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# Comparing Dietary Patterns of Depressed Patients Vs Healthy People in a case-control protocol

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**Comparing Dietary Patterns of Depressed Patients Vs Healthy People in a Case – Control Protocol**

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## Abstract

**Introduction:** Major Depressive Disorder is the leading cause of disability around the world, affecting about 121 million people. The rate of depression is increasing and the World Health Organization (WHO) forecasts that it will be the second most common global burden of disease by the year 2020. Due to the high rate of medication discontinuation by patients and the high rates of recurrence, it is important to consider factors, including nutrition, which may helpful in preventing depression.

The relationships among depression and dietary patterns have been shown in some studies. However, it is worthy to understand this relationship in as many nations as possible to determine whether this may differ among populations. Therefore, this study intends to investigate the relationship between depression and dietary patterns of subjects.

Methods and analysis: In this case-control study, 110 cases and 220 controls will be individually matched based on age, sex and area of residence. The new cases of depressed patients based on DSM-IV criteria will be recruited from two psychiatric clinics in Tehran. For finding the controls, interviewers will go to each patient's living area and invite qualified individuals to participate in the study. Food intakes of all participants will be obtained by semi-quantitative food frequency questionnaire in the past year and then, dietary patterns will be determined by factor analysis. For assessing the relationship of dietary patterns to depression, conditional logistic regression will be used. The results may help to identify nutritional risk factors in depression incidence.

**Ethics and Dissemination:** The study protocol has been approved by Tehran University of Medical Sciences (TUMS) Ethical committee. At the beginning of the study, the written informed consent will be signed and dated by the subjects and the investigator. The results will be easily interpretable and published as soon as possible.

**Key Words**: Major depressive disorder, Diet, Factor analysis, Micronutrients

## Introduction

Depressive Disorder is the leading cause of disability around the world, affecting about 121 million people [1]. Currently, the WHO has specified that depression is ranked 4th on the global burden of disease and forecasts that it will be the second most common global burden of disease by the year 2020 [2-3]. Five of the following symptoms are needed to continue for at least 2 weeks for distinction of major depression: feeling depressed, sad or blue; absence of interest or enjoyment; increased or decreased sleeping; increased or decreased appetite comes with weight change; feeling agitated, feeling of unsettled or slowness; feeling of worthlessness or guilt; low energy; difficulty in concentration; feeling that life is not worthy or suicidal actions [4].

Risk factors of depression include gender, socio-economic status, social support, family history of affective disorders, the loss of a parent before age 10 year, drug abuse, history of physical or sexual abuse in childhood, use of oral contraceptives in women, *u*sing gonadotrophin stimulation for the treatment of infertility in women, stress, genetic backgrounds, medical illnesses such as cancer and diabetes, vascular brain changes and malnutrition [4-5].

Drug therapy in depression has been successful in 60 to 80% of patients; however, fewer than 25% of people with depression receive treatment [1]. Furthermore, depression is a chronic or

recurrent condition. Because of poor compliance of drug use in patients with depression and high rate of recurrence, it is significant to consider other factors, including nutrition-related factors, that may help to prevent unipolar depression [2].

Some evidence has been reported on the relationship between depression and insufficient intakes of some nutrients [2]. For example, tryptophan as a dietary amino acid is the precursor of brain serotonin. Decreased brain serotonin function is considered as a vulnerability factor for affective disorders. Synthesis of serotonin is limited by the inaccessibility of tryptophan [6].

In addition, consumption of specified fatty acids suggests a possible beneficial effect on some mental disorders [7], such as depression in middle-aged women [8]. Omega 3 long chain poly unsaturated fatty acids (PUFA) produce anti-inflammatory eicosanoids that reduce levels of pro-inflammatory cytokines in depressed patients. These PUFAs have antidepressant protective actions. This is characterized by the relationship between lower levels of fish consumption and increased depression incidence [9]. Plausible biological mechanisms linking dietary omega 3 deficiencies to psychiatric illness include: decrease of serotonin and dopamine levels by 50% in animal models, damaged neuronal transport, connectivity, updated apoptosis, and dendritic arborization, such that there is an irreversible impairment in the neuronal pathways that regulate behavior neuroinflammatory processes and disturbance of the hypothalamic pituitary adrenal axis [10].

Traditional analyses in nutritional epidemiology mainly investigate diseases in association with lack of or presence of single or a few nutrients or foods. Although this type of analysis is relatively valuable, it has several conceptual and methodological defects. First, people do not consume individual nutrients. They eat nutriments consisting of the types of foods with

combinations of nutrients which may have alleviating or exacerbating effect. Second, the effect of a single nutrient may be too small to show, but the collective effects of some nutrients existing in a dietary pattern are presumably sufficiently large to be detectable. Third, because nutrient intakes are generally associated with certain dietary patterns, single nutrient analysis may be altered by the effects of dietary patterns. For example, low dietary fat was accompanied with higher intakes of vegetables, fruits, fiber, folate and whole grains. Intakes of these as a dietary pattern may be related to a decreased risk of coronary heart disease (CHD) independently. These dietary components are potential confounders in a study of the relationship between fat intake and coronary disease [11]. Adjustment for these factors in multivariable analyses may not eliminate all the confounding effects because these dietary components may interact with each other [12].

Therefore, this study inclines to investigate the relationship between depression and dietary patterns of subjects, rather than concentrating on one or more specific nutrients intake. Few studies have shown that some dietary patterns have been associated with increased risk of depression [13]. The dietary patterns vary in different countries [14-15]. Therefore, investigations should be repeated for finding various dietary patterns which are related to incidence of depression.

## Aim of the study (Hypothesis)

The purpose of this study is to investigate the relationship between dietary patterns and their types and depression incidence.

## Methods and design

### Study design

An individually matched case-control observational design will be used in this study.

### Objectives

• Comparing the mean of birth rank, education level, and family size between depressed and healthy subjects

• Comparing the mean of cigarettes smoking or use of pipe or hookah per week between the two groups

• Comparing the mean of anxiety and depression scores, weight, height, Body Mass Index (BMI), and physical activity score between the two groups

• Comparing the frequency of unemployment history, occupational status, marital status, life history of traumatic events, childhood history of traumatic events, and family history of alcoholism   between the two groups

• Comparing the mean of daily intake of energy, macronutrients and micronutrients between the two groups

• Comparing the mean of daily intake of energy, macronutrients and micronutrients by the type of dietary patterns

• Comparing the mean of daily intake of energy, macronutrients and micronutrients by the type of dietary patterns between the two groups

• Comparing of depression odds ratio among tertiles of dietary patterns scores

• Comparing of depression odds ratio among tertiles of dietary patterns scores after adjusting the other dependent variables

## Group selection

### Case group

Patients will be diagnosed by a psychiatrist to have major depressive disorder or unipolar depression using the criteria of DSM-IV. They should not have depression history in the past year and should meet the inclusion criteria and do not have exclusion criteria. Symptoms should not begin more than 3 months before the diagnosis. The patients will be recruited from two psychiatric clinics in Tehran (Imam Hossein and Baharloo psychiatric clinics).

### Control group

Individuals who are not diagnosed to have unipolar depression based on Beck Depression Inventory (BDI – II) and have not depression history in the past year will be recruited as control groups. They should meet inclusion criteria and do not have exclusion criteria. For finding the controls, interviewers will go to the each patient's living area and invite qualified individuals to participate in the study.

### Ratio of the case to the control

In this study, the ratio of the cases to the control will be one to two.

**Matching patients with controls**

Matching will be done individually, based on age, sex and residence area. Age categories for matching would be 18-30, 31-40, 41-50 and 51-65 years.

## Inclusion criteria

• major depressive disorder diagnosed in  patients by a psychiatrist with DSM-IV criteria in three categories of mild, moderate and severe based on the Beck Depression Inventory ( BDI – II)

• Lack of major depressive disorder in control group at the time of the study based on the Beck Depression Inventory (BDI – II)

• Maximum period of 3 months intervals from onset of 5 symptoms of depression to beginning of the study

• age 18-65 years and residing in Tehran, the place of the study

**Exclusion criteria**

• Suffering from cognitive impairment or other psychotic illnesses diagnosed by a psychiatrist

• To be severely depressed and the patient is not able to cooperate and answer the questions

• Suffering from hormonal disorders, including Addison, Cushing's disease, hyperthyroidism or hypothyroidism, and hyperparathyroidism according to physician diagnosis or medication intake

• Suffering from chronic diseases including cancer, heart disease, diabetes, stroke, fibromyalgia, kidney or liver failure, multiple sclerosis, and Parkinson disease according to physician diagnosis or medication intake

• History of trauma, bruises, cuts, fractures, bleeding, burns, accidents, and other similar events in the past 3 months which resulted to unconsciousness and hospitalization

• Suffering from chronic and infectious diseases, including HIV, mononucleosis, tuberculosis, viral hepatitis, and pneumonia in the past two weeks

• Alcohol and drug addiction in the present time or their leave in the last 3 months based on confessing to psychiatrist

• To have BMI of 40 kg/m$^2$ and higher

• Pregnancy and lactation in the time of study or in the past year

• To have any type of special diet in the last two months

• To have any type of special diet for more than two months in the past year

## Sample size

Sample size calculations were performed using the software of open Epi with Two-sided confidence, Power=80, ratio of controls to cases=2, percent of controls exposed=25 [16], percent of cases with exposure=40, odds ratio=2 [17]. The sample size was calculated to equal 110 depressed subjects and 220 control subjects.

## Data Collection

### General information

General information, medication use, and some confounders will be obtained with a general questionnaire.

### Anthropometric and blood pressure measurements

Anthropometric measurements including height, weight and waist circumference will be performed for all participants as some confounders. Height will be measured in a standing position without shoes with height gauge and weight will be measured using weight scale with minimal wear. The waist circumference will be measured at the intermediate of the lower margin of rib and iliac crest in standing position and breathing normally without clothes[18]. Blood pressure will be measured after 15 minutes rest in a sitting position.

### Criteria of the Diagnostic and Statistical Manual Disorders, Fourth Edition (DSM –IV)

This criteria is designed by the American Psychological Association[19] and is standardized in Iran [20] .This criterion will be used to diagnose depression in patients admitted to the psychiatric clinics of Imam Hossein and Baharloo in Tehran.

### Beck Depression Inventory (BDI – II)

This questionnaire will be used for quantitative rating of depression in depressed subjects and screening of depression in control group. The criteria is standardized in Iran[21].

### Beck Anxiety Inventory (BAI)

This scale is standardized in Iran [22] and will be used for a quantitative measure of anxiety in the depressed and control groups as a confounder. This scale has 21 items and the total score is between 0-63. Score of 15 or less is normal. Points 16-31, 32-47, and 48-63 are considered mild, moderate, and severe anxiety respectively. Anxiety is measured to adjust as a confounding variable.

**Physical Activity Questionnaire**

Since physical activity can be effective in the incidence of depression, it is necessary to estimate subjects' physical activity as another confounder. A classified physical activity questionnaire based on the metabolic equivalent (MET) will be used which consists of nine levels of activity, from rest and sleep (MET=0.9) up to vigorous activity (MET $\geq$6). The questionnaire was prepared in previous studies in Europe and validated with daily physical activity questionnaire and CSA Accelerometry (Model 7164 Ambulatory Monitor)[23]. Reliability and validity of the questionnaire have been approved, on the teens in the study of Kelishadi and colleagues in Iran [24]. This questionnaire had high reliability and was significantly associated with the results of the International Physical Activity Questionnaire (IPAQ) and 7day records of Iranian youth physical activity. Physical activity is calculated based on metabolic equivalent on hours per day (MET-h/day).

## Dietary analysis

A semi-quantitative food frequency questionnaire is used to determine food intakes during the previous 12 months. The food frequency questionnaire that will be used in this study is the questionnaire designed in the Tehran Lipid and Glucose study in the fourth phase of nutrition cohort; It contains 168 items and its reliability and validity have been confirmed in district 13 of

Tehran[25] . Since the reliability and validity of the questionnaire for the population of the

present study has not been assessed, a pilot study was done to make the necessary changes in the

questionnaire.


**Statistical Analysis**


Dietary patterns will be determined by factor analyses. To examine the relationship between

depression and the characteristics of individuals such as their dietary patterns the tests of $X^2$, Mc-

Nemar, t-test, and Pearson correlation coefficient will be used. Multivariate analyses will be

conducted using a conditional logistic regression model to assess the potential importance of

various variables. In this method, response variable is depression (yes, no). Conditional logistic

regression is used because of matched cases and controls. In addition, this method will be used

for investigating the association of measured values in the two groups:

$$\text{Logit } (y=1) = \alpha_i + \Sigma \beta_i X_i \, (i=1\text{-}n)$$

$\alpha_i$ is random intercept in the equation of conditional logistic regression.

$\beta_i$ is the coefficient of independent variable in regression model including dietary patterns and

other control variables in moderating relation of dietary patterns.


# Ethical issues and Informed Consent Process


The study protocol has been approved by Tehran University of Medical Sciences (TUMS)

Ethical committee. The investigators will provide the subjects with all related information in a

language desired by the subject and at a level of complexity that is understandable to the

subjects. Prior to the subjects' participation in the study, the written informed consent will be

signed and dated personally by the subjects and  the investigator.

## Discussion

Evaluating the patterns of food consumption rather than a nutrient or a few nutrients shows the real effects of nutrients and considers the interactions of nutrients. Food consumption patterns, in addition to biological mechanisms, reflect the complex interactions and relationships between people, cultures and society in which people live and enable us to study of social and psychological mechanisms [17]. According to evidence showing relationship between food and emotion; it seems that understanding the relationship between patterns of food consumption and depression is more promising than studying the relationship between nutrients alone and depression. In a few studies, including studies of Sanchez-Villegas [15], Crawford [26], and Jacka F.N. [14] the association among depression and dietary patterns have been studied. However, these studies did not show consistent results. For example, in the study of Sanchez-Villegas there was a significant inverse relationship between depression and adherence to the mediterranean diet including lower red meat consumption [15]. While the study of Jacka F.N. and colleagues showed subjects with traditional diet including red meat had lower odds of major depression and anxiety compared with those who had western diet [14]. Thus it seems these type of studies should be repeated in various countries, in order to determine whether dietary pattern associated with depression will change according to cultural, social, racial, geographic and environmental conditions [27]. In addition, advising people to use a special dietary pattern is easier than to suggest them to consume a particular nutrient such as cobalamin or folic acid. It is hoped the results of this study may provide a new look in the field of nutritional interventions in patients with depression and may help to identify nutritional risk factors in depression incidence.

**Competing interests and Funding Statement**

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**Authors' contributions**

MK has made substantial contributions to conception and design and has been involved in drafting the manuscript.

GT made substantial contributions to design, revised the manuscript critically, and given final approval of the version to be submitted.

FR has made substantial contributions to conception and revised the manuscript critically.

RM made substantial contributions to design and revised the manuscript critically.

TF has contributed to the literature review and editing the manuscript for English language.

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## Abstract

**Introduction:** Major Depressive Disorder is the leading cause of disability around the world. Due to the high rate of medication discontinuation by patients and the high rates of recurrence, it is important to consider factors, including nutrition, which may be helpful in preventing or treating of depression. The relationship among depression and dietary patterns have been shown in some studies. However, it is worthy to understand this relationship in as many nations as possible to determine whether this may differ among populations. Therefore, this study intends to investigate the relationship between  depression morbidity and dietary patterns in the Iranian population.

**Methods and analysis:** In this case-control study, 110 cases and 220 controls will be individually matched based on age, sex and area of residence. The new cases of depressed patients based on DSM-IV criteria will be recruited from two psychiatric clinics in Tehran. For finding the controls, interviewers will go to each patient's living area and invite qualified individuals to participate in the study. Food intakes of all participants will be obtained by semi-quantitative food frequency questionnaire in the past year and transformed into actual food intakes (gram/day). Dietary patterns will be determined by principal components method. Conditional logistic regression as a multivariate analysis will be used for assessing the relationship of dietary patterns and depression in consideration of the potential role of various variables. The results may help to descript of differences in dietary patterns identified in depressed and healthy people.

**Ethics and Dissemination:** The study protocol has been approved by Ethical committee of Tehran University of Medical Sciences. At the beginning of the study, the written informed consent will be signed and dated by the subjects and the investigator. The results will be easily interpretable and published as soon as possible.

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Risk factors of depression include gender, socio-economic status, social support, family history of affective disorders, the loss of a parent before age 10 year, drug abuse, history of physical or sexual abuse in childhood, use of oral contraceptives in women, *u*sing gonadotrophin stimulation for the treatment of infertility in women, stress, genetic backgrounds, medical illnesses such as cancer and diabetes, vascular brain changes and malnutrition [4-5].

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Therefore, this study was designed to investigate the relationship between depression and dietary patterns of subjects, rather than concentrating on one or more specific nutrients intake. Few studies have shown that some dietary patterns have been associated with increased risk of depression [13]. The dietary patterns vary among countries [14-15]. Therefore, investigations should be repeated for finding various dietary patterns which are related to depression.

## Aim of the study (Hypothesis)

The purpose of this study is to investigate the relation of dietary patterns and their types with depression morbidity.

**Methods and design**

**Study design**

An individually matched case-control observational design will be used in this study.

**Objectives**

• Comparing the mean of birth rank, education level, and family size between depressed and healthy subjects (depression is considered as primary outcome)

• Comparing the mean of cigarettes smoking or use of pipe or hookah per week between the two groups

• Comparing the mean of anxiety and depression scores, weight, height, Body Mass Index (BMI), and physical activity score between the two groups

• Comparing the frequency of unemployment history, occupational status, marital status, life history of traumatic events, childhood history of traumatic events, and family history of alcoholism between the two groups

• Comparing the mean of daily intake of energy, macronutrients and micronutrients between the two groups

• Comparing the mean of daily intake of energy, macronutrients and micronutrients by the type of dietary patterns

• Comparing the mean of daily intake of energy, macronutrients and micronutrients by the type of dietary patterns between the two groups

• Comparing of depression odds ratio among tertiles of dietary patterns scores

• Comparing of depression odds ratio among tertiles of dietary patterns scores after adjusting the other independent variables

## Group selection

### Case group

Patients will be diagnosed by a psychiatrist to have major depressive disorder or unipolar depression using the criteria of DSM-IV. They should not have depression history in the past year and should meet the following inclusion criteria and do not have exclusion criteria. Symptoms should not begin more than 3 months before the diagnosis. The patients will be recruited from two psychiatric clinics in Tehran (Imam Hossein and Baharloo psychiatric clinics).

### Control group

Individuals who are not diagnosed to have unipolar depression based on Beck Depression Inventory (BDI – II) and have not depression history in the past year will be recruited as control groups. For finding the controls, interviewers will go to the each patient's living area and invite qualified individuals to participate in the study.

### Ratio of the case to the control

In this study, the ratio of the cases to the control will be one to two.

### Matching patients with controls

Matching will be done individually, based on age, sex and residence area. Age categories for matching would be 18-30, 31-40, 41-50 and 51-65 years.

### Inclusion criteria

• Major depressive disorder diagnosed in patients by a psychiatrist with DSM-IV criteria in three categories of mild, moderate and severe based on the Beck Depression Inventory (BDI – II)

• Lack of major depressive disorder in control group at the time of the study based on the Beck Depression Inventory (BDI – II)

• Maximum period of 3 months intervals from onset of 5 symptoms of depression to beginning of the study

• Age 18-65 years

• Residing in Tehran, the place of the study

### Exclusion criteria

• Suffering from cognitive impairment or other psychotic illnesses diagnosed by a psychiatrist

• To be very severely depressed and the patient is not able to cooperate and answer the questions

• Suffering from hormonal disorders, including Addison, Cushing's disease, hyperthyroidism or hypothyroidism, and hyperparathyroidism according to physician diagnosis or medication intake

• Suffering from chronic diseases including cancer, heart disease, diabetes, stroke, fibromyalgia, kidney or liver failure, multiple sclerosis, and Parkinson disease according to physician diagnosis or medication intake

• History of trauma, bruises, cuts, fractures, bleeding, burns, accidents, and other similar  events in the past 3 months which resulted to unconsciousness and hospitalization

• Suffering from chronic and infectious diseases, including HIV, mononucleosis, tuberculosis, viral hepatitis, and pneumonia in the past two weeks

• Alcohol and drug addiction in the present time or their leave in the last 3 months based on confessing to psychiatrist

• To have BMI of 40 kg/m$^2$ and higher

• Pregnancy and lactation in the time of study or in the past year

• To have any type of special diet in the last two months

• To have any type of special diet for more than two months in the past year

## Sample size

Sample size calculations were performed using the software of cases with exposure= 40, odds ratio=2 [17]. The sample size was calculated to equal 110 depressed subjects and 220 control subjects. It should be noted that we will include at least 10% more because there will be always incomplete dietary questionnaires that can reduce the final number of participants available for analysis.

## Data Collection

## General information

General information, medication use, and some confounders will be obtained with a general questionnaire.

**Anthropometric and blood pressure measurements**

Anthropometric measurements including height, weight and waist circumference will be performed for all participants. Height will be measured in a standing position without shoes with height gauge and weight will be measured using weight scale with minimal wear. The waist circumference will be measured at the intermediate of the lower margin of rib and iliac crest in standing position and breathing normally without clothes. Blood pressure will be measured after 15 minutes rest in a sitting position.

**Criteria of the Diagnostic and Statistical Manual Disorders, Fourth Edition (DSM –IV)**

This criterion has been designed by the American Psychological Association[18] and was standardized in Iran [19] .This criterion will be used to diagnose depression in patients admitted to the psychiatric clinics of Imam Hossein and Baharloo in Tehran.

**Beck Depression Inventory (BDI – II)**

This questionnaire will be used for quantitative rating of depression in depressed subjects and screening of depression in control group. The criterion has been standardized in Iran[20].

**Beck Anxiety Inventory (BAI)**

This scale has been standardized in Iran [21] and will be used for a quantitative measure of anxiety in the depressed and control groups as a confounder. This scale has 21 items and the total score is between 0-63. Score of 15 or less is normal. Points 16-31, 32-47, and 48-63 are considered mild, moderate, and severe anxiety respectively. Anxiety is measured to adjust as a confounding variable.

**Physical Activity Questionnaire**

Since physical activity can be related to depression, it is necessary to estimate subjects' physical activity as another confounder. A classified physical activity questionnaire based on the metabolic equivalent (MET) will be used which consists of nine levels of activity, from rest and sleep (MET=0.9) up to vigorous activity (MET $\geq$6). The questionnaire has been prepared in previous studies in Europe and it was validated with daily physical activity questionnaire and CSA Accelerometry (Model 7164 Ambulatory Monitor) [22]. Reliability and validity of the questionnaire have been approved in the study of Kelishadi and colleagues in Iran [23]. This questionnaire had high reliability and was significantly associated with the results of the International Physical Activity Questionnaire (IPAQ) and 7day records of Iranian youth physical activity. Physical activity is calculated based on metabolic equivalent on hours per day (MET-h/day).

**Dietary analysis**

A semi-quantitative food frequency questionnaire will be used to determine food intakes during the previous 12 months. Data from the semi-quantitative food frequency questionnaire will be transformed into actual food intakes (gram/day). The food frequency questionnaire that will be used in this study is the questionnaire designed in the Tehran Lipid and Glucose study in the fourth phase of nutrition cohort; it contains 168 items and its reliability and validity have been confirmed in district 13 of Tehran[24]. Since the reliability and validity of the questionnaire for the population of the present study has not been assessed, a pilot study was done to make the necessary changes in the questionnaire.

**Statistical Analysis**

Dietary patterns will be determined by exploratory factor analysis. We will enter extracted food groups into the factor analysis and will use a principal components method to determine number of factors or dietary patterns. It will be used varimax rotation to identify major dietary patterns based on number of food groups. Since in this manner, each participant will be received a factor score for each explored dietary pattern, we categorized participants by tertiles of dietary pattern scores.

To examine the relationship between depression and the characteristics of individuals such as the scores of the tertiles of their dietary patterns, it will be used the tests of $X^2$, Mc-Nemar's chi square, paired t-test, and Pearson correlation coefficient. Multivariate analyses will be conducted using a conditional logistic regression model to assess the potential importance of various variables. In this method, response variable (primary outcome) is depression (yes, no). Conditional logistic regression is used because of matched cases and controls. In addition, this method will be used for investigating the association of measured values in the two groups:

$$\text{Logit } (y=1) = \alpha_i + \Sigma \beta_i X_i (i=1-n)$$

$\alpha_i$ is random intercept in the equation of conditional logistic regression.

$B_i$ is the coefficient of independent variable in regression model including dietary patterns and other control variables in moderating relation of dietary patterns.

**Ethical issues and Informed Consent Process**

The study protocol has been approved by Tehran University of Medical Sciences (TUMS) Ethical committee (91-03-161-19374). The investigators will notify the subjects with all related information in a language desired by the subject and at a level of complexity that is

understandable to the subjects. Prior to the subject's participation in the study, the written informed consent will be signed and dated personally by the subjects and the investigator.

## Limitation

A case-control study cannot determine the temporal relationship between the dietary patterns and depression. It can generate the results that just help to descript of differences in dietary patterns identified in depressed and healthy people.

## Discussion

Evaluating the patterns of food consumption rather than a nutrient or a few nutrients shows the real effects of nutrients and considers the interactions of nutrients. Food consumption patterns, in addition to biological mechanisms, reflect the complex interactions and relationships among people, cultures and society in which people live and it will enable us to study social and psychological mechanisms [17]. According to evidence showing relationship between food and emotion; it seems that understanding the relationship between patterns of food consumption and depression is more promising than studying the relationship between nutrients alone and depression. In a few studies, including studies of Sanchez-Villegas [15], Crawford [25], and Jacka F.N. [14] the association among depression and dietary patterns have been studied. However, these there is controversy regarding the results of those studies. For example, in the study of Sanchez-Villegas there was a significant inverse relationship between depression and adherence to the mediterranean diet including lower red meat consumption [15]. While Jacka et al., showed subjects with traditional diet including red meat had lower odds of major depression and anxiety as compared to those who had western diet [14]. Thus it seems these types of studies should be

repeated in various countries, in order to determine whether dietary pattern associated with depression will change according to cultural, social, racial, geographic and environmental conditions [26]. In addition, advising people to use a special dietary pattern is easier than to suggest them to consume a particular nutrient such as cobalamin or folic acid. Hopefully these results provide a new look in the field of nutritional interventions in patients with depression.

## Competing interests and Funding Statement

## Authors' contributions

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GT has made substantial contributions to design, revised the manuscript critically, and given final approval of the version to be submitted.

FR has made substantial contributions to conception and revised the manuscript.

RM has made substantial contributions to conception and design.

TF has contributed to the literature review and editing the manuscript for English language.

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# Comparing Dietary Patterns of Depressed Patients Vs Healthy People in a Case – Control Protocol

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## Abstract

**Introduction:** Major Depressive Disorder is the leading cause of disability around the world. Due to the high rate of medication discontinuation by patients and the high rates of recurrence, it is important to consider factors, including nutrition, which may be helpful in preventing or treating of depression. The relationship among depression and dietary patterns have been shown in some studies. However, it is worthy to understand this relationship in as many nations as possible to determine whether this may differ among populations. Therefore, this study intends to investigate the relationship between depression morbidity and dietary patterns in the Iranian population.

**Methods and analysis:** In this case-control study, 110 cases and 220 controls will be individually matched based on age, sex and area of residence. The new cases of depressed patients based on DSM-IV criteria will be recruited from two psychiatric clinics in Tehran. For finding the controls, interviewers will go to each patient's living area and invite qualified individuals to participate in the study. Food intakes of all participants will be obtained by semi-quantitative food frequency questionnaire in the past year and transformed into actual food intakes (gram/day). Dietary patterns will be determined by principal components method. Conditional logistic regression as a multivariate analysis will be used for assessing the relationship of dietary patterns and depression in consideration of the potential role of various variables. The results may help to descript of differences in dietary patterns identified in depressed and healthy people.

**Ethics and Dissemination:** The study protocol has been approved by Ethical committee of Tehran University of Medical Sciences. At the beginning of the study, the written informed consent will be signed and dated by the subjects and the investigator. The results will be easily interpretable and published as soon as possible.

**Key Words:** Major Depressive Disorder, Diet, Micronutrients, Factor Analysis, Principal Components Method

## Introduction

Depressive disorder is the leading cause of disability around the world, affecting about 121 million people [1]. Currently, World Health Organization (WHO) has specified that depression is ranked 4th on the global burden of disease and forecasts that it will be the second most common global burden of disease by the year 2020 [2-3]. Five of the following symptoms are needed to continue for at least 2 weeks for distinction of major depression: feeling depressed, sad or blue; absence of interest or enjoyment; increased or decreased sleeping; increased or decreased appetite comes with weight change; feeling agitated, feeling of unsettled or slowness; feeling of worthlessness or guilt; low energy; difficulty in concentration; feeling that life is not worthy or suicidal actions [4].

Risk factors of depression include gender, socio-economic status, social support, family history of affective disorders, the loss of a parent before age 10 year, drug abuse, history of physical or sexual abuse in childhood, use of oral contraceptives in women, *u*sing gonadotrophin stimulation for the treatment of infertility in women, stress, genetic backgrounds, medical illnesses such as cancer and diabetes, vascular brain changes and malnutrition [4-5].

Drug therapy in depression has been successful in 60 to 80% of patients; however, fewer than 25% of people with depression receive treatment [1].  Furthermore, depression is a chronic or recurrent condition. Because of poor compliance of drug use in patients with depression and high rate of recurrence, it is important to consider other factors, including nutrition-related factors, which may help <mark>to prevent or treat</mark> unipolar depression [2].

Some evidence has been reported on the relationship between depression and insufficient nutrient intakes [2]. For example, tryptophan as a dietary amino acid is the precursor of brain serotonin. Decreased brain serotonin function is considered as a vulnerability factor for affective disorders. Synthesis of serotonin is limited by the inaccessibility of tryptophan [6].

 In addition, consumption of specified fatty acids suggests a possible beneficial effect on some mental disorders [7], such as depression in middle-aged women [8]. Omega 3 long chain poly unsaturated fatty acids (PUFA) produce anti-inflammatory eicosanoids that reduce levels of pro-inflammatory cytokines in depressed patients. These PUFAs have antidepressant protective actions. This is characterized by the relationship between lower levels of fish consumption and increased depression incidence [9]. Plausible biological mechanisms linking dietary omega 3 deficiencies  to psychiatric illness include: decrease of serotonin and dopamine levels by 50% in animal models, damaged neuronal transport, connectivity, updated apoptosis, and dendritic arborization, such that there is an irreversible impairment in the neuronal pathways that regulate behavior  neuroinflammatory processes and disturbance of the hypothalamic pituitary adrenal axis [10].

Traditional analyses in nutritional epidemiology mainly investigate the association between diseases and lack or presence of single or a few nutrients or foods. Although this type of analysis

is relatively valuable, it has several conceptual and methodological limitations. First, people do not consume individual nutrients. They eat nutriments consisting of various foods with combinations of nutrients which may have alleviating or exacerbating effects. Second, the effect of a single nutrient may be too small to show, but the collective effects of some nutrients existing in a dietary pattern are presumably sufficiently large to be detectable. Third, because nutrient intakes are generally associated with certain dietary patterns, single nutrient analysis may be altered by the effects of dietary pattern. For example, low dietary fat was accompanied with higher intakes of vegetables, fruits, fiber, folate and whole grains. Intakes of these as a dietary pattern may be related to a decreased risk of coronary heart disease (CHD) independently. These dietary components are potential confounders in a study of the relationship between fat intake and coronary disease [11]. Adjustment for these factors in multivariable analyses may not eliminate all the confounding effects because these dietary components may interact with each other [12].

Therefore, this study was designed to investigate the relationship between depression and dietary patterns of subjects, rather than concentrating on one or more specific nutrients intake. Few studies have shown that some dietary patterns have been associated with increased risk of depression [13]. The dietary patterns vary among countries [14-15]. Therefore, investigations should be repeated for finding various dietary patterns which are related to depression.

**Aim of the study (Hypothesis)**

The purpose of this study is to investigate the relation of dietary patterns and their types with depression morbidity.

**Methods and design**

**Study design**

An individually matched case-control observational design will be used in this study.

**Objectives**

• Comparing the mean of birth rank, education level, and family size between depressed and healthy subjects (depression is considered as primary outcome)

• Comparing the mean of cigarettes smoking or use of pipe or hookah per week between the two groups

• Comparing the mean of anxiety and depression scores, weight, height, Body Mass Index (BMI), and physical activity score between the two groups

• Comparing the frequency of unemployment history, occupational status, marital status, life history of traumatic events, childhood history of traumatic events, and family history of alcoholism between the two groups

• Comparing the mean of daily intake of energy, macronutrients and micronutrients between the two groups

• Comparing the mean of daily intake of energy, macronutrients and micronutrients by the type of dietary patterns

• Comparing the mean of daily intake of energy, macronutrients and micronutrients by the type of dietary patterns between the two groups

• Comparing of depression odds ratio among tertiles of dietary patterns scores

• Comparing of depression odds ratio among tertiles of dietary patterns scores after adjusting the other independent variables

## Group selection

### Case group

Patients will be diagnosed by a psychiatrist to have major depressive disorder or unipolar depression using the criteria of DSM-IV. They should not have depression history in the past year and should meet the following inclusion criteria and do not have exclusion criteria. Symptoms should not begin more than 3 months before the diagnosis. The patients will be recruited from two psychiatric clinics in Tehran (Imam Hossein and Baharloo psychiatric clinics).

### Control group

Individuals who are not diagnosed to have unipolar depression based on Beck Depression Inventory (BDI – II) and have not depression history in the past year will be recruited as control groups. For finding the controls, interviewers will go to the each patient's living area and invite qualified individuals to participate in the study.

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In this study, the ratio of the cases to the control will be one to two.

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• Lack of major depressive disorder in control group at the time of the study based on the Beck Depression Inventory (BDI – II)

• Maximum period of 3 months intervals from onset of 5 symptoms of depression to beginning of the study

• Age 18-65 years

• Residing in Tehran, the place of the study

### Exclusion criteria

• Suffering from cognitive impairment or other psychotic illnesses diagnosed by a psychiatrist

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• Alcohol and drug addiction in the present time or their leave in the last 3 months based on confessing to psychiatrist

• To have BMI of 40 $kg/m^2$ and higher

• Pregnancy and lactation in the time of study or in the past year

• To have any type of special diet in the last two months

• To have any type of special diet for more than two months in the past year

## Sample size

Sample size calculations were performed using the software of open Epi with two-sided confidence, power=80, ratio of controls to cases=2, percent of controls exposed=25 [16], percent of cases with exposure=40, odds ratio=2 [17]. The sample size was calculated to equal 110 depressed subjects and 220 control subjects. It should be noted that we will include at least 10% more because there will be always incomplete dietary questionnaires that can reduce the final number of participants available for analysis.

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General information, medication use, and some confounders will be obtained with a general questionnaire.

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