasticity of the central and peripheral nervous systems (Marosi & Mattson 2014). BDNF also promotes the differentiation of neurons from stem cells, enhances neurite synaptogenesis and

outgrowth, stimulates mitochondria biogenesis and prevents programmed cell death/apoptosis. BDNF can also activate receptor tropomyosin-related kinase B (TrkB) enhancing synaptic plasticity, learning and memory by multiple transcriptional and post-transcriptional mechanisms that involve the PI3-kinase – Akt pathway and extracellular signal regulated kinases (ERKs 1 and 2). A decreased serum level of BDNF has been associated with insomnia and sleep deprivation, and it has been demonstrated that subjects suffering from current symptoms of insomnia and depression exhibited significantly lower serum BDNF levels (Castrén & Rantamäki 2010; Schmitt et al. 2016). Similarly, decreased BDNF levels have been detected in several neurodegenerative disorders including Alzheimer's, Parkinson's, and Huntington's diseases (Hock et al. 2000; Ferrer et al. 2000; Howells et al. 2000).

Fasting also induces the expression of the transcription factor peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) (Austin & St-Pierre 2012). PGC1α is considered the main inducer of mitochondria biogenesis which in turn improves neuron bioenergetics and enables synaptic plasticity. PPARα may also influence aging through the regulation of multiple damage and repair processes after exposure to many endogenous or environmental stressors. Moreover PGC1α modulates the expression of Nitric Oxide (NO) which has antioxidant and protective properties in the endothelium contributing to the preservation of brain microvasculature (Borniquel et al. 2006; Bernier et al. 2016) and is also critical for memory by acting on the maintenance of dendritic spines in the dentate gyrus of the hippocampus (Cheng et al. 2012). Interestingly, PGC1α can enhance BDNF expression (Wrann et al. 2013) suggesting a positive feedback mechanism in which BDNF stimulates PGC1α and vice versa.

Fasting being the catabolic stimulus par excellence determines a net decrease of all anabolic hormones including insulin and insulin-like growth factor (IGF-1). Conversely fasting increases AMP-activated protein kinase (AMPK) that stimulates autophagy, an intracellular degradation process that clears misfolded proteins and damaged organelles counteracting the anabolic action of mechanistic target of rapamycin (mTOR) (Wahl et al. 2016). A global reduction in insulin levels and an improved insulin sensitivity can be beneficial for neuron bioenergetics since the insulin-mediated effects on brain vasculature could cause chronic hypoperfusion and that prolonged hyperinsulinemia's pro-inflammatory effects may potentiate neurodegeneration (Craft & Watson 2004).

Regarding other hormonal effects, fasting also regulates leptin, adiponectin, and ghrelin levels that are main regulators of fat metabolism (Stern et al. 2016). Recent data suggest that sleep restriction may decrease levels of adiponectin in healthy subjects and that lower peripheral adiponectin levels have been associated with anxiety, mood, and stress-related affective disorders (Vuong et al. 2020), suggesting a pleiotropic effect of this hormone toward mental health. In particular, fasting lowers leptin levels that are associated with pro-inflammatory state and conversely increases ghrelin and adiponectin levels that have an effect on stimulation of hippocampal synaptic plasticity and on reduction of inflammation, respectively (Yamauchi et al. 2001; Baatar et al. 2011; Kim et al. 2015).
Chronic inflammation is involved in the pathogenesis of most chronic diseases including neurodegenerative diseases. The activation of microglia in the brain in response to injury or during aging determines the production of pro-inflammatory cytokines (i.e. TNFα, IL-1β, IL-6) and reactive oxygen species (ROS). Fasting suppresses inflammation by reducing the expression of pro-inflammatory cytokines such as interleukin 6 (IL6) and tumor necrosis factor α (TNFα) (Aksungar et al. 2007; Arumugam et al. 2010) and increasing the IFN-γ levels that may enhance synaptogenesis, regulate synaptic plasticity and control neurogenesis (Lee 2006). Finally, Chaix et al. (Chaix et al. 2014) investigated the effect of TRF vs. ad libitum feeding in and in vivo study and demonstrated higher concentrations of anti-inflammatory metabolites in TRF group, such as carnosine and anserine, which have shown therapeutic potential against the oxidative stress observed in pathologies characterized by cognitive dysfunctions (Caruso et al 2019a, Caruso et al. 2019b).

Time restricted feeding and chrononutrition

Time-restricted feeding is a form of intermittent fasting in which all nutrient intake occurs within a few hours (usually ≤12h) every day in order to extend the time spent in the fasted state (Di Francesco et al. 2018) without any attempt to alter nutrient quality or calories. The first evidence concerning the effects of a prolonged fasting window date back to studies on Ramadan and to recent ones regarding skipping breakfast or dinner (Garaulet et al. 2013). The mechanisms underlying the beneficial effects of TRF are not only related to the duration of fasting window per se, but also to other pathways involving circadian rhythms.

Circadian rhythms are self-sustained ~24h oscillations in physiology, metabolism and behavior. Although the circadian clock is cell autonomous, the master circadian clock is the hypothalamic suprachiasmatic nucleus (SCN) which mainly uses signals coming from photoreceptive retinal ganglion cell sending ambient light information to ensure that the circadian system match to the daily light\dark cycle (Bodoky et al. 1995). SNC also controls several secondary clocks distributed in the brain (extra-SCN) and in other organs such as liver, pancreas, adipose tissue and skeletal muscle (Rijo-Ferreira & Takahashi 2019) (Roenneberg & Merrow 2016; Stenvers et al. 2019). Light is the determining factor for SCN oscillations, however also timing of food intake affects the phase of the clock in peripheral tissues (Bondolfi et al. 2004), together with other factors. This close relationship between nutrition and circadian rhythms date back to our evolutionary history. For millions of years in the absence of artificial light the activities of our ancestors were delimited by the sunlight; food was probably scarce and primarily consumed during daylight hours, leaving long hours of overnight fasting and resting. With the advent of artificial light and industrialization, humans have undergone prolonged hours of illuminations and consequently extended consumption of foods especially late at night. This misalignment to circadian rhythms may help explain the known association between shift work and several diseases, including cardiovascular disease, diabetes, obesity, certain types of cancer and neurodegenerative diseases (Morris et al. 2012; Stevens et al. 2014). Thus, Time Restricted Feeding protocol seems to be a potential tool to counteract chronodisruption because it may improve the synchronization between an external stimulus, such as feeding, with the endogenous rhythms of central and peripheral clocks (Chaix et al. 2019).

The mechanisms underlying the beneficial effects of TRF are complex and many gene-expression studies indicate that it determines circadian rhythmicity of thousands of hepatic transcripts (Vollmers et al. 2012). In general, TRF restores cycling of metabolic regulators such as CREB (cAMP response element-binding protein), mTOR, AMPK and their downstream signaling pathways, as well as oscillations of the circadian clock and expression of their target genes. A few hours of fasting activates AMPK that determines the inhibition of mTOR activity and phosphorylates CRY proteins promoting their degradation (Lamia et al. 2009) which in turn modulates the repression of CLOCK/BMAL1-mediated transcription of the target genes. Additionally, nicotinamide adenine dinucleotide (NAD+) levels are influenced by fasting. NAD+ concentration regulates SIRT1

that modulates nuclear factors such as PPARg (peroxisome proliferator activated receptor gamma) and cofactors as PGC-1alfa (peroxisome proliferator activated receptor gamma coactivator 1-alpha) with many metabolic effects (Paoli et al. 2019).
On the contrary, feeding determines the activation of the insulin-pAKT-mTOR pathway which in turn determines downstream gene activities that promote anabolic processes, in fact mTOR phosphorylates casein kinase 1 (CK1) and glycogen synthase kinase 3 (GSK3), both of which phosphorylate the circadian clock component PER, altering its stability (Zheng & Sehgal 2010). The mTOR and AMPK pathways also modulate activities of downstream proteins, including the transcription regulators CREB, PPAR, FOXO, Hsf1, HNF, and PGC1 (Inoki et al. 2011).

Time restricted feeding and microbiome

Recent evidence has identified the intestinal microbiota not only as a key player in the responses to stress, anxiety, depression and cognition through the gut-brain axis (Adan et al. 2019) but also as a factors contributing to brain development and function (Salvucci 2019) (Ceppa et al. 2019). These effects are mediated by numerous intestinal peptides (Lach et al. 2018); for example the neuropeptide Y (NPY) regulates the release of GABA (Martin et al. 2018), Glucagon-like-peptide-1 (GLP-1) acts on the modulation response to stress through the HPA axis (Zietek & Rath 2016), Cholecystokinin (CCK) plays a role in anxiety like behavior through the activation of the CCK2 receptors in limbic regions (Ballaz 2017) and Corticotropin-releasing factor (CRF) plays a key role in response to chronic stress regulating cortisol secretion (Fox & Lowry 2013). Moreover, a reduced differentiation and\or a prevalence of detrimental bacterial species over others (also called dysbiosis) determines an increased permeability of the intestinal mucosa (leaky gut). In this condition bacteria easily cross the intestinal barrier, bind to circulating macrophages and monocytes determining an increase in the inflammatory state through the secretion of pro-inflammatory cytokines including TNF-a, IL-1, and IL-6.
Nutrition has a significant effect on function and composition of gut microbiota and it has been demonstrated that a plant-based diets, such as the Mediterrean diet, exert beneficial effects toward gut microbiome by increasing the diversity of intestinal bacteria (St-Onge & Zuraikat 2019). Preliminary studies have shown

a possible correlation between gut microbiota composition (i.e., a modification in the Firmicutes/Bacteroidetes/Clostridium ratio) and depressive state and response to chronic stress (Dash et al. 2015). Interestingly, humans exhibit a daily rhythm in the gut chemical environment. Studies have shown that function and composition of the gut microbiome change during the day (Deplancke et al. 2000; El Aidy et al. 2012; El Aidy et al. 2013). Moreover, both secretion of various digestive agents as gastric acids, saliva, bile, digestive enzymes and intestinal peristalsis decline late at night, suggesting that there is a link between circadian rhythm and microbiome (Hansen et al. 2010). The relationship between gut bacteria and internal clocks appears to be mutual; in fact, a time shift jet-lag in humans induces dysbiosis and dysbiosis itself can contribute to chronodisruption (Schoenfeld et al. 2015). Recent studies (Zarrinpar et al. 2014; Cignarella et al. 2018) suggest that Time Restricted Feeding improves the profile of gut microbiota through an increase in bacteria diversity especially of Lactobacillaceae, Prevotellaceae, and Bacteroidaceae families. Although data are currently limited, the link between circadian rhythms and microbiota offer an interesting rationale to shortening feeding window in order to sustain gut health and consequently counteract the deleterious effects of chronodisruption. An overview of the beneficial effects of IF is displayed in *figure 2*.

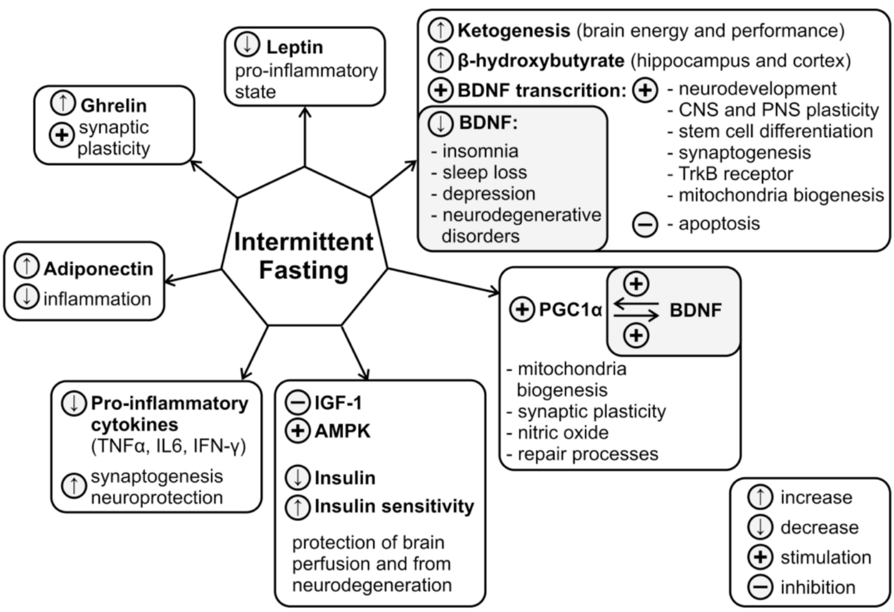

Figure 2. Schematic overview of the beneficial effects of Intermittent Fasting.

TRF and human findings

Although fasting may be promising in neurosciences, existing evidence on the effects of restricting time feeding windows and mental health is mainly derived from observational studies on Ramadan. Ramadan can be considered as a form of TRF in which individuals abstain from all food and drink from sunrise to sunset for approximately 30 days (Ismail et al. 2019). The effects of Ramadan fasting on mental health are heterogenous and domain specific. Studies on Muslims athletes during Ramadan showed that cognitive function was better in the morning, declining in the late afternoon, whereas performance in non-speed dependent accuracy measures was more resilient (Tian et al. 2011). The effects of Ramadan fasting on sleep quality are discordant as some studies show no significant effects while others report detrimental outcomes for sleep quantity and mental alertness (Boukhris et al. 2019). A reduction in REM sleep time during Ramadan, probably due to the consumption of a traditional large late meal before going to rest that leads to an increase in nocturnal body temperature which can disrupt sleep(Roky et al. 2000). Even though these studies are interesting, there are some issues that do not allow to appropriately compare Ramadan fasting to other forms of TRF; the duration of the fasting window varies based on geographical location and year, foods and drink consumption are extremely variable in each population and the cycle of eating and fasting is reversed as compared to natural circadian rhythms. Although expanding the fasting time window during the day seems to be beneficial, shifting food intake to the late hours as during Ramadan can partially reverse circadian rhythms. Eating in misalignment with circadian clocks may effect several cardiometabolic endpoints and the evidence is conflicting as some of the studies conducted during orthodox religious fasting reported that time restricted eating may be associated with better metabolic and glycemic profile (Karras et al. 2020a, Karras et al 2020b), while others that it may worsen glucose tolerance(Scheer et al. 2009; Morris et al. 2015; Wefers et al. 2018) reducing the overall benefits of fasting.

To our knowledge there are very few interventional studies exploring the effects of TRF or early time restricted feeding on humans and they mainly concern metabolic aspects such as weight reduction and\or insulin resistance.

For instance, Sutton et al. (Sutton et al. 2018) found that a 5-week of 8-h early time restricted feeding improved insulin levels, insulin sensitivity, b cell

responsiveness, blood pressure, and oxidative stress levels in men with prediabetes even though food intake was matched to the control arm and no weight loss occurred. Maintaining adequate blood pressure prevents cerebral microhemorrhages which contribute to cognitive impairment, geriatric psychiatric syndromes and gait disorders(Ungvari et al. 2017). These findings are also relevant because metabolic syndrome is another major risk factor for a variety of neurological diseases(Farooqui et al. 2012).
Moro et al. (Moro et al. 2016) also showed that TRF may reduce blood levels of many markers of inflammation such as TNFα, Il-6, and IL-1b, and, at the same time, may increase blood levels of adiponectin. Recent data have shown that sleep restriction may decrease levels of adiponectin in healthy individuals (Simpson et al. 2010) but intermittent fasting can raise the levels of this hormone (Cornelissen 2018). Moreover, lower adiponectin levels have been associated with anxiety and stress-related affective disorders (Vuong et al. 2020), suggesting an important effect of adiponectin on mental health.
Recently Jamshed et al.(Jamshed et al. 2019) firstly demonstrated that early TRF (eTRF) can increase BDNF levels in humans, a neurotrophin that plays a fundamental role in neuronal growth, development, and survival. Moreover, they found that 4 days of early TRF changes the expression of 6 circadian clock genes and upregulation of both SIRT1 and LC3A that have a role in autophagy. Autophagy has been shown to play a determinant role in protecting against multiple chronic disorders such as diabetes, heart disease, cancer, and neurodegenerative diseases, by recycling used and damaged proteins and organelles.

Limitations of time restricted feeding

TRF appears to be the most tolerable and promising IF protocol because it allows to induce benefits of a total fasting without reducing global calories and nutrients intake through the modulation of the timing of the feeding\fasting window during the day (Hatori et al. 2012).
Although there are several issues that should be taken into account when recommending TRF as a therapeutic strategy for a disease, because, as ay other treatment, it is not free from possible side effects and contraindications. In fact it is not recommended to prescribe an intermittent fasting protocol to patients at risk of malnutrition including those with a neurological disease such as persons

with Parkison’s Disease or Alzheimer's Disease (Włodarek 2019). Care should be also taken for diabetic patients on insulin therapy who may experience hypoglycemia. The same caution must be paid to patients with acute infection, renal stones, gastroesophageal reflux and eating disorders who may experience post-restriction hyperphagia. In the clinical practice fatigue, insomnia, nausea and headache are commonly present and considered as minor adverse effects of fasting (Finnell et al. 2018).

CONCLUSIONS

To date many interrelated cellular mechanisms are believed to contribute to the potential beneficial effects of TRF on the nervous system including improved cellular bioenergetics, enhanced neurotrophic factor signaling, reduced accumulation of oxidatively damaged molecules, and reduced neuro-inflammation. In particular time restricted eating exert neuroprotective mechanisms by up-regulating neurotrophic factors (BDNF and FGF2), protein chaperones (HSP-70 and GRP-78) and reducing levels of pro-inflammatory cytokines such as TNFα, IL-1β and IL-6. Fasting improves neurogenesis and synaptic plasticity, two essential mechanisms which can delay cognitive decay and neurodegenerative diseases. Interestingly, the effects of time restricted eating seem to be particularly relevant when the window of eating is in the first part of the day (early TRE) in line with circadian rhythms.

In our studies individuals having a feeding time window of 10 hours (FTW-10) or less were less likely to have impaired cognitive health; the association was significant also for those individuals having breakfast. No association was found between FTW-10 and overall mental health in the whole sample, despite individuals older than 70 years old undergoing a FTW-10 were less likely to have mental health distress than others with no restricted time feeding. Even though the results revealed possible beneficial effects of time restricted eating toward cognitive health, future studies are needed in order to confirm these results and better elucidate the mechanisms underlying the cross-talk between time restricted eating and brain health.

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