The association between vitamin D, depression and diabetes mellitus type 2

Bachelor thesis psychology and health

Author: Lotte van Dammen (227610)

Supervisor: Dr. Paula M.C. Mommersteeg

Second reviewer: Drs. Corinne Stoop

Tilburg University

School of social and behavioral sciences

Department Medical Psychology

June 2012

Abstract

Vitamin D has been suggested to be associated with the development of depression and diabetes mellitus type 2. This literature review examined the relation between vitamin D, depression and diabetes type 2. Based on a literature search, 18 articles were selected, 9 examining vitamin D and depression, 8 articles examining the relation between vitamin D and diabetes, and one contemporary clinical trial investigating all of the variables. The results contain strong evidence for the causal relation between vitamin D and the development of depression. Less consistent findings were found about vitamin D and the development of diabetes type 2. During the literature search the important role of BMI and PTH levels became clear. Recommendations were made according to future studies on the relation between vitamin D, depression, diabetes type 2 and BMI.

Keywords: Depression, Vitamin D, Diabetes Mellitus type 2, Review.

Table of contents

Introduction

Diabetes mellitus is a chronic disease, which is characterized by high blood sugar (glucose) levels which is caused by insulin deficiency. People who suffer from diabetes can't derive energy from sugar in a sufficient way. Insulin plays a crucial role in this disease. Insulin is a hormone produced by the pancreas; this hormone regulates carbohydrates and fat metabolism. Glycated hemoglobin (or HbA1c) can be measured in the blood to find out the amount of sugar in the blood (Yatan & Sagar, 2011). Diabetes can be distinguished into two types, type 1 and type 2. Diabetes type 1 is a form involving little or no production of insulin by the pancreas. It often has an early onset and involves medication and monitoring of blood-sugar levels. Diabetes type 2 is characterized by problems with insulin-receptors. This type of diabetes has often a late onset, and is associated with reduced physical activity and overweight. Medication and monitoring of blood-sugar levels are often necessary (WHO, 2011). It is estimated that worldwide about 346 million people have diabetes mellitus (WHO, 2011). In 2004 an estimated 3,4 million people died from the consequences of high blood sugar levels (WHO, 2011). Between 2005 and 2030 the number of deaths caused by diabetes is expected to double (WHO, 2011). In this review diabetes type 2 will be discussed, in which the body doesn't use the insulin effectively. Diabetes type 2 is also called adult-onset or non-insulin-dependent diabetes. It is estimated that 90% of the patients with diabetes have diabetes type 2. Physical inactivity and obesity play a role in the development of diabetes type 2 (WHO, 2011). Diabetes type 2 is the focus of attention of the present review, as we seek risk factors for the development of diabetes type 2. A novel risk factor in the development of diabetes has recently gained attention: low levels of vitamin D (Holick, 2007). The study from Vacek et al. (2012) found an important role of vitamin D in cardiovascular health and diabetes, and found that vitamin D deficiency was related to reduced survival.

Vitamin D is a steroid vitamin which promotes the intestinal absorption and metabolism of calcium and phosphorus (Medterms, 2003). There are several terms used to describe vitamin D, and therefore a brief explanation of each is given. Vitamin D2 or ergocalciferol is synthesized by plants. Vitamin D3 or cholecalciferol is synthesized in the human skin when it has been exposed to ultraviolet rays from sunlight. Food may contain vitamin D2 or D3 (mayoclinic, 2011). Norman et al. (1980) reported that arginine-induced insulin secretion was impaired in the vitamin

D-deficient rat pancreas, and that it was improved by dietary vitamin D repletion. Hence it is interesting to find out more about vitamin D and the relation with diabetes onset.

A person gets vitamin D in its body by sunlight, oily fish and food (supplements). Vitamin D from the sun and food is metabolized in the liver into 25-hydroxyvitamin D (from now on abbreviated to 25(OH) D). The serum 25(OH) D is also the substance that can be measured to indicate the amount of active vitamin D in a person; this serum 25 (OH) D is the storage form of vitamin D. After hydroxylation in the liver the 25(OH) D serum is transported to the kidneys and then it is called 1,25-dihydroxyvitamin D, which is the active form of vitamin D (Jorde et al., 2008). The amount of vitamin D in a human body can be measured by blood levels. There are 2 standards to report the amount of 25(OH) D, ng/mL and nmol/L, and 1 nmol/L = 0.401 ng/mL. The amount of vitamin D intake from foods and sun is reported in IU (International Unit), and 1 IU is 0.025 μg cholecalciferol/ergocalciferol (Armas et al, 2004). It has been estimated that over one billion people worldwide have vitamin D deficiency or insufficiency (Holick, 2007). The term for low levels of vitamin D is *hypovitaminosis*, and is characterized by levels of the 25(OH) D serum lower than 10 ng/mL. Vitamin D *deficiency* is characterized by levels of 25(OH) D serum less than 20 ng/mL and vitamin D *insufficiency* is a level lower than 30 ng/mL (Thatcher, 2011). Optimal levels of 25(OH)D serum levels are above 30 ng/mL, and the levels can be influenced by sun exposure and food, as well as vitamin D supplements (Thatcher, 2011).Vitamin D has been found to play a role in the risk of developing several conditions as diverse as; infectious diseases, cardiovascular diseases, diabetes mellitus, cancer, multiple sclerosis, allergy, asthma, depression, psychiatric disorders and pain (Thatcher 2011, Holick 2007). The role of vitamin D in developing diabetes was shortly discussed above. The relevance of vitamin D in developing depression will be examined in more detail. The reason for this examination is that there has been little or no research done about the relation between vitamin D and depression. May et al (2010) investigated the association of vitamin D levels with incident depression, in a group of patients with cardiovascular disease. Depression is a known risk factor for cardiovascular disease. In this study a brief explanation was given for the possible relation between vitamin D and depression. Vitamin D receptors and enzymes are present in the brain, which makes it plausible for vitamin D to be related to brain activity and depression. Another mechanism involves parathyroid hormone levels, which increase when vitamin D levels are low.

The term for high parathyroid hormone levels is hyperparathyroidism, and this is often accompanied by depressive disorders (Espiritu, 2011).

Depression is a common mental disorder, characterized by; feeling blue, disturbed appetite, sleeping disturbances, poor concentration and loss of interest in daily activities (WHO, 2011). About 121 million people worldwide suffer from a depression, and an estimated 850.000 people each year commit suicide while suffering from a depressive period (WHO, 2011). There is a difference between a clinically classified major depression and depressive symptoms. Depressive symptoms can be determined with self-report questionnaires. A clinically classified major depression is determined by a professional. In this thesis both will be discussed, because both are reliable ways to determine a depression.

As was discussed above the described fields are associated: a relationship was found between vitamin D and depression (Milaneschi et al, 2010), vitamin D and diabetes mellitus (Pittas et al, 2006) and diabetes mellitus and depression (Anderson et al, 2001).

Research (Pan et al, 2010) shows a bidirectional relation between depression and diabetes. In addition, there is also a relationship between vitamin D and depression (Milaneschi et al, 2010), and between vitamin D and diabetes (Pittas et al, 2006). Based on these findings, we can conclude that there is an association between vitamin D, depression and diabetes mellitus.

There are several questions that arise based on other research and reviews. We know that vitamin D, depression and diabetes mellitus are associated with one other. The questions that can be answered based on the available literature are: What does the current literature state about the direction in which these variables are related? In order to make statements about causality, different questions need to be answered related to the direction of de relation between the variables. First of all, does vitamin D insufficiency precedes and leads to the development of diabetes type 2 and depression? If this is the case, do depressive symptoms decrease after ingesting vitamin D supplements, and does the chance of developing diabetes type 2 decrease after ingesting vitamin D supplements? Can it be stated by reason, that vitamin D a mediator is between diabetes type 2 and depression?

The present review aims to address these questions by examining the role of vitamin D in the development of diabetes and depression in several studies. The reason for only examining the

effect of vitamin D on the development of diabetes type 2 and depression consists of two assumptions; it is possible that depression is associated with low vitamin D levels, because depressed people often don't go out much, and have a less healthy diet (Schneider et al, 2000). However, the influence of low vitamin D levels on the development of a depression is less clear, and it is interesting to find out if low vitamin D is associated with the development of depression. Diabetes type 2 often develops in older people who are overweight and with too little physical activity. Once again, this may prohibit healthy intake of vitamin D via sunlight or diet. This is a possible explanation why diabetes type 2 is associated with low vitamin D levels. It is less clear why vitamin D influences the risk of developing diabetes type 2, this may also be influenced by a process of metabolizing vitamin D in the human body. It is important that we learn more about the association between these variables. Depression and diabetes type 2 are common, more and more people are developing these conditions. It should be clear what the relation is between these conditions and what the influence of vitamin D is. We aim to clarify and combine previous findings in the present thesis.

Methods

In order to examine the association between vitamin D, diabetes mellitus and depression a search for scientific reviews and articles was done. The search engine PubMed was used with the following terms: Terms for depression: “depression” OR “major depression disorder[mesh]” OR “depressive symptoms[mesh]”. Terms for diabetes: “diabetes mellitus type 2[mesh]” OR “adult onset diabetes[mesh]” OR “diabetes type 2”. Terms for vitamin D: “vitamin D” AND “insufficien*[mesh]” OR “deficien*[mesh]”. Three searches have been done, consisting of the following combination of search terms.

Research question 1: What is the relation between diabetes and vitamin D? Search 1: (“diabetes mellitus type 2” OR “adult onset diabetes” OR “diabetes type 2”) AND “vitamin D” AND (“insufficien*” OR “deficien*”) = rendered 126 articles, from which 8 were included in thesis.

Research question 2: What is the relation between depression and vitamin D? Search 2: (“depression” OR “major depression disorder” OR “depressive symptoms”) AND “vitamin D” AND (“insufficien*” OR “deficien*”) = rendered 122 articles, from which 9 were included in thesis.

Research question 3: What is the relation between depression, diabetes and vitamin D? Search 3: (“depression” OR “major depression disorder” OR “depressive symptoms”) AND (“diabetes mellitus type 2” OR “adult onset diabetes” OR “diabetes type 2”) AND “vitamin D” = rendered 2 articles, from which 1 was included in thesis.

The selection criteria are shown in the following Flowchart (Figure 1) :

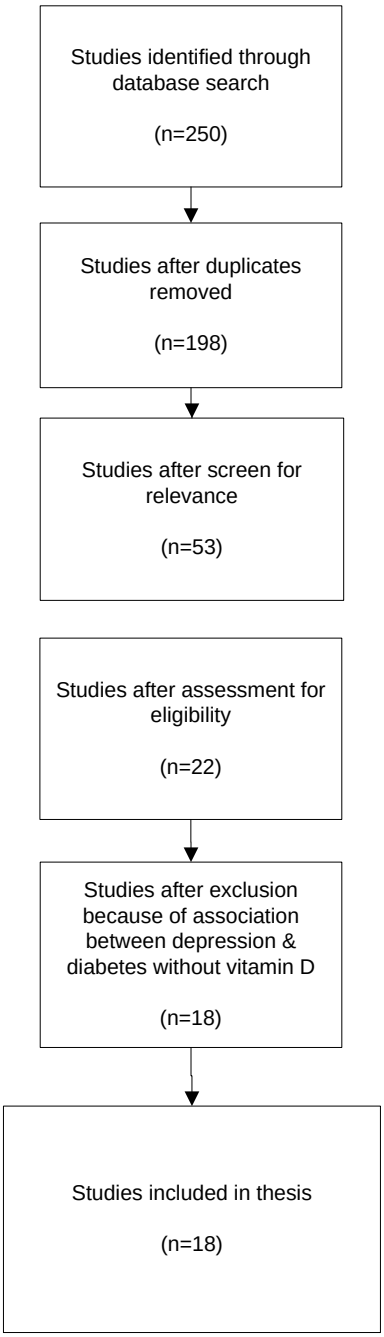

Fig. 1 FlowChart of selecting articles included in the review

The articles used for this review were retrieved from PubMed and described in the FlowChart (Figure 1). The criteria for relevance are that the article must describe a relation between either vitamin D and depression (search 2), or between vitamin D and diabetes (search 3). The criteria for eligibility are that the article must describe the influence of vitamin D on the development of either diabetes or depression. After taking the inclusion and exclusion criteria in consideration, 18 articles were selected for this review, additional relevant articles were found based on references searches of the articles. Every article was checked for relevant references, and 1 additional article was found by a reference search, the article from Jorde et al. (2008) was retrieved by the reference list of the article from Chan et al. (2011).

Results

From the 18 articles, 1 article studied the relation between vitamin D, depression and diabetes. There are 9 articles discussing the relation between vitamin D and depression. The relation between vitamin D and diabetes was examined in 8 articles. In order to investigate the quality of the studies used in this thesis, a summarizing table reports information about the mean age of participants, numbers of participants and other information (Table 1).

Vitamin D and depression

The primary findings of vitamin D and depression are given in Table 1. From the 9 studies about depression and vitamin D, 6 found a significant relation between the variables. The three studies that didn't support this relation were cross-sectional studies investigating the prevalence of depression. Five studies, from the total nine, were prospective cohort studies, examining the role of vitamin D with follow-up research. The final study from the total nine studies, investigated the effect of an intervention with vitamin D supplements.

In sum, three cross-sectional studies (Scheider et al. (2000), Pan et al. (2009) and Zhao et al. (2010)) found no significant association between vitamin D and depression. The five prospective cohort studies (Bertone-Johnsonet al. (2011), Chan et al. (2011), May et al. (2010), Milaneschi et al. (2010) and Hoogendijk et al. (2008)) found a significant association between vitamin D and the development of depression. The intervention study from Jorde et al. (2008) found a significant effect of vitamin D supplementation on depression.

Schneider et al (2000) examined the relation between a major depression and vitamin D with 30 patients with major depression (diagnosed with DSM-III-R). The 25(OH) D and 1,25(OH)2 D levels were measured by immune assays. The results were that the 25(OH) D levels in patients with MDD were not significantly lower than the healthy controls, whereas 1,25(OH)2 D levels were significantly lower than the healthy controls ($p < 0.01$). Furthermore the 1,25(OH)2D levels correlated positively with depression ($r = 0.29$; $p < 0.001$). The authors suggested in the discussion that patients with MDD suffered from malnutrition and less exposure to sunlight.

Pan et al. (2009) examined the association between depressive symptoms and 25(OH) D levels in Chinese inhabitants. A total of 3,262 community residents, 50-70 years old, participated in this cross-sectional study. Depression was measured with the CES-D, vitamin D concentration was measured with radioimmunoassay. Confounding factors include: age, sex, urban/rural, body mass index, physical activity level, smoking status, social activity level, marital status, household income, and number of chronic diseases. The prevalence of depressive symptoms was lower in the top tertile of vitamin D, than in the lowest tertile (7,2% versus 11,1%, $\chi^2 = 8.088$, $p = 0.0045$). Higher levels of vitamin D were significantly associated with a lower risk for having a depression, (unadjusted association: odds ratio (OR) =0.62, 95% confidence interval (CI) = 0.46–0.83, p=0.001). This association was attenuated when controlling for confounding factors, and was no longer significant when controlling for geographic location. The assumption is that southern regions have more sun and thus more vitamin D. This means that the risk of developing a depression depends on vitamin D levels and geographic location. The prevalence of depression had a strong geographic disparity, and 25(OH) D levels differed among cities. Analysis with geographic location as a modifier failed to find differences in vitamin D levels in different cities. This may have influenced the results, that there is no association between 25(OH) D and depression, when controlled for confounding factors. If there was a significant difference between northern cities (less sunlight, thus vitamin D) and southern cities, further research about this effect could be done.

Zhao et al (2010) studied the association between serum concentrations of 25(OH) D, parathyroid hormone and depression, and found no significant associations. It was a cross-sectional, populations-based sample, including 3,916 participants, older than 20 years living in the US. National Health and Nutrition examination Survey and the Patients Health Questionnaire-9 were used as indicators of depressive symptoms for this study. For people suffering from moderate-to-severe depression the prevalence of hypovitaminosis D was 5.3% (95% CI 4.3- 6.5), for participants suffering from a major depression the prevalence was 2.3 %(95% CI 1.7- 3.1), and for people suffering from a minor depression the prevalence of hypovitaminosis D was 3.8 % (95% CI 3.0- 4.6). This suggests that there is no increased chance of having a depression when vitamin D levels are low. The unadjusted OR of having a moderate-to-severe depression or major depression decreased linearly with increasing quartiles of 25(OH) D (p<0.05 for trends). After adjusting for potential confounders, like demographic factors, no significant

associations were found. Their conclusion is that there needs to be further research to confirm that there is no association between vitamin D and depression.

There was a significant association between vitamin D and depression in the study of Bertone-Johnson et al. (2011). They conducted a cross-section and prospective analysis. The intake of vitamin D from foods and supplements were compared to the risk of depressive symptoms. The participants were 81,189 women joining the Women's Health Initiative, aged between 50 and 79 years. Questionnaires were used to measure vitamin D intake by foods and supplements. The Burnam scale (a short version of the CES-D) and antidepressant medication were used to assess the depressive symptoms. Women with an intake of >800 IU vitamin D per day had a lower prevalence for depressive symptoms with an odds ratio of 0.79 (95% CI: 0.71, 0.89; $p < 0.001$) compared to women who reported a total intake of <100 IU vitamin D per day. Another analysis was done concerning women without evidence of depressive symptoms at baseline. An intake of >400 IU vitamin D compared with <100 IU vitamin D per day from food sources was associated with 20% lower risk of depressive symptoms at year 3 (OR: 0.80; 95% CI: 0.67, 0.95; $p = 0.001$). In contrast, vitamin D *supplements* did not appear to decrease the risk of developing depressive symptoms. This study concluded that intake of vitamin D from food, but not supplements, decreases the risk of developing a depression in postmenopausal women.

The study from Chan et al. (2011) examined the association between vitamin D and psychological health in Chinese older men in Hong Kong. In 939 community-dwelling Chinese men >65 years, the serum 25OHD, depression, or depressive symptoms, and cognitive functioning was measured. After a 4-year follow up data on depression status were available in 629 men. Multivariate logistic regression analyses were performed controlled for confounding factors. Men in the highest quartile of 25OHD levels (>=92 nmol/L) compared with the lowest quartile (<=63 nmol/L) had a decreased adjusted odds ratio for depression of 0.46 (95% CI: 0.22-0.98, *p*-trend=0.004). Confounding factors include: demographics, number of diseases, smoking, alcohol use, body mass index, physical activity, mobility limitations, dietary intake, season of blood measurement, and serum parathyroid hormone level. A significant inverse association was found between serum 25OHD and incident depression at 4 years. It must be noted that there was a small number of incident depression at 4 year follow up (4%). Depressive symptoms were measured by means of self-report (CES-D).

The association of vitamin D levels with incident depression was studied by May et al. (2010). The participants were 7,358 cardiovascular patients, 41% were men, with a mean age of 73 years. Vitamin D levels were stratified in 4 categories: >50 (optimal [O] n = 367), 31 to 50 (normal [N] n = 2,264), 16 to 30 (low [L] n = 3,402), and <15 (very low [VL] n = 1,325). These levels of vitamin D were compared with depression. The mean follow-up time was 1 year, and the maximum was 6 years. Days to depression, and event free survival were measured at 5 times, and the following adjusted hazard ratio's were found: VL [HR] 2.70 [1.35-5.40], p = .005; L, HR 2.15 [1.10-4.21], p = .03; N, HR 1.95 [0.99-3.87], p = .06. This association remained when controlled for PTH levels, sex, age and diabetes. During the winter months the association was even stronger. The conclusion of this study is that there is an association between vitamin D and incident depression, and this may be influenced by PTH levels.

Milaneschi et al. (2010) examined the relationship between 25(OH) D and depressive symptoms over a 6 year follow-up. It was part of a population-based cohort study in Italy and a total of 531 women and 423 men aged 65 years and older participated. The serum 25(OH) D levels were measured by collecting blood samples; depressed mood was measured by the CES-D. The following covariates were selected: age, gender, education, smoking habit, alcohol use, MMSE score, body mass index (BMI), season of data collection, number of prescribed and no prescribed drugs, and use of antidepressants and vitamin D supplements. The results were that, when adjusted for the covariates, women with low 25(OH) D levels (<50 nmol/L) had a significantly higher risk of having depressive mood over the follow-up (hazard ratio = 2.0; 95% confidence interval = 1.2-3.2; p = 0.005). Men with low vitamin D levels tended to have higher risk of having a depressed mood (hazard ratio = 1.6; 95% confidence interval = 0.9-2.8; p = 0.1). The conclusion is that this study suggest that hypovitaminosis D is a risk factor for the development of depressive symptoms in people older than 65.

A population based cohort study from Hoogendijk et al. (2008) examined the relationship between depression, decreased 25(OH) D levels and PTH levels. One thousand two hundred eighty-two community residents aged 65 to 95 years participated in this study. Depression was measured by self-reports (CES-D) and interviews (DIS). Levels of 25(OH) D and PTH were assessed from blood samples. Confounding factors include: Age, sex, smoking status, BMI, number of chronic diseases, serum creatinine concentrations, urbanization, physical activity and

season of data acquisition. The result of this study was that the levels of 25(OH) D were 14% lower in 169 participants with minor depression and 14% lower in 26 persons with major depressive disorder compared to the 1087 controls (p <.001). The beta value containing the highest 25(OH) D levels (27ng/mL) was −3.35 (−4.51 to −2.19) (p <.001), high levels of vitamin D have a significant negative relation with depression. The conclusion from this study was: There is an association of depression status and severity with decreased serum 25(OH) D levels in older individuals.

Jorde et al. (2008) studied the effects of vitamin D supplementation on the symptoms of depression in a randomized double blind trail. The trail consisted of 441 Norwegian citizens, with a mean age of 47 and 36% were men. The Beck Depression inventory was used to assess depression symptoms. Confounding factors include: age, sex, smoking, BMI, calcium levels, PTH levels and physical activity. Subjects with levels of 25(OH) D <40 nmol/L scored significantly higher on depressive symptoms than subjects with 25(OH) D levels >40 nmol/L (p <0.05). In the groups given vitamin D supplementation, but not the placebo group, there was a significant improvement in BDI scores after 1 year (p <0.05). It must be noted that overweight and obese participants with 25(OH) D levels <40 nmol/L had higher depression scores compared to overweight participants with 25(OH) D levels >40 nmol/L. The conclusion of this study is that there is a relation between 25(OH) D and symptoms of depression, and this may be causal, considering the intervention outcome.

Nine articles were discussed regarding the relation between vitamin D and depression. The cross-sectional studies from Schneider et al. (2000), Zhao et al. (2010) and Pan et al. (2009) found no significant relation between vitamin D and depression, the 6 studies on incidence of depression did find a significant relation. Bertone-Johnsonn et al. (2010) and Chan et al. (2010) found a significant inverse association between vitamin D and depression. The studies on incidence by Milaneschi et al. (2010), May et al. (2010) and Hoogendijk et al. (2008) found a significant association between vitamin D and depression. The study from Milaneschi et al. (2010) found that low vitamin D is a *risk factor* for the development of depression. The first research question in this review focuses on the preceding and leading of vitamin D insufficiency to depression. Milaneschi et al. (2010) and Jorde et al. (2008) found that this is indeed the case. The intervention study from Jorde et al. (2008) found a significant effect from vitamin D

supplements on depression, the risk of developing a depression was significantly lower when vitamin D supplements were ingested. The second research question focuses on the effect of vitamin D supplements on depression, and from this intervention study it can be concluded that vitamin D supplements indeed have a significant effect on depression. This implicates a causal relationship between vitamin D and depression.

Vitamin D and Diabetes Mellitus

In sum, 7 out of 8 studies found a significant association between diabetes and vitamin D, and the study from Avanell et al. (2009) didn't rule out a protective role of vitamin D. Two studies were cross-sectional (Renzaho et al, 2011 and Shankar et al, 2011), 5 prospective (Mattila et al, 2007, Liu et al, 2010, Lindqvist et al, 2010, Grimnes et al, 2010 and Pittas et al, 2006) and the last study was an intervention study, where the effect of vitamin D supplementation was studied by Avanell et al. (2009). For more information see table 1.

In a cross-sectional study from Renzaho et al. (2011) the demographics were described of 49 African migrants living in Melbourne. In 88% of the participants vitamin D insufficiency occurred, and the participants were at high risk for developing diabetes type 2 or cardiovascular disease. The risk was measured by measuring the following factors: being overweight, hypertension, insulin resistance and cholesterol. Considering the voluntary nature of the study, and the small number of participants, the results cannot be easily generalized to a bigger community. The authors suggest that a study with vitamin D intervention can give more evidence for the existing relationship between vitamin D and diabetes type 2.

In a cross-sectional population based study from Shankar et al (2011) 12,719 US adults who filled out the National Health and Nutrition Examination Survey were used. Adjustments were made for age, sex, season, race, smoking, geographic region, alcohol intake, BMI, physical activity, vitamin D intake, hypertension and cholesterol. Compared with the highest quartile, the odds ratio of pre-diabetes for the lowest quartile was 1.47 (1.16–1.85) $p = 0.001$. The conclusion from this study is; low levels of vitamin D are associated with pre-diabetes in US adults.

In a longitudinal cohort study in 4,097 Finland survey participants examined by Mattila et al. (2007), the relation between serum 25(OH) D levels and subsequent risk of diabetes type 2 was observed. Adjustments were made for age, sex and month when the blood samples were collected. After a follow-up of 17 years the relative risk of diabetes for the highest quartile compared to the lowest quartile of 25(OH) D serum was 0.60 (0.36-0.98) p=0.01. Showing that higher levels of 25(OH) D were associated with a significant decreased diabetes risk. Thus high vitamin D levels are good. When further adjustments were made for BMI, smoking, education and exercise the relative risk was no longer significant: 0.70 (0.42-1.16) p=0.07. These findings showed a significant positive association between high levels of vitamin D and decreased risk of developing diabetes type 2.

Liu et al. (2010) used a subsample of the Framingham Offspring Study to examine the relation between vitamin D status and incidence of diabetes type 2. Adjustments were made for age, sex, waist circumference, parental history of diabetes type 2, hypertension, cholesterol, impaired fasting glucose and diet. In this prospective cohort study, the plasma 25(OH) D levels from 3066 participants were collected. In total 133 participants developed diabetes type 2 after 7 years. Compared to the lowest quartile, those in the highest quartile of predicted 25(OH) D levels had a 40% lower incidence for developing diabetes type 2 HR: 0.60 (0.37- 0.97) (p = 0.03). They suggested that maintaining the vitamin D status can lower the risk of developing diabetes type 2.

The correlation between sun exposure and diabetes type 2 was analyzed by Lindqvist et al. (2010) in a prospective cohort study. During an 11 year follow-up 24,098 Swedish women answered an inquiry. Women with active sun exposure were at 30% less risk for developing diabetes type 2, compared to the women with non-active sun exposure. Also the women with more sun exposure had a lower risk (ranging from 40-60%) of developing diabetes type 2. A possible explanation is that BMI is a high risk for diabetes type 2, and vitamin D influences this. Overall, this study supports that sunlight is involved in glucose metabolism, and BMI appears to mediate this association.

In a prospective population based study from Grimnes et al. (2010) 6119 Norwegian citizens were included. During an 11 year follow-up period, the risk of developing diabetes type 2 was measured in relation to vitamin D levels. Adjustments were made for age, sex, BMI, physical activity and smoking behavior. Vitamin D levels were measured every month, and

diabetes was defined using a hospital journal-based end-point registry. The risk for the development of diabetes in the highest quartile was used as reference, the hazard ratios for the third, second and first quartiles were: non smokers: 1.00 (0.62–1.61), 1.50 (0.97–2.31) and 1.89 (1.25–2.88), smokers: 1.79 (0.77–4.19), 2.33 (1.02–5.35) and 2.68 (1.18–6.08). In this analysis the ratios were adjusted for age and sex. Adjustments for BMI rendered the findings nonsignificant. The conclusion of this study is that the risk of developing diabetes type 2 increases when vitamin D levels are low, but this may be partially mediated by, once again, BMI.

Pittas et al. (2006) examined 83,779 female nurses in a prospective study. The purpose of this study was to determine the relation between vitamin D and calcium intake and the risk of developing diabetes type 2. During a 20 year follow-up 4,843 cases of diabetes type 2 were documented. Adjustments were made for age, sex, smoking, BMI, physical activity, family history of diabetes, hypertension and alcohol consumption. The RR for diabetes type 2 was 0.87 (0.75–1.00) $p = 0.04$, comparing the highest with the lowest category of vitamin D from supplements assessment. When adjusted for the confounding factors, no relationship was found. However, the relative risk for diabetes type 2 is: 0.67 (0.49–0.90) when comparing the daily intake of vitamin D >800 IU and calcium 1,200 mg versus <400 IU vitamin D and 600 mg calcium. Thus vitamin D and calcium may play a role in the development of diabetes type 2.

Avanell et al. (2009) analyzed a substudy of a randomized placebo-controlled trail of vitamin D3 supplementation and diabetes type 2. From the RECORD trail 5,292 osteoporotic patients participated in a 62 month's during trial with vitamin D3 supplementation, 800 IU daily. The development of diabetes type 2 was measured by self-report from the participants. A total of 2,5% of the participants in the vitamin D3 group developed diabetes type 2, whereas in the control group 2,2% developed diabetes type 2. The adjusted odds ratio is: 1.11, 95% CI 0.77–1.62, $p = 0.57$. This does not support the assumption that vitamin D3 protects against diabetes type 2, however the confidence intervals do not rule out a protective effect of vitamin D3. The authors suggest that following research should focus on higher doses of vitamin D supplementation.

Eight articles were discussed regarding the relation between vitamin D and diabetes. Two cross-sectional studies from Renzaho et al. (2011) and Shankar et al. (2011) found that low vitamin D levels has been associated with risk having of diabetes. The prospective studies from

Pittas et al. (2006), Liu et al. (2010) and Lindqvist et al. (2010) found a higher risk of developing diabetes when vitamin D levels are low. Mattila et al (2007) found a significant inverse association between vitamin D and diabetes in a longitudinal design. These findings from Mattila support the statement that vitamin D insufficiency leads to and precedes diabetes. Grimnes et al (2010) found a significant higher risk of developing diabetes when vitamin D was low, but not if controlled for BMI. The intervention study from Avanell et al (2009) found no significant effect from vitamin D supplementation on the risk of developing diabetes mellitus type 2. The authors noted that the vitamin D supplements didn't contain high levels of vitamin D, which may have influenced the results. The third research question in this review can be answered based on the findings from the study done by Avanell and colleagues (2009); the chance of developing diabetes mellitus type 2 does not decrease after ingesting vitamin D supplements.

Vitamin D, depression and diabetes

A contemporary clinical trail from Manson et al. (2012) is currently running. It is a large randomized, double blind, placebo-controlled, 2X2 factorial trail of vitamin D. The influence of vitamin D status on diabetes development and depression will be examined, during a 5 year follow-up among 20.000 US men and women. The participants will be given vitamin D3, 2000 IU per day. From 6000 participants the blood samples will be collected after 5 years, and every year questionnaires will be assessed.

Discussion

The aim of this review was to clarify the relation between vitamin D, depression and Diabetes Mellitus type 2. The relation between depression and diabetes was already established by past research, and is claimed to be bidirectional. The relation between de other variables was examined by a literature study. The first research question examined in this thesis is: What does the current literature state about the way in which diabetes mellitus, vitamin D and depression are related? The question consists of several elements. [1] Does vitamin D insufficiency precedes and leads to the development of diabetes type 2 and depression? [2] Do depressive symptoms decrease after ingesting vitamin D supplements, [3] and does the chance of developing diabetes type 2 decrease after ingesting vitamin D supplements. [4] Can it be stated by reason, that vitamin D a mediator is between diabetes type 2 and depression?

Vitamin D and depression

Jorde et al. (2008) and Milaneschi et al. (2010) discussed the relation between vitamin D and depression, and they found a possible important effect of body mass index. Both studies found that BMI plays a role in the association between vitamin D and depression and further research is necessary. May et al. (2010), Jorde et al. (2008) and Hoogendijk et al. (2008) investigated the possible role of PTH in the development of depression. The outcome of all 3 studies was that low vitamin D levels are accompanied by significantly higher PTH levels.

Vitamin D and Diabetes Mellitus

It must be noted that the studies from Lindqvist et al. (2010) and from Grimnes et al. (2010) found a possible mediation effect of BMI on the relation between vitamin D and diabetes. Further research in necessary to confirm the possible mediation effect, and the implications this brings along for the overall association.

The answer to the first research question is that indeed, vitamin D insufficiency precedes and leads to depression and diabetes type 2. This can be concluded from the longitudinal studies examined in this review. Milaneschi et al. (2010) and Jorde et al. (2008) found that this is the case. The intervention study from Jorde et al. (2008) found a significant effect from vitamin D supplements on depression, the risk of developing a depression was significantly lower when vitamin D supplements were ingested. The second question is answered by the claim that depressive symptoms decrease after taking vitamin D supplements. This can be concluded from the intervention study from Jorde et al. (2008), in which the participants had a lower risk of developing a depression when vitamin D supplements were ingested. This implies a causal effect. The third research question is answered by the finding that the chance of developing diabetes type 2 doesn't significantly decrease after taking vitamin D supplements. This can be concluded from the intervention study (Lindqvist et al, 2010) in which no significant effect of vitamin D supplementation, on risk of developing diabetes was found.

From the literature study done in this review, one variable showed up in several papers. Four studies found a potential role of BMI in the relation between vitamin D, depression and diabetes. In one study from Grimnes et al (2010) the influence of vitamin D on diabetes even rendered nonsignificant when controlled for BMI. If the role of BMI is important in the relation between vitamin D, depression and diabetes, more information is necessary. It has been proposed that obesity leads to low vitamin D levels (Jorde et al, 2010). Because vitamin D is hydrophobic it may move out of the circulation and get into the large amount of adipose tissue in persons with a high BMI, with low circulation blood vitamin D levels as a result. It is also possible that low vitamin D levels increase the risk of obesity, which was found by Mc Carty et al. (2006). Vitamin D may modulate the catabolic and anabolic activity of adipocytes according to Zemel et al. (2010). From the study Gilbert-Diamond et al. (2010) it is known that low vitamin D levels are associated with a significant increase in adiposity. This was measured by BMI, skin fold thickness and waist circumference. In contrast, the study from Young et al. (2009) didn't find any significant associations of vitamin D levels with BMI. In the research from Xiao-Mei et al. (2011) vitamin D levels < 50 nmol/L were associated with new-onset obesity in adults.

The fourth research question, involving a mediation effect of vitamin D on the relation between depression and diabetes type 2, can be answered now. It is possible that the relation

between vitamin D and BMI influences the relation between both depression and diabetes. In order to confirm this hypothesis, further research is necessary. With the information gathered in this review, it can't be stated by reason that vitamin D mediates between depression and diabetes. Therefore the relation between vitamin D and diabetes is not clear yet. Also the possible important influence of BMI on this set of interactions between variables needs more attention and investigation.

The nature of the relationship between vitamin D, BMI, depression and diabetes remains unclear. For example; if vitamin D levels are low because a person is obese, the risk of developing diabetes type 2 and/or depression is higher. Another possibility is; if a person is obese, vitamin D levels may be low, and therefore the risk of developing diabetes type 2 and/or depression is higher. To test if one of these hypotheses is correct, research with path analysis can be performed. To confirm the outcome of the study from Avanell et al. (2009) it is necessary to perform more intervention studies that find no significant effect of vitamin D supplementation on the risk of developing diabetes type 2. It is also possible that there is a significant effect, but Avanell and colleagues found no effect because of the relative low daily doses of vitamin D. At last it is also possible that PTH levels contribute to the relation between vitamin D, BMI, diabetes and depression.

PTH levels are related to diabetes, as was discovered in the research from Murakami et al. (2008) and also to depression (Hoogendijk et al, 2008). May et al. (2010), Jorde et al. (2008) and Hoogendijk et al. (2008) investigated the role of PTH in the development of depression. The outcome of all 3 studies was that low vitamin D levels are accompanied by significantly higher PTH levels. This is rather confusing because high PTH levels are related to depression, and low PTH levels to diabetes. Røislien et al. (2011) found that PTH a mediator is between obesity and vitamin D. The contemporary clinical trail from Manson et al. (2012) will assess the relation between all variables discussed above. Possibly this study will give answer on the yet unknown relation between vitamin D, depression, diabetes, obesity and PTH levels.

The causal relation found by Jorde et al. (2008) has an important clinical implication. People with low vitamin D levels should take vitamin D supplements to prevent the development of depression. Since depression is common and vitamin D insufficiency as well, this has potentially a great impact on the current prevention of depression. From the prospective research

studying the relation between vitamin D and diabetes it can be concluded that there is a relation between them. The risk of developing diabetes type 2 is higher when vitamin D levels are low. This must be interpreted with caution, because there was no causal relationship found between vitamin D and diabetes type 2 by Avanell et al. (2011). This does not mean that the association found by the five prospective studies and two cross-sectional studies does not exist. The clinical consequences are that people high at risk for diabetes type 2 should take vitamin D supplements as prevention for the development of diabetes type 2. Because diabetes is a widespread disease the prevention of this disease is important, and vitamin D may play a role in this.

The strength of this review is the innovative design. Most reviews investigate the relation between two variables, and control for others. In this review the information was gathered and put together about three variables and finally the influence of two other variables was also integrated. Furthermore the present thesis contains contemporary studies from 2000-2012 which implicates an original topic.

A limitation of this review is that the authors used different levels of 25(OH) D serum to indicate vitamin D insufficiency. Most articles used quartiles to analyze the vitamin D levels, but it is difficult to compare articles when the quartiles aren't the same. Another limitation is the difference in measurement of depression. This may affect the comparison of the results from the different articles. However, the results are reliable and interpreted well.

In conclusion, this review examined the relation between vitamin D, depression and diabetes mellitus type 2. The main outcome from the 18 studies is that there is an association between vitamin D, depression and diabetes type 2. There is a causal relation between vitamin D and depression, and an association between vitamin D and diabetes. Also it is important to note that BMI may play a crucial role in the interaction between these variables, and this needs more research to confirm. The influence of PTH levels on vitamin D, depression and diabetes is not clear, and research in this area is recommended.

References:

Anderson, K.E. Freedland, R.E. Clouse, P.J. Lustman, (2001). The prevalence of comorbid depression in adults with diabetes: a meta-analysis, Diabetes Care 24 1069–1078.

Armas, L.A.G., Hollis, B.W., Heaney P.W. (2004). Vitamin D2 is much less effective than vitamin D3 in humans. The Journal of Clinical Endocrinology & Metabolism. vol.89 no. 11 5387-5391

Avanell, A., Cook, J.A., et al. (2009) Vitamin D supplementation and type 2 diabetes: a substudy of a randomized placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). Age Ageing (2009) 38 (5): 606-609.

Bertone-Johnson, E. R., S. I. Powers, et al. (2011). Vitamin D intake from foods and supplements and depressive symptoms in a diverse population of older women. American Journal of Clinical Nutrition. 94(4): 1104-1112.

Chan, R., D. Chan, et al. (2011). Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. Journal of Affective Disorders 130(1-2):251-259.

Espiritu, R.P., Kearns, A.E. et al. (2011). Depression in primary hyperparathyroidism: prevalence and benefit of surgery. Journal of clinical endocrinology & metabolism. 96(11):E1737-45

Gilbert-Diamond D, Baylin A, Mora-Plazas M, et al. (2010). Vitamin D deficiency and anthropometric indicators of adiposity in school-age children: a prospective study. American Journal of Clinical Nutrition; 92(6):1446–1451.

Grant, W. B. (2011). Low serum 25-hydroxyvitamin D levels and the bidirectional association between depression and type 2 diabetes mellitus in women. Archive of Internal Medicine 171(11): 1041; author reply 1041-1042.

Grimnes, G., N. Emaus, et al. (2010). Baseline serum 25-hydroxyvitamin D concentrations in the Tromso Study 1994-95 and risk of developing type 2 diabetes mellitus during 11 years of follow up. Diabetic Medicine 27(10): 1107-1115.

Holick MF. (2007). Vitamin D deficiency. National English Journal of Medicine; 357(3):266 281.

Hoogendijk, W. J., P. Lips, et al. (2008). Depression is associated with decreased 25 hydroxyvitamin D and increased parathyroid hormone levels in older adults. Archive of General Psychiatry 65(5): 508-512.

Jorde, R., M. Sneve, et al. (2008). Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. Journal of Internal Medicine 264(6): 599-609.

Jorde R, Sneve M, Emaus N, et al. (2010). Cross-sectional and longitudinal relation between serum 25 hydroxyvitamin D and body mass index: the Tromsø Study. European Journal of Nutrition; 49(7): 401-407.

Lindqvist, P. G., H. Olsson, et al. (2010). Are active sun exposure habits related to lowering risk of type 2 diabetes mellitus in women, a prospective cohort study? Diabetes Research and Clinical Practice 90(1): 109 114.

Liu, E., Meigs, J. B., Pittas, A. G., Economos, C. D., McKeown, N. M., Booth, S. L., Jacques, P.F. (2010). Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham Offspring Study. American Journal of Clinical Nutrition; 91:1627–33.

Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, Zaharris E, Macfadyen JG, Danielson E, Lin J, Zhang SM, Buring JE: The VITamin D and OmegA-3 TriaL (VITAL): Rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. Contemporary Clinical Trials. 2012 Jan;33(1):159-71. Epub 2011 Oct 2.

Mattila, C., P. Knekt, et al. (2007). Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diabetes Care 30(10): 2569-2570.

May, H. T., T. L. Bair, et al. (2010). Association of vitamin D levels with incident depression among a general cardiovascular population. American Heart Journal 159(6): 1037-1043.

MayoClinic: vitamin D, 2011 http://www.mayoclinic.com/health/vitamin-d/NS_patient-vitamind

McCarty MF, Thomas CA. (2003). PTH excess may promote weight gain by impeding catecholamine induced lipolysis-implications for the impact of calcium, vitamin D, and alcohol on body weight. Medical Hypotheses. 2003;61(5-6):535–542.

Medterms: vitamin D, (2003): http://www.medterms.com/script/main/art.asp?articlekey=15296

Milaneschi, Y., M. Shardell, et al. (2010). Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. Journal of Clinical Endocrinol Metabolism 95(7): 3225-3233.

Murakami R, Murakami S, Tsushima R, et al. (2008). Glycaemic control and serum intact parathyroid hormone levels in diabetic patients on haemodialysis therapy. Nephrology Dialesis Transplant; 23:315-320.

Norman AW, Frankel JB, Heldt AM, Grodsky GM. (1980). Vitamin D deficiency inhibits pancreatic secretion of insulin. Science; 209:823–825.

Pan A, Lucas M, Sun Q, van Dam RM, Franco OH, Manson JE, et al. (2010). Bidirectional association between depression and type 2 diabetes mellitus in women. Archive of Internal Medicine; 170:1884–91.

Pan, A., L. Lu, et al. (2009). Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. Journal of Affective Disorders 118(1-3): 240-243.

Pittas AG, Dawson-Hughes B, Li T, et al. (2006). Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care; 29:650–656.

Renzaho, A. M., C. Nowson, et al. (2011). Prevalence of vitamin D insufficiency and risk factors for type 2 diabetes and cardiovascular disease among African migrant and refugee adults in Melbourne: a pilot study. Asia Pacific Journal of Clinical Nutrition 20(3):397 403.

Røislien J, Van Calster B, Hjelmesæth J. (2011). Parathyroid hormone is a plausible mediator for the metabolic syndrome in the morbidly obese: a cross-sectional study. Cardiovascular Diabetol. Doi: 10.1186/1475-2840-10-17

Schneider B, Weber B, Frensch A, Stein J, Fritze J (2000). Vitamin D in schizophrenia, major depression andalcoholism. Journal of Neural Transmission, 107:839-842.

Shankar, A., C. Sabanayagam, et al. (2011). Serum 25-hydroxyvitamin d levels and prediabetes among subjects free of diabetes. Diabetes Care 34(5): 1114-1119.

Thacher, T. D. and B. L. Clarke (2011). Vitamin D insufficiency. Mayo Clinic Proceedings 86(1): 50-60.

Vacek JL, Vanga SR, Good M, Lai SM, Lakkireddy D, Howard PA. (2012). Vitamin D deficiency and supplementation and relation to cardiovascular health. American Journal of Cardiology; 109(3):359-63.

World Health Organization: Diabetes, (2011): http://www.who.int/topics/diabetes_mellitus/en/

World Health Organization: Depression, (2011): http://www.who.int/mental_health/management/depression/definition/en/

Xiao-Mei Mai, Yue Chen, et al. (2011). Cross Sectional and Prospective Cohort Study of Serum 25-Hydroxyvitamin D Level and Obesity in Adults. American Journal of Epidemiology: DOI: 10.1093/aje/kwr456

Yatan Pal Singh Balhara, Rajesh Sagar. (2012). Correlates of anxiety and depression among patients with type 2 diabetes mellitus. Indian journal of endocrinology and metabolism; 15(Suppl 1):S50-4.

Yi-Min Hsu, Li-Ting Su, et al. (2011). Diabetes mellitus and risk of subsequent depression: A longitudinal study. International Journal of Nursing Studies, doi:10.1016/j.ijnurstu.2011.09.019.

Young KA, Engelman CD, Langefeld CD, (2009). Association of plasma vitamin D levels with adiposity in Hispanic and African Americans. Journal of Clinical Endocrinology Metabolism;94(9): 3306–3313.

Zemel MB, Sun XC. (2010). Vitamin D modulation of adipocyte function. In: Holick MF, ed. Vitamin D Physiology, Molecular Biology, and Clinical Applications. 2nd ed. New York: Springer Publishing Company: 345–361.

Zhao, G., E. S. Ford, et al. (2010). No associations between serum concentrations of 25 hydroxyvitamin D and parathyroid hormone and depression among US adults. British Journal of Nutrition 104(11): 1696-170

Table 1. Summary of reviewed studies

Author & year of publication	Variables included	N	Specification participants	Design
Avenell et al. (2009)	Vitamin D & Diabetes	5,292	osteoporotic fracture patients	intervention
Bertone-Johnson et al. (2011)	Vitamin D & Depression	81,189	Women's Health Initiative	cross-sectional prospective
Chan et al. (2011)	Vitamin D & Depression	939	Chinese men	cross-sectional prospective cohort
Grimnes et al. (2010)	Vitamin D & Diabetes	6,119	Norway citizens	prospective population based
Hoogendijk et al. (2008)	Vitamin D & Depression	1,282	Dutch citizens	population based cohort
Jorde et al. (2008)	Vitamin D & Depression	441	Norway citizens	intervention
Lindqvist et al. (2010)	Vitamin D & Diabetes	24,098	Swedish women	prospective cohort
Liu et al. (2010)	Vitamin D & Diabetes	3,066	population based participants	prospective cohort
Manson et al. (2012)	Vitamin D, Diabetes & Depression	20	US citizens	intervention
Mattila et al. (2007)	Vitamin D & Diabetes	4,097	Finland Survey participants	longitudinal cohort
May et al. (2010)	Vitamin D & Depression	7,358	cardiovascular patients	prospective follow-up
Milaneschi et al. (2010)	Vitamin D & Depression	954	Italian 65+ women and men	population based cohort
Pan et al. (2009)	Vitamin D & Depression	3,262	community residents	population based cross sectional
Pittas et al. (2006)	Vitamin D & Diabetes	83,779	female nurses	prospective
Renzaho et al. (2011)	Vitamin D & Diabetes	49	migrants	cross-sectional
Schneider et al. (2000)	Vitamin D & Depression	25	psychiatric patients	cross-sectional
Shankar et al. (2011)	Vitamin D & Diabetes	12,719	US citizens	cross-sectional population based
Zhao et al. (2010)	Vitamin D & Depression	3,916	US adults	cross-sectional population based

Author & year of publication	cut-off scores vitamin D	Follow-up time	% men	Mean age	Effect Size	p-value
Avenell et al. (2009)	daily dose: 800 IU	5 years	15%	77 years	OR 1.11 (0.77-1.62)	0.57
Bertone-Johnson et al. (2011)	high>= 800 IU low <= 100 IU	3 years	0%	50-79 years	OR 0.79 (0.71-0.89)	< 0.001
Chan et al. (2011)	high >=92 nmol/L low <=63 nmol/L	4 years	100%	73 years	OR 0.46 (0.22-0.98)	0.004
Grimnes et al. (2010)	quartiles	11 years	39%	58 years	HR non-smoke: 1.89 (1.25-2.89)	< 0.001
Hoogendijk et al. (2008)	quartiles 15-27 ng/mL	1 year	52%	76 years	beta −3.35 (−4.51 to −2.19)	< 0.001
Jorde et al. (2008)	<40 nmol/l low >40 nmol/l high	1 year	36%	47 years	none	< 0.05
Lindqvist et al. (2010)	none	11 years	0%	25-64 years	OR 0.7 (0.6-0.9)	none
Liu et al. (2010)	quartiles	7 years	46%	54 years	HR 0.60 (0.37-0.97)	0.03
Manson et al. (2012)	90 nmol/L optimal	5 years	unknown	53 years	none	unknown
Mattila et al. (2007)	quartiles	17 years	47%	53 years	RR 0.60 (0.36-0.98)	0.01
May et al. (2010)	ng/mL high>50 low<15	1 year	41%	73 years	HR 2.70 (1.35-5.40)	0.005
Milaneschi et al. (2010)	low <50 nmol/l	6 years	44%	74 years	HR women 2 (1.2-3.2)	w:0.005
Pan et al. (2009)	tertile 26-65 nmol/l	none	unknown	50-70 years	OR 0.62 (0.46-0.83)	0.002
Pittas et al. (2006)	high>= 800 IU <400 IU Low	20 years	0%	46 years	RR 0.67 (0.49-0.90)	< 0.001
Renzaho et al. (2011)	<50 nmol/L	none	59%	42 years	correlation	none
Schneider et al. (2000)	none	none	44%	58 years	none	> 0.05
Shankar et al. (2011)	quartiles 17-34 ng/mL	none	48%	44 years	OR 1.47 (1.16-1.85)	0.001
Zhao et al. (2010)	quartiles 15-26 ng/mL	none	48%	>20 years	HR Maj Dep 0.23 (0.06-0.79)	0.11

Author & year of publication	Outcome
Avenell et al. (2009)	No influence on risk of developing diabetes
Bertone-Johnson et al. (2011)	Support of inverse association between Vitamin D and depression
Chan et al. (2011)	Significant inverse association between vitamin D and depression
Grimnes et al. (2010)	Significant risk of developing diabetes when low vitamin d, but not when adjustment for BMI
Hoogendijk et al. (2008)	Association between depression and vitamin D, adjusted for confounding variables
Jorde et al. (2008)	Possible causal relation between vitamin D and depression
Lindqvist et al. (2010)	30% lower risk of developing diabetes when vitamin D is high
Liu et al. (2010)	Higher vitamin D status is associated with decreased risk of T2D.
Manson et al. (2012)	Unknown
Mattila et al. (2007)	Significant inverse association between vitamin D and risk of diabetes.
May et al. (2010)	Vitamin D levels are associated with incidence of depression
Milaneschi et al. (2010)	Low vitamin D is a risk factor for developing a depression in older people
Pan et al. (2009)	No association between vitamin D and depressive symptoms
Pittas et al. (2006)	23% chance of diabetes when total of >800 IU/day
Renzaho et al. (2011)	Low vitamin D is associated with risk of diabetes development
Schneider et al. (2000)	Vitamin D is not involved in the pathopsysiology of depression
Shankar et al. (2011)	Low vitamin D is associated with risk of prediabetes
Zhao et al. (2010)	No significant association between vitamin D and depression