Risk factors for depression. New evidence on selenium deficiency and depressive disorders

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Summary

Aim. This study aims to evaluate the effect of selenium deficiency on depressive disorders with adjustment for possible confounders. Its importance among non-dietary and dietary risk factors for depression is discussed using empirical evidence.

Material and method. A structural equation model was fitted using diagonally weighted least squares estimation with adjusted chi-square test statistic (WLSMV). The average daily intake of selenium and other nutrients was calculated to verify their possible association with self-reported depressive disorders. The effect of dietary patterns was adjusted for possible confounders, including the presence of chronic diseases, life problems, pain levels, physical activity, and income. The study was performed on a sample of 9,354 men and women aged 45–65 of the Polish-Norwegian Study (PONS) cohort.

Results. The model shows a significant effect of low selenium intake (standardised total effect of 0.133), high lipids intake (0.102) and low iron intake (0.065) on depressive disorders. Other dietary factors fail to make a significant contribution to depressive disorders, according to the model (p > 0.05). Among the considered non-dietary risk factors, home stress (0.181), pain (0.179) and low income (0.178) show a strong correlation with depression. Pain mediates a small part of the effect of morbidity (0.140). Depressive disorders are also associated with work problems (0.123) and low physical activity (0.024).

Conclusions. Selenium intake is most strongly related to depression among all the dietary factors considered. In the model, the effect of dietary risk factors on depressive disorders is moderate when compared to non-dietary variables. Chronic pain, low income, and morbidity are the main correlatives of depressive disorders.

Key words: depression, risk factors, selenium

Introduction

Depression refers to multi-cause disorders characterised by the absence of a positive affect, low mood, and a range of associated emotional, cognitive, physical, and behavioural symptoms [1]. The International Classification of Diseases (ICD-11)
Krzysztof Czaderny categorises depression into affective, cognitive, and neurovegetative symptoms that significantly affect the individual’s ability to function [2]. This study aims to identify the relationship between dietary patterns and depressive symptoms. Particular attention is devoted to the risk factor of selenium deficiency.

Latent (unobserved) variables are statistical data concepts that represent theoretically-driven constructs. Due to their complexity, they can be measured only to a certain degree by indicators. Depression is a classic example of a latent variable and cannot be measured directly. Structural equation modelling is a flexible multivariate statistical framework used to analyse associations between observed variables and latent traits measured by multiple indicators. Besides depression, the latent variables analysed in the current study are home stress, work stress, and long-term health problems. A structural equation modelling approach has been previously employed to identify risk factors for depression and anxiety; however, the proposed models did not include dietary intake variables [3–4]. In the current study, the average daily intake of selenium and other nutrients was calculated to verify their possible association with self-reported depressive disorders.

Structural equation modelling is a confirmatory technique. It requires a theoretical framework for designing and interpreting models. Low selenium intake was found to be related to depression in experimental studies already in the 1990s [5–8]. The evidence was provided by randomised controlled trials [5–9], surveys that collect biological specimens [10], case-control studies [11], and recently, Geospatial Information System analyses [12]; however, the specific nature of the relationship between selenium deficiency and depression is subject to debate. A few studies have suggested no evidence of a relationship between selenium intake and mood disorders [13] or described this relationship as statistically non-significant after taking into account control variables [10].

Some variables that have been suggested to contribute to depression were introduced into the proposed model, including pain [14–16], morbidity [17], low income [18–19], low physical activity [3], and stress [20]. Dietary control variables taken into account are the intakes of iron [21], lipids [22], calcium [23], zinc [24], fibre [25], folate [26], and carbohydrates [27], as well as body mass index [3].

**Material and method**

The fundamental criterion and hypothesis in structural equation modelling with categorical variables is that the empirical covariance matrix $\Sigma$ is equivalent to the model-implied covariance matrix $\Sigma(\theta)$ of $x^*$ and $y^*$, which are latent continuous indicators of binary or ordinal variables $x, y$, while $\theta$ is a vector of model parameters. The structural equation model consists of structural and measurement submodels. The latent variable submodel is given by [28-30]:

\[
\Sigma(\theta) = \Lambda \Phi \Lambda^T + \Psi
\]
Here $\alpha$ is a vector of intercepts, and $B$ and $\Gamma$ are matrices of regression coefficients describing the relationship between the latent variables. Latent endogenous and exogenous variables are given by vectors $\eta$ and $\xi$, respectively. Regression residuals are given by vector $\zeta$. A reflective measurement model assumes that there is a causal relationship flowing from the construct towards latent continuous indicators [28, 29]:

$$y^* = v_y + A_y \eta + \varepsilon,$$

$$x^* = v_x + A_x \zeta + \delta,$$

where $v_y$ and $v_x$ are vectors of intercepts $A_y$ and $A_x$—matrices of measurement slopes (factor loadings), and $\varepsilon$ and $\delta$ are vectors of residuals also known as measurement errors. In a formative measurement model, latent continuous indicators $y^*$, $x^*$ as a group jointly form a composite measure:

$$\eta = \Pi_y y^* + \mu_y,$$

$$\xi = \Pi_x x^* + \mu_x,$$

where $\Pi_y$ and $\Pi_x$ are coefficients capturing the effect of latent continuous indicators on the latent variables, while $\mu_y$ and $\mu_x$ are disturbance terms. A path diagram is a graphical representation of the hypothesised relationships between variables included in the structural equation model. Theoretical constructs are depicted as ovals while manifest variables are represented by rectangles. The arrows between variables represent regression paths (direct effects). Standardised estimates can be used to compare the effect sizes of predictors independent of the scaling.

The structural equation model was fitted by a weighted least square estimator using a diagonal weight matrix with standard errors and mean- and variance-adjusted chi-square test statistic that use a full weight matrix (WLSMV) estimation [29]. WLSMV is an appropriate choice for modelling categorical data [28]. It is free from the assumption of multivariate normal distribution of observed variables, which applies to the maximum likelihood method in structural equation modelling [30]. Empirical results show that WLSMV performs better than the conventional weighted least squares (WLS) when the tested model is large (15 or more variables) [31].

Goodness of fit of the structural equation model was assessed by the root mean square error of approximation (RMSEA), comparative fit index (CFI), and Tucker-Lewis Index (TLI). RMSEA is an absolute fit index, whereas CFI and TLI are relative fit indices. According to conventional criteria, RMSEA values below 0.05, and CFI and TLI values of 0.95 or higher indicate a good fit of the model [32–33]. A model generating approach was adopted to construct the final model, where the initial model was modified by introducing calculated nutrient intakes. Nutrient intake was estimated using a food frequency questionnaire based on tables of food composition and nutritive value [34]. Dietary intake variables with an insignificant effect on the presence of depressive symptoms were excluded from the model. An invariance testing
strategy [35] was used for cross-validation of the results. Provided with evidence of a well-fitting model for the combined calibration and validation subsamples, testing proceeded for the equivalence of the factor loadings, observed variable intercepts, and structural regression paths across the two random subsamples (robust chi-square difference testing: \( \chi^2 = 19.9; p = 0.224 \)).

Four constructs were specified in the structural equation model, corresponding to one reflective and three formative (composite) variables. Four sets of indicators were chosen to operationalise the study constructs (Table 1). The reliability of the reflective measurement model of depression was assessed by the categorical omega coefficient [36]. Being the most common measure of internal consistency, Cronbach’s alpha [37] assumes tau-equivalence, which is hardly ever met [38]. The obtained values of reliability coefficients indicate good internal consistency and construct validity. Reliability estimates for the depression measurement model are presented in Table 1. In the current study, depression level is based on subjective measures.

The analysis is based on the baseline data from individuals aged 45–64 years enrolled in the *Polish-Norwegian Study* (PONS) [39, 40]. The study was set in the south-eastern part of Poland (Świętokrzyskie Province) and its recruitment units were located both in urban and rural areas. Data were collected through face-to-face interviews in 2010–2011. The PONS study is an open-ended prospective study with broad research aims. The data collection was financed by the Polish-Norwegian Research Fund. The structural equation model is based on survey responses of 9,354 men and women of the Polish-Norwegian Study cohort. In the structural equation modelling, missing data were handled by univariate and bivariate listwise (pairwise) deletion. WLSMV was shown to be consistent under the assumption of missing at random with respect to observed independent variables in the model (MARX) [41]. Most frequently, cases were deleted due to incomplete income data due to item nonresponse (independent variable). Thirteen missing data patterns with the number of cases not exceeding 30 were observed in the data under analysis. The analysis was performed using *Mplus* Version 7.
### Table 1. Latent and observed variables in the structural equation model

<table>
<thead>
<tr>
<th>Variable group</th>
<th>Observed variables</th>
<th>Data type of observed variables</th>
<th>Measurement model</th>
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<tbody>
<tr>
<td><strong>Depressive disorders</strong> (latent variable $\eta_1$)</td>
<td>$y_1$ – Feeling sad, worried, or depressed for a period longer than 2 weeks, in the past 12 months. $y_2$ – Loss of interest in things that used to give pleasure (hobby, work, or other activities) in the past 12 months. $y_3$ – Feeling tired, without energy in the past 12 months. $y_4$ – Troubles with falling asleep in the past 12 months. $y_5$ – Greater difficulties concentrating and focusing in the past 12 months. $y_6$ – Thinking about the death (own, of a relative, or generally) in the past 12 months. $y_7$ – Feeling helpless and worthless in the past 12 months.</td>
<td>Binary variables.</td>
<td>Reflective indicators. Scale reliability: categorical $\omega=0.821$, Cronbach’s $\alpha=0.802$.</td>
</tr>
<tr>
<td><strong>Presence of chronic diseases</strong> (latent variable $\xi_1$)</td>
<td>$x_1$ – Coronary heart disease, angina, or myocardial infarction diagnosed by a medical doctor. $x_2$ – Circulatory insufficiency (heart failure) diagnosed by a medical doctor. $x_3$ – Asthma diagnosed by a medical doctor. $x_4$ – Arterial hypertension diagnosed by a medical doctor. $x_5$ – Cancer diagnosed by a medical doctor. $x_6$ – Stroke diagnosed by a medical doctor.</td>
<td>Binary variables.</td>
<td>Formative indicators.</td>
</tr>
<tr>
<td><strong>Work stress</strong> (latent variable $\xi_2$)</td>
<td>$x_7$ – Loss of job in the past 12 months. $x_8$ – Failure at work in the past 12 months. $x_9$ – Changing jobs in the past 12 months.</td>
<td>Binary variables.</td>
<td>Formative indicators.</td>
</tr>
</tbody>
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Results

The median selenium intake in the PONS sample is 73 μg/day. The European Food Safety Authority has set the daily adequate intake for selenium at 70 μg for adults and adolescents aged 15 and over [42]. The level of potentially dangerous intake of the element was estimated to be 400–500 μg/day. Exceeding the tolerable upper intake levels for selenium may cause adverse health effects [43]. In the PONS sample no toxic levels of selenium consumption were found. However, more than 40% of study participants report a daily selenium intake lower than 70 μg.

The goodness of fit statistics for the structural equation model illustrated in Figure 1 suggest that there is a good fit between the covariance matrix of the observed data and that implied by the model (RMSEA=0.027; CFI=0.964; TLI=0.958). The chi-square test of model fit is statistically significant (χ²=1161.6, df=145); however, this statistic is very sensitive to negligible sources of ill fit in large samples [28].

Twenty-four percent of individuals reported a presence of the majority of depressive symptoms in the last 12 months (captured by η1). Three percent reported using
Figure 1. Path diagram of the structural equation model

Notes: $\eta_1$ – depressive disorders, $\xi_1$ – presence of chronic diseases, $\xi_2$ – work stress, $\xi_3$ – home stress, $a_1$ – pain, $a_2$ – physical activity, $a_3$ – income, $a_4$ – average daily selenium intake, $a_5$ – average daily lipids intake, $a_6$ – average daily iron intake.

Risk factors for depression in the last 30 days. In order to test the statistical significance of dietary risk factors for depressive disorders, the estimated effects that are based on the pattern of relationships shown in Figure 1 were examined. The standardised and unstandardised total effects on depression are listed in Table 2. The parameter estimates demonstrate that the variables listed in Table 1 are significantly associated with depressive disorders. Home stress, self-reported pain, and low income are the main correlates of depression, i.e. these variables have the highest standardised total effect on depression in the model. Furthermore, the model shows that pain is at least as strongly related to depression as the presence of chronic diseases. However, not all chronic diseases were measured in the sample. The structural equation model suggests the association between morbidity and depression is mostly direct (standardised effect of 0.115); a relatively small part is mediated by physical symptoms (0.025). Both personal life and workplace difficulties are significantly related to depression; however, the estimated effect of the latter is significantly lower. The association of home stress with depression is magnified by capturing the effect of the death or severe illness of a spouse ($x_{13}$).
The model shows that dietary factors are of moderate value in the assessment of a depression score. Selenium deficiency is the strongest risk factor for depressive disorders among the nutritional variables considered in the model. Its association with depressive disorders is highly statistically significant. Interestingly, examination of direct effects shows that the variables of body mass index ($p=0.285$) and intakes of calcium ($p=0.746$), zinc ($p=0.513$), fibre ($p=0.870$), folate ($p=0.723$), and carbohydrates ($p=0.775$) fail to make a significant contribution to depressive disorders in the proposed structural equation model. The selenium intake variable remains statistically significant after adjusting for the above nutritional components, including all of them (standardised effect of $-0.151, p<0.001$). This result is robust to limiting the sample to men or women. Depression is also more frequent in individuals following a diet low in iron and high in lipids.

Table 2. Total effects on depressive disorders ($\eta_i$)

<table>
<thead>
<tr>
<th></th>
<th>Standardised estimate</th>
<th>Unstandardised estimate</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of chronic diseases ($\xi_1$)</td>
<td>0.140</td>
<td>0.148</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Work stress ($\xi_2$)</td>
<td>0.123</td>
<td>0.219</td>
<td>0.003</td>
</tr>
<tr>
<td>Home stress ($\xi_3$)</td>
<td>0.181</td>
<td>0.404</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Pain ($a_1$)</td>
<td>0.179</td>
<td>0.053</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Physical activity ($a_2$)</td>
<td>$-0.024$</td>
<td>$-0.006$</td>
<td>0.044</td>
</tr>
<tr>
<td>Income ($a_3$)</td>
<td>$-0.178$</td>
<td>$-0.010$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Average daily selenium intake ($a_4$)</td>
<td>$-0.133$</td>
<td>$-0.004$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Average daily lipids intake ($a_5$)</td>
<td>0.102</td>
<td>0.005</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Average daily iron intake ($a_6$)</td>
<td>$-0.065$</td>
<td>$-0.010$</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

Discussion

It is little known to the general public that nutrition can directly contribute to depressive disorders. However, in the last two decades a few dozen studies have explored the effect of nutrition on depression and mental illness [44]. Recently, dietary recommendations for the prevention of depression have been postulated. Protective diets include Norwegian or Japanese diets which are high in fish [45].

The proposed model reveals that selenium is the most strongly related to depressive disorders among the nutritional components considered, also when adjusting for possible confounders, including the presence of chronic diseases, stress and pain levels, physical activity, and income. In the proposed structural equation model, the relationship between low selenium intake and depressive disorders remains statistically significant, regardless of specification change and sample selection. The results
of the structural equation modelling support the existing body of research that reports dietary factors to be predictors of depression. The reason selenium affects mood in humans and behaviour in animals is, hypothetically, that selenium influences hormonal activity and neurotransmitters in the brain [46]. The effect of selenium intake on depressive disorders seems to be partly mediated by changes induced by selenium in thyroid function [47].

The level of covariate adjustment varies among the observational studies on selenium deficiency and depression. Most previous observational studies identified the relationship between selenium deficiency and depression with adjustment for possible confounding variables [10, 11]. Recently, in the MASHAD stroke and heart atherosclerosis disorder study based on a 24h dietary recall, selenium was suggested to be a significant predictor of depression. However, selenium intake was the only covariate in the proposed logistic regression model [48]. In randomised controlled trials, supplementation of selenium significantly improved mood and decreased anxiety compared to placebo [5, 6, 9]. In feeding trials, subjects following marginal selenium diets reported more symptoms of depression [7, 8]. However, there are examples of studies in which no significant differences in mood or perceived quality of life scores were observed between doses of selenium, or this relationship is not robust to inclusion of control variables [13, 10]. A new approach to the investigation of the relationship between selenium deficiency and depression was recently presented based on the results of Project FRONTIER, a study of rural health in West Texas, United States. The results supported the link between groundwater selenium exposure and decreased depression symptoms [12].

Some limitations of the study should be named. Dietary data are retrospective. The sample is not representative of the population of the country as a whole [38, 39]. Structural equation modelling is a confirmative technique [28]. Observational studies cannot test causality and control for confounding to the extent that clinical trials can.

In the current study, it is shown that the standardised effect of selenium intake is stronger than that of other nutritional components. Lipid intake has a positive, statistically significant effect on depressive disorders according to the postulated structural equation model. Some previous epidemiological, experimental, and clinical research have favoured the hypothesis that polyunsaturated fatty acids may play a role in the pathogenesis and prevention of depression [22]. Also, the current study is consistent with the results from epidemiological studies on iron deficiency and depression [21].

The proposed structural equation model confirms prior research on the role of physical symptoms in depressive disorders. Chronic pain was found to be common in up to 70% of patients with depressive disorders [14]. In the current study, pain disorders are defined by a single variable. A few studies have explored the association between depression and regional pain disorders, such as back pain or neck pain [15, 16]. Physical illness has been suggested to increase the risk of developing depression,
with a psychological or cognitive mechanism being the most common mechanism of depression [17].

High income inequality, high ratio of debts-to-assets, and low income are also known to be risk factors of depression [18, 19]. Some previous research suggested that income has a rather indirect effect on depression through mediators of employment status and financial strain [19]. Interestingly, there are no statistically significant differences in selenium intake due to income in the PONS sample, which is consistent with the results of previous research [49]. Work and home stress were previously identified in literature as other important risk factors for depressive disorders. Home stress was found to account for a larger part of depression scores than work stress in a medically healthy, employed U.S. sample population aged 30–60 [20]. Similarly, in the current study, the standardised effect of home stress is higher than that of work stress.

Conclusions

The hypothesis that selenium intake is related to depression is supported by the analysed data in the present study. This relationship is highly statistically significant and robust to controlling for physical symptoms, presence of chronic diseases, work and home stress, physical activity, income, and intake of other nutritional components. The results of the structural equation modelling suggest that home stress, pain, and low income have the highest standardised effect on the presence of depressive disorders. Since more than 40% of individuals from the PONS study reported a daily selenium intake lower than the recommended 70 μg, these findings may have public health implications.

References


Risk factors for depression


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