Research
a dietetic practice group of the
Academy of Nutrition and Dietetics

TheDigest

Volume 49, Number 4 – Fall 2014

Depression and Nutrition in the Elderly

Emily Tarleton, MS, RD, LD
University of Vermont Center for Clinical and Translational Science

The Administration on Aging reports that 12.9% of the U.S. population is over the age of 65, but by 2030, almost 20% of the population will be older than 65.[1] Included in these statistics are those aged 90 or above, considered "the oldest of the old" and the fastest growing portion of the population.[2] A majority of older Americans live at home. Ensuring this population has the highest quality of life during their later years is an important public health initiative.[3] Primary care physicians and community health care providers are in a position to identify and manage the health of the elderly to ensure the best quality of care.[4]

Both depressive symptoms and reduced nutrient intake promote a lower quality of life but can be monitored by primary care physicians. Life satisfaction is a predictor of longevity and psychiatric morbidity. Adults who are dissatisfied with life are over 41 times more likely to have depressive symptoms than those who are satisfied with life.[5] While the number of adults >65 years of age tend to be more satisfied with life compared to those 18-64 years of age, it is probable that those who are dissatisfied are at greater risk for depressive symptoms.[5] Depression is a strong risk factor for suicide and has been associated with diseases such as stroke, cardiac disease, and cancer.[6] Even minor depression has been associated with increased use of health services, excess disability, poor health outcomes, and higher mortality.[7] Older adults may not report depression to their physicians because they do not recognize the symptoms[7] or are hesitant to describe feelings of depression or anxiety for cultural reasons.[8] Older adults should be regularly screened and interventions initiated if depression presents.

In this Issue:

The nutrition status of older adults should also be monitored. As we age, our ability to absorb certain nutrients decreases, as does our caloric need. Ensuring older adults have access to, and are able to consume, a nutrient dense diet can help ensure a high quality of life. For older adults, the management of chronic diseases may take priority over prevention or identification of new conditions such as depression or changes in nutrition status; however, both impact quality of life in older adults.

Depression in Older Adults

The prevalence of late-life depression is around 11% in adults older than 60 years as compared to about 19% in those younger than 60 years.[8] Depression in the older population may present itself with different symptoms than younger adults and usually has different causes. Depressive symptoms in older adults are associated with gender (females exhibit higher rates), somatic illness (physical pain in many parts of the body without an identified physical cause), cognitive (anxiety, insomnia) and functional (muscular and joint aches) impairment, and lack of social support (widowhood, low emotional support).[9] Risk factors such as deteriorating health, cognitive decline, diminishing social network, inadequate coping strategies, and stressful life events are especially important to identify in the elderly.[10] Some common symptoms are worry, psychomotor delay, loss of concentration, feelings of hopelessness, fatigue linked to poor appetite, weight loss, and sleep disturbances.[8] Agitation and memory loss can be mistaken for dementia rather than recognized as depression. Further, depression can be difficult to assess in older adults due to medication side effects and underlying medical conditions which cause many of the same symptoms.[7, 8]

Primary care physicians and community health providers should be trained to recognize depression and how it manifests in the older population.[8] Health professionals should be knowledgeable about the increased risk of depression with the presence of risk factors such as loss of a spouse, change in living arrangements, or any change in health, mobility, or independence.[3] Individual coping styles and social support can significantly influence risk for depression.[9] The Patient Health Questionnaire-9,[11] Geriatric Depression Scale,[12] Geriatric Anxiety Inventory,[13] Cornell Scale for Depression in Dementia,[14] and The Neuropsychiatric Inventory[15] are all validated instruments that can be used in the older population to identify depressive symptoms. Due to medication use and health issues, treatment of depression needs to be individualized. Fear of adverse outcomes may cause health care providers to hesitate treating older adults, but the benefits of treatment outweigh the safety and efficacy concerns of current treatments for depression.[7] Both medications and counseling can be part of the prescription for depression at any age. Identifying depression in older adults requires assessing several variables including behavioral, psychosocial, and biological factors. Many of the symptoms for depression are similar to those of dementia, frailty, and age-related failure to thrive. Depression should not be incorrectly labeled as simply "age-appropriate mental changes" and go uninvestigated.

Cardiovascular disease and mortality are well documented results of untreated depression later in life.[4, 6, 16-18] Data from the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) indicate depressive symptoms lasting for over a year are associated with a significantly increased risk of mortality five years later.[4] Older adults newly diagnosed with depression are at high risk for mortality, and those with increasing depression over time have a 70% increase in mortality compared to those with stable depression.[4] However, the relationship between depression and mortality may be confounded, and those who are older but in poor health may report more depressive symptoms due to quality of life issues. Higher mortality rates may be a result of chronic conditions and not necessarily depression.[6] Monitoring and treating symptoms of depression in the elderly may ensure a higher quality of life despite increasing disability and chronic disease and may decrease their risk of mortality.

Nutrition in Older Adults

For older adults, factors such as changes in physical and cognitive status, management of multiple medical conditions, and changes in social and family environments are all barriers to optimal food and

nutrient intake.[19, 20] Several age-related changes in older adults including decreases in taste sensation, secretion of digestive enzymes, salivation, ability to detect thirst, motor ability, renal function, hepatic function, chewing ability, smell, sight, and early satiety can lead to inadequate nutrient intake.[3] Even if intake is sufficient, absorption of vitamins and minerals diminishes with age while chronic disease complications and the use of medication exacerbates malabsorption. The need for fewer calories as we age makes the intake of nutritionally dense foods very important. Fruits and vegetables are a good source of vitamins, minerals, fiber, and antioxidants but may be the hardest for the elderly to obtain. Transportation costs and decreased mobility can complicate travel, inhibiting the consumption of fresh foods. Adequate protein intake is important to lessen the risk of age related muscle loss; preservation of muscle mass is important to maintain bone mineral density and to decrease bone fracture risks.[21] However, high protein foods, other than nuts and legumes, are more expensive, spoil quickly, and can be difficult to prepare. A healthy diet can decrease a person's risk of coronary artery disease, and the intake of adequate calories, vitamins, and minerals aids in the control of many chronic diseases.

In addition to advising the elderly on taking their medications, physicians can also assess the level of food insecurity on patients' nutrition status. The Mini Nutritional Assessment has been used in clinic and community settings as a quick and accurate way to assess nutrient intake in the older population.[22] Dietary restrictions recommended to control chronic disease may overwhelm older patients. They may unnecessarily avoid many healthy foods which can lead to nutrient deficiencies, so a less restrictive diet, when possible, may outweigh health risks.[3]

Nutrition and Depression

Older adults reporting inadequate intake are four times more likely to be depressed.[3] Studies also suggest a link between coronary artery disease, inflammation, and the development of depression.[18, 23, 24] The development of frailty and reductions in muscle skeletal strength may be a result of oxidative stress and inflammation.[25] Research indicates a relationship between nutrition and systemic inflammation.[26] Over the past two decades, research on specific nutrients and depression has grown. Vitamin D, folate, magnesium, zinc, and unsaturated fatty acids research, while inconclusive, has received the most attention. There are no current best practices when it comes to individual nutrient supplementation for depression. Folate and magnesium are consumed in inadequate amounts in older adults: fewer than 50% meet the Estimated Average Requirement (EAR) for folate and magnesium from food sources alone or with the addition of supplements.[27] A majority of older adults consume the EAR for zinc, and nearly all older adults who regularly take a vitamin and mineral supplement meet the EAR for zinc.[27] Vitamin and mineral supplementation can increase the intake of many nutrients, but research indicates only half of older adults use a supplement daily.[27] A diet high in fruits and vegetables, whole grains, and fish would provide the nutrients thought to be low in older adults and may aid in the control of depressive symptoms. Research is now turning to whether dietary patterns play a role in depression.

Vitamin D

The discovery of vitamin D receptors in the central nervous system led to research on its role in depression.[28] Older adults are at risk for vitamin D deficiency because they produce only 25% of the cutaneous vitamin D produced by young adults[29] and may have less exposure to solar radiation with which to synthesize vitamin D due to geographical location and/or increased time spent indoors.[30] In addition, the few foods that naturally contain vitamin D (salmon, mackerel, cod liver oil) are not consumed in adequate amounts.[31] Several studies found higher rates of vitamin D deficiency in older adults with psychiatric disorders, both in the inpatient and outpatient setting.[32-34] The few randomized control trials (RCTs) studying the effect of Vitamin D on depression found low vitamin D in people with symptoms of depression, but supplementation with vitamin D to decrease depressive symptoms has had mixed results.[35-37] Vitamin D plays a significant role in bone health: a low intake can lead to issues with mobility which in turn can lead to frailty and depression later in life.

Data supports the use of vitamin D supplementation to decrease mortality in elderly women,[38] but a recent meta-analysis questions the use of vitamin D supplementation to help prevent falls.[39] The Institute of Medicine recommends supplementation of vitamin D in older adults, and assays should be obtained to assess compliance with supplementation regimens.[7] Older adults may decrease their risk of disability with early vitamin D supplementation. A long-term outcome may be a decrease in depression later in life secondary to sustained mobility.

Folate

Evidence of a relationship between folate intake and depressive symptoms is mixed, and the exact mechanism is not known. One theory claims vitamin B deficiencies can lead to increased homocysteine concentrations, which have been associated with depression.[40] Skarupski and colleagues[40] did not find a relationship between folate and depression in the Chicago Health and Aging Project that looked specifically at depression in the elderly. Jacka and colleagues[41] found a weak association (p=0.06) in women while Nguyen et al[42] found no association in women. However, folate deficiencies have been associated with depression in several other studies,[43-45] specifically in older adults.[46-48] Folate intake in the United States is usually adequate due to fortification of the grain supply, so the relatively low risk of folate insufficiency may explain some of the differences in outcomes. Research has shown the older population is at higher risk for low folate intake due to an overall decreased caloric need and decreased intake of fortified foods, but a link with depression is not certain.[27]

Magnesium

Systemic inflammation is a prominent feature of depression, and magnesium has strong anti-inflammatory effects.[49] National data indicates the majority of the population has magnesium intake below the Recommended Daily Allowance.[50] Magnesium supplementation has been linked to improvement in symptoms of major depression,[51] premenstrual symptoms,[52] postpartum depression[51] and chronic fatigue syndrome.[53] Low magnesium status has been associated with increased depressive symptoms in several different age groups and ethnic populations.[23, 41, 54, 55] Issues in study design have led to inconclusive results and skepticism of magnesium's role in depression. Serum magnesium levels were used to indicate magnesium status in some studies,[54, 56] but its reliability is questionable.[57, 58] Clinical trials have suffered from limited sample sizes[53, 54] and the use of the supplement magnesium oxide[59] which is poorly absorbed.[58] Cross-sectional studies have reported an inverse relationship between magnesium intake and standardized depression scores.[23, 41, 55, 60] One longitudinal study[61] did not find an inverse relationship, although it was underpowered to detect a significant reduction in depression. With varying outcomes and limited sample sizes, consensus on the relationship between magnesium intake and depression has not been reached. Magnesium and folate are found in many of the same foods; therefore, it is important to decipher whether depressive symptoms are a result of inadequacy of one of these nutrients but not the other.

Zinc

Zinc is found in highest concentration in the brain, and zinc deprivation leads to alteration in behavior, learning, and mental function.[17] It also has a lipid protective effect and is a constituent of fatty acid metabolizing enzymes.[62] Zinc's role as an anti-inflammatory and neuroprotective agent led to studies involving depression.[41] Studies in animals have been promising, but human studies have presented mixed outcomes. Zinc's role in depression is questioned due to varying issues with the design of past studies. (RCTs) have suffered from high dropout rates[42, 63] and the use of serum zinc as a marker for zinc status,[64, 65] which is known to be unreliable.[66, 67] Many cross-sectional studies also relied on serum zinc levels[62, 68-70] and were done outside of the U.S.[17, 41, 71] Maserejian et al[72] found an association in women in Boston, but not men. The U.S. tends to have a lower rate of zinc deficiency, and these results point to the need for further investigation of the U.S. population. Studies on zinc supplementation and depression in the elderly are lacking; however, zinc deficiency may only be of concern in older adults who do not take a vitamin and mineral supplement.[27]

Polyunsaturated Fatty Acids

The role of fatty acids in depression is complex. Fatty acids are major structural components of the brain and therefore, may have a protective effect

against depression.[62] The fatty acid composition of membranes in the brain declines with age, but supplementation with essential fatty acids, such as omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), can improve membrane fluidity.[73] Numerous studies have shown diets with reduced levels of omega-3 are associated with major depressive symptoms,[74] and RCTs have reported treatment with omega-3 fatty acids improves depression.[75] A recent meta-analysis established that depression is related to a diet low in omega-3 fatty acids.[76] Omega-3 concentrations affect neuroplasticity, cell survival, and gene expression.[62, 77] A deficiency in omega-3 PUFAs prevents the regeneration of membranes and accelerates cerebral aging, which can contribute to the development of depression.[62] Omega-3 deficient diets are associated with an increase in depression scores on standard behavioral tests and are also associated with a reduction in expression of brain-derived neutrotrophic factor (BDNF), a neurotrophin that plays a role in cell survival.[77, 78] Benefits have been seen with a range of doses between 1 and 9 grams daily.[7]

Fatty acids also have an important role in inflammation.[79] PUFAs influence the production of proinflammatory cytokines, which seem to be elevated in depressed patients.[77] The competition between omega-3 and omega-6 for metabolic enzymes can inhibit the production of proinflammatory eicosanoids.[77] Another link to inflammation is seen in omega-3's relationship with cardiac disease. A study by Parker and colleagues[80] showed that among patients with acute coronary syndrome, those with clinical depression had lower levels of omega-3. Cardioprotective effects have repeatedly been seen in high mono and polyunsaturated diets while high intakes of trans-fatty acids have a detrimental effect on depression.[79] Many researchers argue there is a lack of association between the types and ratios of poly and mono unsaturated fats in the diet, and a diet generally high in mono and poly unsaturated fats and low in saturated and trans-fats is associated with lower depressive symptoms.[81] The health benefits of unsaturated fatty acids go beyond a possible role in depression and have been found to be beneficial in the management of many chronic diseases. Although foods containing unsaturated fats can have a shorter shelf life and are generally more expensive, they can add calories for those with early satiety. Older adults should be encouraged to consume foods containing unsaturated fats.

Mediterranean Diet

The Mediterranean diet pattern (MDP) is believed to decrease the metabolic, inflammatory, and vascular processes that contribute to the risk of developing depressive symptoms.[7, 82] The MDP provides a high level of the nutrients identified as having an impact on depression. This diet pattern includes high levels of magnesium and folate from vegetables and legumes, PUFAs from fish, monounsaturated fatty acids (MUFAs) from olive oil, and antioxidants from vegetables and red wine.[82] Overall, the pattern promotes increased consumption of high fiber foods and unsaturated fatty acids. Lower mortality from cancer and cardiovascular disease as well as overall lower mortality has been associated with the MDP.[24] Luciana et al[82] recently replicated work showing the MDP protects against C-reactive protein-inflammation, and the effect is seen not only in those living in Mediterranean regions but also older adults following the MDP in other parts of the world. People inhabiting Greece and the Greek islands, where most people follow the MDP, have a lower rate of depression and mental disorders with the "oldest of the old" living on the island of Ikaria having the lowest rate.[78, 83] Ikaria has been the subject of many recent articles due to its unusually high numbers of people living to the age of 100 years, pointing to an overall increased survival rate from following the MDP.

The MDP promotes the intake of fruits and vegetables, which are an important component of a healthy diet due to their high content of vitamins, minerals, fiber, and antioxidants. Epidemiological evidence suggests that regular consumption of fruits and vegetables in the recommended amounts is associated with lower risk for chronic diseases[84, 85] and is associated with lower mortality.[86] The most recent recommendation for those > 70 years of age is a combined amount of nine servings (4.5 cups) for males and seven servings (3.5 cups) for females.[87] On average, Americans aged 70 years or older consume only two-thirds of their recommended

servings of fruits and vegetables[88] with only 25% reporting > 5 servings per day.[89] Some studies have shown a high intake of fruits and vegetables inhibits the development of depression via the antioxidant neuroprotective and neurogenerative roles.[24, 73] Depression has been associated with low plasma levels of vitamin C which may reflect poor nutritional status and inadequate antioxidant status.[18] The InCHIANTI study (aging in the Chianti area) concluded that a higher adherence to the MDP was associated with a higher intake of many antioxidants such as beta carotene and vitamins C and E; the intake of these nutrients may partly explain why the MDP has a protective role.[25] Even a modest increase in fruit and vegetable intake can have a marked effect on health in older adults. Just one additional serving of fruits and vegetables has been associated with an approximately 10% increase in the odds of a person reporting health, including mental health, as good or better.[90]

A defining characteristic of the MDP is the high intake of MUFAs, mostly in the form of olive oil and fish. MUFAs, found in olive oil and red wine, are thought to have a beneficial role in managing depressive symptoms because they improve postprandial endothelial function and the binding of serotonin to receptors.[78] Populations with a high consumption of fish, one of the best sources of omega-3 fats, tend to have a lower frequency of depression.[24, 91] The relationship between fish and depression is seen in studies of people older than 65, showing a 66% lower likelihood of having depression with the consumption of 300 grams (~10.5 ounces) of fish weekly.[91]

While the individual foods of the MDP each provide a beneficial protective effect from depression, the overall diet pattern may be more important than any one nutrient or food component. Synergistic effects of the nutrients together may lead to lower rates of depression.[78] It is also possible that individuals following the MDP live healthier lifestyles in general, and the MDP is just one component of a lifestyle that leads to lower depression rates.

Conclusion

The number of people aged 65 years or older increased 21% from 2000 to 2010, a 15.1% faster rate than people younger than 45 years.[92] This shift in age demographics is leading to a greater number of older adults looking for ways to control chronic diseases and maintain physical activity and independence. Depression in the elderly leads to an increased risk of mortality but is a treatable illness and should not be considered a normal effect of aging.[4] People who are not receiving adequate nutrition are more prone to depression.[3] The Mediterranean diet pattern and regular physical activity along with moderate alcohol consumption and not smoking are associated with decreased depressive symptoms later in life.[83] Certain nutrients such as vitamin D, folate, magnesium, zinc, and unsaturated fats contain protective properties and may prove to be therapeutic treatments to depression, but not all studies are conclusive.[93] Some studies have shown that the MDP is more protective than a heart healthy diet of increased fruits and vegetables and low consumption of meat and alcohol and is just as easy to follow.[82] Perhaps the protective effect comes from the cumulative effect of nutrients from the different foods as opposed to isolated nutrients.[24] Decreasing depressive symptoms through better diet and exercise can reduce disability, improve self-image, and help control other chronic diseases as well as total body weight.

These associations can be bidirectional, making it difficult to decipher which caused the other.[94] For example, a bidirectional association can be found with food insecurity and depression. The mental stress of food insecurity can lead to depression, but studies have also found that the physical effects of food deprivation may also lead to depression.[95] Frailty and depression also present a bidirectional relationship, and the direction can be influenced by nutrition. Poor nutrition earlier in life can lead to greater frailty later in life, which in turn leads to a greater risk for depression. Alternatively, depressed older adults can have poor nutrient intake leading to a greater risk for frailty. There are several barriers to conducting conclusive studies in depression and nutrition. Studies involving nutrition are often criticized due to the reliance of self-reported data on food intake. Studying volunteers with chronic diseases may lead to reverse causality in which sick volunteers are counseled to, or of their own volition, change their diet to be

healthier. Healthy participants with sub-clinical depression may change their food intake as their mood disorder changes.[79] A poor diet may be the result of depressive symptoms, or it may be that depressive symptoms result from a poor diet. Prospective designs in which the food is provided to volunteers and compliance is checked using validated clinical measures could help move research in this area.

Researching associations between depression and individual nutrients instead of overall dietary intake may lead to inaccurate assessment of these relationships, since diets are not consumed as individual foods or nutrients. Patients with depressive symptoms exhibit a wide range of behavioral, physical, and sociodemographic factors that play a role in their overall mental health. Nutrition may play a role in mental health early on in life, and thus changing the diet of the elderly may not lead to significant long-term changes in depressive symptoms. Most important, however, is increasing awareness of the need for nutrition and depression screening in the elderly. Preventing decline in mental and nutrition status can greatly improve overall quality and longevity of life of the elderly.

References

1. Administration on Aging. Profile of Older Americans. February 10, 2012. Available at: http://www.aoa.gov/AoARoot/Aging_Statistics/Profile/index.aspx. Accessed October 30, 2012.
2. National Institute on Aging. Available at: http://www.census.gov/prod/2011pubs/acs-17.pdf. Accessed October 30, 2012.
3. Phillips RM. Nutrition and depression in the community-based oldest-old. *Home Health Nurse*. 2012;30(8):462-471.
4. Bogner HR, Morales KH, Reynolds CF, 3rd, Cary MS, Bruce ML. Course of depression and mortality among older primary care patients. *Am J Geriatr Psychiatry*. 2012;20(10):895-903.
5. Strine TW, Chapman DP, Balluz LS, Moriarty DG, Mokdad AH. The associations between life satisfaction and health-related quality of life, chronic illness, and health behaviors among U.S. community-dwelling adults. *J Comm Health*. 2008;33(1):40-50.
6. St John PD, Montgomery PR. Do depressive symptoms predict mortality in older people? *Aging Ment Health*. 2009;13(5):674-681.
7. Kastenschmidt EK, Kennedy GJ. Depression and anxiety in late life: diagnostic insights and therapeutic options. *Mt Sinai J Med*. 2011;78(4):527-545.
8. Beattie E, Pachana NA, Franklin SJ. Double jeopardy: Comorbid anxiety and depression in late life. *Res Gerontol Nurs.* 2010;3(3):209-220.
9. Mamplekou E, Bountziouka V, Psaltopoulou T, et al. Urban environment, physical inactivity and unhealthy dietary habits correlate to depression among elderly living in eastern Mediterranean islands: the MEDIS (MEDiterranean ISlands Elderly) study. *J Nutr Health Aging.* 2010;14(6):449-455.
10. Vink D, Aartsen MJ, Schoevers RA. Risk factors for anxiety and depression in the elderly: a review. *J Affect Disord*. 2008;106(1-2):29-44.
11. Kroenke K, Spitzer R, Williams J. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606-613.
12. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clin Gerontol.* 1986;5:165-173.
13. Pachana NA, Byrne GJ, Siddle H, Koloski N, Harley E, Arnold E. Development and validation of the Geriatric Anxiety Inventory. *Intl Psychogeriatrics.* 2007;19(01):103-114.
14. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. *Biol Psychiatr.* 1988;23(3):271-284.
15. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology.* 1994;44(12):2308.
16. Shah LC, West P, Bremmeyr K, Savoy-Moore RT. Health literacy instrument in family medicine: the "newest vital sign" ease of use and correlates. *J Am Board Fam Med.* 2010;23(2):195-203.
17. Amani R, Saeidi S, Nazari Z, Nematpour S. Correlation between dietary zinc intakes and its serum levels with depression scales in young female students. *Biol Trace Elem Res*. 2010;137(2):150-158.
18. Hamer M, Bates CJ, Mishra GD. Depression, physical function, and risk of mortality: National Diet and Nutrition Survey in adults older than 65 years. *Am J Geriatr Psychiatr.* 2011;19(1):72-78.
19. Fey-Yensan N, English C, Pacheco HE, Belyea M, Schuler D. Elderly food stamp participants are different from eligible nonparticipants by level of nutrition risk but not nutrient intake. *J Am Diet Assoc.* 2003; 103(1):103-107.
20. American Dietetic Associaion. Position of the American Dietetic Association: fortification and nutritional supplements. *J Am Diet Assoc.* 2005;105(8):1300-1311.
21. Beasley JM, Shikany JM, Thomson CA. The Role of Dietary Protein Intake in the Prevention of Sarcopenia of Aging. *Nutr Clin Prac.* 2013;28(6):684-690.
22. Shahar DR, Houston DK, Hue TF, et al. Adherence to Mediterranean Diet and Decline in Walking Speed over 8 Years in Community-Dwelling Older Adults. *J Am Geriatr Soc.* 2012;60(10):1881-1888.
23. Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I, Mykletun A. Association between magnesium intake and depression and anxiety in community-dwelling adults: the Hordaland Health Study. *Aust N Z J Psychiatr.* 2009;43(1):45-52.
24. Akbaraly TN, Brunner EJ, Ferrie JE, Marmot MG, Kivimaki M, Singh-Manoux A. Dietary pattern and depressive symptoms in middle age. *Br J Psychiatr.* 2009;195(5):408-413.
25. Talegawkar SA, Bandinelli S, Bandeen-Roche K, et al. A Higher Adherence to a Mediterranean-Style Diet Is Inversely Associated with the Development of Frailty in Community-Dwelling Elderly Men and Women. *J Nutr.* 2012;142(12):2161-2166.

26. Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. P*rog Neuropsychopharmacol Biol Psychiatr.* 2011;35(3):664-675.
27. Sebastian RS, Cleveland LE, Goldman JD, Moshfegh AJ. Older adults who use vitamin/mineral supplements differ from nonusers in nutrient intake adequacy and dietary attitudes. *J Am Diet Assoc.* 2007;107(8): 1322-1332.
28. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the Vitamin D receptor and 1α-hydroxylase in human brain. *J Chem Neuroanatomy*. 2005;29(1):21-30.
29. Holick MF, Matsuoka LY, Wortsman J. Age, vitamin D, and solar ultraviolet. *Lancet.* 1989;2(8671):1104-1105.
30. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab.* 1988;67(2):373-378.
31. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr.* 2008;87(4):1080s-1086s.
32. Lapid MI, Cha SS, Takahashi PY. Vitamin D and depression in geriatric primary care patients. *Clin Interv Aging.* 2013;8:509-514.
33. Lapid MI, Drake MT, Geske JR, et al. Hypovitaminosis D in psychogeriatric inpatients. *J Nutr Health Aging.* 2013;17(3):231-234.
34. Gronli O, Kvamme J, Jorde R, Wynn R. Vitamin D deficiency is common in psychogeriatric patients, independent of diagnosis. *BMC Psychiatry.* 2014;14(1):134.
35. Lansdowne ATG, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacol.* 1998;135(4):319.
36. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med.* 2008;264(6):599-609.
37. Kjærgaard M, Waterloo K, Wang CEA, et al. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case–control study and randomised clinical trial. *Brit J Psychiatr.* 2012;201(5):360-368.
38. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev.* 2011(7):CD007470.
39. Bolland MJ, Grey A, Gamble GD, Reid IR. Vitamin D supplementation and falls: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol.* 2014.
40. Skarupski KA, Tangney C, Li H, Ouyang B, Evans DA, Morris MC. Longitudinal association of vitamin B-6, folate, and vitamin B-12 with depressive symptoms among older adults over time. *Am J Clin Nutr.* 2010;92(2):330-335.
41. Jacka FN, Maes M, Pasco JA, Williams LJ, Berk M. Nutrient intakes and the common mental disorders in women. *J Affect Disord.* 2012;141(1):79-85.
42. Nguyen PH, Grajeda R, Melgar P, et al. Micronutrient supplementation may reduce symptoms of depression in Guatemalan women. *Arch Latinoam Nutr.* 2009;59(3):278-286.
43. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Predictive value of folate, vitamin B12 and homocysteine levels in late-life depression. *Br J Psychiatry.* 2008;192(4):268-274.
44. Nanri A, Hayabuchi H, Ohta M, Sato M, Mishima N, Mizoue T. Serum Folate and Depressive Symptoms Among Japanese Men and Women: A Cross-Sectional and Prospective Study. *Psychiatr Res.* 2012; 200(2–3):349-353.
45. Morris MS, Fava M, Jacques PF, Selhub J, Rosenberg IH. Depression and folate status in the US population. *PsychotherPsychosom.* 2003;72(2):80-87.
46. Ng T-P, Feng L, Niti M, Kua E-H, Yap K-B. Folate, Vitamin B12, Homocysteine, and Depressive Symptoms in a Population Sample of Older Chinese Adults. *J Am Geriatr Soc.* 2009;57(5):871-876.
47. Beydoun MA, Shroff MR, Beydoun HA, Zonderman AB. Serum Folate, Vitamin B-12, and Homocysteine and Their Association With Depressive Symptoms Among U.S. Adults. *Psychosom Med.* 2010;72(9):862-873.
48. Ramos MI, Allen LH, Haan MN, Green R, Miller JW. Plasma folate concentrations are associated with depressive symptoms in elderly Latina women despite folic acid fortification. *Am J Clin Nutr.* October 1, 2004 2004;80(4):1024-1028.
49. Almoznino-Sarafian D, Berman S, Mor A, et al. Magnesium and C-reactive protein in heart failure: an anti-inflammatory effect of magnesium administration? *Eur J Nutr.* 2007;46(4):230-237.
50. Ford ES, Mokdad AH. Dietary magnesium intake in a national sample of US adults. *J Nutr.* 2003; 133(9):2879-2882.
51. Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. *Med Hypotheses.* 2006;67(2):362-370.
52. Walker AF, De Souza MC, Vickers MF, Abeyasekera S, Collins ML, Trinca LA. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. *J Womens Health*. 1998;7(9):1157-1165.
53. Cox IM, Campbell MJ. Red blood cell magnesium and chronic fatigue syndrome. *Lancet.* 1991;337(8744):757.
54. Barragan-Rodriguez L, Rodriguez-Moran M, Guerrero-Romero F. Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial. *Magnes Res.* 2008; 21(4):218-223.
55. Yary T, Aazami S, Soleimannejad K. Dietary intake of magnesium may modulate depression. *Biol Trace Elem Res.* 2013;151(3):324-329.
56. Imada Y, Yoshioka S-I, Ueda T, Katayama S, Kuno Y, Kawahara R. Relationships between serum magnesium levels and clinical background factors in patients with mood disorders. *Psychiatr Clin Neurosci.* 2002; 56(5):509-514.
57. Ismail Y, Ismail AA. The underestimated problem of using serum magnesium measurements to exclude magnesium deficiency in adults; a health warning is needed for "normal" results. *Clin Chem Lab Med.* 2010;48(3):323-327.
58. Walker AF, Marakis G, Christie S, Byng M. Mg citrate found more bioavailable than other Mg preparations in a randomised, double-blind study. *Magnes Res.* 2003;16(3):183-191.
59. De Souza MC, Walker AF, Robinson PA, Bolland K. A Synergistic Effect of a Daily Supplement for 1 Month of 200 mg Magnesium plus 50 mg Vitamin B6 for the Relief of Anxiety-Related Premenstrual Symptoms: . A Randomized, Double-Blind, Crossover Study. *J Women Health Gender-Based Med.* 2000;9(2):131-139.
60. Huang JH, Lu YF, Cheng FC, Lee JN, Tsai LC. Correlation of magnesium intake with metabolic parameters, depression and physical activity in elderly type 2 diabetes patients: a cross-sectional study. *Nutr J.* 2012;11:41.
61. Derom ML, Martinez-Gonzalez MA, Sayon-Orea Mdel C, Bes-Rastrollo M, Beunza JJ, Sanchez-Villegas A. Magnesium intake is not related to depression risk in Spanish university graduates. *J Nutr.* 2012; 142(6):1053-1059.

62. Irmisch G, Schlaefke D, Richter J. Zinc and fatty acids in depression. *Neurochem Res.* 2010;35(9):1376-1383.
63. Nowak G, Siwek M, Dudek D, Zieba A, Pilc A. Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. *Pol J Pharmacol.* 2003;55(6):1143-1147.
64. Siwek M, Dudek D, Schlegel-Zawadzka M, et al. Serum zinc level in depressed patients during zinc supplementation of imipramine treatment. *J Affect Disord.* 2010;126(3):447-452.
65. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study. *Eur J Clin Nutr.* 2010;64(3):331-333.
66. Wegmüller R, Tay F, Zeder C, Brnić M, Hurrell RF. Zinc Absorption by Young Adults from Supplemental Zinc Citrate Is Comparable with That from Zinc Gluconate and Higher than from Zinc Oxide. *J Nutr.* 2014;144(2):132-136.
67. Maret W, Sandstead HH. Zinc requirements and the risks and benefits of zinc supplementation. *J Trace Elem Med Biol.* 2006;20(1):3-18.
68. Marcellini F, Giuli C, Papa R, et al. Zinc status, psychological and nutritional assessment in old people recruited in five European countries: Zincage study. *Biogerontol.* 2006;7(5-6):339-345.
69. Pepersack T, Rotsaert P, Benoit F, et al. Prevalence of zinc deficiency and its clinical relevance among hospitalised elderly. *Arch Gerontol Geriatrics.* 2001;33(3):243-253.
70. Gronli O, Kvamme JM, Friborg O, Wynn R. Zinc deficiency is common in several psychiatric disorders. *PLoS One.* 2013;8(12):e82793.
71. Yary T, Aazami S. Dietary Intake of Zinc was Inversely Associated with Depression. *Biol Trace Elem Res.* 2012;145(3):286-290.
72. Maserejian NN, Hall SA, McKinlay JB. Low dietary or supplemental zinc is associated with depression symptoms among women, but not men, in a population-based epidemiological survey. *J Affect Disord.* 2012;136(3):781-788.
73. Kumar GP, Khanum F. Neuroprotective potential of phytochemicals. *Pharmacogn Rev.* 2012;6(12):81-90.
74. Jacka FN, Pasco JA, Williams LJ, Meyer BJ, Digger R, Berk M. Dietary intake of fish and PUFA, and clinical depressive and anxiety disorders in women. *Br J Nutr.* 2012:1-8.
75. Silvers KM, Woolley CC, Hamilton FC, Watts PM, Watson RA. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids.* 2005;72(3):211-218.
76. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol Psychiatr.* 2010;68(2):140-147.
77. Owen C, Rees AM, Parker G. The role of fatty acids in the development and treatment of mood disorders. *Curr Opin Psychiatry.* 2008;21(1):19-24.
78. Sanchez-Villegas A, Delgado-Rodriguez M, Alonso A, et al. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. *Arch Gen Psychiatr*. 2009;66(10): 1090-1098.
79. Sanchez-Villegas A, Verberne L, De Irala J, et al. Dietary fat intake and the risk of depression: the SUN Project. *PLoS One.* 2011;6(1):e16268.
80. Parker GB, Heruc GA, Hilton TM, et al. Low levels of docosahexaenoic acid identified in acute coronary syndrome patients with depression. *Psychiatr Res.* 2006;141(3):279-286.
81. Jacka FN, Pasco JA, Mykletun A, et al. Association of Western and traditional diets with depression and anxiety in women. *Am J Psychiatr.* 2010; 167(3): 305-311.
82. Luciano M, Mõttus R, Starr JM, et al. Depressive symptoms and diet: Their effects on prospective i nflammation levels in the elderly. Brain Behav *Immunity.* 2012;26(5):717-720.
83. Panagiotakos DB, Chrysohoou C, Siasos G, et al. Sociodemographic and lifestyle statistics of oldest old people (>80 years) living in ikaria island: the ikaria study. *Cardiol Res Pract.* 2011:679187.
84. Hung HC, Joshipura KJ, Jiang R, et al. Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst.* 2004;96(21):1577-1584.
85. Tamers SL, Agurs-Collins T, Dodd KW, Nebeling L. US and France adult fruit and vegetable consumption patterns: an international comparison. *Eur J Clin Nutr.* 2009;63(1):11-17.
86. Nicklett EJ, Semba RD, Xue QL, et al. Fruit and vegetable intake, physical activity, and mortality in older community-dwelling women. *J Am Geriatr Soc.* 2012;60(5):862-868.
87. Dietary Guidelines Advisory Committee. Report of the Dietary Guidelines Advisory Committee on the 2010 Dietary Guidelines for Americans. Available at: http://www.cnpp.usda.gov/DGAs2010-PolicyDocument.htm.
88. Guenther PM, Dodd KW, Reedy J, Krebs-Smith SM. Most Americans eat much less than recommended amounts of fruits and vegetables. *J Am Diet Assoc.* 2006;106(9):1371-1379.
89. Dehghan M, Akhtar-Danesh N, Merchant AT. Factors associated with fruit and vegetable consumption among adults. *J Hum Nutr Diet.* 2011;24(2):128-134.
90. Sodergren M, McNaughton SA, Salmon J, Ball K, Crawford D. Associations between fruit and vegetable intake, leisure-time physical activity, sitting time and self-rated health among older adults: cross-sectional data from the WELL study. *BMC Public Health.* 2012;12(1):551.
91. Chrysohoou C, Tsitsinakis G, Siassos G, et al. Fish Consumption Moderates Depressive Symptomatology in Elderly Men and Women from the IKARIA Study. *Cardiol Res Pract.* 2011;2011:219578.
92. Howden LM, Meyer JA. Age and Sex Composition: 2010. 2010 Census Briefs. Washington, DC: *U.S. Census Bureau*; 2011.
93. Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Mol Psychiatry.* 2012;18(5):595-606.
94. Scafato E, Galluzzo L, Ghirini S, et al. Changes in severity of depressive symptoms and mortality: the Italian Longitudinal Study on Aging. *Psychol Med.* 2012:1-11.
95. Kim K, Frongillo EA. Participation in food assistance programs modifies the relation of food insecurity with weight and depression in elders. *J Nutr.* 2007; 137(4):1005-1010.