# Determinants of adverse health outcomes in late-life depression

van den Berg, Karen

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The role of vitamine D and frailty

**Karen S. van den Berg**

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# Determinants of adverse health outcomes in late-life depression

## The role of vitamine D and frailty

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## Promotor

Prof. dr. R.C. Oude Voshaar

## Copromotores

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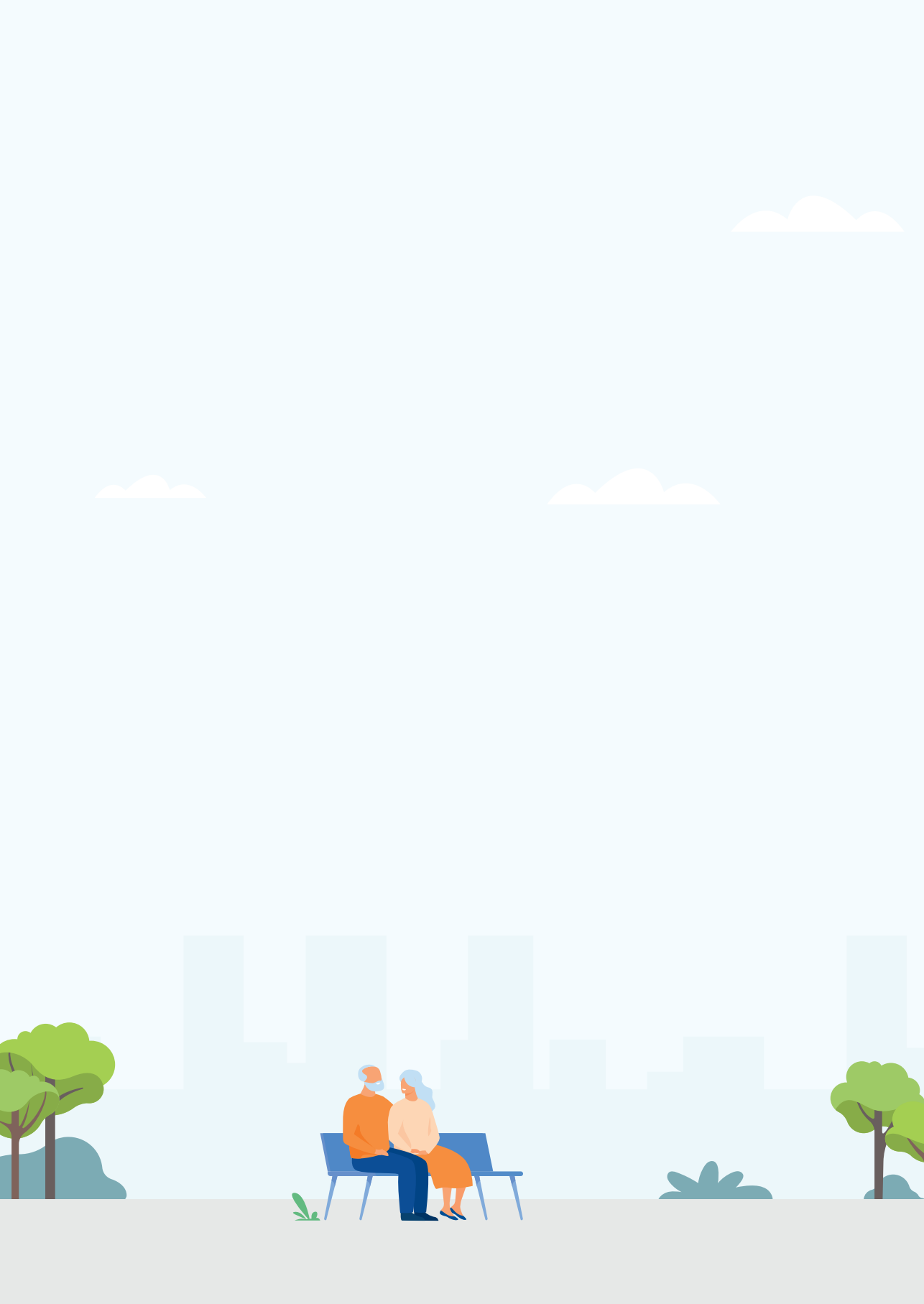

# CHAPTER 1

## INTRODUCTION

**Case report**

*Mrs Z, a 79-year old female, has been admitted to the psychiatric ward in a general hospital. She has no psychiatric history. Her general practitioner referred her because of anhedonia and her belief that she would die soon, even though she was not terminally ill. Mrs Z has been married for 46 years, and she and her husband are a socially active couple who enjoy going out. In the last three weeks, however, she was seated in her chair all day long, with her eyes closed, waiting for death to come. She tells the psychiatrist that she is not feeling particularly sad, although the thought of her impending death makes everything feel pointless to her. She has lost pleasure in everything, and even the visits of her grandchildren, usually a great joy to her, now leave her indifferent. She normally is a hospitable person, but now she can hardly bear any visitors. Hoping they would leave soon, she does not talk to them and asks her husband not to start a conversation with them either. She cannot concentrate on reading or watching television anymore. Due to a loss of appetite, she has hardly eaten in the last three weeks. She often feels sick or dizzy and experiences pains all over her body. The psychiatrist diagnoses a late-onset depressive disorder with psychotic features.*

## LATE-LIFE DEPRESSION

Depressive symptoms are common in later life, and their prevalence increases with ageing. Among persons over 75 years of age, over 17% have clinically relevant depressive symptoms, and 7.2% have a major depressive disorder. Women are more often affected than men[1]. Although the same diagnostic criteria for depression are applied throughout the life span[2], the appearance of depression may differ later in life. Compared to younger persons, depressed older persons present with relatively more somatic symptoms, and less prominent mood symptoms[3]. Cognitive impairment is more common[4]. One of the challenges for old-age psychiatrists and others involved in the treatment of older persons is to determine to what extent somatic symptoms are caused by an underlying somatic disease or by a depression. A depression might present with unexplained physical symptoms[5] or amplify feelings of pain and other somatic complaints[1], but, on the other hand, it also predisposes to a variety of somatic diseases[6] and imposes an increased risk of dying from diseases such as diabetes mellitus type II[7], stroke[8], and myocardial infarction[9]. (Age-related) somatic diseases, in turn, increase the risk of late-life depression[10] and may lead to a more chronic course of the depression[11].

This intertwining of depression and somatic comorbidity involves a risk of both under- and overdiagnosis of depression, if somatic symptoms are incorrectly attributed to a somatic disease, or, on the contrary, if somatic diseases are disregarded[10].

| **Diagnostic criteria for depression (according to DSM 5)** | |
|---|---|
| **Major depressive disorder** | |
| *Primary symptoms (at least one required)* | Depressed mood |
| | Loss of interest and pleasure |
| *Secondary symptoms (at least four required)* | Weight changes / change of appetite* |
| | Sleeping problems* |
| | Psychomotor retardation or agitation* |
| | Fatigue / loss of energy* |
| | Feelings of worthlessness / excessive guilt |
| | Concentration problems / indecisiveness |
| | Suicidality or recurrent thoughts of death |
| **Minor depression** | Less than five criteria present |
| **Atypical subtype** | |
| *Primary symptom* | Mood reactivity to positive events |
| *Other symptoms (at least two required)* | Weight gain / increase of appetite* |
| | Hypersomnia* |
| | Leaden paralysis* |
| | Interpersonal rejection sensitivity |
| **Melancholic subtype** | |
| *Main symptoms (at least one required)* | Anhedonia |
| | Lack of mood reactivity |
| *Other symptoms (at least three required)* | Depression, subjectively different from grief or loss |
| | Severe weight loss / loss of appetite* |
| | Psychomotor agitation / retardation* |
| | Early morning awakening* |
| | Excessive guilt |
| | Worse mood in the morning |

*Somatic symptoms

Besides this comorbidity of somatic diseases, other adverse health consequences that add to the high disease-burden of late-life depression are a decline of physical, social, and cognitive functioning, and decreased self-care, all of which are associated with diminished quality of life and an increased mortality risk[1, 12]. Utilisation of health

services is higher among depressed persons, and entails high societal costs that are not only attributable to the depression treatment[1]. As a result, late-life depression is an important public health problem that, given today's ageing society, will only increase in the next decades. It is important to unravel how depression leads to these negative health consequences and which factors associated with depression play a role.

*Mrs Z, her husband, their daughter and the psychiatrist discuss the treatment plan together. The psychiatrist proposes continuation of the hospitalisation, aimed at activation, with physical therapy to regain muscle strength, as well as electroconvulsive therapy (ECT) because of expected good results in a depression with psychotic features at older age. After an explanation of the side effects of ECT, Mrs Z refuses ECT out of fear for memory problems. Eventually, Mrs Z and the psychiatrist agree on the start of nortriptyline, an antidepressant.*

*At the end of the conversation, the husband of Mrs Z questions how likely it is that his wife will die in the near future, as she herself is so convinced of it. Based on Mrs Z's medical history and her current health status, there are no diseases present that could cause her death soon. Mrs Z denies suicidal thoughts. The psychiatrist wonders what she should say.*

## Association of late-life depression with mortality

Depression has been associated with increased mortality rates in populations of all ages[13] and at older age (>65 years)[14], although other studies have reported null findings[15, 16]. Despite a reassessment of 293 studies, no strong conclusions about the relationship between depression and mortality can be drawn[17]. The authors of this review point out three weaknesses of the current literature. First, a significant publication bias exists, since the largest effect estimates were consistently seen in small samples, with low death rates and brief follow-up. Second, most studies did not adjust for comorbid mental disorders and negative health behaviour (smoking, use of alcohol, physical activity). In eight studies that did adjust for both, no association between depression and mortality was seen. Last, there is a substantial heterogeneity between studies, not only with respect to sample size, duration of follow-up or adjustment for other variables, but also caused by the selection of subjects based on medical conditions in two-third of the studies, and the use of symptom scales instead of psychiatric interviews to diagnose depression. This may have led to overdiagnosis of depression in persons

with somatic symptoms, because in an interview it is easier to distinguish whether a physical complaint is caused by a somatic disease or by a depression. Also, the use of more than forty different symptom scales and different cut-off values may have added to this heterogeneity[17]. Besides these weaknesses in existing studies, the relationship between depression and mortality itself may change over time and thus increase the inconsistency of results. Over the last decades, a downward trend in excess mortality for older persons with major depressive disorder has been observed[18].



Furthermore, depression itself is a heterogeneous condition. It is a syndrome, rather than a distinct entity that can be diagnosed by a certain test, and consequently symptoms and course of depression may vary widely between persons. Therefore, it may be useful to study whether specific subtypes or certain characteristics of depression are differentially related to mortality. Thus far, this has hardly been done. In a population of middle-aged to older persons, patients with a depression with psychotic features had a two-fold increased risk of dying compared to patients with severe non-psychotic depression[19], whereas, in a population-based study among younger and middle-aged adults, atypical features and age of onset were not associated with mortality risk[20]. Regarding severity of depression, a trend towards a dose-response relationship with mortality was observed after direct comparison of mortality in major depressive disorder compared to subthreshold depression[21], although, when compared to non-depressed persons, mortality rates were similarly increased for subjects under and above the threshold for major depressive disorder[20, 21].

In order to further elucidate the relationship between depression and mortality, not only the weaknesses of the current literature should be addressed, through large studies among persons with clinical depression diagnoses, long follow-up duration, and adjustment for covariates[17], but also the association of specific features of depression with mortality.

*Then the daughter of Mrs Z comes up with another question. She recently read an article in the newspaper about vitamin D and depression and searched the internet for more information. She found that older persons with a depression often have low blood levels of vitamin D. She wonders whether a vitamin D pill would be the solution for her mother's depression, as it will probably cause less side-effects than an antidepressant. At admission, the vitamin D level in the blood of Mrs Z was 18 nmol/l, consistent with a vitamin D deficiency. The psychiatrist knows that for women over 70 years of age the daily use of 800 international units of vitamin D is recommended to promote bone health, and therefore supplementation is indicated. However, she is not sure whether vitamin D supplementation would also be a useful intervention for the depression.*

## Vitamin D deficiency - a universal risk factor for age-related conditions

Active vitamin D binds to vitamin D receptors in target tissues, where it regulates gene transcription and is also involved in non-genomic responses[22, 23]. The importance of vitamin D for bone mineralisation and calcium and phosphate metabolism is well-established. Since the discovery of vitamin D receptors in many different locations throughout the human body[24], including the brain[25], research has been focusing on the extra-skeletal effects of vitamin D. The associations of vitamin D deficiency with a wide range of diseases and conditions have been studied, varying from cardiovascular disease[26], cancer[27], and psychiatric disorders[28], to Covid-19[29]. Since vitamin D deficiency can lead to different diseases in different persons, depending on the presence of other risk factors, vitamin D deficiency is considered a universal risk factor for adverse health outcomes. Among these outcomes are depression and frailty[30].

## Vitamin D deficiency and late-life depression

The health benefits of vitamin D are thought to extend to healthy brain function and therefore a deficiency may play a role in mental diseases. Accordingly, in recent years, a lot of research has been conducted into a possible causal relationship between vitamin D deficiency and depression. In the brain, vitamin D receptors have been found in specific areas, such as the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus and substantia nigra[22, 25]. Several of these regions are involved in the pathophysiology of mood disorders[31]. Multiple mechanisms of action by which vitamin D could prevent depression have been proposed. Firstly, through binding to the vitamin D receptor, vitamin D activates gene expression of enzymes involved in the synthesis of neurotransmitters, thus increasing the availability of the neurotransmitters dopamine,

noradrenaline and acetylcholine, and enhancing synapse transmission of acetylcholine[22, 23, 32]. Additionally, vitamin D may exert neuroprotective effects, by protecting the brain from oxidative degeneration through promotion of the gene expression of an enzyme that contributes to the forming of glutathione, the brain's most important anti-oxidant[33], and also by preventing toxic calcium levels by directly influencing the neuronal calcium homeostasis[34, 35]. Furthermore, vitamin D has a powerful enhancing effect on several neurotrophic factors, such as nerve growth factor (NGF), glial-derived neurotrophic factor (GDNF) and neurotrophin 3 (NT-3)[22, 34]. Lastly, vitamin D reduces inflammation by decreasing the expression of inflammatory cytokines[35, 36]. Conversely, depression may actually cause vitamin D deficiency due to a reduction of outdoor activities, leading to less sun exposure and a decreased production of vitamin D in the skin. Loss of appetite and initiative could both lead to an inadequate dietary intake of vitamin D. These reverse causative mechanisms may explain at least partly the association between low vitamin D levels and depression[37].

Results of observational studies among older persons suggest an inverse association between vitamin D levels and depression, although most studies had a cross-sectional design or did not adjust for covariates[38, 39]. However, in the Netherlands Study of Depression in Older Persons, depressed persons had significantly lower vitamin D levels than non-depressed comparisons after adjustment for several covariates[40]. Several randomised clinical trials were conducted exclusively in older persons, of which none observed an effect of vitamin D supplementation on depression[39, 41, 42]. Common limitations were small sample sizes, low vitamin D doses, and short trial durations[39]. In conclusion, it is not clear yet whether vitamin D deficiency plays a causal role in depression, or whether depression causes lower vitamin D levels. Another possibility is that there is no causal relationship whatsoever, and that vitamin D deficiency is an epiphenomenon of depression. To further elucidate this, more well-designed longitudinal and intervention studies in older populations with clinical depression diagnoses are needed, as well as studies with repeated measurements of vitamin D levels.

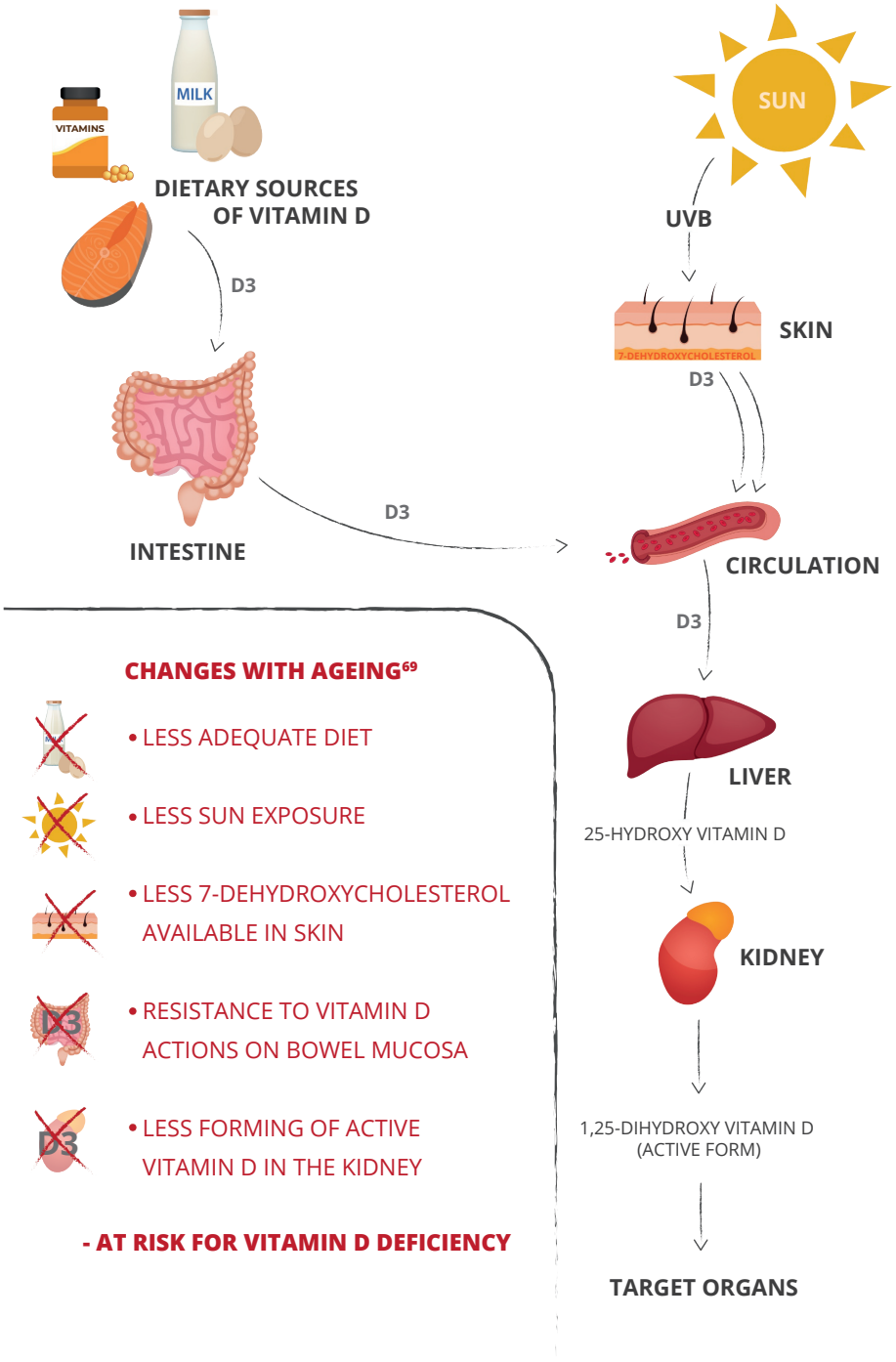


**Fig 1.** Forming of active vitamin D (1,25-dihydroxy vitamin D) in the body, and changes with ageing.

## Vitamin D deficiency and frailty

The concept of frailty can help to understand why health and functional status of persons with similar chronological ages can vary widely[43]. Although the term 'frailty' has been used to describe vulnerable persons in geriatric literature since the 1950s[44], it was not until 2013 that consensus about the concept of frailty was reached. Physical frailty was defined then as 'a geriatric syndrome, characterised by diminished strength and endurance, and reduced physiological functioning, causing a person to be vulnerable for negative health consequences, such as hospitalisation, dependency, and death'[45]. Among the most well-known models to assess frailty is the physical frailty phenotype[46], which marks an underlying physiologic state of multisystem and energy dysregulation and is often used for research purposes. A person is considered frail when three or more of five criteria are present: muscle weakness, slowness, loss of energy, involuntary weight loss, and inactivity[46]. Meta-analysis unequivocally shows an inverse association between vitamin D levels and the frailty phenotype, but good-quality intervention studies are still lacking[47]. Vitamin D deficiency may be linked to frailty through the concept of sarcopenia, the loss of muscle tissue with ageing, which is an important feature of frailty[46]. In muscle tissue, vitamin D might exert genomic effects by stimulating the activity of calcium binding protein in the cell, thus improving calcium handling, and also by promoting the expression of insulin growth factor (IGF), which leads to muscle hypertrophy through muscle cell differentiation and proliferation. Non-genomic effects occur when vitamin D binds to a membrane receptor, which activates two pathways towards a rapid influx of calcium into the cell[48]. Indeed, most observational studies report an association between low levels of vitamin D and muscle dysfunction[48], and a beneficial effect of vitamin D supplementation on muscle strength and physical performance, especially in older women with very low vitamin D levels (<25 nmol/l), was demonstrated in an umbrella-review[49].

*The medical history of Mrs Z includes arthrosis in both hips and high blood pressure. Six years earlier, she received a total hip prothesis on the left side, and a few months ago the right hip was replaced too. She is still in a rehabilitation trajectory after the last operation, but in the last month she has not been exercising anymore. To control the blood pressure, she takes metoprolol 100 mg once daily. She does not use any other medications.*

*A physical examination is performed. Mrs Z weighs 58 kilograms, while her usual weight is 75 kilograms. Her BMI is 19.8 kg/m². Her blood pressure is 120/75. Her muscle strength is low. Mrs Z is convinced that she is not able to walk anymore, although she had been walking with a crutch in the first weeks after the hip surgery. When the nurse eventually manages to get her walking, her pace is very slow. No further explanation was found for the pains Mrs Z experiences in her body. Laboratory examination reveals no irregularities, except for the vitamin D deficiency (18 nmol/l). Magnetic Resonance Imaging (MRI) of the brain shows normal white matter intensities for her age and no other abnormalities.*

*During the admission Mrs Z totally depends on the nurses for her daily care. Her glasses and her dentures bother her, and she does not want to wear them anymore. The consulting geriatrician diagnoses frailty. The psychiatrist wonders how to relate this to the depression of Mrs Z, since some frailty criteria, such as inactivity and slowness, may also be features of the depression.*

## Importance of the association between vitamin D, late-life depression and frailty/mortality

*Frailty & late-life depression*

Frailty often coexists with depression in older persons. Whereas the overall prevalence of frailty in community-dwelling older persons was nearly 11%[50], among persons with depression or depressive symptoms the overall prevalence of frailty was over 40%, with a similar prevalence of depression or depressive symptoms among persons with frailty[51]. Furthermore, odds for incident frailty in persons with depression were almost four, whereas odds for incident depression in persons with frailty were nearly two[51]. Still, the etiological relationship between frailty and depression is not clear. Three models for this relationship have been suggested, considering frailty and depression as either unrelated conditions that are highly prevalent in later life and therefore frequently coexist (model 1), or as different manifestations of the same pathophysiological

mechanisms (model 2), or as highly related but distinct constructs that are each a risk factor for the other (model 3)[52]. It seems unlikely that frailty and depression are fully independent of each other, as postulated in the first model, since frailty and depression share symptoms, such as inactivity, weight loss, slowness, and loss of energy[53]. Also, it was found that the criteria for frailty and depression identify distinct, but highly overlapping subpopulations[54]. In line with the second model, it has been hypothesised that frailty and depression have a common vulnerability factor, since shared symptoms determine some, but not all of the comorbidity of frailty and depression, suggesting that depression reflects a psychological form of vulnerability[55]. Furthermore, several biological mechanisms might play a role in the pathophysiology of frailty as well as depression, such as subclinical cardiovascular disease, inflammation, neuro-endocrine dysregulation, mitochondrial dysfunction, and accelerated cellular ageing[52, 56]. Still, most findings point towards the third model: a bidirectional association between frailty and depression, in which the presence of one is a risk factor for developing the other[51, 57]. Depressed persons might be more susceptible to develop frailty, due to lifestyle factors associated with depression, such as reduced physical activity, inactivity and non-compliance with the treatment of somatic disorders[58]. The use of antidepressants may also contribute to frailty[59]. On the other hand, frail persons may be more prone to depression due to somatic comorbidity, functional limitations, and increased dependency[52].

*Vitamin D, frailty and mortality*

The presence of the frailty phenotype[60] as well as the presence of a larger number of phenotypic criteria[61] are associated with a higher mortality risk. Among older adults, the presence of frailty at psychiatric admission was a strong predictor of mortality, independent of age, gender, multimorbidity, and functional status[62]. Although frailty can be reversible, there might be a point of no return, after which frailty becomes a pre-death phase[63]. Frailty can, therefore, be seen as the final stage of the normal ageing process. Lower vitamin D levels were also independently associated with an increased risk of all-cause and vascular mortality in large meta-analyses of observational studies[64, 65]. An additive joint effect of low vitamin D levels and frailty on mortality was seen in a population sample: the risk of mortality was higher for frail persons with low vitamin D levels than for frail persons with higher vitamin D levels[66]. This raises the question whether frailty is also associated with vitamin D levels and mortality in a sample with late-life depression. Could frailty be a mediating factor in the pathway between vitamin D deficiency and mortality?

### Unravelling the relatedness of vitamin D deficiency, frailty, and mortality in late-life depression

Depression is common in later life, and has many adverse health consequences. The depression itself is rarely the only problem that needs to be dealt with by the patient and the old-age psychiatrist. Unravelling complex cases, in which psychiatric, somatic, and often also social factors play a role, is also the joy of being an old-age psychiatrist. The case of Mrs Z illustrates the multi-factorial nature of late-life depression and some of the questions that may arise in the process of diagnosis and treatment: 'What can I say about the life-expectancy of this person?', 'Should I assess vitamin D levels in all my patients?', 'How bad is a low vitamin D level, do I need to prescribe supplementation?', 'What is the role of somatic diseases?', 'Is this person depressed, frail, or both?' The aim of this thesis is to shed more light on the interrelatedness of vitamin D deficiency, frailty, and mortality in late-life depression, as well as their relations with the depression itself. Previous studies have often been performed in large population cohorts, using symptom scales to assess depression, which may easily lead to confounding by somatic disorders and overdiagnosis of depression. Regarding vitamin D deficiency and frailty, this is particularly a problem. Studies among persons with a clinical depression diagnosis are necessary to unravel this complex matter. In this thesis we focus on vitamin D deficiency, frailty and mortality among patients with a clinical diagnosis of late-life depression.

## CURRENT THESIS

### Background and outline of the thesis

The following questions will be addressed:

*Late-life depression and mortality*

Depressive disorder has been associated with mortality, but literature is not unequivocal[17]. In **Chapter 2**, we present a Cox proportional-hazard analysis to examine whether late-life depression is associated with death, adjusted for lifestyle and somatic comorbidity. We hypothesised to find an association. Secondly, we explore whether specific subtypes and characteristics might be related to mortality.

*Vitamin D deficiency as a universal risk factor for adverse health outcomes*

Vitamin D deficiency and late-life depression are related[39]. Furthermore, a poor vitamin D status is a universal risk factor for many adverse health outcomes, including frailty[47]

and death[65]. In **Chapter 3,** we examine whether vitamin D level predicts the course of late-life depression and mortality. We describe a logistic regression analysis of the association between vitamin D levels at baseline and the presence of depression at the two-year follow-up visit, as well as their association with the course of depressive symptoms over two years. Furthermore, we look at the association of those vitamin D levels with study attrition and mortality. In **Chapter 4**, we examine whether vitamin D level predicts the prevalence and the course of frailty in late-life depression. We report a cross-sectional as well as a longitudinal regression analysis of the association between vitamin D levels at baseline and the presence of frailty at baseline and two-year follow up.



*Age and frailty as main predictors of mortality in late-life depression*

The main predictors of mortality are chronological age and biological age (frailty). Frailty predicts mortality in several chronic conditions, but has never been studied in late-life depression. A particular difficulty in late-life depression is the overlap between the two conditions. In **Chapter 5**, we examine whether frailty may explain mortality in depression. Cox proportional-hazard analyses of the mortality risk by the presence of frailty or frailty components were conducted. Furthermore, we studied whether the mortality risk can be explained by age-related physiological disturbances, among which low vitamin D levels.

*Is vitamin D deficiency an epiphenomenon of late-life depression?*

Whether the association between vitamin D deficiency and late-life depression as well as frailty is causal is still highly debated. Moreover, repeated assessments of vitamin D levels in patients with late-life depression are scarcely available. In **Chapter 6,** we examine whether the change in vitamin D levels over time is associated with either a change in depression, frailty, or both.

*What do we know about the impact of vitamin D in late-life depression outside mental health?*

Since low vitamin D is a universal risk factor for many adverse health outcomes, including frailty and death, which are also very common in depression, it is of utmost importance to study secondary somatic health outcomes in randomised clinical trials evaluating the impact of vitamin D supplementation on depression. In **Chapter 7**, we study whether adverse somatic health outcomes are considered in vitamin D supplementation trials

in depression, and if so, whether supplementation has any impact on these health outcomes. **Chapter 8** is a summary and general discussion of the findings in this thesis.


**Fig 2.** Schematic representation of the triad vitamin D – frailty – mortality in late-life depression *(numbers in arrows refer to the relevant chapters)*

## Appendix 1:

### Study population

For this thesis, we used data obtained from the Netherlands Study of Depression in Older persons (NESDO). NESDO is a multi-centre, prospective cohort study into the course and consequences of late-life depression. From 2007 to 2010, 510 participants aged between 60 and 93 years were recruited from general practices and mental health care institutions. At baseline, data on demographic, psychosocial, biological, cognitive and genetic determinants were collected through interviews, written questionnaires, physical examination, cognitive tests, and collection of blood and saliva samples. 387 persons had a clinical diagnosis of depression, according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). The 132 non-depressed comparisons had never had a diagnosis of depression in their lifetime. From the baseline visit on, postal questionnaires were sent every 6 months to monitor factors such as severity of depressive symptomatology, physical health and use of medication. Follow-up visits were planned at two years and six years after the initial visit, and all measures subject to change were then evaluated again. Vitamin D levels were assessed at baseline and two-year follow-up visits. Attrition was recorded every 6 months by contacting the participant or a contact person if the postal questionnaire was not returned, to inquire about the reasons. At the two-year follow-up assessment, 401 persons were still participating in the study (285 depressed persons and 116 non-depressed comparisons)[67]. A total of 299 older persons, 201 with a depression at baseline and 98 non-depressed comparisons, participated in the six-year follow-up visit[68].

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# CHAPTER 2

## CLINICAL CHARACTERISTICS OF LATE-LIFE DEPRESSION PREDICTING MORTALITY

Karen S. van den Berg, Carlijn Wiersema, Johanna M. Hegeman, Rob H.S. van den Brink, Didi Rhebergen, Radboud M. Marijnissen, Richard C. Oude Voshaar.

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## ABSTRACT

***Objective:*** Depression has been associated with increased mortality rates, and modifying mechanisms are not yet elucidated. We examined whether specific subtypes or characteristics of late-life depression predict mortality.

***Methods:*** A cohort study including 378 depressed older patients according to DSM-IV criteria and 132 never depressed comparisons. The predictive value of depression subtypes and characteristics on the six-year mortality rate, as well as their interaction with somatic disease burden and antidepressant drug use, was analysed with Cox proportional-hazard analyses adjusted for demographic and lifestyle characteristics.

***Results:*** Depressed persons had a higher mortality risk than non-depressed comparisons (HR=2.95 [95%-CI: 1.41-6.16], p=.004), which lost significance after adjustment for age, sex, education, smoking, alcohol, physical activity, number of prescribed medications and somatic comorbidity. Regarding depression subtypes and characteristics, only minor depression was associated with a higher mortality risk when adjusted for confounders (HR=6.59 [95%-CI: 1.79–24.2], p=.005).

***Conclusions:*** Increased mortality rates of depressed older persons seem best explained by unhealthy lifestyle characteristics and multiple drug prescriptions. The high mortality rate in minor depression, independent of these factors, might point to another, yet unknown, pathway towards mortality for this depression subtype. An explanation might be that minor depression in later life reflects depressive symptoms due to underlying aging-related processes, such as inflammation-based sickness behaviour, frailty or mild cognitive impairment that have been associated with increased mortality.

## INTRODUCTION

Psychiatric disorders are associated with increased mortality rates[1, 2, 3]. Only a small proportion of this excess mortality can be explained by unnatural deaths, like suicide or accidents; a much larger part is due to an increased somatic disease burden and/or adverse drug effects as well as an unhealthy lifestyle, unfavourable social health determinants, and less access to health care[3]. According to a recent meta-analysis, the quality of the evidence underlying the association between depression and mortality is generally low and the role of modifying factors needs further elucidation[4]. In the present study, we will explore the modifying role of specific depression subtypes and characteristics, taking somatic comorbidity and use of medication into account.



It is well-known that depression is a heterogeneous disorder[5]. Whether specific subtypes or characteristics of depression are differentially related to mortality has received little attention. Thus far, no dose-response relationship between depressive symptom severity and mortality has been found. Meta-analysis did not show a significant difference between the impact of major depression and minor depression on mortality[6]. In line with this, a more recent population-based study found that a current depressive state predicted mortality irrespective whether the person scored above or below the diagnostic threshold for major depressive disorder. Furthermore, mortality rates did not differ by age of onset or presence of atypical features[7]. This is remarkable, since the atypical subtype of depression has been shown to have the least favourable somatic outcomes[8], and has also been associated with an increased incidence of the metabolic syndrome[9]. However, the latter studies were performed in younger age groups (up to 66 years) only, with low mortality risk. It may, therefore, not be ruled out that atypical depression is related to mortality among depressed older patients, specifically. A similar reasoning holds true for the influence of age of onset of the depressive disorder on mortality risk, as later onset has been found to be associated with a higher family load for vascular disease[10]. Even among middle-aged patients, a later onset of depression is associated with more systemic atherosclerosis[11]. Therefore, in older depressed patients, one may expect the highest mortality risk among patients with a later age of onset.

More in general, depression and somatic disorders have been shown to be closely related. For example, it has been consistently demonstrated that depression is associated with an increased incidence of a multitude of somatic disorders[12], which

all might contribute to a higher mortality risk. In specific groups, such as patients with diabetes mellitus type II[13], stroke [14], and myocardial infarction[15], it has indeed been shown that depression increases mortality risk. On the other hand, somatic disorders have also been found to increase the risk for late-life depression[16, 17]. It may therefore be expected that mortality risk is significantly raised if both a depression and somatic disorder are present. Furthermore, use of antidepressant medication might affect mortality risk in two opposing directions. On the one hand, it might reduce the duration of exposure to the negative lifestyle and somatic consequences of having a depression, and thus decrease mortality. On the other hand, particularly among older persons, antidepressant use might negatively affect survival due to side effects, such as an increased risk of falling[18, 19].

### Aims of the study

The first objective is to examine whether specific subtypes and characteristics of late-life depression predict mortality. We hypothesise atypical depression and late-onset depression to be associated with a higher mortality risk. The second objective is to examine whether the impact of depression (subtypes) on mortality risk is amplified by the presence of somatic comorbidity or antidepressant drug use. We hypothesise that somatic comorbidity is associated with increased mortality rates, and that the joint effect of somatic morbidity and depression on mortality is larger than their individual effects. In addition, we expect that the use of (specific) antidepressants will contribute to the excess mortality risk due to late-life depression.

## MATERIALS AND METHODS

### Sample

The present study was embedded within the Netherlands Study of Depression in Older persons (NESDO)[20, 21, 22]. Briefly, NESDO is a prospective cohort study to examine the determinants, course and consequences of depression in older persons. Between 2007 and 2010, a total of 378 depressed patients were recruited from both mental health institutions and general practices, and 132 non-depressed comparisons were recruited from general practices. Participants were aged 60 to 93. Depressed patients had a diagnosis of major depressive disorder (MDD) (95.0%; n=359) and/or dysthymia (26.5%; n=100) in the previous six months, or minor depression (5.3%; n=20) in the last month, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000). The non-depressed

comparison group had no lifetime diagnosis of depression. Subjects with a (suspected) diagnosis of dementia, a severe primary psychotic or neurodegenerative disorder, a Mini Mental State Examination (MMSE)[23] score <18/30 or insufficient command of the Dutch language were excluded. At baseline, data were gathered about mental health outcomes, demographic characteristics and psychosocial, biological, cognitive and genetic determinants. Follow-up assessments by means of a face-to-face interview were performed two years and six years after baseline using the same measurements as at baseline[21, 22]. Additionally, postal assessments were performed every six months. Interviews were conducted by trained research assistants and audiotaped regularly to control for quality. The ethical review boards of the participating centres approved the study. All participants provided informed consent.



### Mortality

Mortality was recorded at six-month time intervals over the six-years follow-up period. In case the postal questionnaire was not returned, the participant or contact person was contacted, to inquire about reasons for attrition, including death.

### Depression subtypes

Depressive disorders were assessed with the Composite International Diagnostic Interview (CIDI; WHO version 2.1, life time version), and classified as MDD or dysthymia, according to the DSM-IV classification. Additional questions were added to diagnose current minor depression according to the research criteria of the DSM-IV-TR[20]. The 30-item self-report Inventory of Depressive Symptoms (IDS-SR)[24], was used to classify depressive disorders as atypical, melancholic or non-specified depression. In accordance with DSM-IV criteria, and following the algorithm of Novick et al.[25], atypical depression was defined as a positive answer to the IDS-item on mood reactivity, and the presence of two or more positive responses to the IDS-items on hyperphagia, hypersomnia, leaden paralysis and interpersonal rejection sensitivity. Similarly, the algorithm of Khan et al.[26] was used to define melancholic depression as a negative answer to the IDS-SR questions on mood reactivity and loss of pleasure and the presence of three or more positive responses to the IDS-SR items on distinct mood quality, mood worse in the morning, early morning awakening, psychomotor retardation or agitation, anorexia/weight loss, and guilt feelings. This definition is comparable to the DSM-IV criteria for melancholic depression. Patients not classifying for either atypical or melancholic depression were classified as having a non-specified depression.

Finally, depressive disorder was subtyped according to the age of onset. As previously done in other NESDO studies [27, 28], early-onset depression was defined as having had the first depressive episode before the age of 60 years, late-onset depression when at or after the age of 60 years.

### Depression characteristics

Severity of depression was based on the IDS-SR sum score (range 0-84). Higher scores indicate more severe depression. Dimensions of depressive symptoms were measured by the scores on the mood, motivational and somatic subscales of the IDS-SR, as previously defined among older persons[29]. Finally, we studied age of onset as a continuous dimension of the depressive disorder.

### Somatic burden of disease

Participants were asked about current or past cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, COPD, arthritis, cancer, or any other chronic somatic disease, based on previously validated self-report questions and algorithms[30]. The total number of chronic somatic diseases was used as a measure for the somatic disease burden. Somatic diseases were also clustered into cardiovascular diseases (heart diseases and stroke), pulmonary diseases, musculoskeletal diseases (rheumatoid diseases and osteoarthritis), digestive diseases (inflammatory bowel diseases, liver disease, diverticulitis), and cancer. We considered the total number of medications as a proxy measure for the somatic disease burden. At the interviews, names, dosages, and frequencies of use were registered for all drugs participants were using. To calculate the number of medications, all drugs with a unique Anatomical Therapeutical Chemical Classification System (ATC) code at a three-digit level were counted. Dermatological preparations, medications without an ATC code, medications used less than half of the week (except drugs for which non-daily use is common, i.e. bisphosphonates, methotrexate), and for use 'if necessary' were excluded. Antidepressants were clustered into tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) and other antidepressants.

### Covariates

Socio-demographic factors (gender, age, education level) and lifestyle factors were a priori considered as covariates, based on their association with depression and potential effect on mortality. Smoking status (current smoker yes/no) was assessed in the interviews. Units of alcohol use per day were based on the first two questions of the Alcohol Use Disorder Identification Test (AUDIT)[31]. Physical activity was assessed

with the short-form of the International Physical Activity Questionnaire (IPAQ)[32], and classified as low, moderate, or high based on a combination of Metabolic Equivalent of Task (MET)-minutes per week (i.e. ratio of energy expenditure during activity compared to rest multiplied with the number of minutes performing the activity) and type and duration of activities.

**Statistical analysis**

Baseline characteristics of depressed and non-depressed participants were compared using t-tests (or nonparametric Mann-Whitney U tests if clearly non-normally distributed) for continuous variables, and chi-square tests or Fisher's exact tests for categorical variables. Subsequently, Cox proportional-hazard analyses were performed to calculate univariate and multivariate hazard ratios for mortality for each of the depression subtypes (including the different disorders). These analyses were performed in the combined sample of non-depressed participants and those having the specific depression subtype, but excluding the depressed patients not meeting the criteria for the subtype under study. This enabled us to establish the increased mortality risk for that depression subtype compared to the non-depressed controls. In the models examining depression characteristics, we restricted our sample to the depressed participants only, as these characteristics are only relevant in case of the presence of a depression. The observation period for mortality was censored at the end of the six-year follow-up, or earlier in case of study dropout for other reasons than death. The assumption of proportionality of hazard over the follow-up period was checked by visual inspection of the survival curves for participants with or without a depressive disorder. To examine the impact of the different covariates on mortality, we studied the degree to which they confounded the relationship between presence of a depressive disorder (major, minor and dysthymic combined) and mortality. This was done by examining the percentage of change in the regression parameter for depressive disorder from the univariate (unadjusted) model, only including depression status as predictor, to the bivariate (adjusted) model which additionally included the covariate. As a rule of thumb, we will take a change of 10% or more in the regression parameter to indicate substantial confounding. Finally, in a multivariate analysis, all covariates were entered simultaneously. Multicollinearity was checked by a minimum level of tolerance of .20 for all independent variables in the model. To examine modifying effects of somatic disease on the impact of depression on mortality, we tested for interactions of depressive disorder with either somatic disease burden, individual somatic diseases, disease clusters, or number of medications, in the combined sample

of all depressed and non-depressed participants. Whether antidepressant use has a modifying effect on mortality, was subsequently examined by testing for main effects of either antidepressant use as such, or for TCA's, SSRI's or other antidepressants specifically, in the group of depressed participants only. All above tests for modifying effects were performed both with and without control for all covariates, and the tests for antidepressant use were additionally controlled for number of medications other than antidepressants. Analyses were performed using IBM SPSS statistics, version 24.

## RESULTS

### Mortality rate of depressed patients

During the 6-year follow-up, 62 of 378 depressed patients (16.4%) and 8 of 132 comparisons (6.1%) died ($Chi^2$=8.84, df=1, p=.003). There was no drop-out with unknown mortality status. Baseline characteristics of the depressed patients and non-depressed comparisons were presented in table 1. Compared to comparisons, depressed patients on average reported a greater number of chronic somatic diseases and medications, less years of education, lower physical activity, more current smoking, and less alcohol use.

**Table 1.** Baseline characteristics of depressed and non-depressed participants

| | Baseline comparison | | |
|---|---|---|---|
| **Predictors** | **Patients (n=378)** | **Controls (n=132)** | **p-value** |
| · Age at baseline interview, mean (SD) | 70.7 (7.4) | 70.1 (7.2) | .370 |
| · Male sex, n (%) | 128 (33.9) | 51 (38.6) | .322 |
| · Years of education, mean (SD) | 10.4 (3.4) | 12.5 (3.5) | <.001 |
| · Alcohol use (number of drinks a day), median (IQR) | 0.03 (1.18) | 0.53 (1.03) | <.001 |
| · Physical activity | | | .009 |
| o Low physical activity, n (%) | 114 (31.1) | 22 (17.2) | |
| o Moderate physical activity, n (%) | 139 (37.9) | 56 (43.8) | |
| o High physical activity, n (%) | 114 (31.1) | 50 (39.1) | |
| · Currently smoking, n (%) | 100 (26.7) | 11 (8.3) | <.001 |
| · Number of chronic diseases, mean (SD) | 2.1 (1.5) | 1.5 (1.1) | <.001 |
| · Number of medications, mean (SD) | 4.7 (2.9) | 2.6 (2.3) | <.001 |
| · Antidepressant drug use, n (%) | 276 (73.0) | 4 (3.0) | <.001 |
| o Tricyclic antidepressants, n (%) | 82 (21.8) | 2 (1.5) | <.001 |
| o Selective serotonin reuptake inhibitors, n (%) | 105 (27.9) | 1 (0.8) | <.001 |
| o Other antidepressants, n (%) | 106 (28.1) | - | <.001 |

Abbreviations: SD, standard deviation; IQR, Interquartile Range.

Table 2 shows that the hazard ratio (HR) of mortality for depressed patients compared to non-depressed comparisons was 2.95; 95%-confidence interval (CI): 1.41–6.16; p=.004. Nonetheless, the hazard ratio lost statistical significance after adjustment for covariates (HR=1.76 [95%-CI: 0.80–3.86], p=0.162).

**Table 2.** Individual and combined effects of covariates on depression impact on mortality

| | Bivariate models† | | | ΔB‡ for depression | Multivariate model§ | | |
|---|---|---|---|---|---|---|---|
| **Predictors** | **HR** | **[ 95% CI]** | **p** | | **HR** | **[ 95% CI]** | **p** |
| · Depressed patients (versus controls) | 2.95 | [1.41 – 6.16] | .004 | n.a. | 1.76 | [0.80 – 3.86] | .162 |
| *Covariates:* | | | | | | | |
| · Age at baseline interview | 1.07 | [1.04 - 1.11] | <.001 | -7.6% | 1.06 | [1.03 – 1.10] | <.001 |
| · Male sex | 1.81 | [1.13 – 2.89] | .013 | 3.4% | 2.16 | [1.30 – 3.61] | .003 |
| · Years of education | 0.94 | [0.88 - 1.01] | .090 | -6.6% | 1.01 | [0.94 – 1.09] | .809 |
| · Alcohol units per day | 0.61 | [0.34 – 1.09] | .097 | -5.3% | 0.96 | [0.70 – 1.30] | .769 |
| · Physical activity | | | .015 | -7.9% | | | .331 |
| o Low physical activity | 1.00 | Reference | | | 1.00 | Reference | |
| o Moderate physical activity | 0.48 | [0.27 – 0.84] | .011 | | 0.63 | [0.34 – 1.16] | .137 |
| o High physical activity | 0.50 | [0.28 – 0.90] | .020 | | 0.80 | [0.42 – 1.52] | .487 |
| · Currently smoking | 2.00 | [1.21 – 3.29] | .007 | -9.8% | 2.33 | [1.36 – 3.97] | .002 |
| · Number of chronic diseases | 1.17 | [1.00 – 1.35] | .044 | -6.8% | 1.05 | [0.88 – 1.26] | .587 |
| · Number of medications | 1.16 | [1.08 – 1.24] | <.001 | -24.0% | 1.09 | [1.00 – 1.19] | .048 |

† Bivariate model including individual covariate and depression as predictors of mortality, with exception of model for depression, which is univariate model only including depression as predictor.
‡ Change in regression parameter B of impact of depression (versus controls) on mortality when adding the covariate to the univariate model including depression only.
§ Multivariate model including all covariates and depression as predictors of mortality.
Abbreviations: HR, Hazard rate; CI, Confidence Interval; p, p-value.

Table 2 additionally shows the degree of confounding of the relationship between presence of a depressive disorder and mortality by each covariate, i.e. the reduction or increase in the impact of depression status on mortality due to that covariate. The table shows that age, sex, current smoking, and number of medications had a significant effect on the impact of depression, but that only for number of medications (and marginally for smoking) this effect was substantial, causing a drop of 24.0% and 9.8%, respectively, in the depression parameter. For comparison, the drop in the depression parameter for all covariates combined was 42.5% for the multivariate compared to the univariate model.

### Impact of depression subtypes and characteristics on mortality

Table 3 shows unadjusted and fully adjusted (controlled for all covariates) analyses of the impact of depression subtypes and characteristics on mortality. With respect to depression subtypes, the table shows that only for patients with minor depression an increased risk of death was found, compared to non-depressed comparisons. When this result is controlled by adding MDD and dysthymia to the fully adjusted model for minor depression (not shown in table 3; n=510), the impact for minor depression on mortality remains significant (HR= 2.96 [95%-CI: 1.13 – 7.77], p=.028), whereas the impacts of MDD (1.67 [95%-CI: 0.82 – 3.39], p=154) and dysthymia (1.08 [95%-CI: 0.59 – 1.96], p=.811) remain non-significant. The analyses for depression characteristics were done in the group of depressed participants only, since depression characteristics are only relevant in the presence of a depressive disorder. Among depressed persons, none of the depression characteristics were associated with increased mortality.

### Impact of somatic comorbidity on mortality in late-life depression

The presence of a depressive disorder neither interacted with the number of chronic diseases, nor with the number of medications in predicting mortality in both the univariate (p=.208 and p=.861, respectively) and fully adjusted models (p=.261 and p=.602, respectively). Furthermore, we checked whether individual chronic somatic diseases or disease categories interacted with presence of a depressive disorder. No significant interactions were found, either before or after controlling for all covariates (results not shown). Finally, we tested whether individual chronic somatic diseases or disease categories were associated with mortality (results not shown). Only pulmonary diseases predicted mortality (HR=2.13 [95%-CI: 1.6–3.90], p=.014), adjusted for all covariates including depression.

### Impact of antidepressant use on mortality in late-life depression

We also checked whether use of any or specific types of antidepressant drugs were associated with increased mortality rates in the participants with a depressive disorder. We adjusted for the number of medications other than antidepressants. No effects on mortality of antidepressant drug use as such or any specific type of antidepressants were found after adjustment for all covariates and number of medications other than antidepressants (results not shown).

**Table 3.** Associations of depression subtypes and depression characteristics with mortality

| | | Unadjusted | | | Fully adjusted† | | |
|---|---|---|---|---|---|---|---|
| | | HR | [ 95% CI] | p | HR | [ 95% CI] | p |
| **Depression subtypes (versus non-depressed comparisons):** | **Mortality: n/N** | | | | | | |
| *IDS-based subtypes* | | | | | | | |
| · Atypical depression | 4/34 | 2.05 | [0.62 – 6.80] | .243 | 0.84 | [0.14 – 5.06] | .846 |
| · Melancholic depression | 9/51 | 2.23 | [0.78 – 6.46] | .137 | 0.83 | [0.17 – 4.10] | .816 |
| · Depression without specific features | 46/292 | 2.71 | [1.28 – 5.75] | .009 | 1.69 | [0.76 – 3.79] | .200 |
| *DSM-IV-TR based subtypes* | | | | | | | |
| · Major depression, past 6 months | 59/359 | 2.64 | [1.26 – 5.56] | .010 | 1.66 | [0.75 – 3.68] | .211 |
| · Minor depression, past month | 5/20 | 4.83 | [1.58 – 14.8] | .006 | 6.59 | [1.79 – 24.2] | .005 |
| · Dysthymia, past 6 months | 17/100 | 2.82 | [1.21 – 6.59] | .017 | 1.34 | [0.49 – 3.69] | .565 |
| *Age of onset first depressive episode* | | | | | | | |
| · Early onset depression (<60 years) | 38/245 | 2.41 | [1.12 – 5.21] | .025 | 1.88 | [0.81 – 4.33] | .141 |
| · Late-onset depression (≥60 years) | 23/125 | 3.19 | [1.41 – 7.19] | .005 | 1.42 | [0.53 – 3.80] | .488 |
| **Depression characteristics (within depressed patients only):** | **mean (SD)** | | | | | | |
| *Severity of depressive symptoms* | | | | | | | |
| · IDS sum score (range 0 – 84) | 30.1 (5.0) | 0.99 | [0.97 – 1.01] | .277 | 0.99 | [0.96 – 1.01] | .320 |
| *Dimensions of depressive symptoms* | | | | | | | |
| · IDS Mood subscale (range 0-27) | 9.0 (5.2) | 0.97 | [0.92 – 1.02] | .224 | 0.96 | [0.91 – 1.02] | .225 |
| · IDS Motivation subscale (range 0-15) | 5.0 (3.1) | 0.99 | [0.91 – 1.08] | .804 | 0.97 | [0.88 – 1.07] | .539 |
| · IDS Somatic subscale (range 0-24) | 9.8 (4.2) | 0.96 | [0.91 – 1.03] | .266 | 0.99 | [0.92 – 1.05] | .985 |
| *Age of onset (MDD and dysthymia)* | | | | | | | |
| · Age of onset (continuous), years | 48.4 (20.6) | 1.00 | [0.99 – 1.02] | .525 | 1.00 | [0.99 – 1.02] | .815 |

† Adjusted for age, sex, years of education, alcohol use, smoking, physical activity, number of chronic somatic diseases, and number of medications.

# DISCUSSION

## Main findings

Over six years of follow-up, depressed older persons had a higher risk of dying compared to non-depressed older persons. In contrast to our hypotheses, late-onset depression and atypical depression were not specifically associated with increased mortality. After full adjustment, only the presence of minor depression remained

associated with an increased mortality rate. Unlike our hypotheses, neither the number of chronic somatic diseases nor antidepressant drug use were associated with a higher mortality rate, nor exaggerated the effect of depression on mortality. The number of medications, however, explained a substantial portion of the observed relationship between depressive disorder and mortality rate, independent of the presence of chronic diseases.

## Relationship to existing research

*Increased mortality in depressed persons*

Similar to previous meta-analyses[1, 4, 6], we found an increased mortality risk for depressed persons. In line with previous results[4, 33], this association lost significance after adjustment for covariates like lifestyle factors, demographic and illness related variables, implying that other factors than the depression itself play an important role in increased mortality in depression. Our study showed number of medications used to be the main confounder in an older sample, in this respect.

*The role of lifestyle characteristics in depression mortality*

The higher mortality rate among depressed patients can be partially explained by the higher percentage of smokers, in line with well-established associations between smoking and depression[34], and smoking and mortality[35]. However, a more important explanation for the excess mortality in our depressed sample is the number of medications used, independent of the higher number of chronic diseases in the depressed group. A previous study suggests that polypharmacy is associated with increased non-cancer mortality, but only in subjects *without* multimorbidity[36, 37]. In case of multimorbidity, subjects did seem to benefit from a larger number of medications. In our sample, the use of some medications might have been inappropriate for the following reasons. Firstly, a higher prescription rate might be related to a somatic presentation of depression in later life[38]. Secondly, depression itself is associated with increased medical consumption, placing patients at risk of receiving extra prescriptions. Collectively, somatic complaints may lead to more doctor visits and 'force' the doctor into the prescription of drugs, while an underlying somatic substrate might be absent, and the prescribed drugs might do more harm than good. Even 'appropriate' polypharmacy has consistently been associated with falls, fall-related injuries, adverse drug events, hospitalization, and mortality[39].

*Mortality in depression subtypes*

Previously, in a younger population[7], no evidence was found for an association of mortality with atypicality of late onset of the depression, similar to our results. Although we a priori expected these subtypes to be associated with mortality due to their link with metabolic syndrome and vascular disease[8, 9], our negative finding might be explained by the bidirectional association between physical health and depression. Whereas late-onset depression might be partly caused by vascular aging (which we initially hypothesised to also cause a higher mortality risk), patients with early-onset depression might have a higher mortality risk due to a longer duration of exposure to unhealthy lifestyle characteristics associated with having a depression. Our finding of an increased mortality rate for minor depression after adjustment for lifestyle factors and medication use, might point to another, unknown pathway leading to mortality in case of minor depression. This pathway might be age-specific. First, no differential mortality rates were found for depressive symptoms above and below the diagnostic threshold for MDD in a population aged 35-66 years[7]. Second, a meta-analysis, where age was not considered, demonstrated a non-significant, but opposite trend towards an increased mortality rate for MDD compared to minor depression (RR=1.07 [95%-CI: 0.78-1.45][6]. This raises the question whether, in later life, minor depression indeed is a depression subtype or rather a reflection of processes associated with higher biological age, that might be related to depressive symptoms. First, with age, inflammation within the central nervous system increases, sometimes called 'inflamm-ageing', and exposure to cytokines may lead to exaggerated sickness behaviour and 'depression-like behaviour' in older persons[40]. Second, among older persons, frailty is more common. This syndrome is characterised by diminished strength, endurance and reduced physiologic function that increases an individual's vulnerability for developing increased dependency or death[41]. Since criteria for depression and frailty overlap, confounding is inevitable[42]. A third example of a process associated with higher age, is cognitive impairment. Mild cognitive impairment (MCI) has been associated with minor depression[43], and depressive symptoms might be prodromal for a neurodegenerative disorder[44]. Although persons with low scores (<18/30) on the MMSE or with a dementia diagnosis were excluded from our sample, the six years of follow-up might allow mild cognitive impairment to develop.

## Methodological considerations

Important strengths of the present study are the extensive phenotyping of depression in a relatively large sample of depressed older persons, with a high mortality risk.

Nonetheless, the statistical power might still be limited to draw definitive conclusions about smaller subgroups, e.g. specific depression subtypes or antidepressant users, therefore caution is necessary. Furthermore, causes of death were not registered. Their availability could have helped us to further clarify the relationship between depression and mortality. Finally, residual confounding by somatic burden of disease cannot be completely ruled out. The number of chronic diseases does not always reflect the severity and actual relevance of somatic comorbidity. It might be that the number of medications is a better reflection of the actual burden of somatic disease.

**Final conclusions**

Our findings offer opportunities for prevention in clinical practice by targeting smoking and polypharmacy. Since mortality in minor depression seems independent of these factors, another pathway may lead to mortality for this depression subtype. Therefore, minor depression in later life might reflect depressive symptoms due to underlying ageing-related processes, such as inflammation-based sickness behaviour, frailty or mild cognitive impairment that might be associated with increased mortality. The impact of polypharmacy as well as the impact of minor depression on mortality, argues for integration of somatic and mental health care for depressed older persons.

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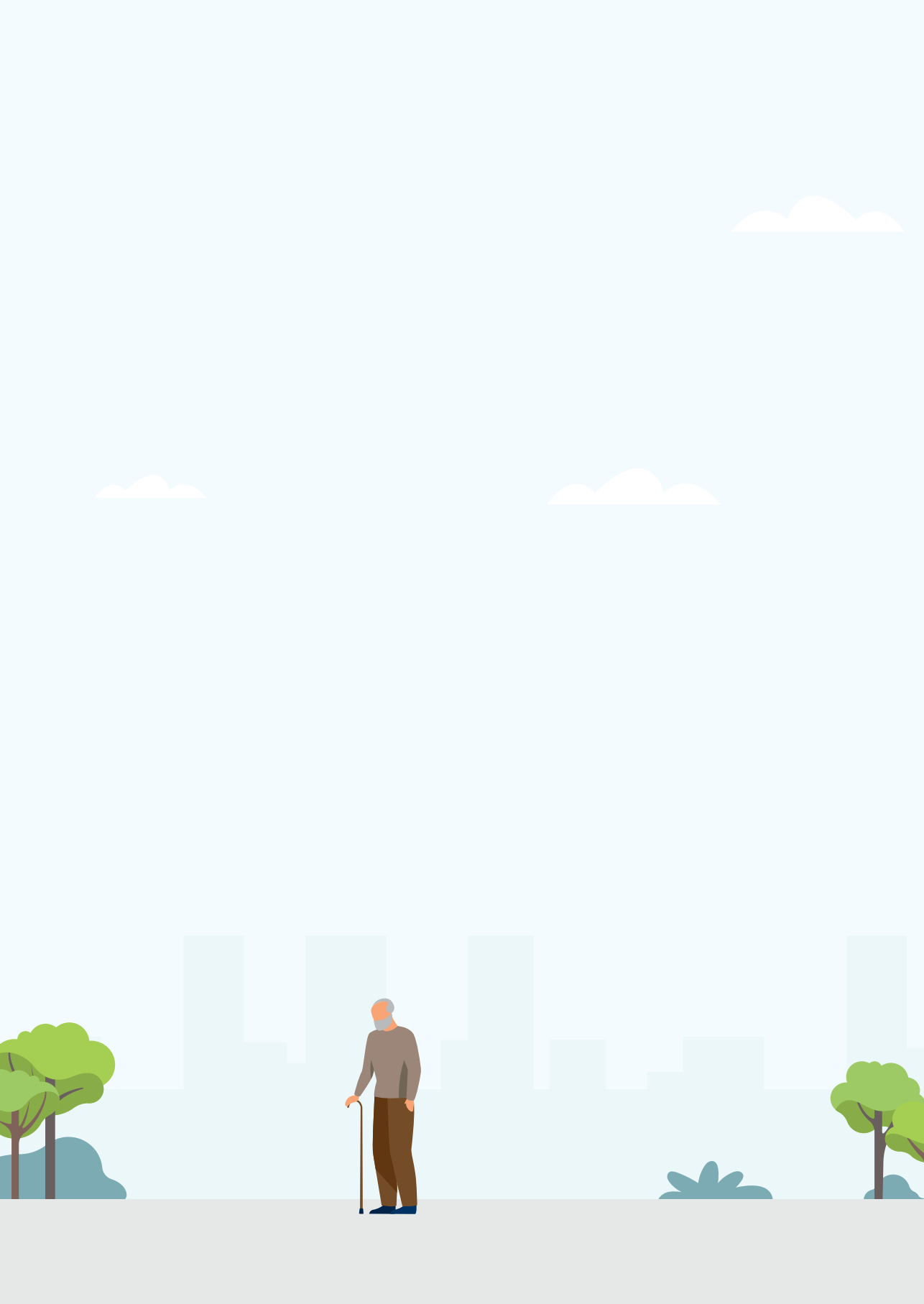

# CHAPTER 3

## VITAMIN D DEFICIENCY, DEPRESSION COURSE AND MORTALITY: LONGITUDINAL RESULTS FROM THE NETHERLANDS STUDY ON DEPRESSION IN OLDER PERSONS (NESDO)

Karen S. van den Berg, Radboud M. Marijnissen, Rob H.S. van den Brink, Paul Naarding, Hannie C. Comijs, Richard C. Oude Voshaar.

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## ABSTRACT

***Objective:*** To study the effect of vitamin D levels on depression course and remission status after two years, as well as attrition and mortality, in an older cohort.

***Methods:*** This study was part of the Netherlands Study on Depression in Older persons (NESDO), a prospective cohort study. 367 depressed older persons (≥60 years) were included. Baseline vitamin D status, reasons for loss to follow up, clinical depression diagnosis at two-year follow up, and six-monthly symptom scores were obtained. Data were analysed by logistic regression and random coefficient models and adjusted for confounders of vitamin D status.

***Results:*** Vitamin D status had no effect on the course of depression or remission, except for a trend towards lower remission rates in the severely deficient subgroup (25-(OH) vitamin D < 25 nmol/l). Patients who died during follow up had significantly lower 25-(OH) vitamin D and 1,25-$(OH)_2$ vitamin D levels than patients with continued participation.

***Conclusions:*** For the total sample we found no effect of vitamin D levels on the course of depression or remission rates. However, we did find an effect of lower vitamin D levels on mortality. This strengthens the interpretation of vitamin D deficiency being a marker for poor somatic health status. The trend towards lower remission rates in the severely deficient subgroup raises the question whether this group could benefit from supplementation. Randomised controlled trials are necessary to study this.

## INTRODUCTION

Vitamin D deficiency is a major public health problem worldwide[1], particularly in older people[2]. Increased prevalence of vitamin D deficiency with age is explained by dietary deficiencies, decreased production of vitamin D in the skin, decreased conversion of calcidiol (25-(OH) vitamin D) to calcitriol (1,25-$(OH)_2$ vitamin D) in the kidney and lack of sunlight exposure in older people[3]. Besides its effect on calcium metabolism and bone health, vitamin D deficiency has been linked to various diseases[4, 5] and proposed to be a universal risk factor for multiple multifactorial diseases[6]. Vitamin D directly affects gene regulation, thereby influencing cell proliferation, vascular calcifications and inflammatory responses, as well as indirectly affects the renin-angiotensin-aldosteron system[6]. In older populations vitamin D deficiency has also been associated with frailty and mortality[7-9]. Increased mortality rates may be explained by the association of vitamin D deficiency with several somatic diseases, particularly cardiovascular disease[10]. A meta-analysis of cross-sectional, population-based studies yielded a pooled odds ratio of 1.31 (95%-confidence interval (95%-CI) 1.00–1.71; p=.05) for association between low vitamin D levels and depression[11]. Furthermore, both younger and older patients suffering from depressive disorder had lower vitamin D levels compared to controls[12, 13]. Current hypotheses about the pathophysiological mechanisms in the association between vitamin D and depression include a role for vitamin D in the regulation of neurotransmitters dopamine, noradrenaline and acetylcholine, as well as an effect on neurotrophic factors[14]. Moreover, vitamin D receptors are found in the prefrontal cortex and parts of the limbic system[15]. These brain areas have been implicated in the pathophysiology of depression[16]. Vitamin D might also reduce concentrations of inflammatory markers associated with depression[17]. A reverse causative mechanism might be that depression leads to decreased sun exposure, poorer dietary intake and more smoking, thereby causing vitamin D deficiency[18].

Longitudinal studies, however, are less consistent and mainly focused on vitamin D as a risk factor for the incidence of depression. Meta-analysis of three cohort studies in middle-aged to older populations[19-21] yielded a significant hazard ratio of depressive symptoms for the lowest vs. the highest vitamin D levels (2.21 (95%-CI 1.40–3.49; p<.001)[11]. Thereafter, in an older cohort no effect of vitamin D levels on the incidence of depressive symptoms was found[22]. To our knowledge, only one study has examined the effect of vitamin D status on course of depression[12]. In this sample of depressed younger adults higher vitamin D levels were associated with better depression outcomes[12]. In

a meta-analysis of randomised controlled trials, vitamin D supplementation did not lead to a reduction of depressive symptoms. However, few participants were (clinically) depressed or vitamin D deficient[23].

Furthermore, nearly all studies have measured 25-(OH) vitamin D levels, while 25-(OH) vitamin D has to be converted in the kidney to the biologically active form, 1,25-$(OH)_2$ vitamin D. In previous cross-sectional analyses, our group found that 1,25-$(OH)_2$ vitamin D was lowered in depression as well[13].

The primary objective of the present study is to examine whether 25-(OH) vitamin D and 1,25-$(OH)_2$ vitamin D levels also predict remission of late-life depression at two-year follow-up, as well as its course. The second objective, essential in an older age sample, is to study the effect of vitamin D on attrition and mortality.

## METHODS

### Sample

The present study was part of the Netherlands Study of Depression in Older persons (NESDO), an on-going cohort study designed to examine the determinants, course and consequences of late-life depression (for details, see[24]). The cohort consisted of 378 depressed patients and 132 non-depressed comparison subjects aged 60 to 93, recruited between 2007 and 2010 from mental health institutions and general practitioners. Data was gathered about mental health outcomes, demographic characteristics and psychosocial, biological, cognitive and genetic determinants. At two-year follow up all measures open to change were evaluated again. Attrition and its reasons were recorded[25]. Interviews were performed by trained research assistants and were audio taped regularly to control for quality. Exclusion criteria were a (suspected) diagnosis of dementia, a Mini Mental State Examination (MMSE)[26] score <18/30 and insufficient command of the Dutch language. The ethical review boards of the five participating centres approved the study. All participants received oral and written information and provided their informed consent. For the present study, we selected the patient group. Eleven patients were excluded due to missing vitamin D levels, leaving a study sample of 367 depressed persons at baseline.

### Depression

At baseline and two-year follow-up, past-six months diagnoses of depression and dysthymia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)-criteria[27] were assessed with the Composite International Diagnostic Interview (CIDI; WHO version 2.1; life-time version), a structured clinical interview[28, 29]. Additional questions were added to diagnose current minor depression according to the research criteria of the DSM-IV-TR[24]. The severity of depressive symptoms was assessed every six months with the Inventory of Depressive Symptoms – Self Report (IDS-SR)[30]. For 28 symptoms, severity and frequency were rated on a scale from 0-3, adding up to total scores ranging from 0-84, higher scores indicating more severe depression. Three subscale scores were derived, reflecting a mood (9 items), motivational (5 items) and somatic (8 items) dimension[31].



### Laboratory testing

Vitamin D levels were assessed at baseline. Serum 25-(OH) vitamin D levels were measured using isotope dilution-online solid-phase extraction liquid chromatography–tandem mass spectrometry, as described previously[32]. Serum 1,25-$(OH)_2$ vitamin D levels were determined by radioimmunoassay. The optimal 25-(OH) vitamin D level has been estimated to be between 50 and 100 nmol/l, since serum levels below 75 nmol/l induce parathyroid hormone (PTH) secretion[33]. Serum 25-(OH) vitamin D levels are often categorised as severely deficient (<10 nmol/l), deficient (10–25 nmol/l), insufficient (25–50 nmol/l), hypovitaminosis D (50–75 nmol/l), and sufficient (≥75 nmol/l)[34, 35]. A recent study reported a reference interval for 1,25-$(OH)_2$ vitamin D between 59 and 159 pmol/l[36].

### Covariates

Based on the literature[37, 38], we a priori selected three sets of covariates. The first set consisted of demographic characteristics (age, gender and years of education) and astronomical season of blood withdrawal (winter: 21 November – 20 February; spring: 21 February – 20 May; summer: 21 May – 20 August; autumn: 21 August – 20 November). The second set included the lifestyle factors smoking (yes/no), use of alcohol and physical activity. We included the Alcohol Use Disorders Identification Test (AUDIT)[39] sum score as a proxy for (subclinical) alcohol dependence severity. To measure physical activity, the number of Metabolic Equivalent of Task (MET)-minutes per week was obtained using the eight-item International Physical Activities Questionnaire (IPAQ)[40]. Parameters of somatic functioning formed the third set of confounders: waist

circumference (centimeters), serum levels of PTH (obtained as described earlier[13]) and glomerular filtration rates (GFR), estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[41]. The number of chronic diseases was assessed by means of self-report questions. This has been proven to be an accurate method when compared to data from general practitioners[42]. The MMSE was used to assess global cognitive functioning (range 0–30), higher scores indicating better cognitive functioning[26]. All covariates were assessed at baseline. Vitamin D supplementation, assessed at baseline and two-year follow-up, was not taken into account, as dosages were low and we were interested in the actual vitamin D levels. Nonetheless, a sensitivity analysis, excluding all patients with vitamin D supplementation will be performed.

**Statistical analysis**

All analyses were performed separately for 25-(OH) and 1,25-$(OH)_2$ vitamin D. Vitamin D levels were standardised using Z-scores. All statistical tests were two-sided, p-values below .05 were considered significant. To meet the test assumptions, 5 positive outliers for 1,25-$(OH)_2$ vitamin D levels, 6 positive outliers for PTH levels and 5 positive outliers for MET-minutes/week were trimmed at the level of the mean plus 3 standard deviations. AUDIT sum scores were log transformed. Vitamin D levels and covariates at baseline were compared by participation status at two-year follow-up, i.e. 'participation', 'death' or 'attrition', using $X^2$ tests for categorical variables and one-way analysis of variance for continuous variables. Odds ratios for the prediction of two years participation status by 25-(OH) vitamin D and 1,25-$(OH)_2$ vitamin D levels were calculated by means of multinomial logistic regression. Because of limited numbers in the 'death' and 'attrition' outcome categories, controlling for covariates was first restricted to season of blood withdrawal in block 1. Then, in block 2, all other covariates were evaluated for inclusion in the analysis using backward elimination. Finally, vitamin D was added in block 3. Effect sizes of 25-(OH) and 1,25-$(OH)_2$ vitamin D were estimated with pseudo $R^2$ according to Nagelkerke. Subsequently, the association between vitamin D levels and depression diagnosis at two-year follow up was analysed using binary logistic regression, adjusted for all covariates. Since in our baseline paper only tricyclic antidepressant (TCA) usage (among all depression characteristics tested) was related to 1,25-$(OH)_2$ vitamin D levels[13], interaction terms for vitamin D and use of a TCA were tested.

Lastly, random coefficient models, a specific type of linear mixed models, were fitted to analyse the effect of 25-(OH) and 1,25-$(OH)_2$ vitamin D levels on the repeated measurements of IDS-SR (sub)scale scores. To correct for the correlation in data caused

by the repeated measurement design, 'patient ID' was added as a random factor and random intercept and random slope were tested for improvement of the model fit. 'Vitamin D' and 'time' were added as fixed factors. The 'vitamin D' x 'time' interaction was added to the model to test the effect of vitamin D levels on the course of IDS-SR scores over time. Subsequently, all covariates were added to the model as fixed factors. In order to preclude contamination of results by vitamin D supplementation, sensitivity analyses were conducted excluding all patients using vitamin D supplementation (n= 30/367; 8,2%). All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 22.0.0.1 (IBM Corp., NY, USA).

## RESULTS



### Study sample and attrition

At baseline (n=367) diagnoses were major depressive disorder (94.8%), dysthymia (25.9%) and minor depression (5.4%). Percentages do not add up to 100% due to double diagnoses. Mean serum levels were 52.66 nmol/l (s.d. 23.25) for 25-(OH) and 138.20 nmol/l (s.d. 49.27) for 1,25-$(OH)_2$ vitamin D. Pearson's rho for the correlation between 25-(OH) and 1,25-$(OH)_2$ vitamin D was 0.56 ($p<.001$). At two-year follow up, 280 patients (76.3%) were still participating: 24 persons had died and 63 were lost to follow up (due to physical illness, n=11; mental illness, n=33; loss of contact/lack of interest, n=19). In table 1 the characteristics of the study population categorised by two-year participation status are presented. Deceased patients had decreased renal function, were more often smokers, and less physically active compared to patients still participating after two years.

**Table 1.** Baseline characteristics of depressed patients stratified by two-year participation status

| | Two-year participation status | | | | | |
|---|---|---|---|---|---|---|
| | Participation | Attrition | Death | | | |
| **Characteristic** | **(n=280)** | **(n=63)** | **(n=24)** | **Statistic** | | |
| Demographic features | | | | | | |
| **Male sex, *n (%)*** | 96 (34.3) | 16 (25.4) | 12 (50.0) | $\chi^2$= 4.83 | df 2 | p= .089 |
| **Age, *mean (SD)*** | 70.6 (7.5) | 70.2 (6.9) | 72.5 (7.3) | F= 0.89 | df 2 | p= .410 |
| **Educational level (years), *mean (SD)*** | 10.6 (3.4) | 10.1 (3.4) | 10.1 (3.6) | F= 0.69 | df 2 | p= .502 |
| Season of blood withdrawal | | | | | | |
| **Winter, *n (%)*** | 51 (18.2) | 11 (17.5) | 10 (41.7) | $\chi^2$=10.26 | df 6 | p= .114 |
| **Spring, *n (%)*** | 84 (30.0) | 18 (28.6) | 4 (16.7) | , | | |
| **Summer, *n (%)*** | 87 (31.1) | 16 (25.4) | 6 (25.0) | | | |
| **Autumn, *n (%)*** | 58 (20.7) | 18 (28.6) | 4 (16.7) | | | |
| Lifestyle factors | | | | | | |
| **Smoking status** | | | | | | |
| **Smoker, *n (%)*** | 67 (23.9) | 18 (28.6) | 11 (45.8) | $\chi^2$=6.35 | df 2 | **p= .042** |
| **Alcohol use** | | | | | | |
| **AUDIT score (0-40), *mean (SD)**** | 2.7 (3.5) | 2.2 (3.1) | 2,5 (4.4) | F= 1.34 | df 2 | p= .262 |
| **Physical activity** | | | | | | |
| **MET-minutes/week, *mean (SD)*[a]** | 2570.6 (2375.5) | 2025.6 (2309.8) | 969,5 (1423.7) | F= 5.91 | df 2 | **p= .003** |
| **Waist circumference (cm), *mean (SD)*** | 92.7 (12.6) | 95.5 (13.0) | 97,7 (13.9) | F= 2.67 | df 2 | p= .071 |
| Physical health | | | | | | |
| **Number of chronic diseases, *mean (SD)*** | 2.5 (1.6) | 2.6 (1.7) | 2.9 (1.8) | F= 1.07 | df 2 | p= .346 |
| **Cognitive functioning** | | | | | | |
| **MMSE score (0-30), *mean (SD)*** | 27.9 (1.8) | 27.3 (2.7) | 27.3 (1.9) | F= 3.16 | df 2 | **p= .044** |
| **Renal function** | | | | | | |
| **eGFR, ml/min/1.73m², *mean (SD)*** | 72.6 (15.6) | 71.2 (14.8) | 65.2 (17.7) | F= 2.61 | df 2 | p= .075 |
| **Serum parathormone (nmol/l), *mean (SD)*[a]** | 7.3 (3.3) | 6.5 (2.6) | 8.7 (4.2) | F= 3.83 | df 2 | **p= .023** |
| **Serum 25-hydroxy vitamin D (nmol/l), *mean (SD)*** | 54.4 (23.6) | 51.0 (21.8) | 36.2 (16.1) | F= 7.27 | df 2 | **p= .001** |
| **Serum 1,25-dihydroxy vitamin D (pmol/l), *mean (SD)*[a]** | 142.9 (46.8) | 127.0 (42.3) | 102.9 (37.7) | F= 10.57 | df 2 | **p< .001** |

*Abbreviations: AUDIT, alcohol use disorders identification test; MET, metabolic equivalent of task, MMSE, mini mental state examination; eGFR, estimated glomerular filtration rate. [a] positive outliers trimmed to mean + 3 SD, * as covariate log-transformation performed, AUDIT sum score of 24 out of the 367 participants (6.5%) was >= 8, indicating harmful alcohol use or alcohol dependence.*

Compared to patients still participating at two-year follow up, deceased patients had significantly lower levels of 25-(OH) vitamin D (F=13.88, df=1, p<.001) as well as 1,25-$(OH)_2$ vitamin D (F=16.57, df=1, p=.001), whereas those lost to follow-up only had lower 1,25-$(OH)_2$ vitamin D (F=6.16, df=1, p=.014).

**Table 2.** Prediction of death and attrition at two-year follow up by standardised vitamin D levels

| | | OR | (95%-confidence interval) | p-value |
|---|---|---|---|---|
| **25-(OH) vitamin D** | | | | |
| Unadjusted | | | | |
| | Participation | 1.00 | | |
| | Attrition | 0.86 | (0.64 – 1.14) | .287 |
| | Death | 0.32 | (0.17 – 0.60) | **<.001** |
| Adjusted for season | | | | |
| | Participation | 1.00 | | |
| | Attrition | 0.84 | (0.62 – 1.14) | .264 |
| | Death | 0.33 | (0.17 – 0.64) | **.001** |
| Adjusted for season + other covariates[a] | | | | |
| | Participation | 1.00 | | |
| | Attrition | 0.83 | (0.60 – 1.14) | .244 |
| | Death | 0.41 | (0.20 – 0.84) | **.014** |
| 1,25-$(OH)_2$ vitamin D | | | | |
| *Unadjusted* | | | | |
| | Participation | 1.00 | | |
| | Attrition | 0.67 | (0.48 – 0.92) | **.015** |
| | Death | 0.29 | (0.16 – 0.54) | **<.001** |
| *Adjusted for season* | | | | |
| | Participation | 1.00 | | |
| | Attrition | 0.67 | (0.48 – 0.93) | **.018** |
| | Death | 0.31 | (0.17 – 0.58) | **<.001** |
| *Adjusted for season + other covariates[b]* | | | | |
| | Participation | 1.00 | | |
| | Attrition | 0.69 | (0.49 – 0.97) | **.031** |
| | Death | 0.31 | (0.15 – 0.61) | **.001** |
| *Participation = reference category* | | | | |

*[a] Gender, parathyroid hormone level, physical activity and smoking status*
*[b] Gender, parathyroid hormone level and smoking status*

Table 2 shows the results of multinomial logistic regression of two-year participation status by vitamin D level. In the fully adjusted models, patients with higher 25-(OH) and 1,25-$(OH)_2$ vitamin D had a significantly lower probability of being in the deceased group than in the group still participating (Nagelkerke's $R^2$: 0.198 for 1,25-$(OH)_2$; 0.179 for 25-(OH) vitamin D).

**Two-year outcome of depression**

At two-year follow up (n=280) diagnoses were major depression (40%), dysthymia (25.4%) and minor depression (3.9%). Using binary logistic regression, we found no effect of 25-(OH) vitamin D (OR 0.87; 95%-CI: 0.69–1.10; p=.256) or 1,25-$(OH)_2$ vitamin D (OR 0.82; 95%-CI: 0.64–1.04; p=.095) on depression status at two-year follow up. After adjustment for all covariates, odds ratios were 0.92 (95%-CI: 0.69–1.22; p=.553) for 25-(OH) vitamin D and 0.90 (95%-CI: 0.66–1.21; p=.471) for 1,25-$(OH)_2$ vitamin D. No interactions between both forms of vitamin D and use of a TCA on depression outcome were found (p=.998 and p=.996, respectively).

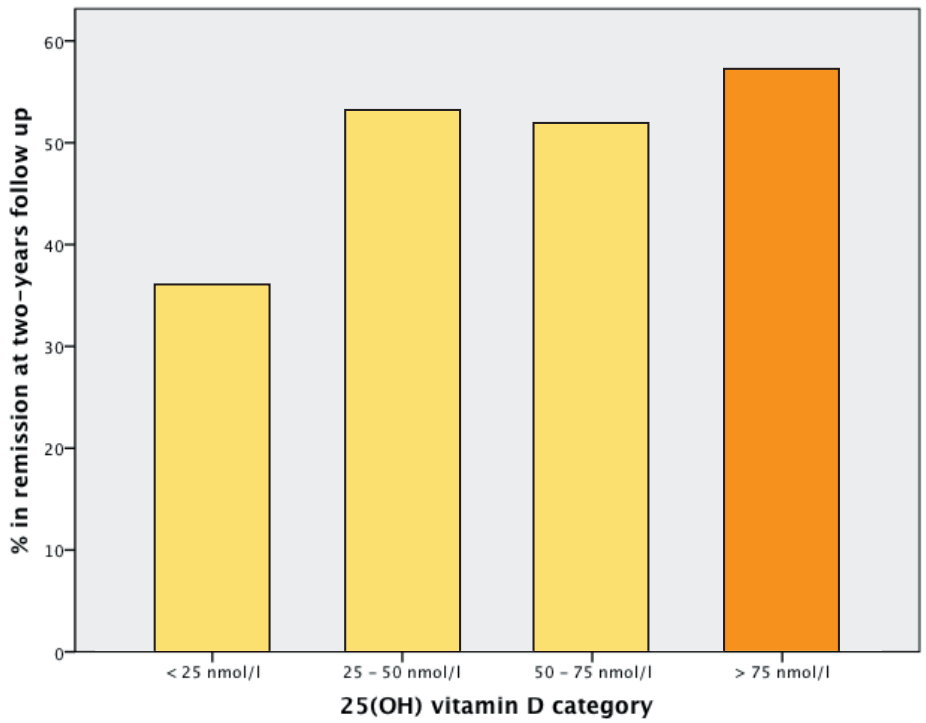

Figure 1 presents the remission rates (i.e. not having a depression diagnosis at two-year follow-up) for the different categories of 25-(OH) vitamin D. Since figure 1 suggests that only vitamin D deficiency (serum levels <25 nmol/l; n=36) might be relevant, we conducted post-hoc logistic regression analyses. Vitamin D deficiency (yes/no) had an odds ratio of 2.03 (unadjusted analysis; 95%-CI 0.87–4.77, p=.103) and 2.19 (after adjustment for all covariates; 95%-CI 0.82–5.89, p=.115) for the prediction of non-remission.

**Two-year course of depressive symptoms**

In all random coefficient models (table 3), models with random slope and random intercept provided the best fit. For both variants of vitamin D and all IDS-SR (sub)scale scores, the interaction of vitamin D with time did not add significantly to the models, hence there is no effect of vitamin D on the course of IDS-SR scores over time.



If added as fixed factor in unadjusted analyses, higher 25-(OH) vitamin D levels yielded significantly lower total IDS-SR scores and somatic subscale scores. These effects disappeared after adjustment for covariates. Post-hoc analyses (not presented) showed that confounding was explained by lifestyle factors (smoking status, waist circumference, physical activity, and alcohol use). What remained after adjustment for all covariates are significant reductions on all IDS-SR (sub)scale scores with subsequent 6-month assessments. Post-hoc tests of vitamin D deficiency (25-(OH) vitamin D <25 nmol/l; yes/no) as determinant of depression course yielded significantly higher total and somatic IDS-SR scores in case of vitamin D deficiency and diminishing scores on all IDS-SR (sub)scales over time, also after adjustment for all covariates. The effects of vitamin D deficiency on the course of the IDS scores remained non-significant.

**Sensitivity analyses**

None of the results changed after excluding the patients using vitamin D supplementation (data not shown).

**Table 3.** Effects of vitamin D, time and interaction of vitamin D with time on repeated inventory of depressive symptomatology (IDS) scores[$]

| | Vitamin D | | Time | | Interaction vitamin D - time | |
|---|---|---|---|---|---|---|
| | **B (s.e.)** | **p-value** | **B (s.e.)** | **p-value** | **B (s.e.)** | **p-value** |
| **25(OH) vitamin D[#]** | | | | | | |
| *Unadjusted* | | | | | | |
| Total IDS score | -1.17 (0.59) | **.048** | -1.27 (0.17) | **<.001** | 0.17 (0.17) | .311 |
| Mood subscale | -0.30 (0.23) | .204 | -0.46 (0.07) | **<.001** | 0.05 (0.07) | .417 |
| Motivational subscale | -0.12 (0.13) | .359 | -0.24 (0.04) | **<.001** | 0.02 (0.04) | .560 |
| Somatic subscale | -0.47 (0.19) | **.013** | -0.30 (0.05) | **<.001** | 0.04 (0.05) | .486 |
| *Adjusted** | | | | | | |
| Total IDS score | -0.32 (0.64) | .624 | -1.19 (0.17) | **<.001** | 0.11 (0.17) | .503 |
| Mood subscale | -0.03 (0.26) | .909 | -0.43 (0.07) | **<.001** | 0.04 (0.07) | .602 |
| Motivational subscale | 0.08 (0.15) | .602 | -0.22 (0.04) | **<.001** | 0.02 (0.04) | .632 |
| Somatic subscale | -0.18 (0.20) | .383 | -0.26 (0.05) | **<.001** | 0.01 (0.05) | .792 |
| **1,25(OH)$_2$ vitamin D[#]** | | | | | | |
| *Unadjusted* | | | | | | |
| Total IDS score | -1.02 (0.59) | .086 | -1.28 (0.17) | **<.001** | 0.06 (0.17) | .705 |
| Mood subscale | -0.33 (0.23) | .157 | -0.46 (0.07) | **<.001** | 0.02 (0.07) | .722 |
| Motivational subscale | -0.19 (0.13) | .148 | -0.24 (0.04) | **<.001** | 0.01 (0.04) | .801 |
| Somatic subscale | -0.20 (0.19) | .285 | -0.30 (0.05) | **<.001** | -0.01 (0.05) | .807 |
| *Adjusted** | | | | | | |
| Total IDS score | -0.31 (0.67) | .640 | -1.19 (0.17) | **<.001** | -0.02 (0.17) | .920 |
| Mood subscale | -0.09 (0.27) | .724 | -0.43 (0.07) | **<.001** | -0.01 (0.07) | .880 |
| Motivational subscale | -0.00 (0.15) | .981 | -0.22 (0.04) | **<.001** | 0.00 (0.04) | .911 |
| Somatic subscale | -0.01 (0.21) | .944 | -0.26 (0.05) | **<.001** | -0.04 (0.05) | .450 |
| **25-(OH) vitamin D deficiency (< 25 nmol/l)** | | | | | | |
| *Unadjusted* | | | | | | |
| Total IDS score | 4.13 (1.98) | **.037** | -1.28 (0.17) | **<.001** | -0.91 (0.57) | .112 |
| Mood subscale | 1.24 (0.77) | .108 | -0.46 (0.07) | **<.001** | -0.20 (0.23) | .376 |
| Motivational subscale | 0.11 (0.45) | .809 | -0.24 (0.04) | **<.001** | -0.17 (0.15) | .238 |
| Somatic subscale | 1.91 (0.63) | **.003** | -0.30 (0.05) | **<.001** | -0.29 (0.18) | .116 |
| *Adjusted** | | | | | | |
| Total IDS score | 4.15 (2.02) | **.041** | -1.21 (0.17) | **<.001** | -0.64 (0.58) | .265 |
| Mood subscale | 1.29 (0.79) | .103 | -0.44 (0.07) | **<.001** | -0.09 (0.23) | .686 |
| Motivational subscale | 0.06 (0.46) | .903 | -0.23 (0.04) | **<.001** | -0.12 (0.15) | .424 |
| Somatic subscale | 2.01 (0.65) | **.002** | -0.27 (0.05) | **<.001** | -0.24 (0.19) | .192 |

** Adjusted for age, gender, educational level, season of blood withdrawal, smoking, use of alcohol, waist circumference, physical activity, cognitive functioning, serum parathyroid hormone level, renal function and number of chronic diseases.*

*$ For all analyses, random intercept plus random slope was best fitting model*

*# Standardised vitamin D scores were used in the analyses*

# DISCUSSION

## Main findings

In a large sample of clinically depressed older people, we neither found an effect of serum 25-(OH) vitamin D or 1,25-$(OH)_2$ vitamin D levels on two-year depression status, nor on the course of depressive symptoms over time. In the subgroup with serious vitamin D deficiency (25-(OH) vitamin D <25 nmol/l, n=36) a trend towards lower remission rates was seen. Interestingly, patients who died during follow up had significantly lower baseline levels of 25-(OH) and 1,25-$(OH)_2$ vitamin D than patients still participating, and significantly lower 1,25-$(OH)_2$ vitamin D levels than those lost to follow up. Since 1,25-$(OH)_2$ vitamin D levels might be normal or raised due to secondary hyperparathyroidism in 25-(OH) vitamin D deficiency, low 1,25-$(OH)_2$ levels probably reflect a more severe deficiency state.



## Vitamin D and depression

As far as we know, this is the first prospective study investigating the effect of vitamin D levels on the course of depression in a clinically depressed, older population. Previous longitudinal research in older populations focused on the incidence of depressive symptoms with respect to vitamin D status and yielded inconsistent results[19-22].On the one hand, the absence of an association might be explained by low incidences of depression and vitamin D deficiency in two population-based cohorts[21, 22]. On the other hand, the positive finding of low vitamin D predicting the onset of depression in the population-based sample of the InChianti study[19] might have been confounded by the chosen cut-off score, as depression was defined as a Centre for Epidemiologic Studies Depression scale (CES-D) score >=16. Consequently, compared to our population where major depressive disorder is the most prevalent diagnosis, more people with mild depressive symptoms might have been included. Furthermore, with a lower cut-off score, depression scores might have been inflated due to symptoms of somatic origin[43, 44]. To our knowledge, only one study has examined vitamin D levels as predictor for the onset of major depressive disorder according to DSM criteria in a middle-aged to older population[20]. This study was based on the medical records of patients with cardiovascular events in whom vitamin D levels were assessed in the clinical process. Confounding by indication, therefore, cannot be ruled out. Acknowledging these inconsistencies and methodological issues of incidence studies, we may still expect an effect of vitamin D on the course of depression in light of the cross-sectional association between depression diagnoses and vitamin D status in our NESDO population[13], as

well as its impact on course in younger adults[12]. So how can we explain our negative finding? Firstly, an older population is more heterogeneous than a younger population. Consequently, due to the presence of multiple potential determinants of the course of depression, a small effect of vitamin D on depression might be masked by increased variability of other determinants in older patients compared to younger ones. Secondly, in the larger Netherlands Study of Depression and Anxiety (NESDA) study (n=922)[12], vitamin D affected the presence of depression diagnoses at follow up only for the vitamin D deficient group (<25 nmol/l). We found a similar trend towards a lower remission rate for the same group. However, due to the small number of severely vitamin D deficient patients in NESDO (n=36) these analyses are underpowered. Moreover, the association of vitamin D deficiency and remission may partly be explained by depression severity, since severe vitamin D deficiency is associated with a higher depression severity (table 3) and depression severity is a negative predictor for remission[45]. Taken together, the results of the NESDA and NESDO studies might be indicative for an association between vitamin D and depression, but only for the lowest vitamin D levels. This supports the hypothesis that the brain is relatively protected from vitamin D deficiency compared to other organs[5].

### Biologically active 1,25-$(OH)_2$ vitamin D

1,25-$(OH)_2$ vitamin D is not routinely measured. Its assessment is recommended in disorders of vitamin D or phosphate metabolism, as 1,25-$(OH)_2$ vitamin D levels may not adequately reflect vitamin D reserves and are thought to be frequently normal or elevated due to elevated serum PTH levels in vitamin D deficiency[46]. We found that lower 1,25-$(OH)_2$ vitamin D levels, just as 25-(OH) vitamin D levels, were associated with mortality. This might indicate that compensatory mechanisms do not always lead to elevated 1,25-$(OH)_2$ vitamin D levels in case of vitamin D deficiency. Furthermore, since cross-sectional results from NESDO demonstrated an even larger effect size for 1,25-$(OH)_2$ vitamin D than for 25-(OH) vitamin D on depression[13], it is possible that low 1,25-$(OH)_2$ vitamin D levels reflect a more severe vitamin D deficiency state than low 25-(OH) vitamin D levels.

### Vitamin D, morbidity and mortality

The association between lower vitamin D levels and mortality is in line with a large meta-analysis demonstrating higher risks for all-cause and cardiovascular mortality for persons with 25-(OH) vitamin D levels in the lowest quintile[47]. Another meta-analysis of 14 studies showed a 29% decrease in all-cause mortality for the highest compared

to the lowest quantiles of 25-(OH) vitamin D[48]. Since 25-(OH) vitamin D levels in these studies are strongly influenced by age, gender, season, education, obesity, physical activity and smoking, it is suggested that vitamin D deficiency is a marker for poor health status rather than a cause of mortality[47]. In line with this interpretation, we also observed that the effect of 25-(OH) vitamin D on total and somatic IDS subscale scores disappears after correction for lifestyle factors reflecting physical fitness (smoking status, waist circumference, physical activity and use of alcohol). However, if only true vitamin D deficiency (25-(OH) vitamin D <25 nmol/l) is taken into account, the effect on total and somatic IDS-SR subscale scores remains significant after correction for all covariates. This might be due to symptoms of somatic diseases resembling depressive symptoms, thereby influencing scores on depression symptom scales.



**Methodological considerations**

Strengths of our study are the large cohort of patients with clinical depression according to DSM-IV criteria, analysing the categorical as well as dimensional perspective, and finally assessing both 25-(OH) vitamin D levels and 1,25-$(OH)_2$ vitamin D levels. There are also some limitations. Firstly, our study is underpowered to detect effects in small subgroups, notably the vitamin D deficient group (<25 nmol/l). Since the mortality rate for our study is 6.5% at two years follow up, this might influence the detection of an effect of vitamin D on depression. Repeating all analyses using a worst-case scenario (all deceased patients still depressed at follow-up or last observation (IDS-SR) carried forward) did still reveal no effect of vitamin D on depression course. Secondly, we did not obtain vitamin D levels at two-year follow-up and do not know whether vitamin D status is subject to change in our population. Some participants were on vitamin D supplementation, probably due to vitamin D-related conditions like osteoporosis. However, a sensitivity analysis excluding all patients on vitamin D supplementation at baseline or at two-year follow up did not reveal a significant effect of vitamin D levels on remission status at two-year follow up, just like the primary analysis. Finally, we do not know the causes of death and thus whether this is due to potentially vitamin D- related causes.

**Conclusions**

A causal role for vitamin D in the pathophysiology of late-life depression seems unlikely. Nonetheless, we should be cautious, as we found a trend towards a less favourable course of depression in the subgroup with true vitamin D deficiency (25-(OH) vitamin D <25 nmol/l), consistent with findings in younger age groups. Of even more interest,

however, is the finding that lower vitamin D levels predicted mortality among depressed older persons. This supports previous observations of vitamin D deficiency as a marker for poor health status, while our results also point to overlap between somatic symptoms and symptoms of depression. This might implicate that in case of depression, vitamin D deficiency is clinically relevant. Randomised controlled trials are needed to examine high-dose vitamin supplementation in depressed (older) patients with vitamin D levels under 25 nmol/l.

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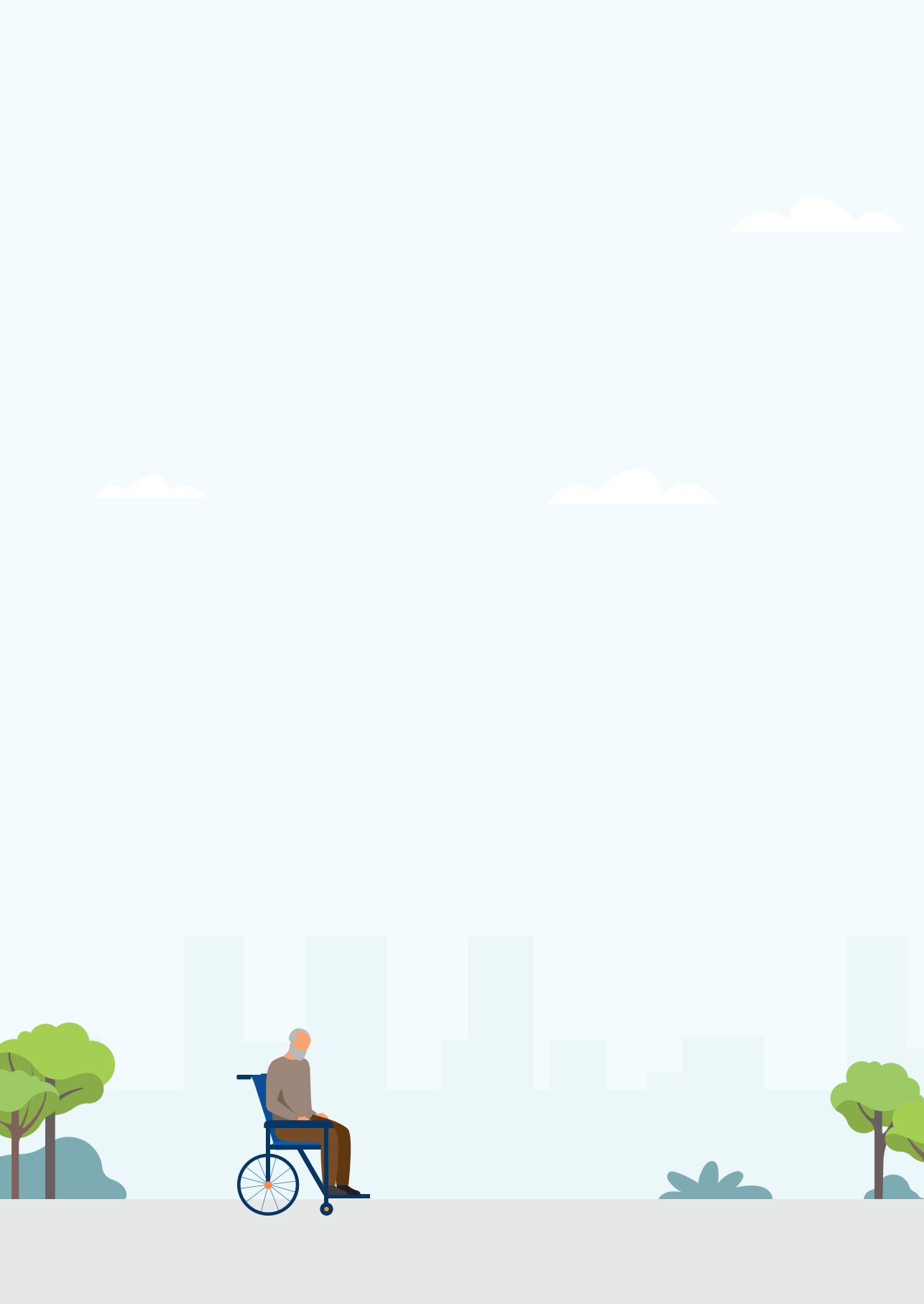

# CHAPTER 4

## VITAMIN D DEFICIENCY AND COURSE OF FRAILTY IN A DEPRESSED OLDER POPULATION

Karen S. van den Berg, Matheus H.L. Arts, Rose M. Collard, Rob H.S. van den Brink, Hannie C. Comijs, Radboud M. Marijnissen, Richard C. Oude Voshaar.

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## ABSTRACT

***Objective*:** To study the association between vitamin D levels and frailty, its components and its course in a depressed sample.

***Methods:*** Baseline and two-year follow-up data from the depressed sample of the Netherlands Study of Depression in Older persons (NESDO), a prospective observational cohort study, were analysed. The 378 participants were aged 60-93, and had a diagnosis of depression according to DSM-IV criteria. Frailty was defined according to Fried's physical phenotype. 25-OH vitamin D measurement was performed by liquid chromatography – tandem mass spectrometry. Linear and logistic regression analyses were performed, adjusted for covariates.

***Results:*** A cross-sectional association between higher vitamin D levels and lower prevalence of frailty was demonstrated (OR 0.64 [95%-CI 0.45 – 0.90], p=.010). Among non-frail depressed patients, higher vitamin D levels predicted a lower incidence of frailty (OR 0.51 [95%-CI 0.26 – 1.00], p=.050). Surprisingly, higher vitamin D levels predicted the persistence of frailty among frail depressed patients (OR 2.82 [95%-CI 1.23 – 6.49], p=.015).

***Conclusions:*** In a depressed population, higher vitamin D levels were associated with a lower prevalence and incidence of frailty. Future studies should examine whether the favourable effect of low vitamin D levels on the course of frailty can be explained by confounding or whether unknown pathophysiological mechanisms may exert protective effects.

## INTRODUCTION

With one billion vitamin D deficient people[1], vitamin D deficiency is a major public health problem worldwide[2]. It is especially common among older persons, mainly due to lack of sunlight exposure, decreased synthesis of vitamin D in the skin and loss of renal function with aging[3]. The role of vitamin D in calcium and phosphate metabolism is well-known. Recently, knowledge about its extra-skeletal effects has been expanding. Vitamin D receptors are widely distributed in the body, and have been, among others, localized in the skeletal muscles[4] and the brain[5]. Epidemiological studies have shown associations between hypovitaminosis D and several conditions, such as depression[6, 7] and physical frailty[8-14]. A key feature of frailty, and potential link with vitamin D deficiency, is sarcopenia, the loss of skeletal muscle[15]. In older persons, a consistent relationship between hypovitaminosis D and muscle dysfunction has been demonstrated[16], as well as a positive effect of vitamin D supplementation on balance and muscle strength[17]. While vitamin D indirectly affects muscle function by its impact on the calcium and phosphate balance, its direct effects are supposed to stimulate synthesis of proteins involved in contractility, proliferation and distribution of muscle cells[18]. Yet, frailty is more multifaceted than sarcopenia alone[19]. Frailty has been defined as a medical syndrome, with multiple causes and contributors, characterised by diminished strength, endurance and reduced physiologic function that increases an individual's vulnerability for developing increased dependency or death[19]. Meta-analysis of longitudinal population-based studies showed increased odds of low vitamin D levels on incident frailty[20]. Although frailty-experts consider vitamin D supplements useful for frail persons with vitamin D deficiency[19], intervention studies are currently lacking[21]. In spite of a consistently found association between low vitamin D levels and depression[6], the potential causal mechanism is still debated. Recently, it was demonstrated that vitamin D levels did not predict the course of depression in a sample of older persons. Instead, lower vitamin D levels were associated with mortality[22]. Since frailty and late-life depression have been reciprocally related in the population[23, 24], frailty might be a somatic pathway underlying this association. The present study aims to evaluate the cross-sectional and longitudinal association of vitamin D and frailty in a cohort of depressed older persons.

## MATERIALS AND METHODS

### Sample

Data were obtained from the Netherlands Study of Depression in Older persons (NESDO), a cohort study designed to examine the determinants, course and consequences of late-life depression[25, 26]. In total, 378 depressed patients and 132 non-depressed controls, aged 60 to 93, were recruited from mental health institutions and general practitioners between 2007 and 2010. Depressed patients had a diagnosis of major depressive disorder (95.0%) and/or dysthymia (26.5%) in the previous six months, or minor depression (5.6%) in the last month, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[27] and assessed by the Composite International Diagnostic Interview (CIDI; WHO version 2.1, life time version). Controls had no lifetime diagnosis of depression. Subjects with a severe primary disorder, such as a psychotic disorder, a primary diagnosis of dementia, or suspected for dementia according to their clinician, as well as subjects with a Mini Mental State Examination (MMSE)[28] score <18/30 or insufficient command of the Dutch language were excluded. The cut-off on the MMSE was lowered from 24 to 18 in order to be able include the more severely depressed patients with transient cognitive decline due to their depressed state. This was considered possible, as clinicians experienced in the diagnostics of dementia had to exclude all patients they suspected from an underlying dementia. At baseline, data were gathered about mental health outcomes, demographic characteristics and psychosocial, biological, cognitive and genetic determinants. Measures subject to change were evaluated again at follow-up. Interviews were performed by trained research assistants and audiotaped regularly to control for quality. If necessary, participants were visited at home. The ethical review boards of the participating centres approved the study. All participants provided informed consent.

Of the 378 depressed patients, 352 with complete data on frailty and vitamin D were included in the cross-sectional analyses. Excluded persons (n=26) were lower educated (8.5 vs. 10.6 years, t=2.98, df=376, p=.003), more often frail (63.6% vs. 29.0%, $\chi^2$=6.10, df=1, p=.014) and scored higher on the Inventory of Depressive Symptomatology (IDS-SR)[29]: 36.7 vs. 29.7 points (interpretation: 0-13 not depressed; 14-25 mildly depressed; 26-38 moderately depressed; ≥39 severely depressed); t= -2.51, df=371, p=.012 than participants. Since actual vitamin D levels were available, vitamin D supplementation was not taken into account in cross-sectional analyses. Nonetheless, sensitivity analyses without supplementation users (n=14) were performed.

At two-year follow-up, 285 initially-depressed patients still participated, 26 had died and 67 were lost to follow-up for other reasons. Participants with missing frailty data (n=30) or baseline vitamin D data (n=5), and users of vitamin D supplementation (n=18) were excluded, leaving a sample of 235 persons for longitudinal analyses. Compared to participants, excluded persons (n=143) were less educated (9.7 vs. 10.9 years, t=3.16, df=376, p=.002), had more chronic diseases (2.8 vs. 2.4, t=-2,29, df=259,2, p=.023), used less alcohol (Alcohol Use Disorders Identification Test (AUDIT)[30] sum score 2.2 vs. 2.8 (range 0-40); Mann-Whitney U p=.021), were more often smokers (32.2% vs. 23.0%; $\chi^2$=4.10, df=1, p=.043) and more often frail at baseline (32.9% vs. 26.4%, $\chi^2$=4.21, df=1, p=.040). For 22 of 26 deceased persons complete baseline frailty and vitamin D data were available. They were included in the sensitivity analyses and considered frail at follow-up.

## Health outcomes



*Vitamin D levels*

Serum 25-(OH) vitamin $D_3$ levels were measured at baseline using isotope dilution-online solid-phase extraction liquid chromatography–tandem mass spectrometry, as described previously[31]. Method characteristics are the following: limit of quantitation 4.0 nmol/l, intra-assay coefficient of variation <7.2% and inter-assay coefficient of variation <14.1% for three concentrations between 20 and 150 nmol/l; recovery ranges from 93 to 98% and linearity was acceptable ($r^2$ = 0.9972). The accuracy of 25-(OH) vitamin $D_3$ levels was established using (the National Institute of Standards and Technology, Gaithersburg, MD, USA) reference material to establish true values for calibration standards. Calibration standards, quality control samples and patient samples were stable for 6 days at 6˚C (coefficient of variation < 11%). Samples were stable for at least three freeze-thaw cycles (coefficient of variation <3%). The optimal 25-(OH) vitamin D level is thought to be between 75 and 100 nmol/l, above which point studies found parathyroid hormone levels (inversely related to vitamin D) beginning to level off[1].

*Frailty*

According to Fried's physical frailty phenotype, frailty was defined as the presence of ≥ 3 out of 5 dichotomous criteria: exhaustion, weakness, slow walking speed, inactivity, and unintended weight loss[15]. These criteria were operationalised as follows[32]:

- *Weakness*: low handgrip strength, measured by two squeezes with the dominant hand in a dynamometer. Cut-off values depended on body mass index and varied between 29-32 kg for men and 17-21 kg for women[15].
- *Unintended weight loss*: positive answer to the CIDI question about unintended weight loss (≥ 1 kg/week, for ≥ 2 consecutive weeks), or a body mass index (BMI) < 18.5 kg/m$^2$.
- *Slowness*: time on a six-meter walking test ≥ 8 seconds for men ≥ 173 cm or women ≥ 159 cm height, or ≥ 9 seconds for men < 173 cm and women < 159 cm height.
- *Low physical activity:* no daily activities such as walking or gardening, and the performance of sports less than once a week, assessed with the International Physical Activity Questionnaire (IPAQ)[33].
- *Exhaustion:* a score of 3 or 4 out of 4 points on one or both of the IDS-SR[29] questions about energy level and leaden paralysis / physical energy.

The primary outcome measures were incident frailty (the presence of frailty at follow-up in a person without frailty at baseline) and persistent frailty (the presence of frailty at follow up in a person with frailty at baseline). Secondary outcome measures were the continuous dimensions underlying the individual frailty components of the Fried model, i.e. highest value for handgrip strength in kilograms (weakness), weight in kilograms (weight loss), six-meter walking time in seconds (slowness), number of Metabolic Equivalent of Task (MET)- minutes per week[33] (physical inactivity) and sum scores of the two IDS-SR[29] questions about energy level and leaden paralysis / physical energy (exhaustion).

**Covariates**

Based on their association with vitamin D level, depression or frailty, we a priori selected age, gender, years of education, astronomical season of blood withdrawal, smoking, use of alcohol, cognitive functioning, number of chronic diseases, renal function and depression symptom score as covariates[7, 34]. Use of alcohol was assessed by AUDIT sum scores[30]. The number of chronic diseases was assessed by means of self-report questions, an accurate method when compared to data from general practitioners[35]. The MMSE was used to assess global cognitive functioning (range 0–30)[28]. Glomerular filtration rates (GFR) were estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[36] formula to assess renal function. Severity of depressive symptomatology was assessed by IDS-SR[29] scores.

### Statistical analysis

Vitamin D levels were standardised using Z-scores. The different groups, based on frailty status, were compared with T-tests, ANOVA and chi-square tests. Non-parametric tests were performed in case of a skewed distribution. The cross-sectional and longitudinal association between vitamin D and frailty was analysed using logistic regression, with the presence of frailty (yes/no) as the dependent parameter. The association between vitamin D level and the individual frailty components was analysed by linear regression. At follow-up, frailty components were adjusted for their own baseline value, in order to assess their course. Continuous values for walking speed were log transformed to achieve a normal distribution. Analyses were adjusted for all covariates. Missing covariates were imputed with the group mean (IDS score n = 2, AUDIT sum score n = 2, smoking status n = 2). Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0.0.1. (IBM Corp., NY, USA). All statistical tests were two-sided, p-values at or below .050 were considered significant.



## RESULTS

### Cross-sectional analyses

At baseline, 102 of 352 participants (29.0%) were frail. Persons with frailty were on average older, had had less years of education, used less alcohol, had more chronic diseases, higher severity of depression, worse cognitive functioning and lower vitamin D levels than non-frail persons (see Table 1). Lower vitamin D levels were associated with the presence of frailty. Regarding the individual frailty components, higher vitamin D levels were associated with more physical activity and greater grip strength (see Table 2). Exclusion of users of vitamin D supplementation (n=14) neither altered the association with frailty (adjusted OR for frailty 0.64 [95%-CI 0.45 – 0.92], p=.015) nor the association with the individual frailty components (results not shown).

**Table 1.** Baseline characteristics, stratified by baseline frailty status.

| Characteristic | Non-frail (n = 250) | Frail (n = 102) | Statistic |
|---|---|---|---|
| Age (years); mean (sd) | **69.7 (6.9)** | **73.2 (8.1)** | **T -3.83, df 163.8, p <.001** |
| Female sex; n (%) | 159 (63.6%) | 72 (70.6%) | $\chi^2$ 1.57, df 1, p .210 |
| Years of education; mean (sd) | **10.9 (3.5)** | **9.7 (3.3)** | **T 2.98, df 350, p .003** |
| Currently smoking; n (%) | 65 (26.0%) | 24 (23.5%) | $\chi^2$ 0.166, df 1, p .683 |
| Alcohol usage (AUDIT sum score, 0-40); median (IQR) | **2.0 (4.0)** | **1.0 (3.0)** | **Mann-Whitney U p .003** |
| Renal function (CKD-EPI, ml/min/1.73m$^2$); mean (sd) | 72.6 (14.8) | 69.7 (17.3) | T 1.55, df 350, p .123 |
| Number of chronic diseases; mean (sd) | **2.3 (1.5)** | **3.0 (1.8)** | **T -3.63, df 348, p <.001** |
| Severity of depression (IDS-SR score, 0-84); mean (sd) | **26.6 (11.9)** | **37.3 (12.4)** | **T-7.53, df 348, p <.001** |
| Cognitive functioning (MMSE score 0-30); median (IQR) | **28.0 (2.0)** | **28.0 (3.0)** | **Mann-Whitney U p .005** |
| 25-(OH) vitamin D (nmol/l); mean (sd) | **56.1 (22.7)** | **43.9 (21.6)** | **T -2.81, df 350, p .005** |
| Season of blood withdrawal | | | **$\chi^2$ 9.19, df 3, p .027** |
| - Winter; n(%) | 41 (16.4%) | 28 (27.5%) | |
| - Spring; n(%) | 70 (28.0%) | 33 (32.4%) | **$\chi^2$** 0.66, df 1, p .415 |
| - Summer; n(%) | 76 (30.4%) | 26 (25.5%) | $\chi^2$ 0.85, df 1, p .357 |
| - Autumn; n(%) | **63 (25.2%)** | **15 (14.7%)** | **$\chi^2$ 4.63, df 1, p .032** |

**Bold** = statistical significance (p≤.050)
Abbreviations: sd = standard deviation; IQR: interquartile range; df: degrees of freedom, AUDIT: Alcohol Use Disorders Identification Test; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; IDS-SR: Inventory of Depressive Symptomatology, self-report; MMSE: Mini-Mental State Examination.

**Table 2.** Cross-sectional association of standardised vitamin D levels and prevalence of frailty and the individual frailty components (n = 352)

| Model | Frailty (n = 352) | Individual frailty components | | | | |
|---|---|---|---|---|---|---|
| | | Slowness* (n = 349) | Exhaustion (n = 344) | Physical inactivity (n = 343) | Weakness (n = 352) | Weight loss (n = 352) |
| | OR [95%-CI] p-value | B (se) p-value | B (se) p-value | B (se) p-value | B (se) p-value | B (se) p-value |
| 25-OH vitamin D | 0.53 [0.40–0.70] **p < .001** | -0.07 (0.02) **p .002** | -0.18 (0.09) **p .047** | 559.99 (125.21) **p <.001** | 2.54 (0.61) **p <.001** | 0.64 (0.77) p .407 |
| 25-OH vitamin D + covariates† | 0.64 [0.45–0.90] **p .010** | -0.02 (0.02) p .448 | -0.15 (0.10) p .126 | 481.88 (133.71) **p <.001** | 1.22 (0.51) **p .016** | 0.38 (0.76) p .616 |

**Bold** = statistical significance (p≤.050)
Abbreviations: OR = odds ratio, 95%-CI = 95%-confidence interval, B = Beta, se = standard error.
* logtransformed
†Covariates in final model: sexe, age, level of education, severity of depressive symptomatology, number of chronic diseases, cognitive functioning, renal function, smoking status, use of alcohol, season of blood withdrawal.

### Longitudinal analyses

At two-year follow-up, 173 of the 250 participants without frailty at baseline, participated again. Of those, 21 (12,1%) had become frail. Compared to the persistently non-frail, participants with incident frailty were older (mean 74.0 (standard deviation (s.d.) 7.8) vs. 68.6 (s.d. 6.5) years, p=.001), had more chronic diseases (mean 2.9 (s.d. 1.6) vs. 2.1 (s.d. 1.4), p=.011) and lower scores for cognitive functioning (median 27.0 (interquartile range (IQR) 3) vs 28.0 (IQR 2), p=.002). Remission of depression at follow-up did not differ between the persistently non-frail (n=86; 56.6%) and the incident frail (n=9; 42.9%, p=.236). There were no significant differences with respect to the other variables (results not shown). As shown in Table 3, a significant association between higher baseline vitamin D levels and lower odds for incident frailty at two-year follow-up was found. When deceased persons were considered incident frail as well, this association was even stronger. Regarding the individual frailty components, only the association between higher baseline vitamin D levels and more physical activity at follow-up was significant.



Of the 102 baseline-frail persons, 62 participated again at two-year follow-up. Frailty had remitted in 31 persons (50%). Participants with persistent frailty were older (mean 75.9 (s.d. 8.6) vs 70.5 years (s.d. 7.1), p=.009) and had less renal function at baseline (mean GFR 68.1 ml/min/1.73m$^2$ (s.d. 17.4) vs 77.7 ml/min/1.73m$^2$ (s.d. 14.6), p=.022) compared to persons with remission of frailty. Among persistently frail persons, depression had remitted less often (n=8, 25.8%) than in persons with remitted frailty (n=21; 67.7%; p=.001). The other variables did not differ significantly (results not shown). In fully adjusted analyses (see Table 4), higher vitamin D levels were associated with higher odds of persistent frailty at follow-up. As depression remitted significantly less often in persistently frail patients, we checked post-hoc the interaction between baseline vitamin D level and the presence of depression at two-year follow-up. This interaction term, however, was not significant. Furthermore, the impact of vitamin D levels on persistence of frailty was neither present in the univariate analyses, nor in the sensitivity analyses. A stepwise procedure demonstrated that adjustment for use of alcohol amplified the effect of higher vitamin D levels on persistence of frailty the most. Regarding the individual frailty components, higher vitamin D levels were associated with increased exhaustion. For the other frailty components, no significant association with vitamin D levels was found.

**Table 3.** Association of standardised vitamin D levels and incidence of frailty and change of the individual frailty components

| Model | **Incident frailty (n = 173)** | **Incident frailty or death (n = 182)** | **Individual frailty components** | | | | |
|---|---|---|---|---|---|---|---|
| | | | Slowness* (n = 172) | Exhaustion (n = 173) | Physical inactivity (n = 173) | Weakness (n = 170) | Weight loss (n = 171) |
| | OR [95%-CI] p-value | OR (95%-CI) p-value | B (se) p-value | B (se) p-value | B (se) p-value | B (se) p-value | B (se) p-value |
| 25-OH vitamin D | 0.58 [0.33 – 1.01] p .054 | 0.49 [0.29 – 0.82] **p .006** | -0.04 (0.03) p .144 | -0.11 (0.12) p .341 | 410.33 (214.64) p .058 | 1.15 (0.80) p .152 | -0.90 (1.14) p .434 |
| 25-OH vitamin D + covariates† | 0.51 [0.26 – 1.00] **p .050** | 0.42 [0.23 – 0.78] **p .006** | -0.02 (0.02) p .458 | -0.01 (0.11) p .929 | 518.78 (229.34) **p .025** | 0.50 (0.56) p .372 | -1.14 (1.09) p .296 |

**Bold** = statistical significance (p≤.050). Abbreviations: OR = odds ratio, 95%-CI = 95%-confidence interval, B = Beta, se = standard error. *logtransformed. †Covariates in final model: sexe, age, level of education, severity of depressive symptomatology, number of chronic diseases, cognitive functioning, renal function, smoking status, use of alcohol, season of blood withdrawal

**Table 4.** Association of vitamin D levels (standardised) and persistence of frailty and change of the individual frailty components

| Model | **Persistent frailty (n = 62)** | **Persistent frailty or death (n = 75)** | **Individual frailty components** | | | | |
|---|---|---|---|---|---|---|---|
| | | | Slowness* (n = 62) | Exhaustion (n = 61) | Physical inactivity (n = 62) | Weakness (n = 62) | Weight loss (n = 60) |
| | OR [95%-CI] p-value | OR [95%-CI] p-value | B (se) p-value | B (se) p-value | B (se) p-value | B (se) p-value | B (se) p-value |
| 25-OH vitamin D | 1.73 [0.98 – 3.07] p .061 | 1.28 [0.77 – 2.13] p .347 | -0.09 (0.07) p .188 | 0.51 (0.20) **p .014** | -109.63 (291.21) p .708 | 1.39 (1.33) p .300 | 1.14 (2.05) p .579 |
| 25-OH vitamin D + covariates† | 2.82 [1.23 – 6.49] **p .015** | 1.65 [0.82 – 3.31] p .162 | -0.05 (0.06) p .464 | 0.52 (0.24) **p .034** | -275.92 (307.91) p .375 | 0.29 (1.19) p .805 | 0.23 (2.16) p .915 |

**Bold** = statistical significance (p≤.050). Abbreviations: OR = odds ratio, 95%-CI = 95%-confidence interval, B = Beta, se = standard error. *logtransformed. †Covariates in final model: gender, age, level of education, severity of depressive symptomatology, number of chronic diseases, cognitive functioning, renal function, smoking status, use of alcohol, season of blood withdrawal

# DISCUSSION

## Main findings

In a cohort of depressed, older persons, lower vitamin D levels were cross-sectionally associated with greater odds of prevalent frailty, which is mainly driven by the components physical inactivity and weakness. In persons without frailty at baseline, lower vitamin D levels doubled the odds of incident frailty and were associated with a further decrease of physical activity at two-year follow-up. In the subgroup of baseline-frail participants, frailty had remitted in 31 of 62 participants (50%) two years later. Remarkably, higher vitamin D levels were associated with persistent frailty over time, irrespective of the fact that improvement of frailty was significantly associated with remission of depression.

## Comparison to the literature

Our cross-sectional findings are in line with previous studies, reporting associations between lowest vitamin D levels and presence of frailty according to the Fried phenotype[8-10, 12, 37, 38]. Regarding the individual frailty components, we found that lower vitamin D levels were associated with weakness and physical inactivity, while other studies have demonstrated associations solely with weakness[9] or with all frailty components except weight loss[10, 38]. Due to these inconsistencies, it is neither possible to draw conclusions about whether low vitamin D levels are related to frailty as an overall-concept (which might include more than just the sum of the individual components) nor to generalize conclusions about the driving factors of the association. We may have found less associated frailty components than some other studies[10, 38] due to the presence of depression in our sample. Since depression and frailty are thought to be reciprocally associated[23, 24], frailty prevalence rates are expected to be higher within a depressed population. In our sample the frailty rate was 29.9%, whereas in community-dwelling populations this rate was 9.9%[39]. Furthermore, depression has been associated with lower vitamin D levels in our population[7], and other populations[6]. Therefore, an association between vitamin D levels and frailty (and its components) might be harder to detect in a depressed sample.

Since frailty had remitted in half of the baseline-frail participants, our longitudinal data underline that frailty is a dynamic process, as previously stated in a frailty consensus paper[19]. In our depressed population, this dynamism might be partly confounded by overlap between frailty and depression[40]. Nevertheless, the impact of vitamin D

on the improvement of frailty was independent of depression status at follow-up. In line with our finding, a recent meta-analysis of seven longitudinal studies showed a pooled odds ratio of 1.27 (95%-CI 1.17 – 1.38) for incident frailty for lowest vitamin D levels[41]. Potential mechanisms explaining this prospective association include 1) the development of sarcopenia and muscle weakness, due to regulatory effects of vitamin D on calcium and mineral homeostasis and protein signaling pathways[21], 2) secondary hyperparathyroidism, caused by low 1,25 $OH_2$ vitamin D and low calcium, leading to decreased bone mineralization and increased bone resorption, thus increasing fracture risk[21, 42], and finally 3) the possible involvement of vitamin D deficiency in inflammation and activation of the immune system, which might play a role in the pathogenesis of auto-immune diseases and the development of frailty[21, 42, 43]. In our sample, lower vitamin D levels at baseline predicted a decrease of physical activity at follow up. In other, population-based samples, low vitamin D levels were associated with physical inactivity/low energy expenditure as well as slowness[12, 44] or none of the individual frailty criteria[45]. The presence of depression might explain why the association between low vitamin D levels and decrease of physical activity stands out. Previously, low vitamin D levels were suggested to be a marker of poor health in our sample[22]. Since poor health might add to increasing physical inactivity over time, and depression itself can also cause physical inactivity[46], this might have amplified the association in our sample. In line with our unexpected finding of an association between lower vitamin D levels and remission of frailty, the population-based InChianti study[47] also reported baseline frail participants with low vitamin D levels to be more likely to transit to pre-frailty (the presence of only 1 or 2 frailty criteria) at follow up. Despite this replication, our finding might still be considered a chance finding, due to the small sample of baseline frail persons (n=62). Confounding by indication (vitamin D supplementation in frail persons) is less likely, since we excluded persons using supplementation at follow-up. Intermittent supplementation during the follow-up period is unlikely to result in the strong effects we found. A third possibility is residual confounding, since a reciprocal association between frailty and depression exists[23, 24]. Symptoms of depression might lead to a false-positive diagnosis of frailty, as the operational criteria of depression and frailty identify overlapping subpopulations[48, 49]. However, this does not fit with our finding that the effect of vitamin D levels on frailty is not moderated by an effect of vitamin D on remission of depression. At last, a more plausible explanation might be that inactive behaviour due to depression might lead to lower vitamin D levels. Upon remission of depression, frailty status also improves (partly due to overlap/confounding with depression, partly true improvement), while vitamin D levels can stay behind. In our

baseline-frail subgroup, depression had remitted significantly more often in participants with remitted frailty at follow up, than in the persistently frail. Nonetheless, taken into account that hitherto two studies reported this unexpected effect, it still might reflect yet unknown pathophysiological pathways that remain to be elucidated.

**Limitations**

First, a dichotomous outcome measure for frailty has been used, and pre-frailty was not taken into account. Second, we did not have access to causes of death. Being able to include only people who died from frailty-related causes in the sensitivity analyses would have led to more accuracy. Now sensitivity analyses are likely an overestimation, and primary analyses an underestimation of the effect. Last, vitamin D levels were measured at baseline only. However, vitamin D levels seem to be relatively consistent over time[50].

**Conclusion / clinical implications**

In our depressed population, like in community-based populations, lower vitamin D levels were associated with greater prevalence and incidence of frailty. Future studies should examine whether the favourable effect of low vitamin D levels on the course of frailty can simply be explained by confounding or whether unknown pathophysiological mechanisms may exert protective effects. This is highly relevant, as vitamin D supplementation is generally seen as a potential treatment strategy for frailty as well as late-life depression.

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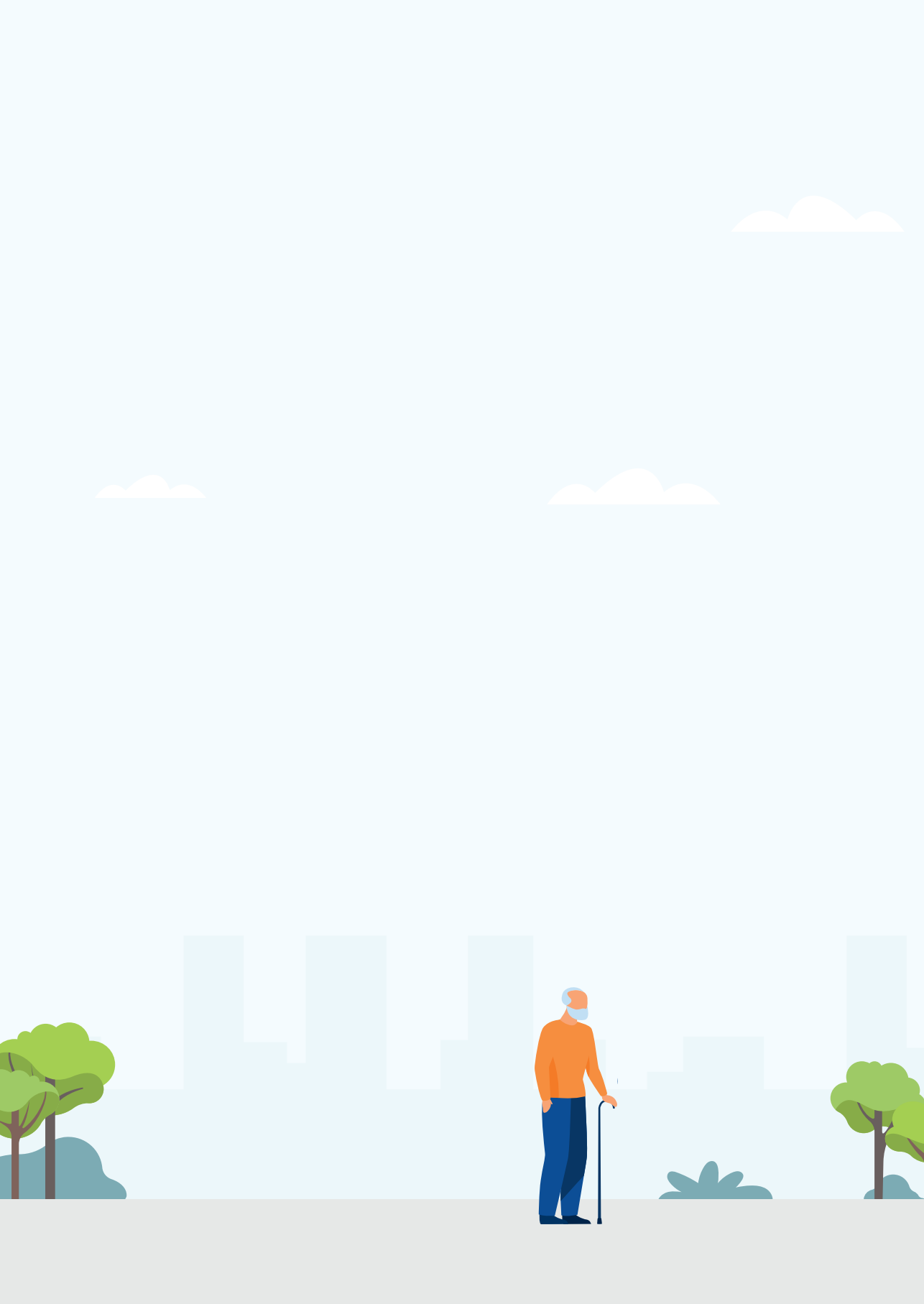

# CHAPTER 5

## FRAILTY AS A PREDICTOR OF MORTALITY IN LATE-LIFE DEPRESSION: A PROSPECTIVE CLINICAL COHORT STUDY

Matheus H.L. Arts, Karen S. van den Berg, Radboud M. Marijnissen, Linda de Jonge, Annette J.M. Hegeman, Rose M. Collard, Hannie C. Comijs, Ivan Aprahamian, Paul Naarding, Richard C. Oude Voshaar.

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## ABSTRACT

***Objectives:*** Frailty is a clinical phenotype that predicts negative health outcomes including mortality and is increasingly used for risk stratification in geriatric medicine. Similar to frailty, late-life depression is also associated with increased mortality rates. Therefore, we examined whether frailty and frailty-related biomarkers predict mortality among depressed older patients.

***Methods:*** Among 378 older patients (≥60 years) with a depressive disorder (DSM-IV criteria) we examined whether frailty predicts time-to-death during a six-year follow-up using Cox-regression analyses adjusted for confounders. Baseline data were collected between 2007 and September 2010. Frailty was defined according to Fried's criteria (muscle weakness, slowness, exhaustion, low activity level, unintended weight loss). Similarly, we examined the predictive value of three inflammatory markers, vitamin D level, and leucocyte telomere length, and whether these effects were independent of the frailty phenotype.

***Results:*** During follow-up, 27/103 (26.2%) frail depressed patients died compared to 35/275 (12.7%) non-frail depressed patients (p<.001). Adjusted for confounders, the number of frailty components was associated with an increased mortality rate (HR=1.38 [95%CI: 1.06–1.78], p=.015). All biomarkers were prospectively associated with mortality, but only higher levels of hsCRP and lower levels of vitamin D were independent of frailty associated with mortality.

***Conclusions:*** In late-life depression, frailty identifies older patients at increased risk of adverse negative health outcomes. Therefore, among frail-depressed patients, treatment models that include frailty-specific interventions might reduce mortality rates.

## INTRODUCTION

Depressive disorder is increasingly recognised as a disorder of accelerated aging based on its association with many physiological and cellular markers of aging[1]. In line with this theory, meta-analyses have shown that depression is associated with excess mortality which cannot be explained by suicide[2, 3]. A reassessment of 293 studies included in 15 systematic reviews, however, found evidence for pronounced publication bias in favour of positive findings, bias due to pre-selection on medical conditions, and insufficient control for confounders, especially comorbidity and lifestyle[3]. Furthermore, most studies in these reviews had assessed depression with depressive symptom severity scales instead of formal diagnostic criteria of the DSM or ICD[3]. Self-report depressive symptom scales may be falsely inflated by the presence of comorbid chronic somatic diseases[4] and thereby confound the association between depression and mortality. The four studies that had assessed depressive disorders according to DSM criteria yielded a pooled hazard rate of 1.2 [95%CI:0.8–1.6] for mortality which was not statistically significant anymore[3]. More well-controlled studies of excess mortality in depressed patients according to DSM-IV criteria are needed to explore which characteristics may explain the potential relationship between depression and mortality.



Frailty is characterised by cumulative declines in multiple physiological systems, accompanied by an increased vulnerability to stressors[5]. In geriatric medicine, frailty is increasingly used for risk stratification to identify patients at increased risk of adverse health outcomes, including mortality, and to deliver patient-centred care[6]. Frailty might be a pathway that may explain excess mortality in depression. In a population-based cohort study of men aged 75+ years, the crude mortality hazard of 4.3 for a DSM-IV defined depressive disorder dropped to 1.8 after additional correction for frailty[7]. The other way around, the prospective association of frailty with mortality differs between disease clusters and seems smallest for patients with neuropsychiatric disorders[8]. To our knowledge, prospective association between frailty and mortality has never been examined in clinically depressed patients. This is relevant as frailty and depression have a complex relationship. Firstly, depression and frailty share many risk factors and consequences[9]. Secondly, at a population level, frailty and depression often identify the same subgroup of persons, especially older persons with high levels of depressive symptoms[9]. Thirdly, many operationalisations of the frailty concept include criteria that may overlap with a depressive disorder, like psychomotor retardation, fatigue, weight loss, and feelings of exhaustion. A meta-analysis estimated that 40.4% of depressed

older persons are frail and that 38.6% of frail persons are depressed[10]. Furthermore, the sparse longitudinal studies showing a bidirectional association between depression and frailty[10]. Nonetheless, only four studies in this meta-analysis have assessed depression according to formal diagnostic criteria. In the Netherlands Study of Depression in Older persons (NESDO), we showed that only 27.2% of the patients suffering from a DSM-IV defined depressive disorder were physically frail[11].

Many aging-related biomarkers are associated with both frailty as well as depressive disorder. Whether these biomarkers represent common pathophysiology or mediates the prospective association from frailty to depression or vice versa needs further study. In the NESDO-study, we did not find consistent associations between late-life depression and low-graded inflammatory markers[12] or leucocyte telomere length (LTL)[13], whereas lower vitamin D levels were only cross-sectionally but not prospectively associated with late-life depression[14, 15]. Consistent with the literature on frailty, we found that within NESDO, physical frailty was associated with low-graded inflammation[16], a shorter LTL[17], and lower vitamin D levels[18]. Collectively, these results may point to frailty as a moderating factor to adverse outcomes like death among depressed older adults.

To our knowledge, only one study has examined whether frailty predicts mortality in psychiatric patients[19]. In that study among a mixed group of 120 older psychiatric inpatients, among which 41 depressed patients, frailty predicted mortality within 5 years. This effect was independent of chronological age, somatic disease burden, functional status and neuropsychiatric symptoms[19]. The present study, embedded in the Netherlands Study of Depression in Older persons (NESDO), examines the prospective association of the physical frailty phenotype as well as associated biomarkers with mortality in 378 clinically depressed older patients. We hypothesise that physical frailty as well as physiological and cellular biomarkers of aging are prospectively associated with the 6-year mortality rate.

## METHODS

### Study population

The present NESDO-study included 378 depressed subjects aged ≥60 years who meet the criteria for a DSM-IV depressive disorder using the Composite International Diagnostic Interview (CIDI-version 2.1)[20]. Of these 378 patients, 95% had a past 6-month major depressive disorder, 26.5% a past 6-month dysthymia, and 5.6% a

past-month minor depression (numbers do not add up to 100% as 26.5% have two depressive disorders). Exclusion criteria were an established or suspected diagnosis of a neurocognitive disorder, a Mini-Mental State Examination-score (MMSE)[21] <18, a history of a psychotic disorder, and insufficient mastery of the Dutch language. Since a severe depressive disorder may interfere with cognitive testing, we accepted an MMSE score as low as 18 in case the patient was neither diagnosed with nor suspected to have an underlying neurocognitive disorder. The overall aim of NESDO is to examine the course and consequences of depressive disorders in older persons. All participants underwent a baseline examination at one of the five research locations or at their homes. This baseline examination included a structured psychiatric diagnostic interview (CIDI 2.1)[20], cognitive testing, physical examination, blood collection, and several observer-rated and self-report questionnaires. Baseline data collection started in 2007 and was finished in September 2010. This assessment was repeated at two- and six-year follow-up for all baseline characteristics amenable to change. In between, every six months, up to six years, postal questionnaires were sent to monitor depressive symptom severity (amongst other measures). Reasons for dropout (including mortality) were explored and registered at 6-months intervals parallel to postal questionnaires and site vistis[22]. The ethical review boards of all participating study centres have approved the NESDO-study protocol and all participants have provided written informed consent[20, 22].



**Physical frailty phenotype**

The physical frailty phenotype was assessed according to the Fried criteria and classified as frail when at least three out of the five criteria were present, including weight loss, weakness, exhaustion, slowness and low physical activity[11, 23]. Weakness was defined as the maximum handgrip strength (as measured by two squeezes with the dominant hand in a dynamometer) below a cut-off stratified by sex and body mass index (BMI). Slowness was defined as a time ≥8 seconds for men ≥173 cm or women ≥159 cm tall, or ≥9 seconds for men <173 cm and women <159 cm tall on a six-meter walking test. Exhaustion was defined as scoring positive (score 2 or 3) on one of the two items regarding energy level and exhaustion of the Centre for Epidemiological Studies Depression (CES-D) scale. Low physical activity was defined as doing no daily activities such as walking or gardening, and the performance of sports less than once a week, as assessed with the International Physical Activity Questionnaire[24]. Finally, unintended weight loss was based on a positive answer to the CIDI question about unintended weight loss (≥1 kg/week, for ≥ 2 consecutive weeks) or a BMI <18.5 kg/m$^2$.

## Aging and frailty biomarkers

Fasting blood samples were obtained at baseline in the morning around 8 am and kept at −80°C for subsequent analyses of biomarkers. Based on availability in the NESDO study, we have chosen to explore the following biomarkers. Low-graded inflammation: We assessed plasma levels of C-reactive protein (CRP), Interleukin-6 (IL-6) and Neutrophil Gelatinase Associated Lipocalin-2 (NGAL-2). High-sensitivity plasma levels of CRP were measured in duplicate by an immunoturbidimetric assay (Tina-quant CRPHS, Roche Diagnostics, Mannheim, Germany). Intra- and inter-assay coefficients of variation were 2% and 2%, respectively. Plasma IL-6 levels were measured in duplicate by a high sensitivity ELISA (PeliKine Compact™ ELISA, Sanquin, Amsterdam, the Netherlands). Intra- and inter-assay coefficients of variation were 8% and 12%, respectively. Finally, the plasma NGAL-2 levels (ng/ml) were measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA)[25]. The intra- and inter-assay coefficients of variation were 2% and 5%, respectively. Neutrophil Gelatinase-Associated Lipocalin-2 (NGAL-2) is a 25-kDa protein of the lipocalin superfamily and a critical component of innate immunity to bacterial infection. It has recently been identified as a neuroinflammatory marker in depressed and/or cognitively impaired patients[25]. NGAL-2 expression is triggered by TNF receptor 1 signaling and able to induce a pro-apoptotic signaling cascade by attenuating Akt phosphorylation of the protein kinase B (PKB)/Akt pathway. Vitamin D: Serum 25-(OH) vitamin D levels were measured at baseline using isotope dilution-online solid-phase extraction liquid chromatography–tandem mass spectrometry, as described previously[14]. *Leucocyte Telomere Length (LTL):* LTL was determined by Telomere Diagnostics, Inc. (TDx, Menlo Park, CA, USA). Quantitative polymerase chain reaction (qPCR) was used to compare the telomere sequence copy number (T) in each patient's sample to a single-copy gene copy number (S), relative to a reference sample. The intra-assay coefficient of variation (CV) was 5.1% and the inter-assay CV was 4.6%. The resulting T/S ratio was proportional to mean TL. The T/S ratio was converted to base pairs (bp) by the following formula: bp=3274+2413x((T/S-0.0545)/1.16)[26].

## Covariates

As covariates we included the most important determinants of death, i.e. sociodemographic data (age, sex, and years of education, partner status), lifestyle characteristics, somatic disease burden, and depressive symptom severity at baseline. Lifestyle characteristics included smoking (yes/no), number of alcoholic drinks based on the Alcohol Use Disorder Identification Test (AUDIT)[27], physical activity in MET-

minutes based on the International Physical Activity Questionnaire (IPAQ)[24], and body mass index (BMI in kg/m$^2$). The somatic disease burden was quantified as the number of chronic somatic diseases under treatment as well as the number of prescribed medications. The total number of self-reported chronic diseases was determined by well-validated algorithms[28], and included lung disease, cardiovascular disease, diabetes, osteoarthritis or rheumatic disease, cancer, ulcer, intestinal problems, liver disease, epilepsy, and thyroid gland disease. To calculate the number of medications, all drugs with a unique Anatomical Therapeutical Chemical Classification System (ATC) code at a three-digit level were counted. Dermatological preparations, medications without an ATC code, medications used less than half of the week (except drugs for which non-daily use is common, i.e. bisphosphonates, methotrexate), and for use 'if necessary' were excluded. Data on drug use were collected at the interviews (and checked by medication containers). In addition, analyses were also adjusted for insomnia and depressive symptom severity because depression and sleep have both been associated with death. Depressive symptom severity was measured by the well-validated 30-item self-rating Inventory of Depressive Symptomatology (IDS)[29]. Additionally, sleep was measured with the self-report 5-item Insomnia Rating Scale (IRS)[30]. Finally, models including vitamin D levels were additionally adjusted for the astronomical season of blood collection.



**Data analysis**

Baseline characteristics are presented stratified for frail and non-frail depressed patients and tested by Student's t-tests or Mann-Whitney U for continuous variables and chi-square tests for categorical variables. Cox's regression (proportional-hazard analysis) models were used to investigate the effect of frailty upon time to attrition due to death. Survival time ranged from baseline till either death (outcome) or censored at time of study dropout or end of the follow-up (at six years). The presence of frailty (yes/no) and the number of frailty components present (range 0-5) were the primary variables of interest. In order to explore the impact of frailty in more depth, we also examined the impact of specific frailty components, i.e. 1) the impact of each of the five Fried frailty criteria (yes/no), 2) gait speed and handgrip strength as continuous, unidimensional proxies for frailty, and finally 3) two frailty dimensions based on the principal components analysis (PCA) with direct oblimin rotation on the five components of the Fried Frailty Phenotype as described before[15]. The Cox proportional-hazard assumption was checked by visual inspection of the survival curves for patients with and without meeting the frailty criteria. Hazard rates are presented bivariate as well as adjusted for age, sex, level of education, smoking, alcohol use, physical activity,

insomnia, depressive symptom severity, cognitive functioning, number of chronic somatic disease, and number of prescribed medications. Thereafter, we examined whether the three inflammatory markers, vitamin D level, and LTL (independently) were prospectively associated with mortality using separate bivariate and multivariate Cox-regression models with time to death as the dependent variable (similarly built and checked as the frailty models, but excluding frailty characteristics). Analyses of vitamin D levels were additionally adjusted for season of blood collection. In order to be able to compare the effect size of the different underlying mechanisms, we calculated Z-scores of each variable. Before calculating Z-scores, gait-speed, handgrip strength, hsCRP and IL-6 were log-transformed in order to achieve a normal distribution. For NGAL-2, three outliers were trimmed at 3 times the standard deviation in order to achieve a normal distribution. Finally, significant inflammatory markers, vitamin D levels, and/or LTL length were added simultaneously with frailty in a final model in order to examine whether the results were independent or can be explained by shared variance. All p-values <.05 were considered statistically significant. Analyses were conducted in SPSS version-25.

## RESULTS

### Sample

The baseline characteristics of the study sample (n=378) are presented in table 1, stratified by the presence of frailty. Patients with missing data varied between none (age, sex, level of education) and six (alcohol use). Compared to non-frail patients, frail patients were significantly older, less educated, more severely depressed, drank less alcohol and had more chronic somatic diseases. Both groups did not differ with respect to sex and smoking status.

**Table 1.** Baseline characteristics, stratified by frailty status

| Characteristics[a]: | | Non-frail depressed patients | Frail depressed patients | Statistics |
|---|---|---|---|---|
| | | (n=275) | (n=103) | |
| **Socio-demographics:** | | | | |
| · Age (years) | mean (SD) | 69.6 (6.9) | 73.7 (7.9) | t=-5.0, df=376, p<.001 |
| · Female sex | n (%) | 179 (65.1%) | 71 (68.9%) | $Chi^2$=0.5, df=1, p=.482 |
| · Level of education (years) | mean (SD) | 10.7 (3.5) | 9.7 (3.2) | t=2.7, df=376, p=.008 |
| · Partner relationship (yes) | n (%) | 149 (54.2) | 49 (47.6) | $Chi^2$=1.3, df=1, p=.252 |
| **Lifestyle characteristics:** | | | | |
| · Alcohol use (number of drinks/day) | median (IQR) | 0.06 (1.18) | 0.03 (0.53) | Z=-2.33, p=.020 |
| · Smoking (yes) | n (%) | 75 (27.4%) | 25 (24.8%) | $Chi^2$=0.3, df=1, p=.611 |
| · Physical activity (MET-minutes) | mean (SD) | 2908 (2561) | 1009 (1452) | t=30.6, df=365, p<.001 |
| · Body Mass Index ($kg/m^2$) | mean (SD) | 26.1 (4.2) | 27.0 (5.0) | t=5,7, df=375, p=.056 |
| **Psychopathology:** | | | | |
| · Depressive symptom severity | mean (SD) | 27.5 (12.3) | 37.2 (12.4) | t=-6.8, df=371, p<.001 |
| · Mini Mental State Examination | mean (SD) | 27.9 (1.7) | 27.1 (2.5) | t=3.8 df=375, p<.001 |
| · Insomnia Rating Scale | mean (SD) | 10.2 (5.4) | 11.7 (5.8) | t=-2.2, df=358, p=.026 |
| **Physical functioning:** | | | | |
| · Number of chronic diseases | median (IQR) | 2.0 (2.0) | 2.0 (2.0) | Z=-2.2, p=.026 |
| · Number of prescribed medications | mean (SD) | 4.4 (2.8) | 5.5 (3.0) | t=-3.4, df=373, p=.001 |
| **Markers of biological aging** | | | | |
| · hsCRP (mg/l) | median (IQR) | 1.74 (3.17) | 2.17 (3.52) | Z=-1.04, p=.297 |
| · IL6 (pg/l) | median (IQR) | 0.49 (1.09) | 0.55 (2.26) | Z=-1.46, p=.145 |
| · Lipocalin-2 (ng/l) | mean (SD) | 59.9 (21.8) | 67.9 (26.1) | t=-3.0, df=367, p=.003 |
| · 25-OH vitamin D (nmol/l) | mean (SD) | 54.6 (23.9) | 41.7 (24.1) | t=4.2, df=365, p<.001 |
| · Leucocyte telomere length (bp) | mean (SD) | 5048 (400) | 4990 (392) | t=1.2, df=366, p=.218 |

Abbreviations: SD, standard deviation; IQR, interquartile range; bp, basepairs.

[a] Number of patients with specific missing data per characteristic: n=0 for age, sex, level of education, and partner status; n=1 for the MMSE, and BMI; n=5 for depressive symptom severity, smoking, and number of prescribed medications; n=6 for alcohol use, n=9 for IL6 and Lipocalin-2; n=10 for leucocyte telomere length; n=11 for vitamin D, and physical activity; n=13 for hsCRP, and n=18 for insomnia.

## Frailty as determinant of mortality

During the 6-year follow-up, a total of 27/103 (26.2%) frail depressed patients died compared to 35/275 (12.7%) non-frail depressed patients ($Chi^2$=9.9, df=1, p=.002). Adjusted for covariates, the HR of frailty was 2.43 [95%CI: 1.33 – 4.43], p=.004.

Table 2 presents the unadjusted and adjusted prospective association between frailty and mortality. As shown, frailty is associated with an increased mortality risk, irrespective of being classified as present/absent or by the number of components met. Regarding the individual frailty components, only weight loss reached statistical significance, and regarding frailty dimensions, only performance based physical frailty reached significance (see table 2).

**Table 2.** Association of the different frailty measures with 6-year mortality by separate multivariate statistics (Cox-regression) among depressed patients[a]

| | Unadjusted | | | Fully adjusted[a] | | |
|---|---|---|---|---|---|---|
| **Predictors** | **HR** | **[ 95% CI]** | **p-value** | **HR** | **[ 95% CI]** | **p-value** |
| Fried Frailty Index: | | | | | | |
| · Frailty, dichotomous | 2.13 | [1.23 – 3.70] | .009 | 2.89 | [1.47 – 5.68] | .002 |
| · Frailty, number of components | 1.28 | [1.04 – 1.58] | .020 | 1.50 | [1.11 – 2.01] | .007 |
| Presence of FFI components (yes): | | | | | | |
| · Exhaustion | 1.29 | [0.75 – 2.21] | .358 | 1.36 | [0.72 – 2.56] | .342 |
| · Weight loss | 1.80 | [1.05 - 3.09] | .033 | 1.95 | [1.08 – 3.53] | .028 |
| · Low physical activity level | 0.98 | [0.57 – 1.70] | .942 | 0.89 | [0.45 – 1.77] | .741 |
| · Low gait speed | 1.62 | [0.92 – 2.87] | .095 | 1.71 | [0.88 – 3.32] | .113 |
| · Low handgrip strength | 1.56 | [0.88 – 2.79] | .129 | 1.54 | [0.81 – 2.94] | .192 |
| Frailty proxies, (uni)dimensional: | | | | | | |
| · Gait speed, log(s) | 3.74 | [0.92 - 15.2] | .066 | 4.41 | [0.78 – 25.0] | .093 |
| · Handgrip strength, log(kg) | 0.82 | [0.21 – 3.25] | .779 | 0.16 | [0.02 – 1.06] | .057 |
| Frailty dimensions (PCA): | | | | | | |
| · Performance based FFI[b] | 1.29 | [1.00 – 1.66] | .046 | 1.47 | [1.04 – 2.09] | .031 |
| · Vitality based FFI[b] | 1.19 | [0.91 – 1.56] | .203 | 1.29 | [0.99 – 1.66] | .055 |

[a] n=340 due to missing values on specific covariates.
Adjusted for age, sex, years of education, partner status, alcohol use, smoking, physical activity, body mass index, depressive symptom severity, sleep, cognition, chronic somatic diseases, number of prescribed medications.
[b] Performance based FFI was based on three components, i.e. gait speed, handgrip strength and low physical activity, whereas vitality based FFI was based on weight loss and exhaustion.
Abbreviations: HR, hazard ratio; CI, confidence interval; FFI, Fried Frailty Index; s, seconds; kg, kilogram.

## Biomarkers as determinants of mortality

Except for the level of IL-6, all biomarkers were significantly associated with the mortality rate, although the impact of NGAL-2 lost statistical significance in the fully adjusted model. Higher hsCRP levels was prospectively associated with increased mortality rates, whereas higher vitamin D levels and LTL were protective (see table 3).

**Table 3.** Separate bi- and multivariate Cox-regression to examine the independent effect of physiological and cellular markers of biological ageing[a]

| | Unadjusted analyses | | | Adjusted analyses[b] (frailty not included in model) | | |
|---|---|---|---|---|---|---|
| **Predictors** | **HR** | **[ 95% CI]** | **p-value** | **HR** | **[ 95% CI]** | **p-value** |
| Inflammatory markers: | | | | | | |
| · hsCRP | 1.45 | [1.11 – 1.88] | .006 | 1.42 | [1.08 – 1.86] | .011 |
| · Interleukin-6 | 1.29 | [0.99 – 1.69] | .061 | 1.31 | [0.98 – 1.75] | .072 |
| · Lipocalin-2 | 1.45 | [1.13 – 1.85] | .003 | 1.32 | [0.99 – 1.75] | .056 |
| Vitamin D[c]: | | | | | | |
| · 25-OH vitamin D | 0.57 | [0.40 – 0.80] | .001 | 0.57 | [0.39 – 0.83] | .003 |
| Telomere length: | | | | | | |
| · Leucocyte telomere length | 0.63 | [0.45 – 0.87] | .005 | 0.68 | [0.47 – 0.98] | .040 |

[a] All characteristics are expressed as Z-score, to be able to compare the HR of the individual makers.
[b] Adjusted for age, sex, education, partner status, alcohol use, current smoking, physical activity, body mass index, depressive symptom severity, sleep, cognition, chronic somatic diseases, and prescribed medications.
[c] All analysis additionally adjusted for astronomical season.
Abbreviations: HR, Hazard ratio; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; DB, change in the B of frailty (either dichotomous (yes/no) or sum score of components) after the predictor under study is added to the final multivariate model.

Subsequently, we included the three significant biomarkers (hsCRP, LTL, vitamin D) to the fully adjusted frailty models. The HR of the presence of frailty remained significant (HR=2.85 [95%CI:1.40–5.77], p=.004) as well as the HR of the sum score (HR=1.29[95% CI:0.98–1.68], p=.065). In these models, LTL lost significance, whereas hsCRP and vitamin D remained independently of frailty associated with mortality (in the dichotomous frailty model: HR of hsCRP = 1.37 [95% CI: 1.04 – 1.81], p=.026; HR of vitamin D = 0.59 [95% CI: 0.41 – 0.86], p=.005).

## DISCUSSION

In line with a recent meta-analysis on the relationship between frailty and mortality[31, 32], we found a prospective association between physical frailty and mortality over a 6-year follow-up among patients suffering from late-life depression. This association remained significant even when adjusted for depression severity, lifestyle characteristics and somatic morbidity. Moreover, the impact of frailty on mortality in late-life depression was independent of inflammatory markers, leucocyte telomere length, and vitamin D, whereas hsCRP and vitamin D were also prospectively associated with mortality independent of frailty[33]. The concept of frailty has been introduced to explain (and identify) older persons at increased risk for disability and death. Demonstrating a prospective association between a specific frailty model and mortality is generally regarded as the ultimate validation of these models. Meta-analyses of 19 longitudinal studies demonstrated that the Frailty Index, based on the deficit accumulation model, consistently predicts mortality[32]. The deficits accumulation model postulates that the proportion of at least 30 ageing-related health deficits reflects biological age on top of chronological age[34]. Nonetheless, this model can be criticised to be merely a model of multimorbidity, as chronic diseases as well as disease severity states are included as health deficits[34]. Currently, many studies have shown that the Fried Frailty Phenotype is also associated with increased mortality rates[35], although a meta-analysis is not available. Within the UK biobank, involving 493,737 persons, the Fried Frailty Phenotype predicted mortality independent of multimorbidity[35]. These authors argue for more research on the impact of frailty across different disease contexts. This may be especially important for a mental health context, as the impact of the frailty phenotype is less in patients with neuropsychiatric diseases compared to other chronic disease clusters[8]. This might be explained by overlapping criteria between frailty and (neuro)psychiatric disorders[8]. To our knowledge, this is the first study on the impact of frailty in a homogeneous sample of psychiatric patients. Moreover, in contrast to previous studies, we adjusted for multimorbidity as well as lifestyle characteristics. We found most robust results for the original operationalisation of the Fried Frailty Phenotype, showing that frailty is more than the sum of its components. Previously, we reported that within the NESDO-study, the mortality rate was significantly higher among depressed patients compared to the non-depressed comparison group[22]. However, when adjusted for demographic, lifestyle and somatic comorbidity, this difference lost significance[18]. This latter finding points to the importance of adequate adjustment for confounders. Previous studies on the association between

depression and mortality have been criticised for incomplete correction for potential confounders[3]. Frailty is a clinical phenotype which is supposed to result from many different pathophysiological mechanisms[33]. Studies on the biology of frailty are booming and a large number of frailty-related biomarkers have been proposed, in particular representing inflammatory, endocrine, and metabolic pathways[33, 36]. In this study, we have focused on immunosenescence, vitamin D deficiency and shortened LTL. Of the three inflammatory markers, IL-6 and NGAL-2 became non-significant due to shared variance with frailty, whereas increased hsCRP remained independently associated with mortality. Immunosenescence manifests itself by a decline of B- and T-cell function and an impaired response to chronic antigenic stimuli[37]. Paradoxically, it creates a condition of chronic low-level inflammation, also called "inflamm-ageing"[37], and is characterised by elevated levels of the inflammatory cytokine IL-6 and the non-specific acute phase reactant CRP[38]. Both frailty and depression have been associated with higher serum levels of CRP and IL-6[39], albeit frailty more consistently compared to depression[40]. Previously, we have shown that physical frailty is associated with low-graded inflammation in late-life depression[16].



We found that shorter LTL was associated with mortality in our sample, independent of lifestyle and somatic disease burden. Telomere length, as a marker of cellular aging, has been associated with increased mortality rates and the onset of various age-related diseases. With each cell division some telomeric DNA is lost, leading to apoptosis when a critical length is reached. Next to replication, endogenous factors may also cause telomere shortening, including inflammation, metabolic dysregulation and oxidative stress[41]. These mechanisms become more prominent with chronological aging. Shortened LTL is also consistently associated with depression earlier in life[1], but the association seems to be lost in older age samples[26]. Thus far, the limited studies reported only a weak association between telomere length and frailty[17]. Nonetheless, LTL and frailty share variance in explaining mortality in our sample. In our study, higher vitamin D levels were protective for death. One of the key features of frailty, and a potential link with vitamin D deficiency, is the loss of skeletal muscle, or sarcopenia[23]. In older persons, a consistent relationship between hypovitaminosis D and muscle dysfunction has been demonstrated, as well as a positive effect of vitamin D supplementation on balance and muscle strength[42]. A recent dose-response meta-analysis showed an association between low-levels of vitamin D and higher risk for frailty[43]. Although frailty-experts consider vitamin D supplements useful for frail persons who are vitamin D deficient[44], intervention studies into the effect of vitamin

D supplementation on frailty are currently lacking[45]. Previously, we have shown that physical frailty in late-life depression is associated with low vitamin D levels[18]. Moreover, low vitamin D levels are consistently associated with (late-life) depression[18], although causality has been questioned and they are merely seen as a marker of poor health[15]. We found that lower vitamin D has a strong association with mortality in late-life depression, independent of depressive symptom severity and independent of frailty. This suggests that randomised controlled trials of vitamin D supplementation in late-life depression should have mortality as an end point instead of improvement of depressive symptoms.

For proper interpretation, some methodological issues need to be addressed. Strengths of this study are the relatively large sample of patients with a confirmed depressive disorder as well as the comprehensive assessment of depression characteristics and confounding factors. However, some limitations should also be acknowledged. First of all, the Fried Frailty Phenotype[23] has been criticised for taking little account on variables including cognitive and emotional domains in the older adult. However, using the Fried criteria for studying frailty in a psychiatric sample enables us to disentangle mental disorders, cognitive aging and physical frailty. Moreover, the frailty phenotype is a well validated instrument and is widely used in frailty research[46]. Secondly, we did not have access to causes of death. On one hand, inclusion of only older adults who deceased from frailty-related causes in the sensitivity analyses would have led to more accuracy. On the other hand, even if causes of death are known, it is arbitrarily which causes of death should be considered frailty related. Moreover, our sample size was too small to conduct subgroup analyses for patients with specific somatic comorbidity patterns. Therefore, we adjusted all analyses for the number of chronic somatic conditions as a dimensional indicator of multimorbidity and for the number of prescribed drugs as a severity marker of comorbid chronic diseases. Finally, we adjusted only for covariates at baseline, while fluctuations in covariates over time, for example in depressive symptom severity, may additionally impact on the mortality.

The management of frailty is an important clinical priority, especially for health professionals working with middle aged and older persons. While frailty has been largely neglected in mental health care, future studies should focus on the clinical implications of frailty across different psychiatric disorders to facilitate the development of interventions to modify frailty and ameliorate its effects in these vulnerable patients. In light of the many mechanisms underlying frailty, we should adopt a wider range of

interventions when targeting frailty in late-life depression. Of the mechanisms explored in the present study, shared variance with leucocyte telomere length seems relevant regarding mortality whereas inflammation and vitamin D seems to have independent effects on the risk of mortality. While the effectiveness of vitamin D supplementation in the treatment of depression is still debated[44, 45], one may hypothesise that vitamin D supplementation in late-life depression might be able to prevent adverse health effects like mortality. A recent network analyses on interventions for frailty pointed to the importance of physical activity interventions with nutritional supplementation as most promising[47].

Since frailty is identifiable in depressed older adults and prospectively associated with mortality independently of the extent of multimorbidity, sociodemographic, and lifestyle characteristics, we hope that these findings will contribute to the evolution of mental health-care services to better meet the needs of our increasingly complex patient populations.



**CLINICAL POINTS:**

- Physical frailty is increasingly recognised as an important concept for risk stratification in somatic medicine, but largely neglected in mental health care.
- Frailty is associated with increased mortality rates in depressed patients, independent of somatic comorbidity and lifestyle.
- The pathophysiology of frailty may guide development of treatment strategies to lower excess mortality associated with psychiatric disorders.

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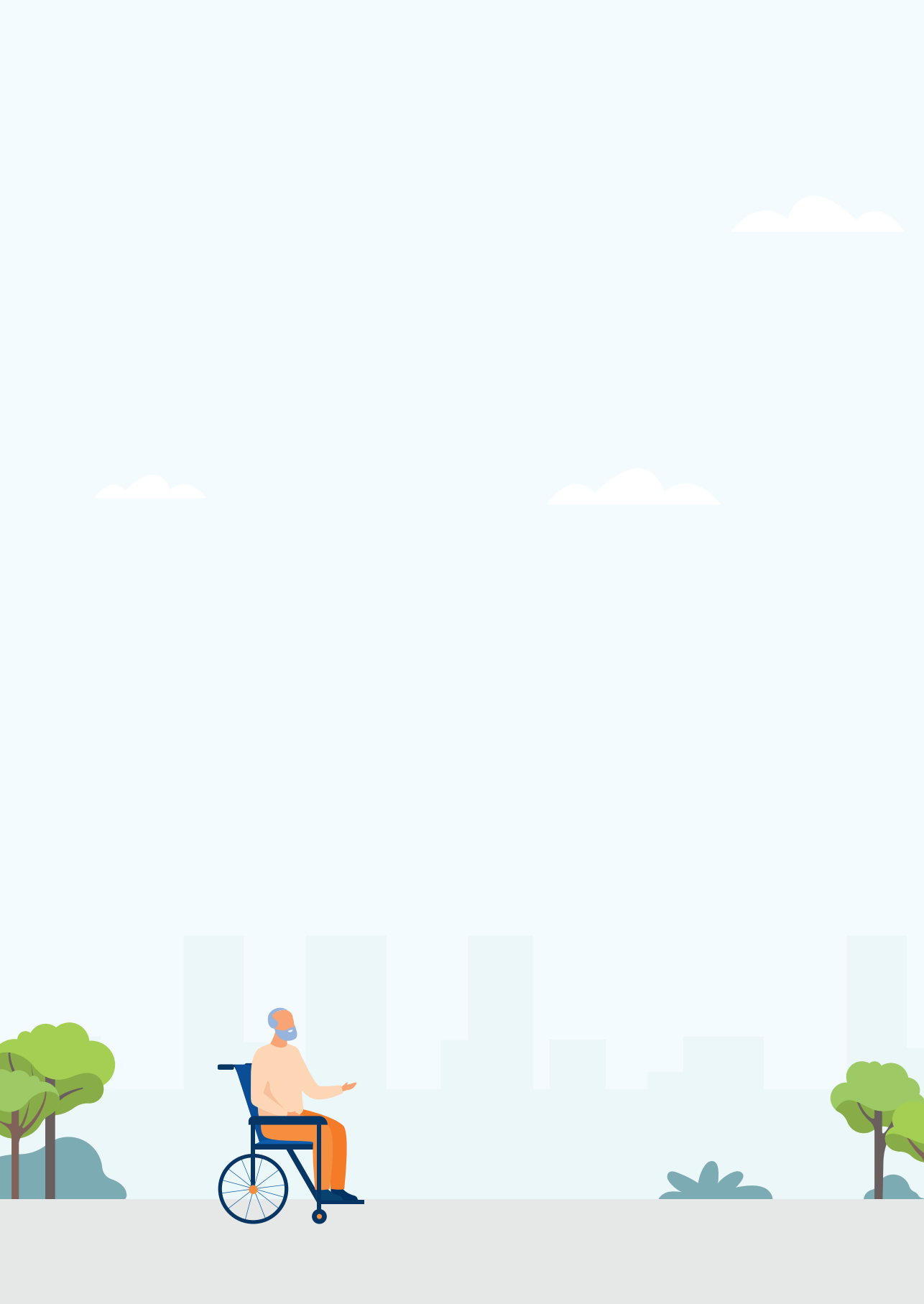

# CHAPTER 6

## A PROSPECTIVE STUDY INTO CHANGE OF VITAMIN D LEVELS, DEPRESSION AND FRAILTY AMONG DEPRESSED OLDER PERSONS

Karen S. van den Berg, Johanna M. Hegeman, Rob H.S. van den Brink,
Didi Rhebergen, Richard C. Oude Voshaar, Radboud M. Marijnissen.

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## ABSTRACT

***Objectives:*** While vitamin D is involved in frailty as well as depression, hardly any study has examined the course of vitamin D levels prospectively. The objective of this study is to examine whether a change of vitamin D in depressed older adults is associated with either depression course, course of frailty, or both.

***Methods:*** The study population consisted of 232 of 378 older adults (60-93 years) with a DSM-IV defined depressive disorder participating in the Netherlands Study of Depression in Older persons, a prospective clinical cohort study. Baseline and two-year follow-up data on depressive disorder (DSM-IV diagnosis), symptom severity (inventory of depressive symptoms), frailty phenotype (and its individual components), and vitamin D levels were obtained. Linear mixed models were used to study the association of change in vitamin D levels with depression course, course of frailty, and the combination.

***Results*:** Vitamin D levels decreased from baseline to follow-up, independent from depression course. An increase in frailty was associated with a significantly sharper decrease of vitamin D levels over time. Post-hoc analyses showed that this association with frailty might be driven by an increase of exhaustion over time and counteracted by an increase in walking speed.

***Conclusions:*** Our findings generate the hypothesis that vitamin D supplementation in late-life depression may improve frailty, which may partly explain inconsistent findings of randomised controlled trials evaluating the effect of vitamin D for depression. We advocate to consider frailty (components) as an outcome in future supplementation trials in late-life depression.

## INTRODUCTION

About half of the older persons has a vitamin D deficiency[1]. In addition to negative effects on bone health, low vitamin D levels are associated with higher prevalence of multimorbidity[2]. Associations of vitamin D with several age-related conditions as well as the presence of nuclear vitamin D receptors in various organ systems, has stimulated vitamin D research in geriatric medicine. Nonetheless, causality between vitamin D deficiency and many health conditions, in particular depressive disorder and frailty, remains elusive.

Meta-analyses of observational studies have identified cross-sectional as well as longitudinal associations of low vitamin D levels with depressive symptoms[3-5]. A causal effect is biologically plausible, as nuclear vitamin D receptors have been found in brain regions involved in depression[6]. Furthermore, vitamin D is involved in the regulation of growth factors, monoamine neurotransmitters, and neuroinflammation[7, 8]. Nonetheless, reverse causation cannot be excluded since depression-related behaviour easily results in less sun exposure[9]. Moreover, meta-analyses of vitamin D supplementation trials among depressed persons did not show an overall reduction of depressive symptoms[10-12]. Apart from this, the largest vitamin D supplementation trial among 18,353 persons did not reveal any effect on the prevention of depression over a five-year follow-up[13].



Meta-analysis also demonstrated an inverse association between frailty and vitamin D levels[14]. Again, a causal effect is biologically plausible as nuclear and non-nuclear vitamin D receptors are involved in calcium/phosphate homeostasis in muscle cells, as well as muscle cell differentiation and proliferation[15]. Low vitamin D levels have been consistently associated with declined muscle function[16]. A meta-analysis of randomised-controlled trials into the effect of vitamin D supplementation among persons >60 years demonstrated a beneficial effect on muscle strength and balance[17]. Although sarcopenia is a core concept underlying frailty[18, 19] the evidence to improve frailty by vitamin D supplementation is still insufficient[20]. Since depression and frailty are bidirectionally associated[21], the association between vitamin D deficiency and depression might be confounded by frailty. Furthermore, prospective studies into the association of vitamin D and depression almost without exception lack follow-up assessment of vitamin D levels. Therefore, the present study examines whether change of vitamin D levels over two years in older persons with a depressive disorder is related to course of depression

and/or course of frailty. We hypothesise that vitamin D levels will improve over time in case of remission of the depression and further deteriorate in case of non-remission. In addition, we hypothesise that vitamin D levels over time are inversely associated with frailty over time.

## METHODS

### Study sample

The present study is part of the Netherlands Study of Depression in Older persons (NESDO), a multi-centre prospective cohort study, designed to examine the determinants, course and consequences of late-life depression[22, 23]. Between 2007 and 2010, 378 depressed persons were recruited from both mental health institutions and general practices, and 132 non-depressed comparisons were recruited from general practices. Participants were aged 60 to 93. In the present study, only depressed persons were included. Depressed persons had a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR[24]) diagnosis of major depressive disorder (MDD; 95.0%) and/or dysthymia (26.5%) in the previous six months, or minor depression (5.3%) in the last month. Reasons for exclusion from NESDO were a primary diagnosis of psychotic or bipolar disorder, or (suspicion of) dementia, a Mini Mental State Examination[25] score <18/30, and insufficient command of the Dutch language. For the present study, we additionally excluded patients using vitamin D supplementation. Participants were assessed at baseline and two-year follow-up. Data were obtained about mental health outcomes, demographic characteristics as well as psychosocial, biological, cognitive and genetic determinants. Trained research assistants conducted the interviews. The ethical review boards of the participating centres approved the study. All participants provided written informed consent. Data are available on request from the authors.

### Measures

*Vitamin D*

Vitamin D levels were similarly assessed at baseline and two-year follow up. Serum 25-(OH) vitamin D levels were measured using isotope dilution-online solid-phase extraction liquid chromatography–tandem mass spectrometry, as described previously[26]. The limit of quantitation was 4.0 nmol/l and the intra-assay coefficient of variation was <7.2%.

*Depression*

Depression was diagnosed at baseline and two-year follow-up by the Composite International Diagnostic Interview (CIDI; WHO version 2.1, lifetime version). Depressed persons who no longer fulfilled the DSM-criteria for any depressive disorder at follow-up were classified as remitters. The severity of depression was assessed with the 30-item self-report version of the Inventory of Depressive Symptoms (IDS-SR[27]) at baseline and two-year follow-up.

*Frailty*

Frailty was assessed according to the frailty phenotype[18] and a severity score (0-5) was assigned, based on the number of criteria met[28]: *weakness:* maximum handgrip strength (as measured by two squeezes with the dominant hand in a dynamometer) below a cut-off stratified by sex and body mass index (BMI)[18]; *slowness:* time on a six-meter walking test ≥8 seconds for men ≥173 cm or women ≥159 cm tall, or ≥9 seconds for men <173 cm and women <159 cm tall; *exhaustion:* a score of ≥3 out of 4 points on one or both of the IDS questions about energy level and leaden paralysis/physical energy; *low physical activity:* no daily activities such as walking or gardening, and the performance of sports less than once a week, as assessed with the International Physical Activity Questionnaire (IPAQ[29]); and *unintended weight loss:* a positive answer to the CIDI question about unintended weight loss (≥1 kg/week, for two or more consecutive weeks) or a BMI <18.5 kg/m$^2$. Post-hoc, we examined the change in the individual frailty components over time, namely maximum grip strength (in kilograms), time on the six-meter walking test (in seconds), sum score of the two exhaustion questions from the IDS (range 2-8), Metabolic Equivalent (MET)-minutes per week (i.e. energy requirements of the physical activities performed, expressed as multiples of the resting metabolic rate) calculated from the IPAQ, and weight (in kilograms).

*Covariates*

Based on their association with vitamin D level and depression[30], the following covariates were selected: astronomical season of blood withdrawal at baseline and follow-up (winter 21 November – 20 February; spring 21 February – 20 May; summer 21 May – 20 August; autumn 21 August – 20 November), as well as baseline assessments of age, sex, years of education, smoking, physical activity, renal function, waist circumference in cm, and number of chronic diseases. The level of physical activity was classified as either sufficient or insufficient according to the WHO as based on the validated norm scores of the IPAQ[29, 31]. Glomerular filtration rates (GFR) were estimated by the Chronic Kidney Disease

Epidemiologic Collaboration (CKD-EPI[32]) formula to assess renal function. The number of chronic diseases was assessed by means of self-report, as previously validated[33].

*Statistical analysis*

Baseline characteristics were compared by chi-square tests, t-tests for independent samples, and non-parametric tests for 1) study participants versus dropouts and 2) included participants stratified by depression status at follow-up. P-values <.05 were considered significant. Random coefficient mixed effect models were used to study the associations between change in vitamin D levels on the one hand and depression course and course of frailty on the other. The dependent variable in these analyses was vitamin D level, corrected for season of blood withdrawal, as assessed at baseline and two-year follow-up. To determine the best-fitting model, models with random coefficients for intercept and/or slope per subject were compared using the likelihood ratio test. For all analyses, a random intercept model was the best fitting model. In separate analyses the association of change in vitamin D with the following independent variables was examined: depression course, as assessed by (1) remission (yes/no), and (2) change in IDS score over the follow-up period; and course of frailty as assessed by (3) change in frailty score, and by (4) change in each individual frailty component score. Presence of an association was tested by the interaction of the independent variable with the variable 'time', which indicated assessment of vitamin D level at baseline or follow-up. This interaction shows whether the change in vitamin level from baseline to follow-up is associated with the independent variable and will be indicated in short as 'the interaction between change in vitamin D level and the independent variable'. All independent variables were coded so that a positive regression coefficient (i.e. the estimate of the effect studied) indicates that an increase in health (e.g. remission of depression or reduction of frailty) is related to an increase in vitamin D level.

In a final analysis, the strongest associations of change in vitamin D level with depression course (either analysis 1 or 2 above) and course of frailty (analysis 3 or 4) were compared and checked for mutual independence by including both interactions in the model. For this selection, effect sizes (ES) of the strength of an association were computed, by dividing the regression coefficient for the above interaction by the standard deviation of the outcome variable (i.e. vitamin D level for all analyses) at baseline and multiplying it with the standard deviation at baseline of the independent variable (for continuous variables) or 1 (for categorial variables). Analyses were performed using IBM SPSS statistics version 24 and were adjusted for all covariates.

# RESULTS

## Study sample

Of the 378 depressed persons included in NESDO, 232/378 (61.4%) participated in the present study (dropout at follow-up: n=93; vitamin D level missing at baseline or follow-up: n=29; vitamin D supplementation: n=24). At baseline, excluded persons were more frequently frail than participants (37% versus 26%; $\chi^2$=5.28, df=1, p=.022) and had a lower vitamin D level (49.5 [22.4] versus 54.5 [23.6] nmol/l; t=1.97, df=365, p=.050), but did not differ with respect to age, sex or depressive symptom severity.

**Table 1.** Characteristics of the study sample, stratified by depression status at two-year follow up

| Characteristic | Non-remitted depression N = 112 | Remitted depression N = 120 | Statistic |
|---|---|---|---|
| Age (year) – mean (sd) | 70.8 (7.8) | 69.9 (7.1) | t 0.86, df 230, p .390 |
| Sex (male) – n (%) | 42 (37.5%) | 43 (35.8%) | $\chi^2$ 0.07, df 1, p .792 |
| Education (years) – mean (sd) | 10.7 (3.7) | 10.8 (3.3) | t 0.11, df 230, p .910 |
| Number of chronic diseases – mean (sd) | 2.4 (1.6) | 1.7 (1.1) | t 3.87, df 230, p<.001* |
| Sufficient physical activity (IPAQ†-based) – n (%) | 80 (71.4%) | 88 (73.3%) | $\chi^2$ 0.78, df 1, p .377 |
| Currently smoking – n (%) | 30 (26.8%) | 25 (20.8%) | $\chi^2$ 1.06, df 1, p .303 |
| Waist circumference (cm) – mean (sd) | 94.8 (13.7) | 90.8 (11.2) | T 2.42, df 230, p .016* |
| Renal function (CKD-EPI‡ (ml/min/1.73 $m^2$)) – mean (sd) | 70.8 (17.3) | 74.8 (14.4) | t 1.91, df 230, p .057 |
| IDS§ score (0-84) – mean (sd) | 33.6 (12.2) | 25.6 (11.9) | t 5.04, df 228, p<.001* |
| Frailty present – n (%) | 31 (27.7%) | 26 (21.7%) | $\chi^2$ 1.44, df 1, p .230 |
| Frailty score (0-5) – mean (s.d.) | 1.9 (1.3) | 1.5 (1.3) | t 2.16, df 210, p .032* |
| Frailty components | | | |
| · *Grip strength (kg) – mean (s.d.)* | 28.6 (11.3) | 29.4 (12.4) | t -0.51, df 230, p.661 |
| · *6-meter walking time (s) – mean (s.d.)*¶ | 7.8 (4.0) | 6.8 (3.7) | U 5439.0, p .019* |
| · *Exhaustion (score 2-8) – mean (s.d.)* | 4.9 (1.6) | 4.4 (1.6) | t 2.52, df 223, p .012* |
| · *MET††-minutes / week – mean (s.d.)* | 2480.2 (2260.1) | 2751.5 (2375.5) | t 0.88, df 223, p .381 |
| · *Weight (kg) – mean (s.d.)* | 76.1 (15.3) | 72.5 (13.9) | t 1.89, df 230, p .061 |
| Season of blood withdrawal – n (%) | | | |
| · *Winter* | 18 (16.1%) | 23 (19.2%) | $\chi^2$ 1.12, df 3, p .772 |
| · *Spring* | 35 (31.3%) | 31 (25.8%) | |
| · *Summer* | 36 (32.1%) | 38 (31.7%) | |
| · *Autumn* | 23 (20.5%) | 28 (23.3%) | |
| 25-OH vitamin D (nmol/l) | | | |
| · *Baseline* | 54.1 (24.1) | 54.9 (23.1) | t -0.26, df 230, p .797 |
| · *Two-year follow-up* | 50.4 (23.0) | 46.8 (19.7) | t 1.23, df 230, p .207 |

† International Physical Activity Questionnaire
‡ Chronic Kidney Disease Epidemiology Collaboration
§ Inventory of Depressive Symptomatology
¶ skewed distribution; Mann-Whitney U test performed, corrected for tied ranks
†† Metabolic Equivalent
* statistically significant (p <.050)

The characteristics of the study sample (n=232), stratified by depression status at follow-up, are presented in table 1.

### Change of vitamin D over time

In the remitted subgroup, vitamin D levels decreased more over the two years follow-up period (t for paired observations 4.83, p=<.001) than in the non-remitted subgroup (t=1.82, p=.071). However, linear mixed models showed that – also after controlling for covariates - change in vitamin D did not depend on depression status at follow-up (see table 2). Nonetheless, an increase in vitamin D was associated with a decrease of the IDS score. Each point reduction on the IDS was related to a vitamin D level increase of 0.22 nmol/l (s.e. 0.11; p=.049; ES is 0.12).

**Table 2.** Interaction between change in vitamin D and depression course

| Interaction with | F | p | Course type | Estimate (standard error) | Effect size (95-%-confidence interval) |
|---|---|---|---|---|---|
| *Disease model:* | | | | | |
| Depression status at follow-up[†] | 3.16 | .077 | Remission | -4.61 (2.60) | -0.20 (-0.41; 0.02) |
| | | | Non-remission (=reference) | 0 | |
| *Dimensional depression model:* | | | | | |
| Change in IDS[‡] score | 3.90 | .049* | Each point less on IDS[‡] | 0.22 (0.11) | 0.12 (0.00; 0.24) |

[†] adjusted for age, sex, years of education, season of blood withdrawal (baseline and follow-up), smoking, physical activity, number of chronic diseases, and waist circumference
[‡] Inventory of Depressive Symptoms
* statistically significant (p <.050)

The interaction between course of frailty and change in vitamin D level are presented in table 3. As shown, an increase in vitamin D levels proved to be related to a decrease in continuous frailty score: each frailty criterion less was related to a vitamin D increase of 3.04 (s.e. 1.14) nmol/l (ES=0.17, p=.008). Post-hoc analyses suggested that an increase of vitamin D over time was in particular associated with decreasing scores on exhaustion and an increasing six-meter walking time (i.e. a slower gait speed), although results were not statistically significant (exhaustion: ES=0.10, p=.054; walking time: ES=-0.11, p=.066).

**Table 3.** Interaction between change in vitamin D and course of frailty

| Interaction with | F | p | Course type | Estimate (standard error) | Effect size (95-% Confidence intervall) |
|---|---|---|---|---|---|
| *Severity of frailty:* | | | | | |
| · Change in frailty score† | 7.08 | .008* | Each frailty criterion less | 3.04 (1.14) | 0.17 (0.04; 0.29) |
| *Frailty components:* | | | | | |
| · Change in grip strength† | 0.07 | .799 | Each additional kg grip strength | 0.04 (0.16) | 0.02 (-0.13; 0.18) |
| · Change in 6-meter walking time†§ | 3.41 | .066 | Each second walking time less | -0.67 (0.36) | -0.11 (-0.23; 0.01) |
| · Change in exhaustion† | 3.75 | .054 | Each point less on exhaustion questions | 1.54 (0.80) | 0.10 (-0.00; 0.21) |
| · Change in MET¶-minutes‡ | 0.19 | .668 | Each additional 1000 MET-minutes | 0.21 (0.48) | 0.02 (-0.07; 0.11) |
| · Change in weight† | 1.44 | .232 | Each additional kg | 0.32 (0.26) | 0.20 (-0.12; 0.52) |

† adjusted for age, sex, years of education, season of blood withdrawal (baseline and follow up), smoking, physical activity, number of chronic diseases, and waist circumference
‡ adjusted for age, sex, years of education, season of blood withdrawal (baseline and follow up), smoking, number of chronic diseases, and waist circumference
§ Δ 6-meter walking time is normally distributed
¶ Metabolic Equivalent of Time
* statistically significant (p<.050)



## Combined analyses on frailty and depression

In the final analysis (see table 4), we examined the association of vitamin D with either change in depression (IDS score) or frailty (number of components) when controlled for each other. This analysis showed that an increase in vitamin D level over a two-year follow-up remained significantly associated with improved frailty scores when adjusted for the change in depression (ES is 0.13; p=.042), whereas no independent association with the change in depression was found.

**Table 4.** Combined interactions of depression course and course of frailty with change in vitamin D

| Interaction with | F | p | Course type | Estimate (standard error) | Effect size (95-% confidence interval) |
|---|---|---|---|---|---|
| Change in frailty score† | 4.19 | .042* | Each frailty criterion less | 2.47 (1.21) | 0.14 (0.01; 0.27) |
| Change in IDS‡ score† | 2.02 | .157 | Each point less on IDS | 0.18 (0.13) | 0.10 (-0.04; 0.23) |

† adjusted for age, sex, years of education, season of blood withdrawal (baseline and follow up), smoking, physical activity, number of chronic diseases, and waist circumference
‡ Inventory of Depressive Symptomatology
* statistically significant (p <.05)

# DISCUSSION

## Main findings

In our large sample of depressed older persons, vitamin D levels decreased over a two-year follow-up. Increasing vitamin D levels were associated with improvement of depressive symptom severity as well as frailty. Nonetheless, analysing the association between vitamin D with depressive symptom severity and frailty simultaneously revealed only an independent effect with frailty. Post-hoc analyses showed that the association of increasing vitamin D levels with decreasing frailty over time may be driven by the frailty component of exhaustion and counteracted by the frailty component of walking speed.

## Vitamin D and depression

Although meta-analyses of longitudinal studies demonstrated that baseline vitamin D level is related to depression course[3, 4], in other studies only cross-sectional associations have been found, which could be due to residual confounding or reverse causality[9, 34]. The only prospective study up till now with multiple vitamin D assessments as in our study, demonstrated an association between increasing vitamin D levels and decreasing depressive symptom scores, but only in the youngest cohort (55-65 years) with vitamin D levels <58.6 nmol/l and not in persons >65 years[35]. Since we did not find an independent association of depression course with change in vitamin D, our results do not support a causal relationship in any direction between a clinical depression diagnosis and vitamin D deficiency. We found a significant association between increasing IDS scores and decreasing vitamin D levels, which lost significance after addition of the association with frailty to the model. This is an important finding, since in the majority of studies included in meta-analyses into the association between vitamin D and depression[3, 4] depression was defined as a score above a cut-off on a depressive symptom scale and none of the included studies adjusted for physical frailty. Due to overlapping criteria, self-reported depressive symptom scales may easily be confounded by the severity of physical frailty[36-38].

## Vitamin D and frailty

In line with our results, significant associations between low vitamin D levels and frailty were demonstrated in a prospective study[39] and a meta-analysis of cross-sectional studies[40]. Previously, an association between lower baseline vitamin D levels and prevalence and incidence of frailty was demonstrated among depressed older

persons[41]. Since sarcopenia is considered a main feature of frailty[19], vitamin D deficiency might contribute to frailty by decreasing muscle function. In case of deficiency, the direct and indirect molecular effects of vitamin D on the muscle cell decline, as well as its anti-inflammatory properties, which may contribute to the prevention of frailty. Furthermore, hyperparathyroidism may arise, leading to loss of muscle function[42]. On the other hand, frailty may, similar to depression, contribute to low vitamin D levels by reduction of sunlight exposure due to decreased outdoor activities.

The finding that (remission of) depressive disorder was not associated with change in vitamin D levels and the association between changes in depressive symptoms and vitamin D levels disappeared after correction for frailty, may point to confounding of self-report depressive symptom severity by frailty. Frailty and depression are closely associated, with meta-analyses classifying 40.4% of depressed patients as being frail and 38.6% of frail persons as being depressed[21]. Furthermore, frailty and depression have overlapping diagnostic criteria, such as exhaustion, weight loss, reduced activity and psychomotor slowness. Our findings lead to the hypothesis that, in light of this high level of comorbidity and overlapping diagnostic criteria[36-38], confounding by frailty of studies into the association between depression and vitamin D is indeed likely. This hypothesis fits with the results of an Australian cohort study showing a crude mortality hazard of 4.3 for depression among males >75 year, which dropped to 1.8 after additional correction for frailty[43].



Subsequent analyses showed that the longitudinal association between vitamin D and frailty might be driven by subjective feelings of exhaustion. Signs of exhaustion may clinically easily be mixed up with symptoms of depression. Although exhaustion was measured by two items from the IDS questionnaire, it is known that self-report items of exhaustion are strongly associated with performance on a physical graded exercise test[44] and predictive of cardiovascular disease[45]. This means that in a depressed older population, feelings of exhaustion might be a better indicator of physical health than of depression. Interestingly, the frailty component slowness showed a trend in the opposite direction (p=.066), but this effect was apparently not strong enough to nullify the association between vitamin D and frailty severity.

**Limitations**

Compared to other studies, we found a strong decrease in vitamin D (-6.0 nmol/l) in two years. In most population-based studies, vitamin D levels were relatively stable during

follow-up[46-49]. In the subgroup >65 years of the Longitudinal Aging Study Amsterdam vitamin D decreased on average 6.9 nmol/l in 13 years[35]. An explanation for our comparable decrease in a shorter time might be that normal behavioural changes with ageing that add to lower vitamin D levels, such as less dietary intake of vitamin D and less time spent outdoors[50], might have been amplified in our depressed population. Another explanation is our exclusion of participants on vitamin D supplementation, since in other studies supplementation is considered an important contributing factor to increasing vitamin D levels[46, 48]. Nevertheless, systematic bias cannot be fully excluded. The baseline vitamin D assessments were performed shortly after blood collection, whereas follow-up vitamin D assessments were done after a storage period of at least six years. However, even when duration of storage would have affected the absolute values at follow-up, this would not have biased the association with change in depression or frailty. Finally, our follow-up period of two years was relatively short, compared to other studies on tracking of vitamin D levels. Since remission of depression was based on the six months before follow-up, the period for recovering vitamin D levels might have been too short in some patients. This is especially relevant as it is not clear how long it takes for vitamin D levels to restore after resumption of outdoor activities.

**Conclusions and implications**

Among depressed older patients, an increase of vitamin D levels over the course of two-years was not associated with a change in depression, while it was associated with improving frailty scores. Interestingly, frailty and depression are often intertwined, and exhaustion may be a feature of both conditions. Since exhaustion is a probable driving factor in the association between increasing vitamin D levels and improving frailty scores, it may be more related to physical health than to depression. Based on our results, we hypothesise that this might have added to inconclusive findings on the relationship between depression and vitamin D in previous studies. Future supplementation trials should consider inclusion of frailty and exhaustion as outcomes, besides depression parameters.

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# CHAPTER 7

## ADVERSE HEALTH OUTCOMES IN VITAMIN D SUPPLEMENTATION TRIALS FOR DEPRESSION: A SYSTEMATIC REVIEW

Karen S. van den Berg, Radboud M. Marijnissen, Rob H.S. van den Brink, Richard C. Oude Voshaar, Johanna M. Hegeman.

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## ABSTRACT

***Background:*** Vitamin D deficiency is a universal risk factor for adverse health outcomes. Since depression is consistently associated with low vitamin D levels as well as several adverse health outcomes, vitamin D supplementation may be especially relevant for depressed persons. This review examines the potential benefits of vitamin D for (somatic) health outcomes in randomised controlled supplementation trials for depression.

***Method:*** Systematic literature search to assess whether adverse health outcomes, such as frailty, falls, or cognitive functioning, were included in vitamin D supplementation trials for depression, and whether these outcomes were affected by supplementation. The revised Cochrane tool for assessing risk of bias in randomised trials was used.

***Results:*** Thirty-one trials were included. Adverse health outcomes were considered in five studies. Two studies reported some beneficial effect on an adverse health outcome.

***Conclusions and implications:*** While depressed persons are at increased risk of vitamin D deficiency, supplementation trials hardly addressed the common negative health consequences of low vitamin D levels as secondary outcome measures. Well-designed trials of the effects of vitamin D supplementation in late-life depression should explore whether adverse health outcomes can be prevented or stabilised, and whether depression benefits from this improvement.

Systematic review registration number: PROSPERO CRD42020215912

## INTRODUCTION

A poor vitamin D status is considered a universal risk factor for adverse health outcomes. Depending on the presence of other risk factors, vitamin D deficiency may lead to the onset of several diseases[1]. Importantly, almost half of the persons older than 65 years have a vitamin D deficiency[2], which has led to many prevention guidelines on vitamin D supplementation[3]. Vitamin D supplementation may be particularly relevant for depressed persons. Vitamin D deficiency and depression often occur together, as consistently reported in observational studies[4]. Vitamin D deficiency in depression is at least partly a consequence of negative lifestyle effects of depression, such as limited sun exposure and inadequate diet[5]. A causal role is also hypothesised, based on a dose-response relationship between lower vitamin D levels and the incidence of late-life depression[6], and plausible mechanisms such as the neurotrophic effects of vitamin D and its role in the synthesis of neurotransmitters[7-9]. Nonetheless, results of randomised controlled trials (RCTs) evaluating vitamin D supplementation for depression are inconsistent, partly due to heterogeneity of the present studies regarding the assessment of depression, vitamin D status, and vitamin D supplementation regime. One overall meta-analysis of RCTs on vitamin D supplementation in depression demonstrated no effect[10]. Nevertheless, a beneficial effect of vitamin D on depression was observed in two smaller meta-analyses of four studies limited to clinically depressed persons[11] and seven studies without 'biological flaws' (such as inclusion of participants without vitamin D deficiency, or inadequate vitamin D supplementation strategies) among persons with depressive symptoms[12].

Depressive disorder is associated with the onset of a poor health status and several chronic diseases[13]. Therefore, vitamin D supplementation may be particularly relevant for the prevention of these adverse health outcomes. Adverse health outcomes in depression that have also been associated with low vitamin D levels are frailty, poor cognitive functioning, falling, and physical disability[14-17]. Recently, we found that among depressed older persons, a decrease in vitamin D levels over a two-year follow-up was not associated with a change in depressive symptom severity whereas it was associated with frailty and exhaustion[18]. Vitamin D supplementation may thus be relevant to improving the somatic health status among depressed persons (selective prevention).

Therefore, the aim of the present systematic review is to explore whether vitamin D supplementation trials in depression have evaluated adverse health outcomes

secondary to depression, and whether vitamin D supplementation improves adverse health outcomes related to vitamin D deficiency and depression.

## METHODS

### Search strategy

A systematic search was conducted in the electronic databases of PubMed, EMBASE, and PsycInfo, last on 23 November 2020. For each database, a comprehensive search strategy was developed in consultation with a librarian. We combined search terms on depression, vitamin D, study design (randomised controlled trials/reviews), and their derivatives and synonyms (see supplemental information for the complete search strategy). Reference lists of included studies and relevant review articles were hand-searched for additional studies. This systematic review was performed according to the PRISMA guidelines[19]. The protocol was registered at PROSPERO (www.crd.york.ac.uk/prospero; registration number CRD42020215912).

### Eligibility

Eligible studies were peer-reviewed and published randomised clinical trials of vitamin D supplementation with the main focus on depression or depressive symptoms. Studies in English or Dutch were eligible. No restrictions regarding the year of publication were applied. Studies in adult populations in different settings (community samples or clinical populations, i.e. in hospitals, mental health care institutions and nursing homes) were included. Given the low prevalence of adverse health outcomes in younger age groups, studies performed in children/adolescent populations or exclusively in adults under 40 years were non-eligible. Studies among participants with primary diagnoses other than depression, i.e. schizophrenia or dementia, or with a focus on anxiety, well-being or quality of life were excluded. Studies evaluating supplementation of vitamin D in a clear dosing schedule, regardless of administration form (oral/intramuscular), were included, as well as studies giving an additional supplement besides vitamin D, i.e. calcium or fish oil. If dosages were unclear, i.e. if vitamin D was supplemented in the form of a multinutrient (preparations composed of multiple vitamins or nutrients) or a vitamin D-fortified food instead of as a singular vitamin D preparation, these studies were excluded.

### Outcome measures

We assessed whether adverse health outcomes that may be related to vitamin D deficiency as well as depression, such as frailty, falls, somatic chronic diseases, physical disability, or poor cognitive functioning[14-16, 20] were included in vitamin D supplementation trials for depression. We also assessed whether these outcomes were affected by vitamin D supplementation. Since different assessment methods are available for the adverse health outcomes under study, we did not apply any restrictions on the specific instruments. Regarding frailty, we also considered the five components of the frailty phenotype (slowness, physical activity, muscle weakness, exhaustion, and unwanted weight loss)[21]. Due to our focus on health outcomes and not on intermediate factors, we did not assess the effects of vitamin D supplementation on laboratory values, anthropometric measures, psychiatric outcomes other than depression, or other factors related to mental health.

### Data extraction

After a first screening on title and abstract by one of the authors (KvdB), full text versions of all possible eligible papers were evaluated independently for inclusion in the systematic review by two authors (KvdB and JH). Differences in judgement were discussed and resolved. A standardised, piloted form was used for data-synthesis. We determined for each study whether adverse health outcomes were an inclusion or exclusion criterion, stratification variable, covariate, or outcome measure, and recorded the definition and method of assessment used. We also assessed the impact of vitamin D supplementation relative to the control condition on these outcomes. In addition, the following general study data were collected: authors, journal, year of publication, setting (general, psychiatric or somatic population), geographical location, study design, in- and exclusion criteria, diagnostic procedure for depression (clinical diagnosis or symptom score), duration of supplementation and follow-up, age of participants (range, mean, standard deviation), stratification variables, covariates, and other outcome measures. Since both depression and adverse health outcomes pose a risk of drop out from a study, the following data on recruitment and attrition were extracted: the number of patients 1) screened, 2) included, 3) randomised, 4) analysed with intention to treat analysis, 5) completed the study, 6) dropped out, plus reasons for attrition. Details about vitamin D assessment (timing and method; levels of vitamin D at baseline and follow up (mean, range)), method of adjustment for season, vitamin D supplementation (dosage, method of administration, combination with calcium supplementation or other preparations), and control conditions were assessed.

An estimation of the increment of vitamin D with the given vitamin D dosage was calculated, assuming that vitamin D levels would increase with 0.70 nmol/l for each mg (=40 I.U.) of vitamin D supplementation per day[22]. In this way, we assessed whether a sufficient concentration of vitamin D (between 75 and 250 nmol/l) could be achieved, based on the baseline values and the estimated increment, or (if available) on the actual follow-up vitamin D levels.

### Quality assessment

Two authors (KvdB and JH) independently evaluated the quality of the included studies using the revised Cochrane tool for assessing risk of bias in randomised trials (RoB 2)[23]. The following forms of bias for the depression outcome were assessed: bias arising from the randomisation process, due to deviations from intended interventions, due to missing outcome data, in measurement of the outcome, and in selection of the reported result. Each study was assigned an overall score for risk of bias (low risk, some concerns, or high risk of bias) as indicated by the RoB 2. Discrepancies were identified and resolved through discussion by the two assessors (KvdB and JH), and if necessary within the complete study group. Furthermore, physical vulnerability was scored for each study population as high, medium or relatively low, based on the mean age of the population, the presence of somatic comorbidity in the population, and the application of exclusion criteria related to frailty and somatic comorbidity.

### Subgroups

We chose in advance to stratify studies according to diagnostic procedure for depression into 1) a clinical diagnosis of a depressive disorder by a psychiatrist / psychologist or a diagnosis based on a (semi-) structured interview according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), or 2) the presence of depressive symptoms based on a screening questionnaire score for depressive symptomatology. It is important to make this distinction, since the use of symptom questionnaires may lead to overestimation of depression due to misclassification of somatic symptoms as depressive features, particularly in populations with frailty or somatic comorbidity[24].

## RESULTS

### Study selection and characteristics

A total of 2378 records were retrieved by database searching; one additional record was identified through the reference lists. After deleting duplicates, the title and abstract of

1861 records were screened for eligibility. Full-text versions of 65 papers were assessed, and ultimately, 31 vitamin D supplementation trials with depression as primary outcome could be included in the review (see Figure 1).

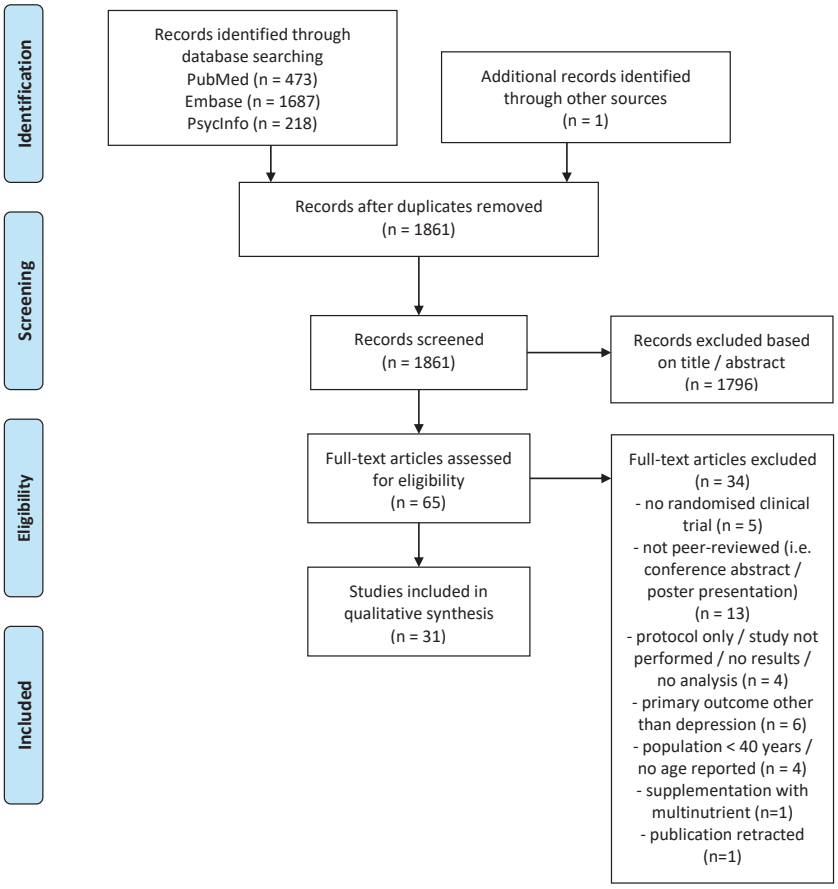


**Fig. 1.** Flow diagram of the selection process of randomised clinical trials.

In 13 studies, inclusion was restricted to persons with a depressive disorder (see Table 1). Among the other 18 studies focussed on depressive symptom severity, two studies exclusively included persons with a symptom score above a cut-off value[25, 26].

**Table 1.** Vitamin D supplementation trials for depression, stratified by the presence of depressive disorder and sorted by physical vulnerability and overall risk of bias.

| Author, year of publication | Study population | Estimated physical vulnerability of population | Mean baseline vitamin D level (intervention group) | Vitamin D dosing schedule | Mean increment of vitamin D (intervention group) | | Adequate supplementation?** | Adverse physical health outcomes, and other included outcome measures | RoB† |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Estimated* | Observed | | | |
| ***Studies in populations with depressive disorder*** | | | | | | | | | |
| Alavi et al., 2019[27] | Psychiatric population, Iran; persons over 60 yrs under treatment for depression, GDS-15 >5 | High | 56.3 nmol/l | 50,000 I.U./week for 8 weeks vs. placebo | 125 nmol | 52.3 nmol/l | Yes | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** GDS-15 | S |
| Wang et al., 2016[29] | Somatic population, Iran; persons >=18 yrs with end-stage renal failure, BDI >=16 and clinical depression diagnosis | High | 54.6 nmol/l | 50,000 I.U./week for 52 weeks vs. placebo | 125 nmol | 46 nmol/l | Yes | ***Adverse physical health outcomes:*** *Comorbidity index:* significant decrease in vitamin D group compared to control group.<br>***Other outcomes:*** BDI-II, markers of bone metabolism, nutrient indices, BMI, hs-CRP | S |
| Zhang et al., 2018[44] | Somatic population, China; persons >=18 yrs with pulmonary tuberculosis and depression (DSM-IV) | Medium | 57.3 nmol/l | 100,000 I.U./week for 8 weeks vs placebo | 250 nmol/l | 10.5 nmol/l | No | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** BDI-II, markers of bone metabolism, nutrient indices, inflammatory biomarkers | S |
| Khoraminya et al., 2013[45] | Psychiatric population, Iran; persons 18-65 yrs with MDD (DSM-IV) and HDRS-17 >=15 | Relatively low | 57.6 nmol/l | 1,500 I.U. + 20 mg fluoxetine/day for 8 weeks vs. placebo + fluoxetine | 26.3 nmol/l | Unknown | Probably | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** HDRS-17, BDI | S |
| Vellekkatt et al., 2020[46] | Psychiatric population, India; persons 18-65 yrs with MDD (DSM 5) | Relatively low | Unknown (<50 nmol/l) | 300,000 I.U. once vs. placebo, follow-up 12 weeks | 62.5 nmol/l | Unknown | Probably | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** HDRS-17, QLES, CGI-SI | S |
| Alghamdi et al., 2020[47] | Psychiatric population, Saudi Arabia; persons 18-65 yrs with MDD (DSM 5) | Relatively low | Unknown (30-50 nmol/l) | 50,000 I.U./week for 3 months vs. standard of care | 125 nmol/l | Around 50 nmol/l (extrapolated from graph) | Yes | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** BDI, serotonin level | H |

**Table 1.** (Continued)

| Author, year of publication | Study population | Estimated physical vulnerability of population | Mean baseline vitamin D level (intervention group) | Vitamin D dosing schedule | Mean increment of vitamin D (intervention group) | | Adequate supplementation?** | Adverse physical health outcomes, and other included outcome measures | RoB† |
|---|---|---|---|---|---|---|---|---|---|
| Amini et al., 2020[48] | Psychiatric population, Iran; women 18-45 yrs with postpartum depression and EPDS >12 | Relatively low | 36.6 nmol/l (vit D + calcium group), 39.8 nmol/l (vit D + placebo group) | 50,000 I.U./2 weeks +/- calcium 500 mg/day for 8 weeks vs. placebo | 62.5 nmol/l | 14.4 nmol/l and 18.2 nmol/l | No | ***Adverse physical health outcomes:*** None ***Other outcomes***: EPDS, calcium, estradiol, inflammatory markers | H |
| Gloth et al., 1999[49] | Psychiatric population, United States; persons 15-61 yrs with SAD (DSM-IV) | Relatively low | 27.5 nmol/l | 100,000 I.U. once vs. phototherapy, follow-up 1 month | 58.3 nmol/l | 20.3 nmol/l | No | ***Adverse physical health outcomes:*** None ***Other outcomes:*** HDRS, SIGH-SAD, SAD-8 | H |
| Hansen et al., 2019[50] | Psychiatric population, Denmark; patients (18-65 yrs) admitted to mood disorder clinic | Relatively low | 43.2 nmol/l | 2,800 I.U./day for 12 weeks vs. placebo, follow-up 6 months | 49 nmol/l | 54.7 nmol/l | Yes | ***Adverse physical health outcomes:*** None ***Other outcomes:*** HDRS-17, major depression inventory; WHO-5 well-being index | H |
| Kaviani et al., 2020[51] | Psychiatric population, Iran; outpatients (18-60 yrs) with clinical diagnosis of mild to moderate depression | Relatively low | 87.1 nmol/l | 50,000 I.U./2 weeks for 8 weeks vs. placebo | 62.5 nmol/l | 40.8 nmol/l | Yes | ***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, oxytocin, serotonin, PTH, weight, BMI, waist circumference, hip circumference, waist-hip ratio, blood pressure | H |
| Marsh et al., 2017[52] | Psychiatric population, United States; persons 18-70 yrs with clinical diagnosis of bipolar depression | Relatively low | 48 nmol/l | 5,000 I.U./day for 12 weeks vs. placebo | 87.5 nmol/l | 22 nmol/l | No | ***Adverse physical health outcomes:*** None ***Other outcomes:*** MADRS, YMRS, HAM-A | H |
| Mozaffari-Khosravi et al., 2013[53] | Psychiatric population, Iran; 20-60 yrs with clinical diagnosis of depression | Relatively low | Unknown; most between 12.5 and 25 nmol/l | 300,000 or 150,000 I.U. once vs. no treatment, follow-up 3 months | 58.3 nmol/l / 29.2 nmol/l | Unknown | Probably / No | ***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, PTH, calcium, phosphate | H |
| Zhu et al., 2020[54] | Psychiatric population, China; persons 18-60 yrs with clinical diagnosis of MDD | Relatively low | 39.1 nmol/l | 1,600 mg/day vs. placebo for 6 months | N/A§ | Unknown | Probably not | ***Adverse physical health outcomes:*** None ***Other outcomes:*** HDRS-17, HAM-A-14, RSAS, RPAS | H |

**Table 1.** (Continued)

| Author, year of publication | Study population | Estimated physical vulnerability of population | Mean baseline vitamin D level (intervention group) | Vitamin D dosing schedule | Mean increment of vitamin D (intervention group) | | Adequate supplementation?** | Adverse physical health outcomes, and other included outcome measures | RoB† |
|---|---|---|---|---|---|---|---|---|---|
| ***Studies in populations with a depressive symptom score above a cut-off value*** | | | | | | | | | |
| De Koning et al., 2019[25] | General population, the Netherlands; persons 60-80 yrs with CES-D >=16, and >=1 functional limitation | High | 46 nmol/l | 1,200 I.U./day for 12 months vs. placebo | 21 nmol/l | 40 nmol/l | Yes | ***Adverse physical health outcomes:*** *Number of functional limitations:* Fewer limitations in vitamin D group compared to placebo (if baseline vitamin D levels >50 nmol/l). *Severity of functional limitations, physical performance, muscle strength, functional mobility, and cognitive functioning:* no differences between intervention groups. ***Other outcomes:*** CES-D, BAI, health-related quality of life | L |
| Yosaee et al., 2020[26] | Somatic population, Iran; persons >20 yrs with obesity and BDI >=10 | Relatively low | 65.2 nmol/l (vitamin D group) / 26.1 nmol/l (vitamin D + zinc group) | 2,000 I.U./day or placebo + zinc or placebo for 12 weeks | 35 nmol/l | 25.6 nmol/l (vitamin D group) / 18.7 nmol/l (vitamin D + zinc group) | Yes / No | ***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, Brain-derived neurotrophic factor, cortisol, blood pressure, weight, BMI, waist circumference | H |
| ***Studies in populations with depressive symptoms regardless of symptom severity*** | | | | | | | | | |
| Raygan et al., 2018[28] | Somatic population, Iran; persons 45-85 yrs with coronary heart disease | High | 36.8 nmol/l | 50,000 I.U./2 weeks + probiotic for 12 weeks vs. placebo | 62.5 nmol/l | 29.5 nmol/l | No | ***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI, glycemic control, hs-CRP, biomarkers of oxidative stress, blood pressure, BAI, GHQ-28 | S |
| Zheng et al., 2019[30] | Somatic population, Australia; persons with knee osteoarthritis | High | 43.7 nmol/l | 50,000 I.U./month for 24 months vs. placebo | 29.2 nmol/l | 40.8 nmol/l | Yes | ***Adverse physical health outcomes:*** None ***Other outcomes:*** PHQ | H |

**Table 1.** (Continued)

| Author, year of publication | Study population | Estimated physical vulnerability of population | Mean baseline vitamin D level (intervention group) | Vitamin D dosing schedule | Mean increment of vitamin D (intervention group) | | Adequate supplementation?** | Adverse physical health outcomes, and other included outcome measures | RoB† |
|---|---|---|---|---|---|---|---|---|---|
| Ghaderi et al., 2017[55] | Somatic population, Iran; persons 25-70 yrs on methadone maintenance treatment | Medium | 34.8 nmol/l | 50,000 I.U./2 weeks for 12 weeks vs. placebo | 62.5 nmol/l | 20.3 nmol/l | No | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** BDI, metabolic status, biomarkers of oxidative stress, PSQI, BAI | L |
| Kjaergaard et al., 2012[56] | General population, Norway; persons 30-75 yrs | Medium | 47.4 nmol/l | 20,000 I.U./week for 6 months vs. placebo | 50 nmol/l | 100.3 nmol/l | Yes | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** BDI-II, HADS, SPAQ, MADRS, BMI, serum calcium, PTH | L |
| Okereke et al., 2020[35] | General population, United States; men >50 yrs, women >55 yrs | Medium | 77 nmol/l (total group) | 2,000 I.U./day + fish oil for 5.3 years (average) vs. placebo | 35 nmol/l | Unknown | Probably | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** PHQ-8, risk of incident or recurrent depression | L |
| Bertone-Johnson et al., 2012[34] | General population, United States; postmenopausal women (50-79 yrs) | Medium | 52.0 nmol/l | 400 I.U./day + calcium 1000 mg vs. placebo, average follow-up 7.0 years | 7 nmol/l | Unknown | Probably not | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** Burnam score, antidepressant use at year 3 | S |
| Jorde et al., 2008[31] | Somatic population, Norway; persons 21-70 yrs with BMI between 28 and 47 kg/m$^2$ | Medium | 52.5 nmol/l (total group) | 40,000 I.U./week + or 20,000 I.U./week + 500 mg calcium/ day vs. placebo for 1 year | 100 nmol/l / 50 nmol/l | 56.9 nmol/l and 35.6 nmol/l | Yes | ***Adverse physical health outcomes:*** *Physical activity:* no difference in IPAQ scores between intervention groups.<br>***Other outcomes:*** BDI, BMI, calcium, PTH | S |
| Jorde & Kubiak, 2018[57] | General population, Norway; persons 40-80 yrs | Medium | 33.8 nmol/l (total group) | 100,000 I.U. once + 20,000 I.U. /week for 4 months vs. placebo | 64.6 nmol/l | 56 nmol/l | Yes | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** BDI-II, calcium and PTH | S |
| Mirzavandi et al., 2020[58] | Somatic population, Iran; persons 30-60 yrs with diabetes mellitus type II | Medium | 39.5 nmol/l | 200,000 I.U./4 weeks twice vs. no treatment | 125 nmol/l | 51.8 nmol/l | Yes | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** BDI, weight, body fat mass, waist-to-hip ratio | S |

**Table 1.** (Continued)

| Author, year of publication | Study population | Estimated physical vulnerability of population | Mean baseline vitamin D level (intervention group) | Vitamin D dosing schedule | Mean increment of vitamin D (intervention group) | | Adequate supplementation?** | Adverse physical health outcomes, and other included outcome measures | RoB† |
|---|---|---|---|---|---|---|---|---|---|
| Omidian et al., 2019[59] | Somatic population, Iran; persons 30-60 yrs with diabetes mellitus type II | Medium | 38.8 nmol/l | 4,000 I.U./day for 3 months vs. placebo | 70 nmol/l | 42.3 nmol/l | Yes | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** BDI, blood pressure, metabolic profile | S |
| Rolf et al., 2017[33] | Somatic population, the Netherlands; persons 18-55 yrs with multiple sclerosis | Medium | 58 nmol/l | 7,000 I.U./day for 4 weeks, then 14.000 i.u./day up to 44 weeks vs. placebo | 245 nmol/l | 168 nmol/l | Yes | ***Adverse physical health outcomes:*** *Fatigue:* no difference in Fatigue Severity Scale scores between groups<br>***Other outcomes:*** HADS-D, inflammatory markers | H |
| Yalaman-chili et al., 2018[36] | General population, United States; women 57-90 yrs with vit D level =<50 nmol/l | Medium | 38.3 nmol/l | 400-4,800 I.U./day for 12 months vs. placebo | 7 – 84 nmol/l | Unknown | Depends on dosage | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** GDS | H |
| Sharifi et al., 2019[60] | Somatic population, Iran; persons 18-50 yrs with mild to moderate ulcerative colitis | Relatively low | 83.3 nmol/l | 300,000 I.U. once vs. placebo, follow-up 90 days | 58.3 nmol/l | 18.8 nmol/l | Yes | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** BDI-II, PTH, calcium | S |
| Frandsen et al., 2014[61] | General population, Denmark; health care professionals 18-65 yrs with SAD symptoms and >= 8 **on** question 2 of SPAQ | Relatively low | 68.3 nmol/l | 2,800 I.U./day for 12 weeks vs. placebo | 49 nmol/l | Unknown | Probably | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** SIGH-SAD, weight, waist circumference, blood pressure, WHO-5 well-being index, absenteeism from work | H |
| Mousa et al., 2018[32] | General population, Australia; persons 20-60 yrs with BMI >25 | Relatively low | 33.3 nmol/l | 100,000 I.U. once and 4000 I.U./day for 16 weeks vs. placebo | 85.6 nmol/l | 23.1 nmol/l | No | ***Adverse physical health outcomes:*** *Physical activity:* no difference in change in IPAQ-MET between intervention groups.<br>***Other outcomes:*** BDI-II, BMI, waist-to-hip ratio, % body fat | H |

**Table 1.** (Continued)

| Author, year of publication | Study population | Estimated physical vulnerability of population | Mean baseline vitamin D level (intervention group) | Vitamin D dosing schedule | Mean increment of vitamin D (intervention group) | | Adequate supplementation?** | Adverse physical health outcomes, and other included outcome measures | RoB† |
|---|---|---|---|---|---|---|---|---|---|
| Vafa et al., 2019[62] | Somatic population, Iran; women 18-45 yrs with anemia and vitamin D <75 nmol/l | Relatively low | 42.6 nmol/l | 1,000 I.U./day + 27 mg iron/day vs. 1,000 I.U./day + placebo for 12 weeks | 17.5 nmol/l | 54.6 nmol/l (vitamin D + iron), 51.4 nmol/l (vitamin D + placebo) | Yes | ***Adverse physical health outcomes:*** None<br>***Other outcomes:*** BDI, BMI, BAI | H |

* Estimated increment of vitamin D level (nmol/l): 0.70 nmol/l for each mg (=40 i.u.) per day (Heaney et al., 2003). If weekly / monthly doses are stated, estimations are based on a calculated daily dose.

** Supplementation is considered adequate if actual follow-up vitamin D levels or baseline vitamin D levels plus the estimated increment are between 75 and 250 nmol/l

† Overall Risk of Bias for the depression outcome: L = low, S = some concerns, H = high

§ Based on the reported dosage of 1600 mg estimated vitamin D levels would be extremely high. The authors were contacted to verify whether the reported dosage is correct, but did not respond.

**Abbreviations:** BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BMI: Body Mass Index; CES-D: Centre of Epidemiologic Studies Depression scale; CGI-SI: Clinical Global Impression – Severity of Illness; DSM: Diagnostic and Statistical Manual of Mental Disorders; EPDS: Edinburgh Postpartum Depression Scale; GDS-15: Geriatric Depression Scale, 15 items; GHQ-28: General Health Questionnaire, 28 items; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Rating Scale; HDRS-17: Hamilton Depression Rating Scale, 17 items; hsCRP = high sensitivity C-reactive protein; I.U.= international units; IPAQ-MET: International Physical Activity Questionnaire – Metabolic Equivalent of Time; MDD: major depressive disorder; PHQ: Patient Health Questionnaire; PTH: parathyroid hormone; PSQI: Pittsburgh Sleep Quality Index; QLES: Quality of Life Enjoyment and Satisfaction; RPAS: Revised Physical Anhedonia Scale; RSAS: Revised Social Anhedonia Scale; SAD: Seasonal Affective Disorder; SIGH-SAD: Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version; SPAQ-SAD: Seasonal Pattern Assessment Questionnaire; YMRS: Young Mania Rating Scale

**Table 2.** Evaluation of risk of bias for the depression outcome.

| Author | Bias arising from randomisation procedure | Bias due to deviation from intended interventions | Bias due to missing outcome data | Bias in measurement of the outcome | Bias in selection of the reported result | Overall risk of bias |
|---|---|---|---|---|---|---|
| ***Studies in populations with depressive disorder*** | | | | | | |
| Alavi et al., 2019[27] | LOW | Some concerns | LOW | LOW | Some concerns | **SOME CONCERNS** |
| Wang et al., 2016[29] | LOW | Some concerns | LOW | LOW | Some concerns | **SOME CONCERNS** |
| Zhang et al., 2018[44] | LOW | Some concerns | LOW | LOW | Some concerns | **SOME CONCERNS** |
| Khoraminya et al., 2013[45] | Some concerns | Some concerns | LOW | LOW | Some concerns | **SOME CONCERNS** |
| Vellekkatt et al., 2020[46] | LOW | LOW | LOW | LOW | Some concerns | **SOME CONCERNS** |
| Alghamdi et al., 2020[47] | HIGH | HIGH | HIGH | HIGH | Some concerns | **HIGH** |
| Amini et al., 2020[48] | LOW | HIGH | HIGH | LOW | LOW | **HIGH** |
| Frandsen et al., 2014[61] | LOW | HIGH | Some concerns | LOW | Some concerns | **HIGH** |
| Gloth et al., 1999[49] | LOW | HIGH | LOW | LOW | HIGH | **HIGH** |
| Hansen et al., 2019[50] | LOW | LOW | HIGH | LOW | Some concerns | **HIGH** |
| Kaviani et al., 2020[51] | LOW | HIGH | HIGH | LOW | LOW | **HIGH** |
| Marsh et al., 2017[52] | LOW | HIGH | HIGH | LOW | LOW | **HIGH** |
| Mozaffari-Khosravi et al., 2013[53] | Some concerns | Some concerns | HIGH | HIGH | LOW | **HIGH** |
| Zhu et al., 2020[54] | Some concerns | HIGH | HIGH | Some concerns | Some concerns | **HIGH** |
| ***Studies in populations with a depressive symptom score above a cut off*** | | | | | | |
| De Koning et al., 2019[25] | LOW | LOW | LOW | LOW | LOW | **LOW** |
| Yosaee et al., 2020[26] | LOW | HIGH | HIGH | LOW | Some concerns | **HIGH** |
| ***Studies in populations with depressive symptoms regardless of symptom severity*** | | | | | | |
| Raygan et al., 2018[28] | LOW | LOW | Some concerns | LOW | LOW | **SOME CONCERNS** |
| Zheng et al., 2019[30] | LOW | HIGH | HIGH | LOW | Some concerns | **HIGH** |

**Table 2.** (Continued)

| Author | Bias arising from randomisation procedure | Bias due to deviation from intended interventions | Bias due to missing outcome data | Bias in measurement of the outcome | Bias in selection of the reported result | Overall risk of bias |
|---|---|---|---|---|---|---|
| Ghaderi et al., 2017[55] | LOW | LOW | LOW | LOW | LOW | **LOW** |
| Kjaergaard et al., 2012[56] | LOW | LOW | LOW | LOW | LOW | **LOW** |
| Okereke et al., 2020[35] | LOW | LOW | LOW | LOW | LOW | **LOW** |
| Bertone-Johnson et al., 2012[34] | LOW | LOW | Some concerns | LOW | Some concerns | **SOME CONCERNS** |
| Jorde et al., 2008[31] | LOW | LOW | Some concerns | LOW | Some concerns | **SOME CONCERNS** |
| Jorde & Kubiak, 2018[57] | LOW | Some concerns | LOW | LOW | LOW | **SOME CONCERNS** |
| Mirzavandi et al., 2020[58] | LOW | LOW | LOW | Some concerns | LOW | **SOME CONCERNS** |
| Omidian et al., 2019[59] | LOW | Some concerns | LOW | LOW | Some concerns | **SOME CONCERNS** |
| Rolf et al., 2017[33] | LOW | HIGH | LOW | LOW | Some concerns | **HIGH** |
| Yalamanchili et al., 2018[36] | LOW | HIGH | Some concerns | LOW | Some concerns | **HIGH** |
| Sharifi et al., 2019[60] | LOW | Some concerns | LOW | LOW | LOW | **SOME CONCERNS** |
| Mousa et al., 2018[32] | Some concerns | HIGH | Some concerns | LOW | LOW | **HIGH** |
| Vafa et al., 2019[62] | LOW | HIGH | Some concerns | LOW | Some concerns | **HIGH** |

Nineteen studies were performed in populations with vitamin D deficiency (mean vitamin D levels <50 nmol/l) at baseline. Baseline vitamin D levels were not reported in one study, and three studies were conducted in populations with sufficient vitamin D levels (>75 nmol/l). In seven studies actual follow-up vitamin D levels did not reach 75 nmol/l, and in another four studies the estimated increment of vitamin D levels was not enough to reach sufficiency. In one study no estimation could be made (see Table 1). Five studies were performed among physically vulnerable populations[25, 27-30]. Overall risk of bias was low in four studies (see Table 2), of which only one was performed in a physically vulnerable population[25].

**Studies including adverse health outcomes**

Five studies included adverse health outcomes. Although frailty was not an outcome measure in any of the studies, three studies assessed one or more frailty components: physical activity was an outcome measure in all of these[25, 31, 32]; one additionally assessed muscle strength[25]. No effect of vitamin D supplementation was demonstrated in any of these studies. De Koning et al. also included the number of functional limitations, severity of functional limitations, functional mobility, and cognitive functioning[25]. Other studies included a comorbidity index[29], and fatigue[33]. De Koning et al. reported fewer functional limitations after supplementation, but only for participants with baseline vitamin D levels above 50 nmol/l (which does not qualify as vitamin D deficiency)[25]. No effect on severity of functional limitations, functional mobility, or cognitive functioning was observed in this study[25]. Wang et al. found a sharper decrease of the comorbidity index in the group with vitamin D supplementation compared to the placebo group[29]. Rolf et al. found no effect of supplementation on fatigue[33]. In four of these studies[25, 29, 31, 33] actual follow-up vitamin D levels reached sufficiency (>75 nmol/l). Only in the study by Mousa et al., mean vitamin D levels were still insufficient (56.4 nmol/l) after supplementation[32]. Of the above five studies including adverse health outcomes, two were conducted in physically vulnerable populations[25, 29], two in populations with medium vulnerability[31, 33] and one with relatively low vulnerability[32]. Only one of these five studies had low risk of bias[25]. Some concerns arose in two studies[29, 31], and risk of bias was high in the two other studies[32, 33]. Thus, the study by De Koning et al. was the only study in a physically vulnerable population with low risk of bias[25].

**Meta-analysis**

Due to the low number and heterogeneity of studies, we could not perform a meta-analysis.

# DISCUSSION

This is the first systematic review focussing on adverse health outcomes related to vitamin D deficiency in vitamin D supplementation trials for depression. While depressed persons can be considered a high-risk group for adverse health outcomes, only five of the 31 trials considered adverse health outcomes as a secondary outcome measure[25, 29, 31-33]. The only high-quality study in a physically vulnerable population reported a beneficial effect on the number of functional limitations[25]. This is in line with our hypothesis that vitamin D supplementation in depression may improve adverse health outcomes. Nevertheless, there are currently too few studies in physically vulnerable populations with depression that have examined the effects of vitamin D supplementation on adverse health outcomes to determine whether depressed persons benefit from supplementation effects on adverse health outcomes.

## Strengths and limitations

*Current literature*

Although we could include 31 studies into the effect of vitamin D supplementation on depression or depressive symptoms in older populations, only one high-quality study[25] remained to draw any conclusions about the effects of vitamin D supplementation on adverse health outcomes related to depression. We encountered a number of shortcomings in the current literature. First, physical vulnerability is particularly relevant in geriatric populations. However, only eight of the 31 included studies were conducted in older populations (mean age >60 years)[25, 27-30, 34-36]. Furthermore, somatic conditions were often reason for exclusion, as well as 'medical conditions likely to result in death within three years'[34] or 'substantial comorbidity' and 'physical conditions severe enough to prevent reasonable physical activity'[36]. Thus, besides finding just a limited number of vitamin D supplementation studies in geriatric populations, in at least three of those studies the most physically vulnerable participants appear to have been excluded [34-36] Still, the inclusion of adverse health outcomes may be useful in younger age groups, as their prevalence is not limited to older ages, and to compare the effects of vitamin D supplementation on depression and other health outcomes across different age groups. Second, at least some concerns about the risk of bias exist in all but four of the 31 studies. Of the five studies that included an adverse health outcome, only one[25] had low risk of bias. Thus, the overall quality of the studies most relevant for the current review is questionable. Moreover, vitamin D dosage should be high enough

to reach an adequate blood level. For bone metabolism and the prevention of falls and fractures, 75 nmol/l is considered sufficient[37, 38], although for extra-skeletal effects no clear target vitamin D levels are known. In four of the studies that included adverse health outcomes, vitamin D levels >75 nmol/l were reached[25, 29, 31, 33]. In one study, vitamin D levels remained insufficient throughout the study[32]. Besides, follow-up duration should be long enough for vitamin D to exert its effect on depression or other outcome measures. The maximum biological response (as in maximum vitamin D level and maximum decrease of bone turnover) is seen at three to six months of supplementation[39]. In contrast, the follow-up duration in 14 of 16 studies reporting a beneficial effect of supplementation on depression was between one and three months, so that these positive findings may be due to chance. However, the studies that included an adverse health outcome had an adequate follow-up duration, varying from 16 weeks[32] to 44 weeks[33] or 1 year[25, 29, 31]. Lastly, to comment on the clinical implications of findings from supplementation studies, results should be applicable to depressed persons in clinical practice. However, generalisability of the current results towards more severely depressed persons (i.e. those treated in mental health care) might be limited as these persons were mostly excluded in the selected studies. In fact, in seven out of thirteen studies in populations with a clinical diagnosis of depression, the presence of severe depression or even the use of an antidepressant was an exclusion criterion. Furthermore, of the 18 studies focussing on depressive symptoms, 16 did not apply a cut-off value and included persons regardless of the severity of depressive symptomatology. Especially in somatically afflicted populations, there is a risk of misattribution of somatic symptoms to depression when symptom questionnaires are used instead of diagnostic interviews[24]. Thus, a beneficial effect on depression, as was reported in seven out of nine somatic populations focussing on depressive symptoms, may rather reflect a decrease of somatic symptoms that were previously misclassified as depressive. Furthermore, generalisability of the results on adverse health outcomes may be reduced since only two out of five studies that included such an outcome were performed in depressed populations. One study included persons with a clinical depression diagnosis and BDI score >= 16[29] and the other only included persons with CES-D scores >= 16[25]. In all of these five studies, major depressive disorder[25] (de Koning et al., 2019), severe depression[29, 33], clinical depression[32], and/or antidepressant use[29, 31] were exclusion criteria.

*Review level*

An important strength of this review is that we are the first to provide a complete overview of adverse health outcomes in vitamin D supplementation trials that target depression or depressive symptoms. We were able to retrieve full text versions of all potentially eligible studies. It is unlikely that we missed any studies in physically vulnerable populations, since we only excluded study populations that were entirely under 40 years of age. A limitation of our review is that the rules for the inclusion of studies in a systematic review about nutrients[40] could not all be followed. Dose-response curves for nutrients – unlike drugs – are presumably non-linear, as once the intake of the nutrient is adequate, an increase of the dose produces no additional effect on the outcome. In order to avoid bias towards null, Heaney recommends to only include studies that are similar with respect to baseline values, supplementation dosages, and conutrient status[40]. Although we could not completely avoid heterogeneity of studies, we were able to quantify the change in vitamin D levels in 22 of the 31 studies, and to determine for all but six of the studies whether supplementation had been adequate (see table 1). Also, several studies were incorporated into larger vitamin D trials that were not primarily designed to study the effect of supplementation on depression and were often performed in populations with low prevalence of depression. Importantly, in these studies that were not primarily designed to target depression, a probability of publication bias is plausible, since more effort may have been put into reporting positive secondary outcomes rather than negative outcomes. However, our stratification by diagnostic modality for the depression (clinical diagnosis – symptom score above a cut-off value – symptom score regardless of symptom severity) might help to interpret the results. Since intention-to-treat analyses allow conclusions about supplementation on a population level, those analyses were of primary interest. However, in 17 out of 31 studies no such analyses were performed; accordingly, we report results of the per-protocol analysis for all studies. Where intention-to-treat analyses were available, results were in line with the results of the per-protocol analysis, except in the study by Jorde et al., in which a beneficial effect of vitamin D supplementation on depression was demonstrated in the per-protocol analysis but not in the intention-to-treat analysis[31].



**Supplementation recommendations**

Although supplementation of 10-20 µg vitamin D per day (depending on skin colour and sun exposure) is recommended for all older persons[41], these guidelines are often not followed[42]. In the Netherlands, general practitioners are encouraged to follow a pragmatic approach and to actively prescribe vitamin D to persons who will likely benefit

from it[43]. So far, depressed persons are not one of the risk groups explicitly identified in these guidelines. While vitamin D levels of 75 nmol/l are considered sufficient for bone metabolism and the prevention of falls and fractures[37, 38], target levels for extra-skeletal effects are unknown. Moreover, while dose-reponse curves are often non-linear (see [40]), a recent dose-response meta-analysis that specifically looked for non-linear dose-response associations between vitamin D levels and depression, only found a linear association[6]. Therefore, future supplementation trials should not only address what the optimal vitamin D level should be, but also whether the dose-response curve for these effects is linear or non-linear. Interestingly, the beneficial effect of vitamin D supplementation on the number of functional limitations in the high-quality D-Vitaal study [25] was only seen in the subgroup with baseline vitamin D levels >50 nmol/l. This post-hoc analysis could be a chance finding, but if not, several explanations may apply. First, in case of severe vitamin D deficiency irreversible effects may have occurred, or secondly, higher target values and/or a longer follow-up duration are needed to improve functional limitations. This latter explanation also challenges the idea of fixed target levels for specific outcomes, as target levels may differ conditional on duration and severity of vitamin D deficiency. Finally, the target level of vitamin D to improve functional limitations in depression might be much higher than previously thought and may only be reached by this supplementation strategy among patients who had >50 nmol/l vitamin D levels at baseline. Regarding the uncertainty of optimal vitamin D levels in depression, we advocate considering depressed persons as at risk for vitamin D deficiency and the associated adverse health outcomes.

## Conclusions and implications

While depressed persons are at increased risk of adverse health effects as well as vitamin D deficiency, supplementation trials in depression have not addressed the common negative health consequences of low vitamin D levels. The findings of the only high-quality study in a physically vulnerable population are in line with our hypothesis that vitamin D supplementation in depression may have beneficial effects on adverse health outcomes. Well-designed trials of the effects of vitamin D supplementation for late-life depression should explore whether vitamin D-related adverse health outcomes can be prevented or stabilised in this vulnerable population. In the meantime, depression should be added to the risk factors for vitamin D deficiency in practical supplementation guidelines.

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# CHAPTER 8

## SUMMARY AND GENERAL DISCUSSION

## SUMMARY

In the past decades, vitamin D has been reconceptualised as a panacea for many chronic adverse health conditions, based on its involvement in many organ systems[1]. The widespread vitamin D receptor within the brain[2] and consistently identified low vitamin D levels in depression[3] have stimulated research in this field. Thus far, however, neither vitamin D deficiency has been proven as an etiological factor in depression, nor vitamin D supplementation as an evidence-based treatment strategy for depression[4]. Previous conclusions were often based on studies performed in general populations with depression diagnosed by using a depression rating scale; the generalisability of these results to depressed populations in clinical practice may therefore be low. The Netherlands Study of Depression in Older persons consists of 378 depressed persons with clinical depression diagnoses, confirmed by a structured diagnostic interview, as well as 132 non-depressed comparisons. This cohort enables us to further unravel the complex association between vitamin D and late-life depression in relation to adverse health outcomes. The aim of this thesis was in particular to study the interrelatedness of vitamin D deficiency, frailty, and mortality in late-life depression, as well as their relationship with depression itself.

Depression has been associated with increased mortality rates, but modifying mechanisms have not yet been identified[5]. Therefore, the study in **Chapter 2** examined whether depression as well as specific subtypes or characteristics of late-life depression predict mortality within NESDO.-We found that the mortality risk was nearly three times higher for depressed persons than for non-depressed comparisons. Nonetheless, after adjustment for demographic factors, negative lifestyle characteristics, medication use and somatic comorbidity, this result lost significance. Thus, increased mortality rates of depressed older persons seem best explained by unhealthy lifestyle characteristics and multiple drug prescriptions. Regarding depression subtypes and characteristics, only minor depression was associated with a higher mortality risk independent of these confounders. An explanation may be that minor depression in later life reflects depressive symptoms due to underlying ageing-related processes, such as inflammation-based sickness behaviour, frailty, and mild cognitive impairment, which have all been associated with increased mortality.

The study in **Chapter 3** aimed to further clarify the interrelatedness between vitamin D, late-life depression and adverse health outcomes with respect to the effect of vitamin

D levels on depression course and remission status after two years, as well as attrition and mortality, among 367 depressed participants of NESDO. In this study, we found neither an effect of vitamin D levels on the course of depressive symptoms, nor on remission rates. Nonetheless, a trend towards lower remission rates in the severely deficient subgroup (vitamin D levels < 25 nmol) raises the question whether this group could benefit from supplementation. Randomised controlled trials including vitamin D deficient persons with depression are needed. Interestingly, lower vitamin D levels significantly predicted excess mortality. This association strengthens the hypothesis that vitamin D deficiency is merely a marker for poor somatic health status. This latter hypothesis was subsequently examined in more depth in the next chapters.

In **Chapter 4**, the study focussed on the association between vitamin D levels and frailty, its components and its course among the depressed participants of NESDO. At baseline, persons with a lower level of vitamin D were more often frail, even when adjusted for lifestyle characteristics and other somatic health indicators. Among depressed persons who were not frail, a higher vitamin D level was protective for the onset of frailty. This could be expected, as vitamin D deficiency is hypothesised to be an etiological factor for frailty, and vitamin D supplementation is currently considered a potential treatment strategy to prevent frailty, although the level of evidence is still weak[6]. An unexpected finding was that higher vitamin D levels were associated with the persistence of frailty over time among frail depressed patients. Interestingly, this counterintuitive finding has been previously reported in another study, but was considered a chance finding[7]. Due to the small sample size, however, we still cannot exclude chance findings, neither we can fully exclude confounding by indication and/or by overlap between frailty and depressive disorder. Future studies should examine whether the favourable effect of low vitamin D levels on the course of frailty can be explained by confounding or whether unknown pathophysiological mechanisms may exert protective effects.

Both frailty and late-life depression predict negative health outcomes including mortality. Therefore, in **Chapter 5** we examined whether frailty and frailty-related biomarkers (inflammatory markers (high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), neutrophil gelatinase associated lipocalin 2 (NGAL-2)), vitamin D level, and leucocyte telomere length) predict mortality during a six-year follow-up among the depressed participants of NESDO, adjusted for other risk factors of mortality. We found a prospective association between physical frailty and mortality. Furthermore,

the number of frailty components was associated with an increased mortality rate. As frailty-related biomarkers may point to underlying pathophysiological pathways of the association between frailty and mortality, we examined whether the increased mortality risk of frailty could (partly) be explained by these biomarkers. This impact of frailty on mortality in late-life depression was independent of inflammatory markers, leucocyte telomere length, and vitamin D. Only higher levels of hs-CRP and lower levels of vitamin D were associated with mortality independent of frailty. Thus, in late-life depression, frailty identifies older persons at increased risk for mortality. Therefore, among frail-depressed persons, treatment models that include frailty-specific interventions might reduce mortality rates.

While vitamin D is involved in frailty as well as depression, hardly any study has examined the course of vitamin D levels prospectively. This is relevant, since vitamin D levels may also change due to frailty- or depression-related behaviour like inadequate food intake or less sunlight exposure. In **Chapter 6**, therefore, we studied whether a change of vitamin D in depressed older persons is associated with either depression course, course of frailty, or both. With two-year follow-up data of 232 depressed participants of NESDO, we studied the association of change in vitamin D levels with depression course, course of frailty and the individual frailty components, and the combination of both. In this depressed group, vitamin D levels decreased over a period of two years, independent of the course of depression. An increase in frailty was associated with a significantly sharper decrease of vitamin D levels over time. Post-hoc analyses showed that this association with frailty might be driven by an increase of exhaustion over time and counteracted by an increase in walking speed. Our findings generate the hypothesis that vitamin D supplementation in late-life depression may improve frailty, in particular exhaustion. This finding may partly explain inconsistent findings of randomised controlled trials evaluating the effect of vitamin D for depression (especially as fatigue is an important symptom of many depressed older persons). We advocate to consider frailty (components) as well as exhaustion as secondary outcome measures in future supplementation trials in late-life depression to address these issues in more depth. **Chapter 7** presents the results of a systematic review that examined to what extent this recommendation has been implemented in previous studies. We performed a systematic literature search to study whether adverse somatic health outcomes associated with vitamin D deficiency and depression were considered as outcomes in vitamin D supplementation trials with depression as the primary outcome in middle-aged to older populations. Five studies addressed one or more adverse

health outcomes. In the only good-quality study in a physically vulnerable population, a beneficial effect of vitamin D on the number of functional limitations was seen[8]. Well-designed trials of the effects of vitamin D supplementation for late-life depression should explore whether adverse health outcomes can be prevented or stabilised in late-life depression.

## Methodological considerations

Although the methodological considerations of the individual studies have already been discussed in the relevant chapters, some overarching methodological considerations can be discussed here.

*Netherlands Study of Depression in Older persons*

The currently available studies into the association of depression with vitamin D as well as mortality rates are characterised by heterogeneity with regard to study design and depression diagnostics, as well as a lack of adjustment for confounders[5]. An important strength of NESDO is the extensive phenotyping of depression in a relatively large clinical sample of older persons with a formally diagnosed depression. This enabled us to study depression subtypes and adjust for confounders, which provides additional knowledge besides findings from major reviews and meta-analyses. However, although NESDO was adequately powered to perform analyses in the whole group, analyses in smaller subgroups, such as persons with severe vitamin D deficiency or specific depression subtypes, may have been underpowered. Furthermore, causes of death were unknown, so we cannot exclude that some NESDO participants may have died from causes not attributable to vitamin D or frailty, such as accidents.

*Physical frailty phenotype*

Throughout the years, several models and instruments to assess frailty have been proposed. The advantage of the physical frailty phenotype[9] in a depressed population is that depression is not among its criteria for frailty. Moreover, the model of Fried considers sarcopenia-related factors, such as muscle weakness and weight loss, that may play an important role in the association between vitamin D deficiency and frailty. However, a limitation of the physical frailty phenotype is that the social and cognitive domain, that have also been associated with adverse health outcomes, are ignored[10]. Furthermore, frailty components such as exhaustion, slowness, and low physical activity may still represent symptoms of depression, and may lead to an overestimation of frailty in a depressed population.

One of the alternatives, the frailty index[11], considers the number of accumulated deficits to determine to which extent a person is frail. These 70 potential deficits cover a wide range of age-related health problems. In this way, a broader definition of frailty is applied, as cognitive problems and deficits related to self-care are also included. However, several depression-related deficits form a disadvantage for its use in a depressed population. Furthermore, although the frailty index offers interesting mathematical properties, such as calculations with the rate of deficit accumulation[12], for research purposes the assessment of 70 deficits is less feasible.

*Vitamin D levels*

A causal relationship between vitamin D deficiency and depression or frailty cannot be proven or rejected based on the results of observational studies only. As depression and frailty may both lead to inadequate food intake and limited sun exposure due to reduced outdoor activity, lower vitamin D levels may just as well be the result of these conditions. Furthermore, vitamin D levels are strongly dependent on the season. Within NESDO, we were able to adjust for physical activity (as a proxy for outdoor behaviour) and for the season of blood withdrawal. Nevertheless, this may not fully cover these reverse causative mechanisms, and therefore residual confounding cannot be excluded. Moreover, in some individuals vitamin D levels may be low for other than behavioural reasons. In the presence of some diseases, internal homeostatic mechanisms to correct an excess of free calcium ions may also result in vitamin D deficiency[1].

A strength of NESDO was the availability of follow-up vitamin D levels, as most longitudinal studies based their conclusions on baseline vitamin D levels, without knowing what happened to vitamin D levels during the follow-up period. To our knowledge, we were the first to assess follow-up vitamin D levels in a depressed older population. In population-based studies, vitamin D levels were relatively stable during follow-up[13]. Although a systematic error cannot be fully excluded, the decrease of vitamin D levels we observed among our depressed participants as well as their non-depressed counterparts is in line with the decrease of vitamin D levels in the older age group from the Longitudinal Amsterdam Study of Ageing[14], and may thus be age-related.

**Case report (epilogue)**

*During the psychiatric hospitalisation, Mrs Z started treatment with nortriptyline and vitamin D supplementation. After three weeks she wanted to go home, as she had the feeling that she would not recover at the psychiatric ward. Once at home, she fell twice and nortriptyline was discontinued because of symptoms of orthostatic hypotension. Afterwards, citalopram was prescribed. This time, she could continue the antidepressant treatment, despite mild side-effects. At first, she remained very inactive and still thought about death often. After two months on citalopram, there was some remission of the depressive symptoms, and she became more active. However, she was still frail and did not dare to exercise on her own at home. She agreed with her general practitioner to temporarily move to a nursing home for geriatric revalidation.*

*Eventually, she would stay there for eight months. When she returned home, her level of functioning had improved and she had not been falling for a couple of months. She did not fulfil the criteria for frailty anymore. Unfortunately, some depressive symptoms were still present. Although the psychotic features had remitted, she still experienced some anhedonia and concentration problems. Nevertheless, she was able to resume most of her activities with her husband. Upon re-assessment, her vitamin D level had reached sufficiency (77 nmol/l).*

## Final conclusions and future perspectives

What can we conclude from this thesis about the role of vitamin D and frailty as determinants of adverse health outcomes in late-life depression? First, no evidence for an etiological role of vitamin D deficiency in depression was found. However, vitamin D deficiency may play a role in the adverse health consequences of depression, such as frailty. Furthermore, in late-life depression, it may not be depression itself but rather its negative health consequences and comorbid conditions, among which frailty and vitamin D deficiency, that lead to an increased mortality risk. Future vitamin D supplementation trials in late-life depression should be carefully designed, and should include frailty and other adverse health outcomes as secondary outcome measures.

## Clinical implications

What do these findings mean to the old-age psychiatrist and others working with persons with late-life depression? Most importantly, clinicians should be alert to

the negative consequences of depression, as these may worsen the prognosis and ultimately lead to death. The presence of frailty and vitamin D deficiency in late-life depression represent an adverse prognosis. Therefore, a treatment plan for a person with late-life depression should include a careful consideration of the possible adverse health outcomes, as well as interventions targeting frailty or other negative lifestyle factors, such as exercise programmes, life style coaching, or reduction of polypharmacy. The findings in this thesis underscore that vitamin D deficiency is a marker of poor health. Although vitamin D supplementation presumably does not directly affect depression, it may improve adverse health consequences of depression. Based on our findings, and although evidence is still limited, we advocate adding older persons with a depression to the risk groups that should be actively supplemented with vitamin D.

**Personal reflection on the process**

Encouraged by the hopeful finding of a cross-sectional association of low vitamin D levels and depression within the NESDO population[15], this thesis took off as a quest to determine the role of vitamin D deficiency in the causation of depression. I wrote my first paper, on the longitudinal association of vitamin D deficiency and depression (Chapter 3), as a research internship in my last year of psychiatric residency. Although the null finding on the longitudinal association between vitamin D and depression was a bit disappointing, we did find an association between lower vitamin D levels and mortality, and I got a taste for conducting research. Back then I already pictured a thesis with a nice yellow cover, titled something like 'the sunshine vitamin for depression'. At that time, follow-up vitamin D levels were not available in NESDO. We shifted our focus to somatic markers and frailty, as a possible mediating factor in the association found between low vitamin D levels and mortality. Afterwards, when I had been working for a while as an old-age psychiatrist, we even left vitamin D completely aside for the paper on mortality and subtypes in late-life depression, again with negative findings on our main hypotheses. We went back on the original vitamin D track after the follow-up vitamin D levels of NESDO came in. No studies had considered the course of vitamin D levels in depression before, so I got new energy. But again, we obtained null results on the association between the change in vitamin D and depression course. However, the association of vitamin D course with frailty was confirmed in this study and generated a new hypothesis, of vitamin D rather being associated with adverse health consequences of depression than depression itself. We worked this out further with a systematic literature review. Looking back, it has been a path of hope and occasional disappointment. I sometimes felt like there would be no end to it, and I was afraid that

after all, I would have only null findings to report. But I have learned that it is precisely the null findings that drive a further deepening and broadening of the subject. And most of all: here it is, the cover with a yellow sun, but with a further developed title: 'Determinants of adverse health outcomes in late-life depression – the role of vitamin D and frailty'.

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# CHAPTER 9

## SAMENVATTING IN HET NEDERLANDS

# SAMENVATTING IN HET NEDERLANDS

## Inleiding

De depressieve stoornis is de meest voorkomende psychiatrische aandoening bij ouderen, met grote impact op de kwaliteit van leven van betrokkenen. Depressieve ouderen zijn ook lichamelijk minder gezond dan niet-depressieve ouderen. Het doormaken van een depressie blijkt zelfs gepaard te gaan met het ontstaan van nieuwe lichamelijke ziekten en vroegtijdig overlijden[1]. Deze hoge ziektelast leidt, mede door de toenemende vergrijzing, ook tot steeds hogere maatschappelijke kosten. Het is daarom belangrijk om te ontrafelen hoe deze negatieve gevolgen van een depressie ontstaan en welke factoren daarbij een rol spelen. De afgelopen decennia is duidelijk geworden dat vitamine D betrokken is bij veel meer processen in het lichaam dan alleen de botontwikkeling. Een tekort aan vitamine D blijkt een universele risicofactor te zijn voor verschillende negatieve gezondheidsuitkomsten[2]. Nadat op veel plaatsen in de hersenen vitamine D-receptoren werden aangetroffen[3], nam ook het onderzoek naar de associatie tussen vitamine D en depressie een grote vlucht. Bij mensen met een depressie vond men verlaagde vitamine D-spiegels in het bloed[4]. Toch is tot op heden noch overtuigend bewijs gevonden voor een oorzakelijk verband tussen vitamine D-deficiëntie en het ontstaan van een depressie, noch voor een antidepressieve werking van vitamine D[5]. Een vitamine D-tekort bij depressie zou ook het gevolg kunnen zijn van minder blootstelling aan zonlicht of een inadequate intake van voeding door depressieve mensen. Met andere woorden: mogelijk is er geen enkel oorzakelijk verband en is vitamine D-deficiëntie slechts een epifenomeen (bijverschijnsel) van depressie. Vitamine D-deficiëntie is ook een risicofactor voor het ontstaan van frailty. In dit proefschrift verstaan we onder frailty lichamelijke kwetsbaarheid: een situatie waarin relatief kleine stressoren het evenwicht tussen de verschillende fysiologische systemen makkelijk kunnen ontregelen, waardoor een cascade aan negatieve gezondheidseffecten ontstaat. Frailty kan op verschillende manieren in kaart worden gebracht. In het frailty-model volgens Linda Fried is sarcopenie, het verlies van spierweefsel en -functie met het ouder worden, een belangrijk kenmerk[6]. Depressieve ouderen blijken vaker frail te zijn dan ouderen in de algemene populatie[7]. Meest waarschijnlijk is er sprake van een wederzijds verband tussen frailty en depressie, waarbij de aanwezigheid van de ene conditie een risicofactor is voor het ontwikkelen van de andere[7, 8]. Het vroegtijdig onderkennen van frailty is belangrijk, omdat dit mogelijkheden biedt de behandeling hierop aan te passen, om complicaties te voorkomen en in sommige gevallen zelfs de mate van frailty (kwetsbaarheid) te verminderen. Het frailty-concept

wordt in toenemende mate succesvol ingezet in de somatische gezondheidszorg, maar binnen de ouderenpsychiatrie wordt hier nog weinig aandacht aan besteed. Hoewel inmiddels voor veel chronische ziekten is aangetoond dat de mate van frailty een belangrijke voorspeller is voor overlijden, is dit nooit onderzocht bij ouderen met een depressie. Studies naar de relatie tussen depressie enerzijds en vitamine-D deficiëntie en frailty anderzijds zijn veelal uitgevoerd in de algemene bevolking. In deze studies werd depressie meestal gemeten met vragenlijsten naar depressieve symptomen. Bij ouderen kan dit makkelijk leiden tot overdiagnosticering van depressie, doordat symptomen van een lichamelijke ziekte, zoals vermoeidheid of slaapproblemen, worden gescoord als depressieve klachten. Zeker als het gaat over vitamine D-deficiëntie en frailty, waarbij de kans groter is dat er ook somatische klachten spelen, is het de vraag of de resultaten van eerdere onderzoeken wel te generaliseren zijn naar de klinische praktijk van de geestelijke gezondheidszorg (GGZ).

Het doel van dit proefschrift is om vanuit de klinische praktijk, dus uitgaande van een oudere patiënt met een depressieve stoornis, het onderlinge verband tussen vitamine D-deficiëntie, frailty en mortaliteit te ontrafelen. Hiervoor hebben we gebruik gemaakt van de database van de Nederlandse Studie naar Depressie bij Ouderen (NESDO). Deze studie werd uitgevoerd onder 510 ouderen, waarvan er 378 een depressie hadden en 132 ouderen nooit in hun leven een depressie doormaakten. In NESDO werd de diagnose depressie door middel van een diagnostisch interview vastgesteld. Het doel van de NESDO was om de determinanten, het beloop en de gevolgen van de depressie op latere leeftijd te onderzoeken. Daarvoor werden van alle deelnemers gegevens verzameld over verschillende psychosociale, biologische, cognitieve en genetische factoren. Deze uitgebreide database biedt de mogelijkheid om het complexe verband tussen vitamine D en depressie bij ouderen in relatie tot negatieve gezondheidsuitkomsten op te helderen.



## Inhoud van dit proefschrift

*Depressie bij ouderen en mortaliteit*

In eerdere onderzoeken werd depressie in verband gebracht met een verhoogde kans op overlijden, al is nog niet duidelijk welke mechanismen daaraan ten grondslag liggen[9]. In **hoofdstuk 2** beschrijven we een studie binnen de NESDO-populatie waarin we hebben onderzocht of het risico op overlijden voorspeld wordt door het hebben van een depressie, of door de aanwezigheid van bepaalde subtypes of kenmerken van de

ouderdomsdepressie. We vonden dat het mortaliteitsrisico bijna drie keer zo hoog was voor de depressieve groep dan voor de niet-depressieve controlegroep. Nadat we de resultaten hadden gecorrigeerd voor demografische factoren, kenmerken van een ongezonde levensstijl, medicatiegebruik en somatische comorbiditeit was dit verschil echter niet meer significant. De verhoogde kans op overlijden van depressieve ouderen lijkt het best verklaard te kunnen worden door ongezonde leefgewoonten en het gebruik van verschillende medicamenten naast elkaar. Van de verschillende subtypes en kenmerken van depressie die we onderzocht hebben, was alleen de beperkte depressieve stoornis (*minor depression*) geassocieerd met een verhoogd risico op overlijden, ook na correctie voor mogelijke confounders. Een verklaring hiervoor zou kunnen zijn dat de diagnose beperkte depressieve stoornis bij ouderen wellicht gesteld wordt op basis van depressieve symptomen door onderliggende processen gerelateerd aan veroudering, zoals ziektegedrag door inflammatoire reacties, frailty of milde cognitieve achteruitgang, die alle samenhangen met een verhoogd risico op overlijden.

*Vitamine D-deficiëntie als universele risicofactor voor negatieve gezondheidsuitkomsten*

Het doel van de studie in **hoofdstuk 3** is om de onderlinge verbanden tussen vitamine D-deficiëntie, depressie bij ouderen en negatieve gezondheidsuitkomsten verder op te helderen. Hiervoor werd bij de 367 depressieve deelnemers aan de NESDO gekeken naar de samenhang van de vitamine D-spiegel met het halfjaarlijkse beloop van de depressieve symptomen, de remissiestatus na twee jaar, uitval uit de studie en overlijden. We vonden geen verband tussen de vitamine D-spiegel en het beloop van de depressieve symptomen of de remissiestatus. Desalniettemin leek er bij de deelnemers met een ernstige vitamine D-deficiëntie (vitamine D-spiegel < 25 nmol/l) minder vaak sprake van remissie van de depressie, hoewel dit verschil niet significant was. Om te onderzoeken of deze groep baat zou kunnen hebben bij suppletie met vitamine D zijn gerandomiseerde placebogecontroleerde studies nodig. We vonden tevens dat lagere vitamine D-spiegels samenhangen met een significant hoger risico op mortaliteit. Dit verband versterkt de gedachte dat vitamine D-deficiëntie vooral een teken van een slechte somatische gezondheidstoestand is. Deze hypothese hebben we nader uitgediept in de volgende hoofdstukken.

In **hoofdstuk 4** keken we bij de depressieve deelnemers van de NESDO naar de associatie tussen vitamine D- spiegels en frailty, waarbij we ook de verschillende

frailty-componenten en het beloop van frailty meenamen. Bij aanvang van de studie bleken de deelnemers met een lagere vitamine D-spiegel vaker frail te zijn, zelfs als de resultaten gecorrigeerd werden voor leefgewoonten en andere somatische gezondheidsindicatoren. Onder de depressieve personen die bij aanvang van de studie niet frail waren, bleek een hogere vitamine D-spiegel te beschermen tegen het ontstaan van frailty. Dit was zoals we van tevoren hadden verwacht, omdat gedacht wordt dat vitamine D-deficiëntie een etiologische factor zou kunnen zijn voor frailty, en vitamine D-suppletie een potentiele behandeling om frailty te voorkomen. Het bewijs hiervoor is echter nog niet overtuigend[10]. Een onverwachte bevinding was dat bij de deelnemers die zowel depressief als frail waren hogere vitamine D-spiegels verband hielden met het persisteren van frailty over de tijd. Een soortgelijke uitkomst in een andere studie[11] werd destijds beschouwd als een toevalsbevinding. Vanwege de beperkte groepsgrootte kunnen wij een toevalsbevinding ook niet uitsluiten. Ook zou deze contra-intuïtieve uitkomst veroorzaakt kunnen worden door confounding door indicatie of overlap tussen frailty en depressie. In toekomstige studies zou onderzocht moeten worden of dit gunstige effect van lage vitamine D-spiegels op het beloop van frailty verklaard kan worden door confounding van de resultaten, of dat er sprake is van een beschermend effect door nog onbekende pathofysiologische mechanismen.

*Leeftijd en frailty als belangrijkste voorspellers van mortaliteit bij ouderen met een depressie*

Bij ouderen zijn zowel frailty als een depressie voorspellend voor negatieve gezondheidsuitkomsten, waaronder mortaliteit. Daarom hebben we in **hoofdstuk 5** onderzocht of frailty voorspellend is voor overlijden gedurende de zes jaar dat de depressieve deelnemers aan NESDO vervolgd werden. Nadat gecorrigeerd was voor andere risicofactoren voor mortaliteit, vonden we een prospectief verband tussen fysieke frailty en mortaliteit. Bovendien hing ook het aantal aanwezige frailty-componenten samen met een verhoogde kans op overlijden. Biomarkers gerelateerd aan frailty zouden mogelijk in de richting kunnen wijzen van onderliggende pathofysiologische verklaringen voor het verband tussen frailty en mortaliteit. Daarom hebben we onderzocht of het verhoogde risico op overlijden bij frailty (gedeeltelijk) kan worden verklaard door inflammatoire parameters (ultrasensitief C-reactief proteïne (CRP), interleukine-6 (IL-6), neutrofiel gelatinase-geassocieerd lipocaline-2 (NGAL-2)), vitamine D en de telomeerlengte van de leukocyten. De impact van frailty op de mortaliteit in de ouderdomsdepressie werd deels verklaard door verhoogde inflammatoire parameters, verkorte telomeren en een verlaagde vitamine D-spiegel.

Alleen hogere spiegels van ultrasensitief CRP en lagere spiegels van vitamine D hielden daarnaast ook onafhankelijk van frailty verband met de mortaliteit.

Het concept frailty kan dus helpen om onder depressieve ouderen degenen met een verhoogd risico op sterfte te identificeren. Voor mensen die zowel frail als depressief zijn zouden interventies gericht op frailty mogelijk kunnen bijdragen aan het verminderen van de sterfte.

*Is vitamine D-deficiëntie een epifenomeen van depressie bij ouderen?*
Hoewel een vitamine D-tekort geassocieerd is met zowel frailty als depressie, zijn er weinig studies waarin gekeken is naar het prospectieve beloop van vitamine D-spiegels in relatie tot deze condities. Dit is van belang omdat gedrag dat samenhangt met frailty of depressie, zoals een ontoereikende intake van voeding of verminderde blootstelling aan de zon, van invloed kan zijn op de vitamine D-spiegel in het bloed. Daarom hebben we in **hoofdstuk 6** onderzocht of een verandering van de vitamine D-spiegel bij depressieve ouderen samenhangt met het beloop van de depressie, het beloop van frailty en de verschillende frailty-componenten, of beide. Hiervoor hebben we de baseline- en tweejaarsdata van 232 depressieve deelnemers aan NESDO gebruikt. We vonden dat in deze groep de vitamine D-spiegel gemiddeld genomen daalde, onafhankelijk van het beloop van de depressie. Een toename van frailty hing samen met een significant sterkere daling van de vitamine D-spiegels over de tijd. Post-hoc analyses wezen uit dat deze samenhang met frailty mogelijk werd gedreven door een toename van uitputting over de tijd en werd tegengegaan door een toename van de loopsnelheid. Op basis van deze bevindingen ontstond de hypothese dat vitamine D-suppletie bij een depressie op oudere leeftijd mogelijk zou kunnen zorgen voor een afname van frailty, en dan in het bijzonder van uitputting. Dit zou mogelijk deels de eerdere inconsistente bevindingen in gerandomiseerde gecontroleerde trials naar het effect van vitamine D-suppletie op depressie kunnen verklaren, zeker omdat vermoeidheid een belangrijk symptoom is bij veel depressieve ouderen. Wij pleiten er daarom voor om frailty (-componenten) en uitputting mee te nemen als secundaire uitkomstmaten in toekomstige vitamine D-suppletie onderzoeken bij ouderen met een depressie, zodat dit meer diepgaand onderzocht kan worden.

*Wat is er bekend over het effect van vitamine D bij depressieve ouderen op fysieke gezondheidsuitkomsten?*

In **hoofdstuk 7** presenteren we de resultaten van een literatuuronderzoek, waarbij we onderzocht hebben in hoeverre de voorgaande aanbeveling al in de praktijk is gebracht in eerdere studies. We voerden een systematische literatuurreview uit, waarbij we hebben gekeken of negatieve gezondheidsuitkomsten die samenhangen met vitamine D-deficiëntie en depressie werden meegenomen als uitkomsten in vitamine D-suppletie onderzoeken die primair gericht waren op personen van middelbare of oudere leeftijd met een depressie. Van de 32 studies die we vonden, hadden er vijf één of meer negatieve gezondheidsuitkomsten als uitkomst. Van de studies die uitgevoerd werden in fysiek kwetsbare populaties was er slechts één van goede kwaliteit. In deze studie werd een gunstig effect van vitamine D-suppletie op het aantal functionele beperkingen gezien[12]. In de toekomst zijn goed opgezette studies naar de effecten van vitamine D-suppletie bij ouderen met een depressie nodig om te exploreren of hiermee negatieve gezondheidsuitkomsten kunnen worden voorkomen of gestabiliseerd.

## Conclusies

Wat kunnen we aan de hand van dit proefschrift concluderen over de rol van vitamine D en frailty als determinanten van negatieve gezondheidsuitkomsten bij ouderen met een depressie? Ten eerste vonden we geen aanwijzingen voor een etiologische rol van vitamine D-deficiëntie in het ontstaan van een depressie. Wel zou vitamine D-deficiëntie een rol kunnen spelen in het ontstaan van de negatieve gevolgen van een depressie op de gezondheid, zoals frailty. Bovendien is het waarschijnlijk niet de depressie zelf, maar zijn het eerder de negatieve gevolgen en comorbide condities, zoals frailty en vitamine D-deficiëntie, die leiden tot een verhoogd risico op sterfte van ouderen met een depressie. Als laatste zouden studies die het effect van vitamine D-suppletie bij ouderen met een depressie bestuderen zorgvuldig opgezet moeten worden, met medeneming van frailty en negatieve gezondheidsuitkomsten als secundaire uitkomstmaten.

## Klinische implicaties

Wat betekenen deze bevindingen voor de ouderenpsychiater en anderen die werken met mensen met een depressie op latere leeftijd? Het meest belangrijk is dat clinici alert zijn op de negatieve gezondheidsgevolgen van een depressie, omdat deze leiden tot een slechtere prognose en uiteindelijk mogelijk tot de dood. De aanwezigheid van frailty en vitamine D-deficiëntie bij ouderen met een depressie weerspiegelt een ongunstiger prognose. Daarom dient in de behandeling van een oudere met een depressie

zorgvuldig onderzoek gedaan te worden naar de aanwezigheid van mogelijke negatieve gezondheidsconsequenties. In het behandelplan zouden interventies opgenomen moeten worden gericht op preventie van frailty en ongunstige leefstijlfactoren, zoals oefenprogramma's, leefstijlcoaching of reductie van polyfarmacie. De bevindingen in dit proefschrift onderstrepen dat vitamine D-deficiëntie een teken is van een slechte gezondheidstoestand. Hoewel vitamine D-suppletie vermoedelijk de depressie niet direct zal beïnvloeden, kunnen hierdoor mogelijk wel de negatieve gevolgen van een depressie voor de gezondheid verbeteren.

Hoewel het bewijs nog steeds beperkt is, raden wij op basis van onze bevindingen aan om ouderen met een depressie te scharen onder de risicogroepen voor vitamine D-deficiëntie, bij wie vitamine D-suppletie actief nagestreefd dient te worden.

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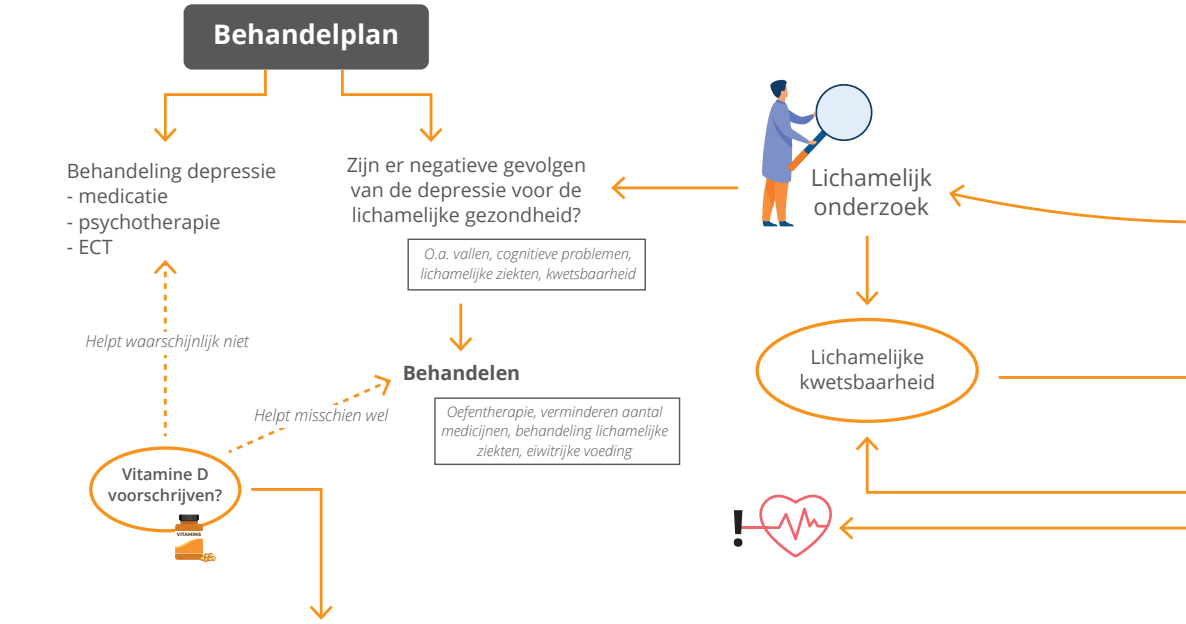


## Toekomstig onderzoek:

**Vitamine D geven aan depressieve ouderen**


**Kijken naar:**

- effect op depressie
- effect op negatieve lichamelijke gevolgen van depressie

**Komt een depressieve oudere bij de psychiater...**

**Vooruitzichten** *op basis van de uitkomsten van de Nederlandse Studie naar Depressie bij Ouderen*


Na 6 jaar

Grotere kans op +

Bloed prikken


Na 6 jaar

**Vitamine D tekort**


Na 2 jaar

Grotere kans op lichamelijke kwetsbaarheid

2 jaar later

Geen verband met het beloop van de depressie

**Toename vitamine D tekort**

Verband met verergering kwetsbaarheid

# ADDENDUM

LIST OF PUBLICATIONS

CURRICULUM VITAE

ACKNOWLEDGEMENTS

PREVIOUS SHARE DISSERTATIONS

# LIST OF PUBLICATIONS

**Van den Berg KS**, Marijnissen RM, van den Brink RHS, Oude Voshaar RC, Hegeman JM. Frailty and other somatic health indicators in vitamin D supplementation trials in depression: a systematic review. Ageing Res Rev. 2021 Nov;71:101442. doi: 10.1016/j.arr.2021.101442.

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# CURRICULUM VITAE

Karen van den Berg werd geboren op 6 maart 1982 in Apeldoorn. In 2000 slaagde zij voor het atheneum aan CSG de Heemgaard in Apeldoorn en studeerde daarna een jaar Gezondheidswetenschappen aan de Universiteit Maastricht. Na het behalen van het propedeutisch examen stapte zij in 2001 over naar Geneeskunde aan de Radboud Universiteit in Nijmegen. In het kader van haar studie ging zij in 2005 naar Australië voor een onderzoeksstage aan de Sydney Melanoma Unit. In 2008 liep zij een coschap ontwikkelingslanden in Suriname, waar zij onder andere werkzaam was in het Psychiatrisch Centrum Suriname te Paramaribo.

Het artsexamen behaalde zij in 2008. Naderhand werkte zij als basisarts op de afdelingen Psychiatrie en Interne Geneeskunde in Ziekenhuis Rijnstate te Arnhem. In 2010 begon zij aan de opleiding tot psychiater bij Pro Persona in Arnhem/Wolfheze, met als aandachtsgebied de ouderenpsychiatrie. Onderdeel hiervan was een onderzoeksstage in het UMCG te Groningen naar de rol van vitamine D in het beloop van de ouderdomsdepressie, onder supervisie van dr. R.M. Marijnissen en prof. dr. R.C. Oude Voshaar. Na de opleiding zette zij dit onderzoek voort als promotietraject.

Na haar registratie als psychiater in oktober 2015 werkte zij korte tijd op de acute opname-afdeling voor ouderen bij Altrecht. Sinds januari 2016 is zij werkzaam als psychiater in het St Antonius ziekenhuis in Utrecht. In haar patiëntgerelateerde werkzaamheden ligt de focus op de medisch-psychiatrische unit, de POP-poli (psychiatrie tijdens de zwangerschap en kraamperiode) en elektroconvulsietherapie (ECT). Daarnaast is zij een van de kartrekkers van de implementatie en ontwikkeling van het elektronisch patiëntendossier (Epic) en het bijbehorende depressie-zorgpad voor de afdeling Psychiatrie & Psychologie. Na haar promotie zal zij dit verder uitbreiden met toegepast onderzoek binnen het waardegedreven zorg depressieproject. In de coronaperiode was zij als voorzitter van de werkgroep psychosociale ondersteuning intensief betrokken bij de inrichting en coördinatie van de psychosociale ondersteuning van medewerkers, patiënten en naasten. Ook was zij mede-ontwikkelaar van verschillende infographics ten behoeve van de ondersteuning van zorgmedewerkers.

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