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Research paper

Dietary magnesium intake and the incidence of depression: A 20-year follow-up study

Teymoor Yary [a], Soili M. Lehto [b,c], Tommi Tolmunen [c], Tomi-Pekka Tuomainen [a], Jussi Kauhanen [a], Sari Voutilainen [a], Anu Ruusunen [c,*]

[a] University of Eastern Finland, Institute of Public Health and Clinical Nutrition, P.O. Box 1627, 70211 Kuopio, Finland
[b] Institute of Clinical Medicine, University of Eastern Finland, P.O. Box 1627, 70211 Kuopio, Finland
[c] Department of Psychiatry, Kuopio University Hospital, P.O. Box 100, 70029, KYS, Kuopio, Finland

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ABSTRACT

Background: Depression is a major global public health concern. The aetiology of depression is partly unclear; however, intake of nutrients, such as magnesium, have been suggested to affect depressive symptoms and modify depression risk.
Methods: This research is a part of the Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study, conducted on a sample of 2320 Eastern Finnish men aged 42–61 years old at the baseline. Magnesium intake was assessed by a 4-day food record. Hospital discharge diagnosis of unipolar depressive disorder was used as an outcome variable.
Results: Participants in the middle tertile of dietary magnesium intake had a statistically significantly decreased risk of getting a hospital discharge diagnosis of depression compared to participants in the lowest tertile of magnesium intake (HR 0.49, CI 0.25–0.95, $P=0.035$) in the prospective setting after multivariable adjustments. In addition, an inverse association between magnesium intake and the risk of depression was found when the combined middle and highest tertiles of magnesium intake were compared with the lowest tertile (HR 0.53, CI 0.29–0.95, $P=0.033$).
Limitations: Our findings may not be generalizable to individuals below middle-age or women. Moreover, we were unable to consider cases with mild depression in the longitudinal setting.
Conclusions: The results of this study suggest that magnesium intake may have an effect on the risk to develop depression. Further studies are needed to investigate whether sufficient magnesium intake could have implications for prevention or treatment of depression.

1. Introduction

Depression is a major public-health problem in both developed and developing countries (Strine et al., 2008; Yary and Aazami, 2011). It is associated with several somatic diseases such as cardiovascular disease and diabetes mellitus, and has a negative effect on the quality of life, life expectancy and the economy (Li et al., 2008) despite of all the currently available treatment modalities.

The role of nutrients in the etiology of depression has received more attention during the past years. Among nutrients, magnesium has been shown to be involved in the function of a range of hormones (Serefko et al., 2013), neurotransmitters (Serefko et al., 2013; Yary, 2013), neuronal membrane fluidity (Serefko et al., 2013) and neurotoxicity (Laudato et al., 2013). The N-methyl-D-aspartate antagonistic and gamma-aminobutyric acid A agonistic effects, and reduction in the release of adrenocorticotrophic hormone (ACTH) have also been suggested for the possible antidepressant mechanisms of action of magnesium (Murck, 2002). Moreover, higher intake of magnesium is associated with lower levels of inflammation markers such as C-reactive protein (CRP) (Bo et al., 2006), and low-grade inflammation has been shown to play a role in the development of depression (Ford and Erlinger, 2004).

Chronic administration of magnesium has been observed to reduce depression-like behavior in the olfactory bulbectomy rat model of depression (Pochwat et al., 2015). In addition,

Abbreviations: ACTH, adrenocorticotropic hormone; BDNF, brain-derived neurotrophic factor; CVD, cardiovascular diseases; CRH, corticotropin releasing hormone; CRP, C-reactive protein; HR, hazard ratio; HPA, hypothalamic–pituitary–adrenal; IL-6, interleukin 6; LTPA, leisure-time physical activity; NMDA, N-methyl-D-aspartic acid; PVN, paraventricular hypothalamic nucleus; PKC, protein kinase C; KIHD, The Kuopio Ischemic Heart Disease Risk Factor

* Corresponding author.
E-mail address: anu.ruusunen@kuh.fi (A. Ruusunen).

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antidepressant-like activity of magnesium has also been found in mice (Poleszak, 2007). In humans, both low (Banki et al., 1985) and high (Widmer et al., 1992) blood magnesium concentrations have been reported in depressed subjects. However, some factors limit the usability of blood magnesium measurements; for example, serum magnesium levels reflect only a small part of the total body content of magnesium (Reinhart, 1988), and they may not be a sensitive marker for reflecting mild magnesium insufficiency or the intracellular magnesium pool (Del Gobbo et al., 2012). Therefore, dietary intake of magnesium may be preferable when investigating the association between magnesium and depression. Several previous studies have suggested an inverse association between magnesium intake and depression (Jacka et al., 2009; Tarleton and Littenberg, 2015; Yary et al., 2013). However, these previous studies have been conducted in cross-sectional settings. The aim of this study was to examine the associations between dietary intake of magnesium and the incidence of depression among middle-aged Finnish men in a prospective setting.

2. Subjects and methods

2.1. Study population

The Kuopio Ischemic Heart Disease Risk Factor (KIHD) study was designed to investigate risk factors for cardiovascular disease, atherosclerosis, and related outcomes in a population-based, randomly selected sample of men from Eastern Finland (Salonen, 1988). The baseline examinations were carried out from 1984 to 1989. A total of 2682 men who were 42, 48, 54, or 60 years old at baseline (82.9% of those eligible) were recruited in two cohorts. The first cohort consisted of 1166 men who were 54 years old, enrolled from 1984 to 1986, and the second cohort included 1516 men who were 42, 48, 54, or 60 years old, enrolled from 1986 to 1989. The baseline examinations were followed by the 4-year examination round (1991–1993) in which 1038 men from the second cohort (88% of those eligible) participated. At the 11-year examination round (1998–2001), all men from the second cohort were invited, and 854 men (95% of the eligible) participated. During the 20-year examination round, all eligible participants from the first and second cohorts were invited to the study site. The baseline characteristics of the entire study population have earlier been described in detail (Salonen, 1988). The KIHD study protocol was approved by the Research Ethics Committee of the University of Kuopio. All subjects gave a written informed consent for participation. Subjects with current depressive symptoms ($n=287$) or missing data at baseline were excluded, leaving 2320 men for final analyses.

2.2. Assessment of depressive symptoms and depression

The 18-item Human Population Laboratory (HPL) Depression Scale, designed for screening of depressive symptoms among general population samples, was used to assess depressive symptoms at baseline (Kaplan et al., 1987). A cut-off score of five or more was used to detect individuals with elevated depressive symptoms ($n=287$) (Tolmunen et al., 2004). In order to enhance the analyses on causality, these subjects were removed from the analyses leaving total 2320 subject for the final analyses.

Depressive disorders during the follow-up were obtained by computer linkage to the National Hospital Discharge Register in 2010. The average follow-up time for the cohort was 21.3years. Depression was diagnosed based on the International Classification of Diseases 8 (ICD-8) (years 1985–1986), ICD-9 (1987–1995) and ICD-10 (1996–2010). The following diagnoses were considered as depression during the follow-up: major depression (ICD-9: 2961-, ICD-10: F32.1-3, F33.1-3), a depressive disorder, otherwise unspecified (ICD-9: 2968A, ICD-10: F32.9, F33.9), chronic depression (ICD-8: 300.41, ICD-9: 3004A, ICD-10: F34.1) and adjustment disorder with depressive symptoms (ICD-9: 3090A).

2.3. Assessment of nutrients intake

The baseline dietary intakes of magnesium, zinc and other nutrients were assessed by a 4-day food recording. Nutrient intakes were calculated using Nutrica® software (The Social Insurance Institution of Finland, Turku, Finland), and the loss of vitamins during food preparation was taken into account. Nutrica contains a large database comprising 1300 food items and dishes and 30 nutrients, including dietary magnesium, zinc, fats and vitamins.

2.4. Assessment of other variables

Study participants completed questionnaires assessing their background, marital status and education, as previously described (Salonen et al., 1992). Smoking status (never, past or current smoking), the type (cigarettes, cigars) and the amount smoked per day were assessed using questionnaires. Alcohol consumption (grams/week) was assessed with a structured quantity-frequency method using the Nordic Alcohol Consumption Inventory for drinking behavior over the previous 12 months (Kauhanen et al., 1992). Leisure-time physical activity was assessed using the 12-Month Leisure-Time Physical Activity (LTPA) Questionnaire (Lakka and Salonen, 1992). A trained nurse checked and completed the questionnaire during an interview. The energy expenditure from LTPA was expressed as kcal per day. The weight and height of the subjects were measured by the study nurse, and the body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in meters. A positive history of cardiovascular diseases (CVD) was coded based on the following criteria: first, all subjects had at least one of the following physician-diagnosed conditions: myocardial infarction, angina pectoris, other coronary conditions, cardiomyopathy, cardiac insufficiency or stroke. Second, all also used nitrates at least once per week, and had angina pectoris according to the World Health Organization angina pectoris questionnaire (the Rose Angina Questionnaire, RQ), a validated instrument to assess symptoms of typical angina pectoris in the general population (Rose, 1962).

2.5. Statistical analysis

The associations between dietary intake of magnesium (presented as tertiles) and baseline variables including age (years), smoking status (never, previous, and current), marital status (married or living as a couple, not married, separated or divorced, widowed), education (years), alcohol intake (g/week), leisure-time physical activity (kcal/day), BMI (kg/m^2), zinc intake (mg/d), magnesium intake (mg/d), history of CVD (yes vs no) and history of diabetes (yes vs no) were examined using chi-square test and *t*-test. The association between incident depression and tertiles of magnesium intake was tested by Cox's proportional hazard's regression model, adjusted for all the listed baseline variables.

Previous papers from the same data have showed that the utilized sample sizes appear to be satisfactory for assessing the role of nutrient intake on the risk of depression in a prospective setting (Tolmunen et al., 2004). Also, a meta-analysis on depression prevention in male populations indicated that the same effect size level may be sufficient for studies related to potential means for prevention (Jane-Llopis et al., 2003). All analyses were conducted with the SPSS statistical software (version 22; SPSS Inc., Chicago, IL). Two-tailed *P* values below 0.05 were considered to