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Nutrition and depressive symptoms

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SUMMARY

Introduction

Depression is one of the most prevalent and disabling mental disorders, and causes a significant burden to both individuals and society. Major depressive disorder is characterised by emotional and behavioural alterations, including depressed mood and loss of interest or pleasure as core symptoms. Depressive symptoms are linked to a decreased quality of life and functioning, physical morbidity and mortality. Due to its high and increasing prevalence, affecting 350 million people globally, depression is a major contributor to the global disease burden. Therefore, attention to prevention is very important.

Evidence for a link between nutrition and depression is growing; nutritional factors may modulate physiological pathways that affect depression risk, such as neurotransmitter processes, neuroprogression, oxidative stress, mitochondrial function and inflammation. Nutrient status, including vitamin B₁₂ and vitamin D status, has been studied in relation to depressive mood. A link between the intake of specific food groups, such as fruit, vegetables, fish, coffee, olive oil, whole grains and sweets, and depressive symptoms has also been suggested. In addition, 'healthy' dietary patterns may be associated with less depressive symptoms, whereas 'unhealthy' dietary patterns might relate to more depressive symptoms. It has also been proposed that the link exists in the reverse direction: depressive mood may change diet. However, evidence for associations between nutritional factors and depression is inconclusive and limited, indicating the urgent need for more high-quality, longitudinal, potentially bidirectional studies on nutritional factors and depressive symptoms.

After a general introduction, *Chapter 1* describes the overall aim of this thesis: to investigate longitudinal associations of nutrient status, food groups and dietary patterns with depressive symptoms in adults.

Specific research questions are:

1. What is the longitudinal association between *nutrient status* and depressive symptoms?
 - a. What is the association between serum vitamin B₁₂ and (subsequent) depressive symptoms?
 - b. What are the associations between (change in) serum vitamin D and (change in) depressive symptoms?
2. What is the bidirectional, longitudinal association between *food group intakes* and depressive symptoms?
3. What is the association of depressive symptoms and history with *diet quality indices*?

Data from two ongoing, population-based cohort studies of general older populations are used to examine these longitudinal associations: the Dutch Longitudinal Aging Study Amsterdam (LASA) and the Italian Invecchiare in Chianti (InCHIANTI) study. The research questions are addressed in the three parts of this thesis.

Part I: Nutrient status and depressive symptoms

In *Chapter 2*, the cross-sectional and prospective associations between vitamin B₁₂ concentration and depressive symptoms were investigated in the oldest LASA cohort of 1205 participants aged ≥65 years. Serum vitamin B₁₂ at baseline was not cross-sectionally associated with the severity of depressive symptoms. In addition, no prospective associations were found of baseline vitamin B₁₂ with course of depressive symptoms nor with incidence of depression (Center for Epidemiologic Studies Depression scale (CES-D) ≥16 and/or antidepressant use) over 16 years, except for an unexpected higher risk of depression in younger participants with higher vitamin B₁₂ concentrations (aged 64.8-73.4 years at baseline). As serum vitamin B₁₂ and plasma total homocysteine are inversely correlated with each other, the analyses were repeated using baseline homocysteine concentration as determinant. Homocysteine also showed no cross-sectional nor prospective associations with depressive symptoms, supporting the null findings of vitamin B₁₂. This study in older adults does not confirm previously shown associations of vitamin B₁₂ concentration with depressive symptoms.

Chapter 3 describes cross-sectional and prospective 6-year associations between 25-hydroxyvitamin D (25(OH)D) concentration and depressive symptoms. To gain a better understanding of the underlying mechanisms, the second aim was to explore the mediating role of physical functioning in the prospective association. In both the older (≥65 years at baseline, *n*=1282) and younger (55-65 years at baseline, *n*=737) LASA cohort, baseline serum 25(OH)D was cross-sectionally not associated with the severity of depressive symptoms in the fully-adjusted models. In the older cohort, sex was an effect modifier in the prospective associations, and older women with baseline 25(OH)D concentrations <30 nmol/l experienced 23% more depressive symptoms in the following 6 years, compared to women with 25(OH)D concentrations >75 nmol/l. Reduced physical performance partially mediated this association. No significant associations were found in older men and in the younger cohort. The findings indicate no associations of vitamin D status with severity and course of depressive symptoms, except for an inverse association in older women.

A more detailed investigation on the longitudinal association between serum 25(OH)D and depressive mood is described in *Chapter 4*. Two 25(OH)D measurements were used to study the association between change in serum 25(OH)D and parallel change in depressive symptoms over time. Change in serum 25(OH)D was not associated with change in depressive symptoms in the older LASA cohort (*n*=173) over a period of 13 years and also not in the younger cohort over 6 years with a baseline 25(OH)D concentration above 59 nmol/l (*n*=225). However, in participants from this younger cohort with a lower baseline 25(OH)D (*n*=225), an increase in serum 25(OH)D of 10 nmol/l was associated with a decrease of 0.62 points in CES-D score. An increase in vitamin D concentration might be protective against depressive mood but only in middle-aged adults with a low vitamin D concentration.

Part II: Food groups and depressive symptoms

Chapter 5 reports on the prospective associations – in two directions – between food group intakes and depressive symptoms in 1058 participants (aged 20-102 years) of the InCHIANTI study. Four times repeated measurements of both dietary intake and CES-D scores were fully used in time-lag models. Associations were investigated of intakes of thirteen food groups with 3-year changes in CES-D scores over a 9-year period, and vice versa. Higher intakes of fish and shellfish were associated with a decrease and sweet foods with an increase in CES-D scores. In the reverse direction, higher CES-D scores were associated with decreased intakes of vegetables and red and processed meat, and increased intakes of dairy and savoury snacks. No significant associations in either direction were found for fruit, nuts and legumes, potatoes, whole grain bread, olive oil, sugar-sweetened beverages, and coffee and tea. In this sample of mainly older adults, bidirectional, longitudinal associations between food group intakes and depressive symptoms were found. However, bidirectional associations for a single food group were not found, which excludes reverse causality as reason for the observed associations.

Part III: Depressive symptoms and dietary patterns

In *Chapter 6*, associations between depression determinants and diet quality were investigated in 1322 LASA participants aged ≥ 55 years. Next to current depressive symptoms (1), short-term changes in depressive symptoms (2) and long-term history of depressive symptoms (3) were used as determinants. Scores on three *a priori* diet quality indices in 2014/2015 were used as outcomes: the Mediterranean Diet Score (MDS), Alternative Healthy Eating Index (AHEI) and Dietary Approaches to Stop Hypertension diet (DASH). Cross-sectionally, current depressive symptoms (CES-D ≥ 16) were associated with lower MDS and AHEI scores in men but not in women. Chronic/recurrent depressive symptoms over 2 to 5 years (CES-D ≥ 16 in both 2011-2013 and 2015/2016) were also associated with lower MDS scores and a trend for lower AHEI scores, compared to no depressive symptoms (CES-D < 16 at both cycles). History of depressive symptoms over 2 to 14 years (ever CES-D ≥ 16 from 2001-2003 to 2011-2013) was associated with lower MDS and AHEI scores in men only. None of the depression determinants was consistently associated with the DASH score, and emerging and remitted depressive symptoms were also not associated with any diet index. This study suggests that current and past depressive symptoms are related to poorer diet quality, particularly in men.

Conclusion

In *Chapter 7*, a summary of the main findings of this thesis is provided, and methodological strengths and limitations are considered. Furthermore, recommendations for future studies and implications for public health and clinical practice are discussed.

It is concluded that in older adults, vitamin B₁₂ concentration is not associated with subsequent depressive symptoms. Higher vitamin D concentrations were found to be associated with less subsequent depressive symptoms but only in specific population groups. In mainly older adults, intake of fish was found to be inversely and sweets positively associated with subsequent

depressive symptoms. In the reverse direction, depressive symptoms were found to be related to a decrease in the intakes of meat and vegetables, and an increase in the intakes of dairy and savoury snacks. Last, both current and past depressive symptoms were, particularly in older men, found to be associated with a lower diet quality. Overall, this work shows some longitudinal associations but the modest effect sizes and several null associations prompt us to be cautious about the existence of bidirectional links between nutrition and depression.

In light of this thesis as well as previous literature, currently, specific nutrients seem to be of less importance in relation to depressive symptoms compared to intake of food groups and whole dietary patterns. Reversely, depressive mood appears to be negatively related to subsequent diet quality, i.e. related to less healthy food groups and dietary patterns.

Eating a healthy diet is recommended for the general population because of its beneficial effect on physical health and, potentially and partially supported by this thesis, also on mental health. However, evidence on the causality and bidirectionality of the diet-depression link is still limited. Future research is warranted to further examine the role of food group intakes and dietary patterns in the course and development of depression as well as to explore if and how depressive mood influences dietary intake. This knowledge is required for strategies to prevent depressive symptoms and the optimal nutritional care of depressed persons.