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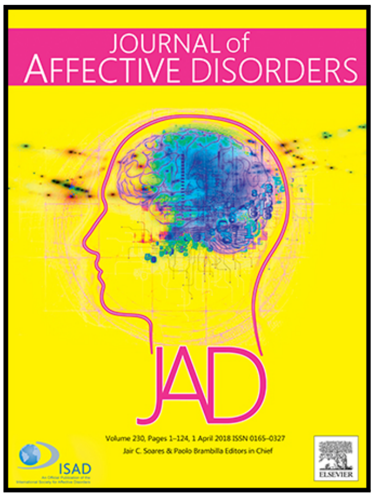

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Limitations:

- 1-Although the Constances cohort was designed as a randomly selected representative sample of French adults, the current sample may not be representative of the general population.
- 2-The cross-sectional nature of the analyses warrants the results to be confirmed by longitudinal analyses.
- 3-Additional confounding factors might have not been considered which increases the possibility of residual confounding.

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Abstract

Background: The association between depression and the metabolic syndrome remains poorly understood. Diet and physical activity may partly explain this association. **Methods:** Baseline data on 64,861 subjects from the French population-based Constances cohort was analyzed. Depressive symptoms were determined with the Center of Epidemiologic Studies Depression (CES-D) scale. A CES-D score $\geq$ 19 combined with self-reported limitations related to depressive symptoms was used to define depression. The metabolic syndrome was defined according to the International Diabetes Federation criteria. Dietary patterns were determined with a food frequency questionnaire and a principal component analysis. Physical activity was measured with 3 questions resulting in a composite 6-point scale. Associations between depression and the metabolic syndrome were estimated through logistic regression and path analysis. **Results:** The odds-ratios (95% confidence interval) for the association between depression and the metabolic syndrome, adjusting for age, sex, education and income, was 1.75 (1.57-1.96). The path analysis showed that 23% of this association was explained by diet and physical activity, 67% being attributed to physical activity. **Limitations:** The cross-sectional nature of the analyses warrants the results to be confirmed by longitudinal analyses. **Conclusion:** Diet and physical activity might partially explain the association between depressive symptoms and metabolic syndrome but other factors (e.g. inflammatory factors) are involved.

Keywords: depression, metabolic syndrome, diet, physical activity.

Significant outcomes:

Diet and physical activity explained 23% of the association between depression and the metabolic syndrome.
Much of this association was not related to behavioral factors measured in the Constances cohort study.
Physical activity had a higher contribution than diet in explaining the association between depression and the metabolic syndrome.

Limitations:

1-Although the Constances cohort was designed as a randomly selected representative sample of adults living in France, the current sample may not be representative of the general population.

2-The cross-sectional nature of the analyses warrants the results to be confirmed by longitudinal analyses.

3-Additional confounding factors might have not been considered which increases the possibility of residual confounding.

Introduction

Depression is associated with an increased risk of metabolic syndrome that contributes to the poor cardiovascular health of depressed individuals. A meta-analysis showed that individuals with depression had a 1.5 times higher odds of having a metabolic syndrome (1). Although the exact mechanisms underlying this association are poorly known, several hypotheses have been proposed. Depression and metabolic syndrome may share some common alterations of the stress system which could lead to a low grade inflammatory state and to oxidative stress which damages the neurons as well as the pancreatic cells and the endothelium (2). They may also share some environmental risk factors, such as low socioeconomic status (3, 4). Finally, this association may be mediated by health-related behaviors, such as poor diet or low physical activity, which could represent clinically relevant targets for preventive interventions (5).

Accumulating evidence demonstrates that poor diet and sedentary behavior are main risk factors for the development of the metabolic syndrome (6-8). These unhealthy lifestyle factors are also more frequent among individuals with depression (8-10). For instance, a recent study has shown that a diet characterized by a high intake of fruits and fish was associated with a lower likelihood of depressive symptoms (11). Furthermore, an higher adherence to French dietary guidelines in adulthood has been associated with a lower rate of chronic or recurrent depressive symptoms (9). Likewise, depression is associated with both increased sedentary behaviors and decreased physical activity (12). Depression may affect dietary patterns and physical activity through altered motivation, whereas the immune and the autonomous nervous system may mediate the other way around (13).

Although both diet and physical activity might be crucial targets for preventive interventions, their contribution to the association between depressive symptoms and metabolic syndrome is poorly understood. More specifically, it remains unclear the extent to which dietary patterns and physical activity may explain the link between depressive symptoms and metabolic syndrome. Such knowledge is yet important because it may help guide preventive measures to reduce the risk of metabolic syndrome among depressed individuals.

To provide an estimate as to how much diet and physical activity contribute to the relationship between depression and the metabolic syndrome, we used data from the large scale French population-based Constances cohort (adults living in France) and examined the potential mediating effects of both diet and physical activity linking depression and the metabolic syndrome. Because sex, age, education and socioeconomic status can influence the risks of depression(14), metabolic syndrome (15) and diet and physical activity (16), analyses were adjusted for these variables.

Aims of the study: Provide an estimate of how much diet and physical activity contribute to the relationship between depression and metabolic syndrome. We hypothesized that (i) depressive symptoms is associated with metabolic syndrome and (ii) dietary patterns and physical activity are significant and substantial mediating factors between depressive symptoms and the metabolic syndrome.

Methods

Population

Constances is a large, population-based, prospective cohort whose recruitment began in 2012 and will continue until the end of 2018 (expected total size is 200,000 subjects), including volunteers aged 18-69 at baseline and living in 21 selected departments (administrative divisions) throughout metropolitan France, in both rural and urban settings (17). Participants were selected among individuals covered by the general insurance scheme or partner health insurance funds (in all, 85% of individuals living in France) using a random sampling scheme stratified on place of residence, age, gender, occupational and socioeconomic status. Eligible individuals were invited by mail to participate in the study. Volunteers completed a self-administered questionnaire on lifestyle, health status, medical history, socio-professional status and attended a Health Screening Center for a comprehensive evaluation including a physical examination and laboratory tests. The Constances cohort study has received the authorization of the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL) and the institutional review board of the National Institute for Medical Research (Inserm) (Authorization number 910486). All subjects included in this study gave an informed consent.

The present analyses were restricted to 64,861 adult participants (**Figure 1**). They were free of cardiovascular diseases at baseline and not following a diet prescribed by a health professional. Further restrictions included having no missing data for the following variables: age, sex, depressive symptoms, physical activity and metabolic syndrome. All individuals who had information on dietary data collected by a food frequency questionnaire were included.

Variables

Depressive symptoms

Depressive symptoms were measured with the self-administered Center of Epidemiologic Studies Depression scale (CES-D). This scale evaluates the frequency of depressive symptoms during the previous week (e.g., I felt depressed, I felt everything I did was an effort, My sleep was restless). Responses range from 0 (hardly ever) to 3 (most of the time), resulting in a global score ranging from 0 to 60. Internal consistency of this scale is generally high (α=0.90 in the Constances cohort). According to the validated cutoff of the French version, a score ≥ 19 for both men and women has a sensitivity/specificity for the diagnosis of major depression: 0.85/0.86) (18). Since major depression is defined by both depressive symptoms and related functional impairment, the combination of a CES-D score ≥ 19 with limitations related to depressive symptoms in the last 6 months was used to increase the specificity of our proxy for depression toward major depression (19). These limitations were self-reported by 2 questions: "For at least 6 months, are you limited, i.e. do you have difficulties because of a health problem, to carry out everyday activities (at home, at work, during leisure) by comparing yourself to people your age?" and "If yes, for what reason(s)?" Participants who answered "Yes, very limited", "Yes, limited" or "Yes, slightly limited" to the first question and "depressive state" to the second question were considered having limitations related to depressive symptoms.

Complementary analyses were based on the sole CES-D score, either as a binary variable based on the cutoff of 19 or as a continuous variable.

Cardio-metabolic variables

Fasting blood samples were taken to measure HDL cholesterol, glycaemia and triglyceridemia (20). Blood pressure was measured after a 5-min rest period, using an automated oscillometric sphygmomanometer. Waist circumference was obtained using a tape meter. Abdominal obesity was defined as a waist circumference ≥94/80 for men/women. Weight and height were measured in health centers and BMI (kg/m^2) was calculated. For descriptive purpose, obesity was defined as a BMI ≥30 kg/m^2. All anthropometric and blood pressure measurements were obtained following standardized procedures(21, 22).

Metabolic syndrome

Metabolic syndrome was defined according to the French National High Authority for Health criteria (HAS) and the International Federation of Diabetes and Joint Interim Statement criteria for the metabolic syndrome (23), which consists of having 3 out of the following 5 criteria: a blood pressure ≥85/130 mmHg or reported treatment for hypertension; triglycerides level ≥1.7 mmol/l or reported treatment for hypertriglyceridemia; HDL-C <1.04/1.29 in men/women; glycemia ≥5.6 mmol/l or reported treatment for diabetes; waist circumference ≥94/80 cm in men/women (23, 24).

Dietary patterns

Dietary patterns were obtained using a qualitative food frequency questionnaire. Each food item on the questionnaire was measured using the question: "How frequently do you consume this item" on a scale ranging from never to more than once per day. Quantity was not measured. Food items included: fruits, vegetables, cereals, milk, meat, fish, poultry, eggs, plant fat, sweetened products, non-alcoholic beverages, alcohol, cold cuts, cheese, chips, fast foods, pre-prepared meals and snacking. Information on whole grain cereals, added fats and water intake were not available and were not part of the analysis. This food frequency questionnaire was designed in order to reflect intake in the French population and data regarding nutritional intake in the Constances cohort has already been published(25). The selected food items are compliant with the nutritional guidelines from the French National Nutrition and Health Program (PNNS)(25).Because food frequency was not normally distributed, each item's square root was calculated and entered into a principal component analysis in order to identify and compute factors underlying the dietary patterns of the population. The varimax rotation was used and eigen values above 1 were retained. Factor loadings of 0.4 and above were considered significant and retained for each index.

Physical activity

Physical activity outside work was determined by a calculated score ranging from 0 (i.e. being very active) to 6 (being not active at all). Questions used for the score's calculation included: i) in the past 12 months have you regularly engaged in gardening, cleaning or handy work?, ii) in the past 12 months have you regularly practiced sport (aside from gardening, cleaning or handy work)? and iii) in the past 12 months have you regularly gone on biking or walking trips (for work or leisure)?

A score of 0 is assigned if the answer is no; 1 if it is equal to yes, less than 15 minutes and yes at least 2 hours depending on the question; and 2 if it is equal to yes, 15 minutes and more or 2 hours and more according to the type of question. These scores were added in order to provide the final one. The final score is only calculated if the 3 questions are answered, otherwise the data is considered missing.

Covariates

Covariates included sex, age, education and household income. Education was categorized into four categories: less than or equal to high school diploma, undergraduate degree, and postgraduate degree or other.

Household monthly income was categorized into three levels: <1500 euros, 1500-2800 euros, ≥2800 euros and does not know or does not want to answer.

Statistical analysis

Descriptive statistics were performed to provide characteristics of the sample by presence or absence of the metabolic syndrome and are presented as means ± standard deviations (SD) or percentages as appropriate.

Missing dietary data were imputed for by using the median value for each dietary component relative to the same age, sex and occupational status (26, 27). The percentage of missing variables from dietary data was 5.74% with the exception of butter, margarine and olive oil for which 50% of the data was missing. The reason for the high percentage of imputation for different types of fat is because not all individuals got the same questions regarding fat consumption. Around half of the sample got a version of the questionnaire with details on types of oils and the other half a question combining all types of fat together.

Dietary patterns were measured with three scores that were derived from the three dietary patterns obtained by the principal component analysis. These scores were used as continuous variables and were divided by their interquartile range in all the analyses so that our analysis offers the possibility to compare an individual in the middle of the upper half of the predictor's distribution with an individual in the middle of the lower half.

The association between depression, dietary patterns and physical activity was determined by logistic regression analysis. For descriptive purpose, the physical activity score was used as categorical variable, in order to provide some insight about the linearity of the relationships. Logistic regression was performed to investigate the association between depressive symptoms and metabolic syndrome, computing odds-ratio (OR) and 95% confidence interval (CI) while adjusting for age, sex, education and income.

To examine the extent to which differences in dietary patterns and physical activity (used as a continuous variable) explained the association between metabolic syndrome and depressive symptoms, we used a path analysis with mediation.

In this model, the total indirect effect represents the total mediating effect of dietary patterns and physical activity in the association between depression and metabolic syndrome, i.e., the total indirect effect obtained by summing indirect effects for physical activity and each dietary pattern; the direct effect represents the effect of depression on metabolic syndrome that is not mediated by dietary patterns and physical activity. The size of the total mediating (i.e., indirect) effect is reported both in absolute terms and as a mediation proportion of the total effect of depression on metabolic syndrome.

The mediation model allows for the possibility of compensatory effects, i.e. that some indirect effects through each dietary pattern can be either positive or negative, more information on how the path analysis works could be found here (28-30).

The mediation model would fully explain the greater prevalence of metabolic syndrome in depressed individuals if the total indirect effect (i.e., the sum of all the specific indirect effects of depression on metabolic syndrome through all types of eating behavior and physical activity) would be positive and there would be no additional (i.e., direct) effect of depressive symptoms on risk of metabolic syndrome. The model was adjusted for age, sex, education and income. Dietary patterns and physical activity were allowed to correlate.

Because we sought to examine simultaneously all path coefficients, no paths in any of the models were fixed to zero. Therefore, goodness of fit measures are not relevant in evaluating these models since they do not inform on the ‘correctness’ of the models but rather provide only a summary of how well the observed correlations match the model when several paths are fixed at zero (29, 31). The default estimator for the analysis was the variance-adjusted weighted least squares (WLSMV), a robust estimator appropriate for ordered categorical and dichotomous variables (32). Standardized estimates indicate how many standard deviations higher (or lower) the mean of the latent variable underlying the binary outcome are expected to be for each increase in an additional unit of the latent factor underlying the continuous predictor or of the categorical predictor, while adjusting for the other factors.

Finally, exploratory analyses were conducted with our main measure of depressive symptoms (CES-D score ≥ 19 with limitations related to depressive symptoms in the last 6 months) and each component of the metabolic syndrome (hyperglycemia, high level of triglycerides, low HDL levels, abdominal obesity and high blood pressure) separately instead of the metabolic syndrome.

Path analyses were conducted using the MPlus software (32). All other statistical analyses carried out with the Statistical Analysis System (SAS, version 9.4, Cary NC). Statistical significance was evaluated with α set a priori at 0.05.

Results

This analysis reports the results of adults living in France from the Constances cohort (aged 18-73) who had data on age, sex, health behaviors (dietary data and physical activity), components of the metabolic syndrome, depressive symptoms and socioeconomic status (measured by income and education). There were a total of 64,861 individuals remaining after exclusion of individuals with reported cardiovascular diseases or dieting because of a health professional's prescription at baseline and with no available data on dietary patterns (Figure 1). Table 1 presents the characteristics of the study participants by presence or absence of the metabolic syndrome. The prevalence of depression, as defined by the combination of a CES-D score ≥ 19 with self-reported limitations related to depressive symptoms in the last 6 months, was 4.3% and 2.7% in the presence or absence of the metabolic syndrome, respectively (17.1% and 15.3%, respectively, when relying only on a score ≥ 19). Of those having the metabolic syndrome, 64% were men.

Table 2 shows factor loadings and variance explained by each dietary pattern. Based on the examination of loadings and on the drop in initial eigenvalues after the third factor, three factors were retained. The three factors were named high fat-high sugar diet, healthy traditional diet and high protein diet. High fat-high sugar loaded higher on ready-to-eat meals, fast foods, pastry and sweets, biscuits, sodas, cold cuts and deli and potato chips. The healthy traditional had higher loadings on milk, vegetables, fruits, bread, cereals and cheese. The high protein diet was so called because of the factor loadings on legumes, meat, poultry, fish and eggs. Data on factor loadings for two and four factors were also obtained and are presented as supplementary tables 1a and 1b.

Depressed individuals had lower odds of following a healthy traditional pattern (OR 0.78 95% CI 0.75-0.80) and a high protein pattern (OR 0.89 95% CI 0.87-0.91) and a higher odd of following a high fat-high sugar pattern (OR 1.23 95% CI 1.20-1.26). Similar relationships were found when using the sole cutoff of CES-D score ≥19 with the following OR (95% CI) for the healthy traditional / high protein / high fat-high sugar patterns: 0.76 (0.74-0.78) / 0.89 (0.87-0.91) / 1.23 (1.20-1.26). Likewise, these dietary patterns were associated with the CES-D score used as a continuous variable with the following regression coefficients (SD) for one interquartile range: -0.10 (0.003) / -0.04 (0.000) / 0.09 (0.003) (all P<0.0001).

Low physical activity was associated with higher odds of being depressed with gradually increased ORs (95% CI) up to 2.88 (2.53-3.29) for individuals not active at all versus those very active (Table 3). Similar relationships were found when using the sole cutoff of CES-D score ≥19 (Table 3) or the CES-D score as a continuous variable: regression coefficients (SD) for one interquartile range: 0.06 (0.00)2 ($P<0.0001$).

Results from the logistic regression showed OR (95% CI) of 1.75 (1.57-1.96) for the association between depression and the metabolic syndrome, adjusting for age, sex, education and income.

Results from the path analysis are summarized on Figure 2 and detailed in supplementary table 2. All the paths for the endogenous variables (variables receiving arrows) in our model were significant except for the association between the high protein dietary pattern and metabolic syndrome. The standardized total effect of depression on metabolic syndrome was 0.117 ± 0.013 ($p<0.05$). The indirect effect through dietary patterns and physical activity was 0.027 ± 0.002 ($p<0.05$). The ratio of total indirect effects (mediated through diet and physical activity) / total effect (i.e., the effect of depression on metabolic syndrome that is mediated through diet and physical activity) was 0.027/0.117=23%. In other words, 23% of the association between depressive symptoms and metabolic syndrome were explained by diet and physical activity in our model, whereas 77% were explained from a direct association between depressive symptoms and the metabolic syndrome. Physical activity and diet explained respectively about two-third (67%) and one-third (33%) of the mediation effect.

To examine the robustness of our results, we performed a series of sensitivity analyses. First, we considered depressive symptoms as defined by solely meeting the CES-D score cut-off of ≥19 (without the combination of self-reported limitations related to depressive symptoms in the last 6 months) or as a continuous and the analyses did change neither the direction nor the significance of the results.

In the logistic regression analyses, the OR (95% CI) using the binary CES-D score for the association with metabolic syndrome was 1.34 (1.26-1.42) whereas the OR (95% CI) using the continuous score (with the interquartile range as unit) was 1.16 (1.13-1.42), adjusting for age, sex, education and income.

As complementary analyses, path analyses models were also performed using alternative definitions of depressive symptoms and results are presented in supplementary table 3. The percentages of mediation remained significant and consistent with our main analysis. With depressive symptoms modeled as either a binary variable (CES-D score ≥19) or a continuous variable, we found that 35% or 45% of the association with metabolic syndrome were explained by diet and physical activity.

Second, we used different sets of exclusion criteria and included individuals with past incident of cardiovascular diseases or having a diet prescribed by a health professional with imputation on dietary data. The percentage of mediation was 38% when using the CES-D cut-off plus limitations.

We also ran analyses by removing individuals with past incident of cardiovascular diseases or having a diet prescribed by a health professional and not imputing on missing items from dietary data. The percentage of mediation was 44% when using the CES-D cut-off plus limitations.

The results of exploratory analyses conducted with each component of the metabolic syndrome separately are now displayed in supplementary tables.

Discussion

Main findings:

This study took advantage of data from the large-scale Constances cohort to test the hypothesis that diet and physical activity may significantly and substantially explain the association between depression and metabolic syndrome. This association was significant in the present study with an increase of 75% of the odds of having a metabolic among depressed individuals, controlling for age, sex, education and income. In accordance with our main hypothesis, the path analysis indicated that 23% of the effect of depression on the risk of metabolic syndrome was mediated through diet and physical activity. Physical activity had a greater explicative role than diet with 67% of the indirect effects attributed to it. These results were robust across sensitivity analyses considering different ways of modeling depressive symptoms and inclusion criteria. Exploratory analyses looking at each component of the metabolic syndrome showed similar results with triglycerides level, HDL-cholesterol and abdominal obesity. As regards hypertension, consistently with several cross-sectional studies (33, 34), the direct effect of depressive symptoms was negative but the indirect effect (mediation by diet and physical activity) was still positive and significant.

Strengths and limitations:

The strengths of our study include the large sample and the design of the Constances cohort that allowed us to study different associations between depression, metabolic syndrome and lifestyle factors. All clinical data have been collected at Health Screening Centers (HSC) in France and routine protocols and checkups are conducted by specialized teams(22). Besides, a field-pilot was performed in 2010 in seven HSCs, which included about 3,500 subjects; it showed a satisfactory structure of the sample and a good validity of the collected data (20). Reciprocal associations found between depressive symptoms, metabolic syndrome, diet and physical activity are consistent with prior findings (7, 9, 35, 36). However, to our knowledge, this is the first study to quantify the contribution of diet and physical activity for the relation between depression and the metabolic syndrome using a path analysis. We have as well used the principal component analysis in order to determine patterns of diet which reflects eating behavior as a whole and does not focus on one particular food group. This is important as diet comes as a multidimensional exposure and not as an isolated consumption of few particular nutrients (37). Moreover, several sensitivity analyses based on different ways of modeling depressive symptoms were performed and supported the robustness of our results.

Limitations include the cross-sectional nature of the data which restricts the possibility of drawing causality. The proposed model could have bidirectional associations among endogenous variables included and that the temporal sequence of the events remains to be determined. More specifically, the present study may not be able to distinguish mediating from confounding effects; however, the path analysis provided quantified information on potential risk factors (i.e. diet and physical activity) that could be targeted in order to prevent the metabolic syndrome in the case of depressive symptoms; the same conclusion may apply for the public health sector: whatever diet and physical activity are mediators, confounders or both, they are both clinically relevant targets to reduce the association between depression and metabolic syndrome.

More limitations include the absence of some dietary data and in particular the impossibility to calculate energy intake which is an important factor for investigating nutritional issues. Data on inflammatory factors was not available which might increase the possibility of residual confounding knowing the associations of both depression and the metabolic syndrome with inflammation (2). Such factors may contribute to the unexplained part of the direct effect.

Dietary intake and physical activity were self-reported in this study which may reduce the accuracy of the collected data. Moreover, ethnic data were not available as they cannot be collected by law in France.

Since no structured interview was used, as in many large-scale studies, major depression per se was not assessed in the present study. However, our main proxy for depression was not only based on a well-validated measure of depressive symptoms(18), but also on self-reported limitations related to depressive symptoms in the last 6 months. Because major depression is not only defined by depressive symptoms but also related functional impairment, the combination of a CES-D score ≥ 19 with limitations related to depressive symptoms in the last 6 months was used to increase the specificity of our proxy for depression toward major depression(38). Indeed, this measure yielded prevalence figures closer to those observed for major depression in general population.

The Constances cohort was designed to be representative of the population living in France; however, by law ethnic data could not formally be collected in France. However data regarding geographic origins of the parents of the participants showed that most of them (90%) were of European origins so that it could limit the generalizability of the current findings to other ethnic groups. Finally, our sample is also restricted to individuals with complete data on main variables of interest; we have however conducted sensitivity analyses including all participants which did not change the interpretation of the results.

Explanatory hypotheses

Evidence from the literature has identified an association between dietary habits and depression. This relationship has been shown to be possibly bi-directional, however it has been difficult to draw conclusions from observational data (39). Depression might affect appetite and food choice toward unhealthy diet through changes in brain functioning (40). A related hypothesis is that high fat-high sugar food might be used by depressed individuals to ameliorate unpleasant affective states, through the stimulation of the reward system (41). Data from clinical trials also show that depressive symptoms could be alleviated by proper diet (42) such as a Mediterranean diet supplemented with nuts. Several underlying mechanisms for the association between depressive symptoms and dietary habits have been proposed. It could be explained by the inflammatory potential of the diet as proposed by a recent French study which has shown that anti-inflammatory diets (determined by the dietary inflammatory index; a score dependent on the type of nutrients consumed) which may buffer the inflammatory potential of bad behaviors such as smoking and sedentarity (36). Some animal data pinpoints the link between mental disorders and gut microbiota (43) as well as inflammatory mechanisms. It has been questioned if the association with gut microbiota is altered by the change of diet that comes along depression. It could also be that microbiota produces some metabolomic modifications such as changes in short-chain fatty acids which could alter the brain function. Some studies are underway to understand if probiotics could influence the psychological state (43).

Epidemiological studies also show a decrease in depressive symptoms with increasing levels of physical activity and decreasing levels of sedentarity (12). Depression may reduce physical activity by biasing decision-making towards a lower exertion of effort(44), whereas randomized controlled trials suggest a causal link between promoting physical activity and alleviating depressive symptoms in both clinical and non-clinical samples(45). Sedentarity has in fact been associated with high levels of proinflammatory cytokines in a recent trial. This inflammation impacts the brain through several pathways involved in mood regulation as well as neuroendocrine function(46). The abovementioned trial has focused on exercise intensity in order to reduce depression and has shown that moderate-intensity exercise may be the optimal to decrease TNFα while enhancing mental health(46). A growing body of literature shows very positive effects of physical activity on mental function through physiological mechanisms that increase endorphins production as well as through a reduction in the inflammatory state. The challenge is to set effective programs for physical activity for people suffering from depression. Some studies seem to show positive effects of exercise interventions for people with mild depressive symptoms, which shows that it is necessary to develop programs that are easy to tackles and that depressed individuals would be able to perform(47).

Concluding remark: Depression is associated with greater risk for metabolic syndrome and 23% of this association may be mediated by diet and physical activity. Although the percentage of mediation was higher with less restrictive definition of depressive symptoms, the majority of this association remained unexplained, even after consideration of socio economic factors. Beyond metabolic syndrome, this result is consistent with the fact that the association between depression and cardiovascular risk is only marginally explained by traditional risk factors (48, 49). Other physiological factors such as genetic or inflammatory factors may provide an elucidation as to how depression is associated with metabolic syndrome over and above lifestyle and socioeconomic factors. Nevertheless, the focus on eating behavior and physical activity for the prevention of the metabolic syndrome in the presence of depressive symptoms is important and future studies targeting these two factors are needed.

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Contributors:

JM and CL take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. JM and CL designed the study; MG and MZ acquired the data; JM, NH and CL performed statistical analysis. All authors contributed to the interpretation of data. JM and CL drafted the article; EKG, CC, EW, FL, MP, SC, MZ and MG revised it critically for important intellectual content.

All authors have read and approved the final manuscript.

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Declaration of interest

Sebastien Czernichow has received before 2018 honoraria for conferences from: Novonordik, Lilly, Astra Zeneca, MSD, BMS, Servier, Covidien, Merck, Sanofi. He also declares holding shares from MyGoodLife.

Frederic Limosin has received honoraria for consultant/board participation for AstraZeneca, Janssen, Lundbeck, Otsuka, Roche and Servier.

Cédric Lemogne has received speaker and consulting fees from Janssen, Lundbeck, Otsuka Pharmaceuticals and Servier.

The other authors have nothing to declare.

Table 1: Participants' characteristics according to metabolic syndrome status

	Metabolic syndrome (N=12,183)	No metabolic syndrome (N=52,678)	P-value
Sociodemographic variables			
Age (years), mean ± SD	53.49 ± 11.5	44.64 ± 13.3	<0.0001
Sex, N (%)			<0.0001
Men	7800 (64.0)	23210 (44.0)	
Women	4383 (35.9)	29468 (55.9)	
Education level, N (%)			<0.0001
≤ high school diploma	6835 (56.7)	19267 (36.8)	
Undergraduate	3385 (28.0)	18963 (36.3)	
Postgraduate	1809 (15.0)	13904 (26.6)	
Other	25 (0.2)	91 (0.1)	
Household income (euros) N (%)			<0.0001
<1500	1279 (10.6)	5475 (10.5)	
[1500-2800]	3396 (28.2)	13098 (25.2)	
≥2800	6680 (55.6)	30556 (58.8)	
Does not want to answer or does not know	656 (5.4)	2800 (5.3)	
Depressive symptoms			
CES-D score ≥19 + limitations, N (%)	529 (4.3)	1405 (2.6%)	<0.0001
CES-D score ≥19, N (%)	2081 (17.0)	8072 (15.3)	<0.0001
CES-D score, mean ± SD	11.0 ± 9.3	10.6 ± 8.7	<0.0001
Diet and physical activity			
High fat-high sugar diet, mean ± SD (max)	-0.04 ± 0.99 (11.0)	0.03 ± 1.00 (9.7)	<0.0001
Healthy traditional diet, mean ± SD (max)	-0.11 ± 0.98 (6.4)	0.04 ± 1.00 (12.2)	<0.0001
High protein diet, mean ± SD (max)	0.05 ± 1.08 (11.0)	-0.004 ± 0.97 (11.0)	<0.0001
Physical activity level outside work, N (%)			<0.0001
0 (very active)	1277 (10.4)	5361 (10.1)	
1	1514 (12.4)	8715 (16.5)	
2	2670 (21.9)	13213 (25.0)	
3	2416 (19.8)	11626 (22.0)	
4	2646 (21.7)	9082 (17.2)	
5	1173 (9.6)	3553 (6.7)	
6 (not active at all)	487 (4.0)	1128 (2.1)	
Cardiometabolic variables			
BMI[c] (kg/m^2), mean ± SD	29.15 ± 4.35	23.71 ± 3.55	<0.0001
Obesity[d], N (%)	4268 (35.4)	2712 (5.2)	<0.0001
Diastolic blood pressure (mmHg), mean ± SD	83.21 ± 9.52	74.29 ± 9.25	<0.0001
Systolic blood pressure (mmHg), mean ± SD	140.57 ± 15.11	124.28 ± 14.87	<0.0001
High blood pressure[e], N (%)	10,834 (88.9)	17,764 (33.7)	<0.0001
Waist circumference (cm), mean ± SD	98.41 ± 10.92	80.94 ± 10.45	<0.0001

Abdominal obesity[f], N (%)	10,827 (88.8)	13,517 (25.6)	<0.0001
HDL cholesterol (mmol/l), mean ± SD	1.29 ± 0.34	1.59 ± 0.37	<0.0001
Low levels of HDL[g], N(%)	4864 (39.9)	5677 (10.7)	<0.0001
Serum triglycerides[j] (mmol/l), geometric mean	1.59	0.88	<0.0001
High levels of triglycerides[h], N(%)	6154 (50.5)	2455 (4.6)	<0.0001
Fasting blood glucose[j] (mmol/l), geometric mean	5.95	5.12	<0.0001
Hyperglycemia[i], N(%)	8926 (73.2)	7583 (14.4)	<0.0001

[a] missing data in 129/453 participants with/without metabolic syndrome
[b] missing data in 172/749 participants with/without metabolic syndrome
[c] missing data in 149/337 participants with/without metabolic syndrome
[d] BMI ≥30 kg/m²
[e] Systolic or diastolic blood pressure ≥85/130 mmHg or treatment
[f] Waist circumference ≥94 cm in men and ≥88cm in women
[g] HDL cholesterol <1.04 mmol/l in men and <1.29 mmol/l in women
[h] Serum triglycerides ≥1.7 mmol/l and/or treatment
[i] Glycemia ≥ 5.6 mmol/l and/or treatment
[j] geometric mean
Difference between the two groups has been compared by t-test or chisquare as appropriate

Table 2: Principal component analysis for dietary patterns showing factor loadings with varimax rotation

	Factor1 (Fat-sweet-salt)	Factor2 (Healthy-traditional)	Factor 3 (High protein)
Milk	11	53*	-6
Vegetables	-21	62*	23
Fruits	-23	63*	15
Bread	3	61*	-2
Cereals	18	44*	24
Legumes	4	8	49*
Ready to eat meals	48*	-7	19
Fast foods	62*	-5	17
Cheese	6	55*	9
Meat	24	11	48*
Poultry	18	2	65*
Fish	-11	15	67*
Eggs	5	6	60*
Butter	29	-3	-1
Margarine	17	12	-9
Olive oil	-27	10	17
Pastry and sweets	46*	12	5
Biscuits	45*	25	-7
Sodas	57*	-13	-7
Energy drinks	23	-12	5
Juices	38	18	-7
Alcohol	-2	-2	16
Cold cuts and deli	40*	7	20
Potato chips	48*	8	12

Printed values are multiplied by 100 and rounded to the nearest integer. Values greater than 40 are flagged by an ''*

Each subject's score on different dietary patterns was calculated using the rotated factor loadings and values were used as continuous.

Table 3: Association of physical activity with depressive symptoms.

	OR (95% CI)	
Physical activity	**CES-D score ≥19 + limitations**	**CES-D score ≥19**
0 (very active)	1	1
1	1.16 (1.06-1.28)	1.16 (1.05-1.27)
2	1.34 (1.23-1.46)	1.34 (1.22-1.46)
3	1.46 (1.33-1.59)	1.45 (1.33-1.59)
4	1.86 (1.70-2.03)	1.87 (1.71-2.05)
5	2.12 (1.92-2.35)	2.18 (1.96-2.41)
6 (not active at all)	2.88 (2.53-3.29)	3.04 (2.66-3.48)

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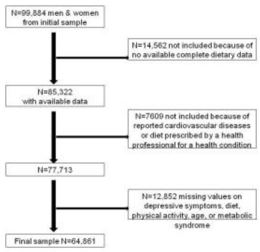

Figure 1: Flowchart for study.

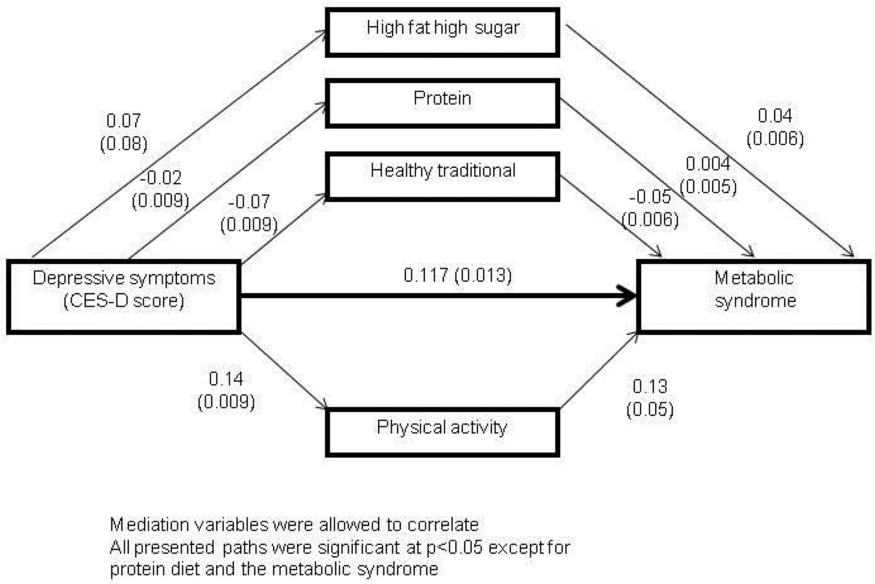

Figure 2: Path model showing mediation effect of eating and physical activity for the association between depressive symptoms and physical activity (confounding variables and association between dietary data and physical activity not shown for model simplification purposes, estimates shown on separate supplementary table)