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Original Article

Assessment of nutritional habits and their impact on clinical symptoms in schizophrenia and major depressive disorder

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ABSTRACT

The results of nutritional interventions with long-chain, polyunsaturated *n*-3 fatty acids (PUFAs) with regard to the course of psychiatric illnesses are inconsistent. Poor dietary habits and associated nutritional deficiencies have recently been identified as potential treatment targets. The aim of our study was to compare the dietary habits of patients with schizophrenia and major depression and relate them to clinical symptoms at the time of illness exacerbation or age at onset. The frequency of consumption of selected foods (PUFA-rich or high glycaemic index foods) was determined using a self-report questionnaire. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) and the Hamilton Depression Rating Scale (HDRS) for schizophrenia and major depression, respectively. Four dietary factors and the distribution of patients within tertiles corresponding to infrequent, less frequent or more frequent consumption of each food group were assessed by factor analysis. The differences in dietary habits observed between the two patient groups were of medium or strong effect size. The consumption of savoury snacks and sweetened beverages changed the negative PANSS scores by 8.1%, while psychopharmacotherapy in schizophrenia mainly influenced the positive PANSS and PANSS total scores. In major depression, the consumption of olive oil and PUFA-rich foods changed the age at onset of illness by 6.6%. Dietary habits had no effect on the severity of clinical symptoms. By reducing the frequency of eating unhealthy foods, schizophrenia patients were able to lower their negative PANSS scores. Patients with major depressive disorder were able to delay the onset of clinical symptoms if they consumed olive oil and PUFA-rich foods more frequently.

KEYWORDS: major depressive disorder, diet, feeding behaviour, psychiatric status rating scales, schizophrenia.

INTRODUCTION

Schizophrenia (SCH), with a prevalence of 1% worldwide, and major depressive disorder (MDD), with a higher lifetime prevalence of 9.9% to 21.0%, are extremely debilitating mental disorders [1]. The clinical features that clearly differentiate these two disorders include not only the aetiology and prevalence, but also the age of onset, the course

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and duration of the illness, the gender ratio, and the depressive and cognitive symptoms. However, there are potential similarities at the molecular level. SCH and MDD are consistently associated with chronic, low-grade peripheral inflammation, deficiency of long-chain polyunsaturated fatty acids of the *n*-3 family (LC-PUFAs) in the membranes of central and/or peripheral cells, cognitive impairment [2-4] and neuroinflammation, at least in a subset of patients [5-8]. Although inflammation is part of the pathological mechanism in psychiatric disorders, the nature of this link is not yet fully understood. The above features, in conjunction with diet, can be considered important factors in the development and progression of the disease. A diet rich in *n*-3 LC-PUFAs, such as green leafy vegetables, fruit, nuts, seeds and oily fish, has an anti-inflammatory effect in cells, whereas a diet in which *n*-6 PUFAs or saturated fatty acids predominate increases cellular inflammation [9, 10]. Dietary LC-PUFAs are potent modulators of peroxisome proliferator-activated receptors (PPARs), a superfamily of nuclear receptors that control glucose and lipid metabolism. Therefore, the type and ratio of dietary fats can have a decisive influence on cell metabolism and inflammatory processes.

Poor dietary habits have been demonstrated in patients with psychiatric disorders, including SCH and MDD [11-13]. Recent evidence suggests that a significant proportion of them are at risk of malnutrition despite being overweight [14]. In addition to consuming foods with low nutritional value and high glycaemic index (*i.e.* an unhealthy diet), patients with MDD exhibit behaviours such as emotional and uncontrolled eating, which have been shown to affect their mood, somatic and cognitive symptoms [15, 16]. An increased rate of long-term obesity has also been linked to depression [17]. Unhealthy dietary habits, including increased consumption of saturated fats, alcohol and sugar and decreased consumption of vegetables, fruit and fish, may also be associated with disturbances in cell signalling, cell transport, mitochondrial function and metabolic traits such as glucose intolerance and lipid abnormalities, which may be important in the clinical expression and pathogenesis of the disease [18]. In non-medicated patients with first-episode SCH, the risk of developing metabolic syndrome is additionally influenced by the use of antipsychotics [19].

Some studies have shown that dietary interventions with *n*-3 LC-PUFAs may reduce the severity of symptoms in the early stages of SCH spectrum disorders or be beneficial in their prevention [20]. The anti-inflammatory properties of the *n*-3 family of LC-PUFAs may also be critical in the prevention and treatment of depression [21, 22]. Recent reviews and meta-analyses confirmed the association between adherence to the Mediterranean diet and higher consumption of unsaturated fatty acids, and lower risk (or alleviation of symptoms) for various mental disorders [20, 23, 24]. The strength of the associations found was generally weak; therefore, further research was suggested.

In this study, we aimed to assess and compare the dietary habits of two groups of patients with different psychiatric diagnoses (SCH and MDD) who received psychopharmacotherapy but no nutritional support/intervention prior to an episode of illness, and to relate the results to specific clinical outcomes. As psychiatric disorders develop over the years, dietary habits could play a role in their development. Therefore, we also investigated whether dietary habits could have influenced age at onset. Smoking status, socioeconomic status, gender, body mass index (BMI), duration of illness and adherence to psychopharmacotherapy, *i.e.* factors that contribute to the severity of symptoms, were also included in the analyses. The results could shed light on whether there is a relationship between dietary habits and symptom severity in SCH and MDD, and provide a rationale for the introduction of nutritional support (*i.e.* counselling to change eating behaviour) during psychiatric treatments.

MATERIALS AND METHODS

Participant recruitment, demographic and clinical data

The study was conducted in accordance with the ethical standards set out in the latest version of the Declaration of Helsinki. The study was reviewed and approved by the Ethics Committee of the University of Rijeka, Faculty of Medicine, Croatia, and the Ethics Committee of the Clinical Hospital Centre Rijeka, Croatia. After a detailed explanation of the procedures, written informed consent was obtained from each participant. A sample of 211 patients with clinical diagnoses of SCH or MDD was recruited

between 2015 and 2018 at the Department of Psychiatry, Clinical Hospital Centre Rijeka, Croatia. Clinical diagnoses were assessed by two trained psychiatrists according to DSM-5 criteria using the structured clinical interview at the last hospital admission. A total of 94 SCH patients and 117 MDD patients from the northern Adriatic region (Primorsko-goranska and neighbouring Istarska counties) who met the following inclusion criteria were included in the study: Age between 18 and 75 years, prescription of psychotropic drugs for at least six months, and ability to complete a questionnaire on dietary habits and provide written informed consent. Clinical data were collected using the Positive and Negative Syndrome Scale (PANSS) and the Hamilton Depression Rating Scale (HDRS) during the last hospitalisation for an exacerbation of the illness. Demographic data and smoking status were collected in face-to-face interviews using a structured questionnaire. Smokers were defined as those who smoked more than one cigarette per day and had been smoking for more than one year. Non-smokers were defined as people who smoked occasionally or had stopped smoking for more than a year. Age at onset was taken from medical records and defined as the patient's age at the time of first hospitalisation for a psychotic or depressive episode. The duration of illness was calculated as the period in years between the age at onset and the actual age of the patient. Non-compliance with psychopharmacotherapy was recorded and defined as non-compliance with treatment recommendations at least one month prior to assessment. BMI was calculated based on patient-reported height and weight. The number of years of completion of a formal programme of primary, secondary or tertiary education served as an indicator of socioeconomic status. The demographic and clinical data are shown in Table 1.

Dietary assessment

The data on the patients' dietary habits were collected using the authors' original questionnaire. The questionnaire consisted of 12 questions on the frequency of consumption of selected foods. Foods commonly included in the Mediterranean diet typical of the geographical region were selected for this study, including fish (oily fish, lean fish and canned fish), fruit (all types of fresh or dried fruit), vegetables (chard, lettuce, kale, cabbage, spinach and other types), nuts (walnuts, hazelnuts, almonds, cashews and other types), dairy products (all types of cheese, yoghurt and butter) and olive oil. The Mediterranean diet is rich in monounsaturated and polyunsaturated fatty acids (PUFA), which are natural ligands of PPAR genes/proteins known to regulate carbohydrate, lipid and protein metabolism [25]. The questionnaire

Table 1. Demographic and clinical data.

		SCH[a] n=94	MDD[a] n=117	χ^2 or Z	P
Males/ Females, n		41/53	22/95	15.324	<0.0001
Age, years	**All**	37 (18.0 - 60.0)	56.0 (28.0 - 75.0)	9.696	0.000
	Males	36.0 (21.0 – 60.0)	59.0 (30.0 – 75.0)	5.489	0.000
	Females	40.0 (18.0 – 60.0)	56.0 (28.0 - 75.0)	7.232	0.000
Age of onset, years	**All**	24.0 (10.0 - 45.0)	48.0 (18.0 - 75.0)	10.145	0.000
	Males	26.0 (16.0 – 44.0)	49.5 (20.0 – 75.0)	5.335	0.000
	Females	24.0 (10.0 - 45.0)	46.0 (18.0 – 75.0)	8.202	0.000
Illness duration, years	**All**	10.0 (0.5 - 41.0)	6.0 (0.5 - 38.0)	-2.500	0.013
	Males	9.0 (0.5 – 32.0)	2.0 (0.5 – 30.0)	-1.944	0.052
	Females	11.0 (0.5 – 41.0)	7.0 (0.5 – 38.0)	-2.493	0.013
Level of education, 0/1/2	**All**	6/69/19	23/69/25	8.376	0.015
	Males	1/34/6	0/15/7	2.986	ns
	Females	5/35/13	23/54/18	4.911	ns
Smokers/nonsmokers	**All**	55/39	67/50	0.033	ns
	Males	16/25	10/12	0.244	ns
	Females	23/30	40/55	0.023	ns

Table 1 continued ..

Obese/nonobese	**All** **Males** **Females**	23/71 29/12 42/11	20/97 18/4 79/16	1.747 0.929 0.349	ns ns ns
n-3 PUFA supplementation, yes/no	**All** **Males** **Females**	18/76 7/34 11/42	17/100 5/17 12/83	0.505 0.297 1.710	ns ns ns
Comorbidities, 0/1/≥2	**All** **Males** **Females**	63/24/7 28/8/5 35/16/2	20/44/53 4/11/7 16/33/46	61.652 14.385 45.016	0.000 <0.001 0.000
Adherence to psychopharmaco-therapy, 0/1	**All** **Males** **Females**	25/69 12/29 13/40	23/94 6/16 17/78	1.428 0.028 0.926	ns ns ns
BMI, kg/m^2	**All** **Males** **Females**	25.3 (15.6 - 52.5) 26.5 (17.8 – 52.5) 24.6 (15.6 – 48.8)	24.6 (15.8 - 53.0) 25.7 (21.0 – 31.0) 24.4 (15.8 – 53.0)	-0.213 0.094 0.314	ns ns ns
PANSS positive symptom score	**All** **Males** **Females**	24.5 (11.0-38.0) 27.0 (12.0-38.0) 23.0 (11.0-37.0)	-	-	-
PANSS negative symptom score	**All** **Males** **Females**	26.0 (15.0-47.0) 27.0 (18.0-44.0) 25.0 (15.0-47.0)	-	-	-
PANSS general psychopathology symptom score	**All** **Males** **Females**	50.0 (28.0-78.0) 52.0 (40.0-78.0) 48.0 (28.0-70.0)	-	-	-
PANSS total score	**All** **Males** **Females**	100.0 (56.0-150.0) 105.0 (74.0-150.0) 97.0 (56.0-149.0)	-	-	-
HDRS score	**All** **Males** **Females**	- - -	20.0 (14.0-31.0) 20.0 (14.0-29.0) 20.0 (14.0-31.0)	-	-

[a]values are given as ratios or medians and ranges; BMI, body mass index; HDRS, Hamilton Depression Rating Scale; Level of education, 0, primary or no education, 1, secondary education, 2, tertiary education; MDD, Major Depressive Disorder; n, number of patients; ns, not significant; PANSS, Positive and Negative Syndrome Scale; SCH, Schizophrenia; Adherence to psychopharmacotherapy, 0, nonadherence 1, adherence; Z, the Mann-Whitney U test.

included red meat, poultry and foods with low PUFA content and high glycaemic index (various types of salty snacks, sweets and sugary or artificially sweetened drinks). Dietary habits were assessed based on daily, weekly, and monthly portions. A 7-point scale was offered for each food: never consumed (point 0), rarely consumed (point 1), one portion per month (point 2), several portions per month (point 3), one portion per week (point 4), several portions per week (point 5) or one or more portions per day (point 6). The questionnaire was designed in such a way that it was possible to differentiate between frequent, less frequent, and infrequent consumers.

Statistical analysis

Statistical analyses were performed with Statistica for Windows, version 14.0.0.15 (©TIBCO Software Inc., USA). Continuous variables (clinical variables, BMI, age and disease duration) were described by medians and ranges, and Kolmogorov-Smirnov tests confirmed the non-normal distribution of the variables. The frequencies of food consumption were compared using chi-square. Spearman rank correlations were calculated between ordinal data sets.

To assess associations between dietary habits and clinical data, ordinal values associated with each

dietary item for the entire cohort (N = 211) were first analysed using principal component-based factor analysis. Four factors (F1-F4) were extracted. Factor loadings > 0.40 identified fruit, nuts, green leafy vegetables (GLVs) and olive oil within F1, lean, oily and tinned fish within F2, red meat, poultry and dairy within F3 and savoury snacks, sweets and soft drinks within F4 (Table 2). Based on a scree test (eigenvalues > 1.0), all four factors were included in the subsequent analyses. First, each factor was categorised into tertiles based on the factor loading values, starting with the most negative and ending with the most positive value; each study participant was assigned to a low, medium or upper tertile, resulting in a specific distribution pattern within each factor. For each factor, the distribution of SCH and MDD patients was based on the assumption that patients in the low tertiles were less likely to consume a particular group of foods, while patients in the medium and upper tertiles were more frequent consumers. The assignment of a patient to a particular tertile was assigned a dummy variable (1 for low tertile, 2 for middle tertile and 3 for upper tertile), and the given distribution patterns were used in the subsequent statistical analyses. The effects of possible strong predictors of age of onset or symptom severity, such as the distribution within the four dietary factors, disease duration, gender, psychotropic drug therapy, smoking status, *n*-3 PUFA supplementation status, presence of comorbidities, socioeconomic status, and/or BMI, were tested using a stepwise multiple regression model. The F value for adding and removing variables was set to 4 and 1, respectively. Differences between data groups were tested post hoc using non-parametric tests for two or more independent samples. Significance was set at $p < 0.05$.

RESULTS

Demographic and clinical data

The two patient groups differed significantly in terms of gender ratio, age at hospitalisation, age at onset, duration of disease, number of comorbidities and socioeconomic status (Table 1). At the time of the study, the MDD patients, who were predominantly female, were significantly older than the SCH patients and had significantly more comorbidities. The average age in the MDD and SCH groups was 56.0 and 37.0 years, respectively. The MDD group also had a lower socioeconomic status: 19.7% (23/117) of patients, all women, had eight years of formal education compared to 6.4% (6/94) in the SCH group. Patients with post-secondary education, *i.e.* more than 12 years of formal education, accounted for about 20% in both groups (19/94 and 25/117 respectively). At the time of the study, the SCH patients had been ill for longer and were significantly older at the onset

Table 2. Factor loading score distribution[a].

Variables	Factor 1	Factor 2	Factor 3	Factor 4
Lean fish	0.320	**0.744**	0.044	-0.042
Oily fish	0.385	**0.681**	0.051	0.049
Tinned fish	-0.253	**0.659**	0.143	0.005
Fruit	**0.768**	-0.057	0.194	0.012
Olive oil	**0.754**	0.131	-0.070	-0.135
Nuts	**0.620**	0.178	0.088	-0.014
Green leafy vegetables	**0.527**	0.087	0.355	-0.265
Savoury snacks and sweets	0.005	-0.116	0.076	**0.837**
Soft drinks	-0.179	0.198	-0.042	**0.761**
Poultry	-0.028	0.100	**0.831**	-0.127
Red meat	0.163	0.337	**0.708**	0.133
Dairy products	0.346	-0.232	**0.533**	0.177

[a]Factor loading scores >0.40 appear in bold.

of the disease (median 24.0 years and 48.0 years respectively). The two groups did not differ with regard to smoking status, BMI or the proportion of obesity, the frequency of *n*-3 LC PUFA supplements or the proportion of patients who did not respond to psychopharmacotherapy (Table 1). There were also no differences in the distribution of BMI categories between the two groups (Supplementary Table 1). The proportion of obese patients (BMI ≥30) was 17.1% in the MDD group and 24.5% in the SCH group. Compared to the women, the male SCH patients had higher scores in all PANSS scales (Table 1). No difference was found between the genders in the HDRS scores of the MDD patients.

Dietary habits and dietary item analyses

In order to compare the dietary habits of the patients in the study, we reduced the number of foods analysed using a factor analysis. Significant differences in the distribution of SCH and MDD patients were found for dietary factors 1, 3 and 4, while the differences for factor 2 did not reach significance (Figure 1). The differences found were of small or medium effect size and mainly associated with the upper and lower tertiles of F1 and F4 [$OR_{F1\ lower\ tertile}$ = 1.884 (95% CI 1.057 - 3.356), P < 0.05; $OR_{F1\ upper\ tertile}$ = 0.439 (95% CI 0.240 – 0.803), P < 0.01; $OR_{F4\ lower\ tertile}$ = 0.286 (95% CI 0.152 – 0.537), P=0.000; $OR_{F4\ upper\ tertile}$ = 4.087 (95% CI 2.222 – 7.517), P=0.000], lower tertile of F3 [$OR_{F3\ lower\ tertile}$ = 2.243 (95% CI 1.254 – 4.014), P < 0.01], and middle tertile of F2 [$OR_{F2\ middle\ tertile}$ = 0.529 (95% CI 0.292 – 0.958), P < 0.05] (Figure 1). With respect to F1, ~40% of SCH patients were distributed in the lower tertile; at the same time, ~40% of MDD patients were distributed in the upper tertile. For F4, 50% of SCH patients were in the upper tertile compared to 20% of MDD patients, while the majority of MDD patients were in the lower tertile. Significantly more SCH patients were in the lower tertile of F3 (> 40%), compared to > 20% of patients in the MDD group (Figure 1).

To better understand the dietary habits of the two groups, we analysed the frequency of consumption of each food item (Table 3). Significant differences in the frequency of food consumption between the two patient groups were found in relation to olive oil, soft drinks, savoury snacks and sweets, fatty fish, GLVs, red meat and poultry (Table 3). Almost 60% of the patients in the study never or rarely consumed olive oil. In the MDD group, 70.9% rarely consumed it. In the SCH group, the percentage was lower, but infrequent consumers of olive oil

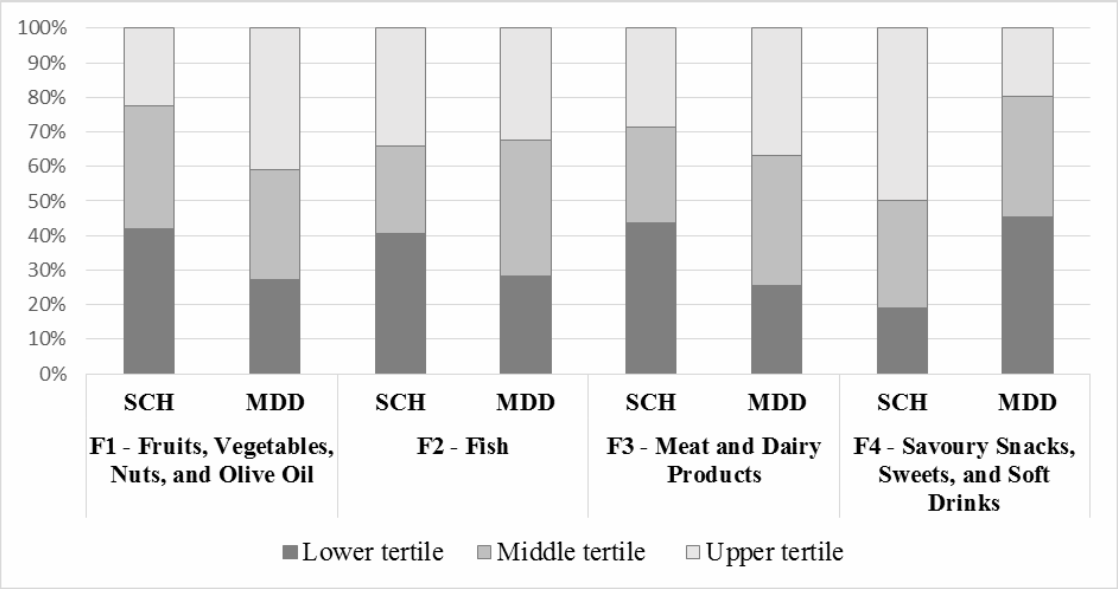

Figure 1. Distribution of the lower, middle and upper tertiles of four nutritional factors in schizophrenia (SCH) and major depressive disorder (MDD).

Table 3. Frequencies of dietary item consumption.

Dietary Items	Frequencies	All		SCH		MDD		χ^2	df	
		n=211	%	n=94	%	n=117	%	SR	t	P
Lean fish	**Often**	7	3.3	4	4.3	3	2.6	1.655	2	0.437
	Less often	144	68.2	60	63.8	84	71.8	0.051	0.745	0.457
	Rarely	60	28.4	30	31.9	30	25.6			
Oily fish	**Often**	0	0.0	0	0.0	0	0.0	6.100	1	0.014
	Less often	138	65.4	53	56.4	85	72.6	0.170	2.493	0.013
	Rarely	73	34.6	41	43.6	32	27.4			
Tinned fish	**Often**	4	1.9	3	3.2	1	0.9	3.496	2	0.174
	Less often	58	27.5	30	31.9	28	23.9	-0.118	-1.711	0.089
	Rarely	149	70.6	61	64.9	88	75.2			
Green leafy vegetables	**Often**	151	71.6	59	62.8	92	78.6	7.902	2	0.019
	Less often	58	27.5	33	35.1	25	21.4	0.179	2.638	0.009
	Rarely	2	0.9	2	2.1	0	0.0			
Nuts	**Often**	46	21.8	14	14.9	32	27.4	5.018	2	0.081
	Less often	88	41.7	41	43.6	47	40.2	0.138	0.017	0.045
	Rarely	77	36.5	39	41.5	38	32.5			
Fruits	**Often**	159	75.4	66	70.2	93	79.5	3.426	2	0.180
	Less often	45	21.3	23	24.5	22	18.8	0.113	1.646	0.101
	Rarely	7	3.3	5	5.3	2	1.7			
Olive oil	**Often**	44	20.8	26	27.7	18	15.4	16.179	2	0.0003
	Less often	43	20.4	27	28.7	16	13.7	0.260	3.896	0.0001
	Rarely	124	58.8	41	43.6	83	70.9			
Savoury snacks and sweets	**Often**	77	36.5	42	44.7	35	29.9	11.671	2	0.003
	Less often	96	45.5	44	46.8	52	44.4	-0.214	-3.174	0.002
	Rarely	38	18.0	8	8.5	30	25.6			
Soft drinks	**Often**	27	12.8	22	23.4	5	4.3	22.431	2	0.0001
	Less often	75	35.5	37	39.4	38	32.5	-0.304	-4.621	0.0001
	Rarely	109	51.7	35	37.2	74	63.3			
Red meat	**Often**	22	10.4	15	16.0	7	6.0	6.299	2	0.043
	Less often	120	56.9	53	56.4	67	57.3	0.145	2.120	0.036
	Rarely	69	32.7	26	27.6	43	36.7			
Poultry	**Often**	108	51.2	38	40.4	70	59.8	8.458	2	0.016
	Less often	94	44.5	50	53.2	44	37.6	0.200	2.944	0.004
	Rarely	9	4.3	6	6.4	3	2.6			
Dairy products	**Often**	188	89.1	85	90.4	103	88.0	0.309	2	0.857
	Less often	18	8.5	7	7.5	11	9.4	-0.038	-0.549	0.584
	Rarely	5	0.5	2	2.1	3	2.6			

SCH, Schizophrenia; MDD, Major Depressive Disorder; SR, Spearman's Rank; n, number of patients; df, degrees of freedom; often, daily or several times a week; less often, once a week or several times a month; rarely, several times a year or never.

were still the most common (43.6%) (Table 3). The consumption of savoury snacks, sweets and soft drinks showed different patterns in the two groups. Only 8.5% of SCH patients compared to 25.6% in the MDD group consumed savoury snacks and sweets occasionally, but only 4.3% of MDD patients compared to 23.4% of SCH patients consumed soft drinks once a week or daily. Regarding red meat consumption, the proportion of daily consumers was low in both groups (16.0% and 6.0% in the SCH and MDD groups, respectively), while the proportion of infrequent consumers was quite high (27.6% and 36.7% in the SCH and MDD groups, respectively). The patients in the study mainly consumed poultry: 40.4% and 59.8% of the SCH and MDD patients consumed it several times a week or daily. A very small percentage of patients rarely consumed poultry: 6.4% and 2.6%, respectively. A significant proportion of SCH and MDD patients rarely or never consumed fish: 43.6% and 27.4% for fatty fish, 31.9% and 25.6% for lean fish and 64.9% and 75.2% for tinned fish. With the exception of tinned fish, most patients consumed fish less frequently (less than several times a week). Nuts were also consumed rather infrequently by the patients in the study. In fact, 41.5% of SCH patients and 32.5% of MDD patients rarely or never consumed nuts. About 40% of each group consumed nuts less frequently. Finally, 37.2% of SCH patients compared to 21.4% of MDD patients consumed GLVs less than once a week.

Although the frequencies were significantly different, the patterns of GLVs consumption were similar in both patient groups. Only the SCH patients (0.9% of all patients in the study) reported not consuming GLVs or consuming them infrequently. Similar frequencies and patterns were found for the consumption of fruit and dairy products. Although most patients consumed at least several portions of fruit and dairy products per week, 24.6% consumed fruit and 9% dairy products less frequently or never.

Correlations between dietary habits and clinical characteristics

Correlations between patients' dietary habits and their clinical characteristics were analysed using multiple regression analyses and non-parametric post-hoc tests (Tables 4 and 5). Three PANSS subscales (positive, negative and general psychopathology scales), the PANSS total score and age at onset were dependent variables for SCH. For MDD, the HDRS score and age at onset were the dependent variables. Dietary factors, BMI, gender, adherence to psychopharmacotherapy, smoking status, socioeconomic status and the presence of comorbidities were analysed as independent predictors. Several predictors were identified. Non-adherence to psychopharmacotherapy was primarily associated with higher positive PANSS scores (β=-0.31, $P < 0.01$) and higher PANSS total symptom scores (β=-0.22, $P < 0.05$) (Table 4), which was later confirmed by post-hoc analyses (Table 5). Gender significantly influenced the PANSS general psychopathology score (β=-0.35, $P < 0.01$) and the PANSS total score (β=-0.30, $P < 0.01$) (Table 4). All PANSS scores were higher in men than in women (Table 1). In the multiple regression analyses, BMI explained 4%-5% of the variation in all PANSS symptoms except the positive PANSS score (Multiple R^2 change, Table 4). Post-hoc analyses confirmed an association between PANSS total score and BMI (Table 5). In all cases, the beta coefficient values indicated a negative correlation between BMI and PANSS symptom severity. Dietary habits for high glycaemic index foods (F4) were also expected to predict PANSS symptom scores for negative and general psychopathology in SCH. More frequent consumption was associated with higher symptom scores (Table 4). Post-hoc tests confirmed the significance of F4 for the negative PANSS score (Z=7.087, $P < 0.05$) (Table 5), with dietary habits describing 8.1% of the variation in the negative PANSS symptom score (Table 4). In MDD patients, dietary habits did not predict symptom severity, but more frequent consumption of healthy foods (F1) was associated with a delay in disease onset (Table 4). Food consumption of F3 and F1 explained altogether 9.5% of the variability observed in age of onset in SCH (Multiple R^2, Table 4), although post-hoc analyses confirmed a significant correlation in MDD but not SCH patients (Table 5). No influence of dietary habits on positive PANSS or PANSS total symptom scores was found in SCH.

Table 4. Summary of multiple regression analyses of clinical features.

Dependent variable	Predictor	Step in/out	β	Multiple R^2	Multiple R^2 change	F	P
PANSS positive symptom score[a]	Psychopharmacotherapy	1	-0.31	0.097	0.097	9.895	0.002
PANSS negative symptom score[a]	Dietary factor 4	1	0.31	0.081	0.081	8.163	0.005
	Body mass index	2	-0.21	0.126	0.044	4.587	0.035
PANSS general psychopathology symptom score[a]	Sex	1	-0.35	0.112	0.112	11.584	0.001
	Body mass index	2	-0.24	0.159	0.048	5.158	0.026
	Dietary factor 4	3	0.23	0.210	0.050	5.746	0.019
PANSS total score[a]	Sex	1	-0.30	0.079	0.079	7.926	0.006
	Psychopharmacotherapy	2	-0.22	0.143	0.064	6.817	0.011
	Body mass index	3	-0.20	0.180	0.037	4.059	0.047
Age at onset[a]	Dietary factor 3	1	-0.22	0.053	0.053	5.101	0.026
	Dietary factor 1	2	-0.21	0.095	0.042	4.258	0.042
Age of onset[b]	Dietary factor 1	1	0.27	0.066	0.066	8.069	0.005
	Comorbidities	2	0.18	0.098	0.032	4.079	0.046
HDRS score[b]	No predictors	-	-	-	-	-	-

[a]Schizophrenia, [b]Major Depressive Disorder; HDRS, Hamilton Depression Rating Scale;
Other predictors: age, illness duration, smoking status, level of education (for age at onset analysis age and illness duration were not included).

DISCUSSION

In the present study, we compared the dietary habits of SCH and MDD patients and investigated possible associations with the severity of the patients' clinical symptoms. We found differences of small (F1-F3) or moderate effect size (F4) between the dietary habits of SCH and MDD patients (Figure 1) and an influence of dietary habits on certain clinical symptoms, *i.e.* PANSS scores for negative symptoms in SCH and age at disease onset in MDD patients (Tables 4 and 5).

Although SCH patients generally had worse eating habits than MDD patients (Table 3), our data suggest poor dietary habits in both groups, which is consistent with previous reports of poor eating habits in people with psychiatric disorders [26, 27]. The vast majority of patients did not regularly consume red meat (~90%) and fish (>95%), while a significant proportion of them did not regularly consume poultry, nuts and olive oil (~50% to ~80%) (Table 3). The percentages for irregular consumption of fruits, groceries and dairy products are lower: about 25%, 28% and 9% of all patients, respectively. Unhealthy foods were consumed more frequently by SCH patients compared to MDD patients: 44.7% and 29.9% consumed savoury snacks and sweets daily or several times a week, respectively. For soft drinks, the percentage of frequent consumers was lower, although the distribution patterns were significantly different between the two groups: 23.4% versus 4.3% (Table 3). This is lower than that in the studies by Sorić *et al.* [28] conducted on a different Croatian SCH sample. They found that 42.9% of SCH patients consumed carbonated soft drinks daily. Fruit and vegetable intake were also below recommended levels and 47.9% had metabolic syndrome. They concluded that dietary interventions can be effective in preventing the development of metabolic syndrome in hospitalised SCH patients. A recent meta-analysis confirmed the non-linear association between increased consumption of sugary or artificially sweetened beverages, type 2 diabetes mellitus, cardiovascular disease and all-cause mortality [29].

Our patients with MDD and SCH may be at higher risk of malnutrition, as irregular consumption of

Table 5. Medians and ranges of the predicted clinical variables in the study.

Variables	Predictor		n	Median (range)	H/Z	P
PANSS positive score[a]	Psychopharmaco-therapy	*Adherence* *Nonadherence*	69 25	24.0 (11.0-38.0) 29.0 (18.0-37.0)	-2.800	0.005
PANSS negative score[a]	Dietary factor 4	*Lower tertile*	18	24.0 (15.0-38.0)	7.087	0.029
		Middle tertile	29	24.0 (15.0-46.0)		
		Upper tertile	47	26.0 (18.0-47.0)		
	Body Mass Index	*< 18.5* *18.5 – 24.9* *25.0 - 29.9* *≥ 30*	5 40 26 23	24.0 (22.0-28.0) 26.6 (18.0-46.0) 27.0 (15.0-44.0) 24.0 (15.0-47.0)	4.412	0.220
PANSS general psychopathology score[a]	Body Mass Index	*< 18.5* *18. – 24.9* *25.0 - 29.9* *≥ 30*	5 40 26 23	52.0 (41.0-55.0) 51.0 (28.0-67.0) 51.5 (36.0-78.0) 46.0 (28.0-70.0)	7.568	0.056
	Dietary factor 4	*Lower tertile*	18	45.5 (36.0-65.0)	4.423	0.110
		Middle tertile	29	50.0 (28.0-65.0)		
		Upper tertile	47	51.0 (36.0-88.0)		
PANSS total score[a]	Psychopharmaco-therapy	*Adherence* *Nonadherence*	69 25	98.0 (56.0-150.0) 107.0 (79.0-149.0)	-2.636	0.008
	Body Mass Index	*< 18.5* *18.5 – 24.9* *25.0 - 29.9* *≥ 30*	5 40 26 23	99.0 (78.0-110.0) 103.5 (70.0-141.0) 102.5 (72.0-150.0) 93.0 (56.0-149.0)	8.443	0.038
Age of onset[a]	Dietary factor 3	*Lower tertile*	41	23.0 (14.0-34.0)	4.392	0.111
		Middle tertile	26	26.0 (10.0-40.0)		
		Upper tertile	27	26.0 (15.0-45.0)		
	Dietary factor 1	*Lower tertile*	39	28.0 (10.0-45.0)	4.308	0.116
		Middle tertile	33	24.0 (14.0-44.0)		
		Upper tertile	22	23.0 (16.0-36.0)		
Age of onset[b]	Dietary factor 1	*Lower tertile*	29	39.0 (18.0-64.0)	11.241	0.004
		Middle tertile	41	49.0 (24.0-68.0)		
		Upper tertile	47	51.0 (18.0-77.0)		
	Comorbidities	*0*	20	40.0 (20.0-66.0)	2.814	0.245
		1	44	49.0 (18.0-64.0)		
		≥2	53	40.0 (20.0-66.0)		

[a]Schizophrenia; [b]Major Depressive Disorder; H, Kruskal-Wallis test; n, number of patients; Z, Mann-Whitney U test; lower tertile: rare consumption, up to once a month; middle tertile: moderately frequent consumption, up to once a week; upper tertile: frequent consumption, several times a week or every day.

fish, meat, nuts and GLVs is usually associated with inadequate intake of essential nutrients and micronutrients such as the *n*-3 family of PUFAs, amino acids, B vitamins and minerals [27, 30-32]. In addition, irregular consumption of olive oil reduces the potential beneficial effects of *n*-9 PUFAs and other bioactive compounds found in extra virgin olive oil on patients' overall health [33]. Regular consumption of foods rich in *n*-3 PUFA is important for everyone's overall health, probably even more so for patients with SCH or MDD. Besides adipose tissue the brain contains the most lipids in the body, and *n*-3 and *n*-6 LC-PUFAs are the main building blocks for neuronal membranes [34]. The synthesis of LC-PUFA is very limited in neurones and also slows down in the liver with increasing age. This applies in particular to the *n*-3 family of LC-PUFAs (EPA and DHA), as the essential alpha-linolenic acid (ALA) obtained from plants can only be converted into LC-PUFAs to a limited extent in the body. The rate of conversion depends on several factors, including the effectiveness of the rate-limiting enzymes (desaturases), the availability of zinc and iron, the composition of fatty acids in the diet and sex hormones. While oestrogen promotes desaturase synthesis in the liver, testosterone suppresses it [35]. Therefore, the brain is dependent on *n*-3 LC-PUFAs in the diet throughout life [36]. The recommended *n*-6/*n*-3 PUFA ratio (4:1) in the human diet is critical for proper fatty acid content of neuronal membranes, phospholipid composition and brain function. The *n*-6 PUFA family (linoleic acid (LA) and arachidonic acid (ARA)) is usually derived from vegetable oils (e.g. sunflower oil, corn oil, etc.). The content of LC-PUFAs in the membrane maintains a balance between inflammatory and anti-inflammatory processes in the cells, as LC-PUFAs are converted into pro-inflammatory eicosanoids (ARA derivatives) or anti-inflammatory eicosanoids (EPA derivatives) and docosanoids (DHA derivatives) [37]. Fruits, GLVs and nuts are good sources of *n*-3 PUFAs, while fish, especially oily fish, are good sources of *n*-3 LC-PUFAs. Meat and dairy products could also be sources of *n*-3 LC-PUFAs, as could proteins, although long-term consumption of increasing amounts of red and/or processed meat has been associated with an increased risk of all-cause mortality [38]. Most of our patients reported infrequent meat consumption (~10% and ~50% regularly consumed red meat and poultry, respectively), but the vast majority frequently consumed dairy products (~90%). Cow's milk and dairy products also provide important nutrients such as bioactive peptides, a variety of fatty acids, vitamins and minerals. It has been reported that three or more servings per day can reduce the risk of cardiovascular disease in the general population [39, 40]. In the multiple regression analysis of our study, F3 dietary habits explained 5.3% of the variation in age at onset in SCH, but post-hoc analyses confirmed no significant effects (Tables 4 and 5). Unfortunately, we do not have data on the consumption of processed meat in our sample.

In this study, we used factor analysis not only to allow comparison of dietary habits between groups of patients with different clinical diagnoses, but also to interpret the correlation analysis. The main findings of our study concerned the effects of high glycaemic index foods on adverse symptoms in SCH and the effects of *n*-3 PUFA-rich foods on age at onset of MDD. Negative symptoms of SCH contribute to physical inactivity and associated metabolic and weight problems in patients [41]. Negative symptoms tend to worsen over time, and current antipsychotic medications are least effective in treating these symptoms [42]. In contrast, as shown in our study, adherence to psychopharmacotherapy can significantly reduce PANSS positive symptom scores (Tables 4 and 5). One of the most important results of our study suggests that PANSS negative symptoms in SCH could be modified by changing eating habits, *i.e.* reducing the consumption of high glycaemic index foods and low content PUFA foods. The pattern of eating unhealthy foods (food F4) described 8.1% of negative PANSS scores. More frequent consumption of F4 foods was associated with a trend towards higher PANSS symptom scores in general psychopathology in SCH (Tables 4 and 5). However, male gender remained the strongest predictor of general psychopathological symptoms in SCH, while BMI and F4 food consumption were not significantly associated with clinical symptoms in the post-hoc analyses (Table 5).

Another important finding of our study is the suspected association between more frequent consumption of *n*-3 PUFA-rich foods, including olive oil (dietary F1), and the later onset of MDD. No predictors were found for other clinical symptoms (HDRS). Dietary F1 predicted 6.6% of the variability in age of onset (F=8.069, P=0.005), while the influence of comorbidities was lower for MDD (3.2%, F=4.079) (Tables 4 and 5).

In our study, no influence of fish consumption on clinical symptoms was found, although a lower risk of mental disorders associated with fish consumption has been documented in the literature [43-45]. A recent lipidomic study pointed to an inflammatory linoleic acid (LA)/arachidonic acid (ARA) pathway as a potential diagnostic marker and treatment target for MDD [46]. Decreased fatty acid content in red blood cells with a reduced *n*-3/*n*-6 ratio has been found in a population of adolescents with depression and also earlier in adults [47]. Deficiencies in docosapentaenoic acid (DPA), DHA and ARA have also been found in the membranes of neuronal and peripheral cells in patients with antipsychotic-naïve and chronic episodes of SCH [48-51]. Low plasma levels of EPA and DHA have been associated with the presence and severity of anxiety in MDD [2]. ALA deficiency alters the composition of brain cell membranes, myelin, nerve endings and mitochondria, leading to neurosensory, cognitive and behavioural disorders [52]. A high daily intake of various types of fruit and vegetables significantly reduced the risk of all-cause mortality in a study and a meta-analysis that showed a health benefit [53, 54]. Therefore, eliminating fish, nuts and other PUFA-rich foods, including meat, may have influenced the age of onset of MDD.

In SCH, we found no correlation between dietary habits and age of disease onset. This discrepancy suggests important etiological differences between the two diseases: SCH is a disease with a significantly earlier age of onset, usually in adolescence, and probably of developmental neurological aetiology. Both diseases are considered multifactorial, suggesting a significant role of environmental factors, as no causative genes have been identified. Diet is likely a strong epigenetic factor that can alter the expression of critical genes in both diseases [55]. Nutritional deficiencies associated with MDD that occur later in life suggest that MDD likely skips the neurodevelopmental stage. These data suggest that the timing and duration of malnutrition in these two psychiatric disorders may be critical and lead to very different clinical outcomes.

The Mediterranean diet improves health and reduces the risk of developing depression [56, 57]. It is characterised by a high intake of olive oil, fish, GLVs and other plant-based, PUFA-rich foods, that have a positive effect on dementia and depression and improve cognitive function [58]. The typical Mediterranean diet traditionally consumed by the general population in the Croatian coastal region is rich in folate, S-adenosylmethionine, essential fatty acids, EPA, DHA, vitamins and minerals, which have antioxidant and antidepressant properties, alleviate negative and cognitive symptoms, are involved in neurotransmitter synthesis and protection against free radicals and toxins, and are essential for brain development, memory and normal ageing [59-64]. A possible explanation for the conflicting results regarding the effects on age at onset in two diseases could be that a healthy and balanced diet should provide essential macro- and micronutrients for proper development and function of the nervous system [65]. Optimal nutrition and the presence of strong social support and secure attachment in early childhood would lead to a reduction in toxic stress and inflammation, healthy brain development and overall health later in life [66]. In this regard, nutritional deficits in early childhood and/or their persistence into adolescence could contribute to the development of SCH.

The Mediterranean diet has profound effects on health, including the consumption of olive oil (in F1), which mainly has antioxidant and anti-inflammatory properties in the body. Recently, daily consumption of olive oil has been associated with increased life expectancy and a decrease in overall mortality in the population [33]. The beneficial effects of olive oil could be related to its oleic acid content, but also to the presence of polyphenols, sterols, tocopherols and other compounds. Foshati *et al.* [67] reported significant improvements in clinical symptoms after a 52-day study with the consumption of 25 ml of extra virgin olive oil per day in a group of severely depressed patients compared to others who consumed the same amount of sunflower oil, which is rich in *n*-6 PUFAs. However, the

results were not significant in patients with mild to moderate depression.

Omega-3 supplementation could also be an option for psychiatric patients, although some studies have shown an adverse effect of omega-3 supplementation characterized by an increase in the risk of depression onset, but not recurrence [68]. An intervention study with a group of young men diagnosed with MDD showed a significant improvement in depressive symptoms, as measured by the Beck Depression Inventory Scale—Version II, in those who received dietary recommendations, including meal plans, portion sizes and recipes. Significantly less improvement was observed in the control group of young, depressed men who received support in the form of conversations about sports and hobbies [69]. Therefore, in addition to psychopharmacotherapy, educational and dietary interventions could have the potential to reduce symptom severity and cognitive performance in SCH and MDD, respectively, and educate psychiatric patients on how simple measures such as dietary and lifestyle interventions (*e.g.*, physical activity) can improve quality of life and well-being (which also enables better adherence to psychopharmacotherapy) [12, 70]. Our results suggest that interventions related to eating habits could be a promising approach as an adjunct therapy in psychiatric disorders, *e.g.* in the treatment of negative symptoms of SCH, but also in the prevention of MDD symptoms. These results support the recent finding that nutritional deficiencies are an important environmental factor associated with the onset of clinical symptoms and/or metabolic complications in psychiatric or neurodegenerative disorders [27]. This is consistent with previous findings that high adherence to dietary recommendations significantly reduces the risk of developing depressive symptoms in adults of different age groups [24]. In a study by Akbaraly *et al.* [71], a lower risk of recurrence of depression was associated with the intake of fruit, vegetables and fibre, which is consistent with our findings of an association between F1 and later age of onset of depressive symptoms. Dietary interventions have the potential to reduce the side effects of antipsychotics and antidepressants and mitigate the effects of medication on nutritional status, such as increased appetite and changes in the gut microbiome that lead to weight gain, gastrointestinal and other side effects, or contribute to systemic inflammation and inflammation in the brain [72-74].

Our study had several limitations: small sample size, lack of assessment of physical activity and nutritional status.

CONCLUSIONS

Although the dietary habits of patients with severe mental illness were generally poor, we have shown that there are significant differences between the dietary patterns of SCH and MDD patients. Our results also support the assumption that SCH patients could better manage their negative symptoms by consuming less unhealthy foods. In MDD, a more frequent inclusion of olive oil, PUFA, and vitamin- and mineral-rich foods in the diet could delay the onset of clinical symptoms.

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CONFLICT OF INTEREST STATEMENT

On behalf of all authors, no conflicts of interest to declare.

Supplementary Table 1. Distribution of body mass index categories.

BMI category	SCH		MDD		χ^2	P
	N	%	N	%		
< 18.5	5	5.3	4	3.4	2.48	0.480
18.5 – 24.9	40	42.5	58	49.6		
25.0 - 29.9	26	27.7	35	29.9		
≥ 30	23	24.5	20	17.1		

BMI, Body Mass Index; MDD, major Depressive Disorder; SCH, schizophrenia

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