



Diet, Inflammation and the Brain

Inflammatory dietary pattern and risk of depression among women



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ABSTRACT

Background: Inflammation is considered as a mechanism leading to depression, but the association between inflammatory dietary pattern and depression risk is unknown.

Methods: Using reduced-rank regression, we identified a dietary pattern that was related to plasma levels of inflammatory markers (C-reactive protein, interleukin-6, tumor necrosis factor α receptor 2), and we conducted a prospective analysis of the relationship of this pattern and depression risk among participants in the Nurses' Health Study. A total of 43,685 women (aged 50–77) without depression at baseline (1996) were included and followed up until 2008. Diet information was obtained from food frequency questionnaires completed between 1984 through 2002 and computed as cumulative average of dietary intakes with a 2-year latency applied. We used a strict definition of depression that required both self-reported physician-diagnosed depression and use of antidepressants, and a broader definition that included women who reported either clinical diagnosis or antidepressant use.

Results: During the 12-year follow-up, we documented 2594 incident cases of depression using the stricter definition and 6446 using the broader definition. After adjustment for body mass index and other potential confounders, relative risks comparing extreme quintiles of the inflammatory dietary pattern were 1.41 (95% confidence interval [CI], 1.22, 1.63; P -trend < .001) for the strict definition and 1.29 (95% CI, 1.18, 1.41; P -trend < .001) for the broader definition of depression.

Conclusions: The inflammatory dietary pattern is associated with a higher depression risk. This finding suggests that chronic inflammation may underlie the association between diet and depression.

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1. Introduction

Depression is a chronic and recurrent illness that affects more women than men, and about 20% of US women are affected during their lifetime (Kessler et al., 2003). Depression is associated with leading causes of morbidity and mortality, including cardiovascular disease (CVD), diabetes, and cancer (Musselman et al., 1998; Pan et al., 2011a; Spiegel and Giese-Davis, 2003). As indicated in a recent literature review (Sanchez-Villegas and Martinez-Gonzalez, 2013), depression shares common mechanisms (e.g., insulin resistance, higher plasma homocysteine levels, endothelial dysfunction, etc.) with cardiometabolic disorders that could explain the link between these diseases. Inflammatory processes

have been also suggested as common link between depression and CVD, diabetes and cancer (Howren et al., 2009). Proinflammatory cytokines may have an adverse effect on neurotransmitters, and inflammatory status and endothelial dysfunction could impair the expression of brain-derived neurotrophic factor (BDNF) (Sanchez-Villegas and Martinez-Gonzalez, 2013). Current evidence indicates that diet could stimulate chronic inflammatory diseases (Bosma-den Boer et al., 2012; Giugliano et al., 2006).

The traditional single-nutrient or food analysis in relation to chronic diseases is challenged by several conceptual and methodological limitations (Hu, 2002). Dietary pattern analysis, which reflect different combinations of food intake, has emerged as a complementary approach that better reflects the complexity of the diet and its relationship with disease risk (Hu, 2002). Therefore, it is also important to consider the overall diet relationship with depression risk, and not only isolated nutrients or foods. To date, only five cohort studies have evaluated the associations between patterns and depression risk. Sanchez-Villegas et al. (2009) noted

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a lower incidence of depression with higher scores on a Mediterranean diet score in the Seguimiento Universidad de Navarra (SUN) cohort. Through the principal component analysis (PCA) among the Australian Longitudinal Study on Women's Health (ALSWH), [Rienks et al. \(2013\)](#) observed that a Mediterranean-style dietary pattern was associated with a lower incidence of depressive symptoms. Using PCA and data of the Whitehall II prospective cohort, [Akbaraly et al. \(2009\)](#) noted a higher odds of depressive symptoms with a "processed food pattern". Using PCA and data of the GAZEL cohort, [Le Port et al. \(2012\)](#) reported that healthy and traditional patterns were associated with lower risk of depressive symptoms in women. However, in our recent analyses among women in the Nurses' Health Study (NHS), no significant association was found between dietary Prudent (high in fruits, vegetables, legumes, fish, poultry, and whole grains) and Western pattern (high in red and processed meats, sweets and desserts, french fries, and refined grains) scores (using PCA) and depression risk ([Chocano-Bedoya et al., 2013](#)).

The reduced rank regression (RRR) is an alternative empirical approach to generating dietary patterns that may be better predictors of disease ([Hoffmann et al., 2004](#)). Unlike analyses using PCA or factor analysis, which derive dietary patterns based on covariance among foods, the RRR method uses information on biomarkers to derive dietary patterns. To our knowledge, no previous study has examined the association between inflammation prone dietary patterns (RRR derived) and depression risk. Here we first derived a dietary pattern that was associated with selected inflammatory biomarkers and then conducted a prospective analysis to determine the relationship of this inflammatory dietary pattern (IDP) with depression risk among participants of the NHS.

2. Methods and materials

2.1. Study population

The NHS is a prospective cohort of 121,700 U.S. female registered nurses aged 30–55 years at enrollment in 1976. Every 2 years, participants provide updated information, via mailed questionnaires, about lifestyle, medical history and newly-diagnosed medical illnesses. Women were first asked to report their use of antidepressants in 1996 and their history of physician-diagnosed depression in 2000. A total of 97,103 women completed one of the 1996, 1998, or 2000 questionnaires. To examine prospectively the relation of IDP to depression, we excluded from the analyses those women who could have had depression before 1996. This group included 36,225 women with an incomplete depression history (i.e. those who did not report their depressive status in 1996, 1998, or 2000, or did not return or answer the 1992 or 1996 Mental Health Index (MHI-5) questionnaires ([Berwick et al., 1991](#); [Yamazaki et al., 2005](#)), a 5-item subscale of the Short-Form 36 Health Status Survey), as well as women who reported in 1996 using antidepressants ($n = 2052$) or had a physician-diagnosed episode of depression in 1996 or before ($n = 3445$), or with an unknown start date ($n = 198$), or reported severe depressive symptoms (score ≤ 52) on the 1992 ($n = 2374$) or 1996 ($n = 2271$) MHI-5 questionnaire. Thus, a total of 50,538 women were considered depression-free in 1996, comprising the baseline population for the current analyses. Further excluding those who had missing values for IDP ($N = 6853$), the final 1996 baseline population included in the IDP and depression analyses comprised 43,685 women.

The study protocol was approved by the Institutional Review Boards of Brigham and Women's Hospital and the Harvard School of Public Health.

2.2. Assessment of exposure

The dietary variables were assessed using validated semiquantitative food-frequency questionnaires (FFQs) ([Willett et al., 1985](#)). In 1984, 1986 and every 4 years since, an expanded 131-item FFQ were sent to participants. Women were asked how often they had consumed a commonly used unit or portion size of each food on average during the previous year, with 9 possible frequency responses ranging from "never" to "more than 6 times a day." Food items were aggregated into 39 food groups on the basis of nutrient profiles and culinary usage ([Hu et al., 1999](#)). We included each type of alcoholic beverage (wine, liquor, beer) separately as food groups in factor analysis. Vitamin and mineral supplements were not included in the patterns. The validity and reproducibility of the FFQ have been evaluated before in a subgroup of participants using four one-week long diet records completed during the previous year and repeated FFQs one year apart ([Salvini et al., 1989](#); [Willett et al., 1985](#)).

2.3. Case ascertainment

We used two definitions for depression, a strict definition that required both self-reported physician-diagnosed depression and regular antidepressant use (i.e. used regularly in the past 2 years), and a broader definition that included women who reported either clinical diagnosis or regular antidepressant use. In 2000, participants were asked to report the year of their first episode of physician-diagnosed depression (1996 or before, 1997, 1998, 1999, or 2000). Thereafter, this information was updated biennially through 2006. Regular antidepressant medication use was first asked in 1996 and then biennially updated through 2006. Hence, the 1996 questionnaire cycle was considered as baseline.

2.4. Covariate assessment

Demographic, lifestyle, behavior, and comorbidity information were collected using the standardized questionnaires mailed to the participants. In the baseline questionnaire (1996), we requested information about age, weight and smoking, menopausal status and use of postmenopausal hormone therapy, and previously diagnosed medical conditions. This information has been updated in the biennial follow-up questionnaires. Marital status and retirement were obtained at baseline (1996) and updated in 2000 and 2004. Education levels of the nurses (registered nurses, bachelor, master and doctorate), and their husband (<high school, high school, college graduate school, graduate school), and ethnicity (White, Black, Amerindian and Hawaiian, Asian) were measured in 1992. Participants were asked to report the hours spent per week on moderate (e.g., brisk walking) and vigorous (e.g., strenuous sports and jogging) exercise, and then the total hours of metabolic equivalent tasks per week (METh/wk) were estimated on the basis of the MET score assigned to each activity. Mental health at baseline was assessed using the MHI-5 score, a subscale of the SF-36 Health Status Survey.

2.5. Laboratory procedures

Between 1989 and 1990, 32,826 women free of diagnosed diabetes, ischemic heart disease, stroke, or cancer provided fasting blood samples in heparin-containing tubes. Women shipped their blood samples overnight in an icepack provided by the study and completed a questionnaire which included information of time of blood draw, weight, and medication use among others. Upon arrival, blood samples were aliquoted into plasma, white blood cells, and red blood cells components and stored in liquid nitrogen freezers with an electronic alarm system; the majority of samples

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