Vitamin D: ultraviolet light and well-being of older people

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CONTENTS

Chapter 1

General introduction

VITAMIN D SYNTHESIS AND VITAMIN D RECEPTORS

Vitamin D is a hormone produced in the skin from 7-dehydrocholesterol (provitamin D) via a non-enzymatic process involving ultraviolet light. The product of this photolysis, previtamin D, undergoes further hydroxylation in the liver to 25-hydroxyvitamin D (25(OH) D_3, calcidiol) by 25-hydroxylase and is converted in the kidney to the biologically active form 1,25-dihydroxyvitamin D_3 (1,25 $(OH)_2$ D_3, calcitriol) through a second hydroxylation by 1-alpha hydroxylase. Recent genome-wide association studies have identified several variants near genes involved in cholesterol synthesis (DHCR7), hydroxylation (CYP2R1, CYP27B1, CYP24A1) and vitamin D transport (GC, vitamin D binding protein) that influence vitamin D status. Genetic variation in these loci can cause vitamin D insufficiency and disease [1,2].

1,25-dihydroxyvitamin D_3 has multiple functions in the regulation of calcium and phosphorus metabolism, immune and cardiovascular systems, skin, muscle function, cellular growth control and possibly numerous other biological processes [3]. These biological activities are mediated by the vitamin D receptor, a nuclear receptor protein which functions to control the expression of genes in a cell-selective manner [1,4]. Most cells and organs in the human body have vitamin D receptors [4-7].

VITAMIN D SIGNALLING AND TARGET ORGANS/ CELLS: DOES VITAMIN D PLAY AN ESSENTIAL ROLE IN BIOLOGICAL PROCESSES OR IN CURING DISEASE?

Observational studies have described inverse associations between vitamin D status and a large number of diseases and health risks such as osteoporosis, fracture risk, fall risk, cardiovascular diseases, malignancies, infections, and autoimmune diseases [8-12]. Recently, a large number of randomised controlled trials (RCTs), meta-analyses of RCT's and Mendelian randomisation studies have investigated causality concerning vitamin D levels and diseases.

VITAMIN D AND BONE MINERAL HOMEOSTASIS

One of the principal functions of vitamin D is to promote calcium absorption from the intestine and maintain calcium homeostasis in the body. Patients with functional mutations in 25-hydroxylase (CYP2R1) develop vitamin D-dependent rickets and respond to physiological doses of calcidiol [13]. Patients with functional mutations in 1-alpha hydroxylase (CYP27B1) develop skeletal defects or classic rickets, muscle weakness and growth retardation, all of which

can be cured with physiological levels of calcitriol [14]. Vitamin D and calcium are substrates in a multifactorial process that maintains bone homeostasis. The multifactorial nature of this process makes it difficult to determine the threshold level of vitamin D at which the balance becomes negative and triggers disease: insufficient mineralisation of the matrix leads to the development of osteopenia or osteoporosis. RCTs and meta-analyses of vitamin D trials show no negative effects on bone density or fracture risk when the baseline level of 25-hydroxyvitamin D is higher than 40 nmol/l [15-19]. Furthermore, a study assessing the genetic and clinical determinants of fracture risk, including genome wide associations and Mendelian randomisation, showed an effect of bone mineral density on fracture risk but no causality regarding vitamin D levels [20]. However, this study was carried out in a healthy population and did not consider the possibility of a threshold-dependent relation to the risk of fractures and vitamin D levels.

VITAMIN D AND FALLS

Vitamin D receptors have also been identified in muscles, where 1,25 $(OH)_2$ D_3 influences calcium uptake and controls protein synthesis in the fast twitch muscle fibres that maintain balance and prevent falls [21]. Reversible muscle atrophy has been observed in individuals with vitamin D deficiency [22]. The RCTs and meta-analyses carried out to examine the effect of vitamin D supplementation in the prevention of falls are inconclusive but do delineate two aspects: vitamin D supplementation is effective in doses 700-1000IU [23] and in people with a low vitamin serum concentration [24]. A recent, large RCT by Scragg et al. that included 5110 participants and an intervention consisting of vitamin D supplementation in monthly doses of 100,000 IE for 3.3 years showed no beneficial effects of vitamin D on the prevention of falls. However, the study population had a mean baseline deseasonalized 25(OH)D concentration of 66 nmol/l and only 25% of the subjects had 25(OH)D levels below 50 nmol/l.

Clinical trials with very high vitamin D supplementation levels of 60,000 IE monthly or 500,000 IU annually showed a counterproductive effect and actually increased the risk of falling [25,26].

VITAMIN D AND CANCER

Preclinical studies have demonstrated that vitamin D can modulate anticancer activities such as antiproliferation, countering in sensitivity to antigrowing signal and evasion of apoptosis [27]. Vitamin D receptor signalling enhances adhesion and suppresses invasive potential [28], as well as playing a role in maintaining genomic integrity and facilitating DNA repair [29]. The effects of vitamin D supplementation on the risk of cancer were discussed in a systematic review of

meta-analyses, which concluded that the studies analysed provided no evidence supporting a causal relationship between low vitamin D levels and cancer [30]. However, the authors of the systematic review noted that people with low vitamin D levels were underrepresented in the RCTs included in the meta-analysis and that studies of longer duration have suggested a beneficial effect of vitamin D supplementation [31,32].

VITAMIN D AND RISK OF HYPERTENSION

Vitamin D corrects abnormalities in calcium homeostasis and regulates the renin-angiotensin system, both of which play a role in the development of hypertension [33,34]. Meta-analyses on the effect of vitamin D supplementation on blood pressure have caused controversy. Two large meta-analyses took into account the effect of supplementation on subgroups with very low baseline 25(OH)D levels: the first study found no effect of vitamin D on blood pressure [35], while the second study found a lower diastolic blood pressure in hypertensive patients with very low baseline 25(OH)D levels [36]. The VIDA study, which recruited 5110 participants, reported a beneficial effect on arterial function in participants with low 25(OH)D levels following supplementation with high monthly doses of vitamin D [37]. Furthermore, a Mendelian randomised trial investigated whether genetic variants that affect circulating concentrations of 25(OH)D also affect blood pressure and risk of hypertension [38]. In phenotypic analyses (N=49,363), an increased 25(OH)D concentration was associated with decreased systolic blood pressure and reduced odds of hypertension.

VITAMIN D AND IMMUNE SYSTEM

1,25 $(OH)_2$ D_3 has a wide range of immunomodulatory effects in innate and adaptive immune cells [39]. Inflammatory immune signals can stimulate the expression of CYP27B1, allowing macrophages to locally produce 1,25 $(OH)_2$ D_3 [40,41]. Active metabolites of vitamin D then enhance the antimicrobial activity of macrophages, allow dendritic cells to become adherent, diminish the secretion of proinflammatory cytokines and enhance secretion of IL-10 (interleukin 10, an anti-inflammatory cytokine) and TNF-alpha (tumour necrosis factor alpha), which modulates T-cell behaviour through effects on antigen presenting cells and cell phenotype and function [39]. High-dose vitamin D supplementation in patients with multiple sclerosis produced pleotropic immunomodulatory effects that included reduction of interleukin 17 levels (IL-17). IL-17 production damages the blood-brain barrier, facilitating the entry of immune cells into the central nervous system [42]. A systematic review and meta-analysis of individual participant's data (11,321 participants) showed that vitamin D supplementation may reduce acute respiratory infections, especially in people with vitamin D deficiency [43]. A retrospective, observational

analysis of 190,000 participants that aimed to determine if circulating 25(OH)D levels are associated with SARS-CoV-2 positivity rates reported that participants with vitamin D serum levels lower than 50 mmol/l had a 54% higher positivity rate compared to those with serum levels of 75-85 nmol/l/ [44].

EFFECTS OF SUN/ULTRAVIOLET LIGHT ON HUMAN HEALTH

The most well-known effect of sun and ultraviolet light on human health is the synthesis of vitamin D in the skin, but other effects have also been described. There is growing evidence that harm due to avoidance of sun exposure might actually outweigh the risks of skin cancer, and that a satisfactory balance is possible [45]. Interestingly, while sunburns appear to double the risk of melanoma, non-burning sun exposure is associated with a reduced risk of melanoma [46]. Furthermore, observational studies have described inverse associations between sun radiation and several cancers such as non-Hodgkin lymphoma and colorectal, breast and prostate cancer [9]. Well described positive effects of sunlight include the prevention and treatment of skin diseases like psoriasis, eczema, vitiligo and acne [47,48].

Epidemiological studies have shown that blood pressure correlates with geographical latitude [49] and that sunlight exposure might reduce both blood pressure and CVD [50,51]. In a competing risk scenario study of 29,518 Swedish women with prospective 20-year follow-up (Melanoma in Southern Sweden cohort), Lindqvist et al. showed that longer life expectancy among women with active sun exposure habits was related to a decrease in CVD and non-cancer/non-CVD mortality [50]. The skin has the potential to contribute to cardiovascular homeostasis by increasing the circulating nitric oxide (NO) metabolite pool. Laboratory studies investigating the effect of ultraviolet light type A on blood pressure demonstrated that both skin and dermal vasculature contain biologically significant stores of nitric oxide (NO) that can be directly mobilized by UV type A radiation [52,53]. NO is a key vasoprotective molecule canonically produced in the cardiovascular system. It is an important determinant of peripheral vascular resistance and blood pressure, as well as being associated with vasorelaxation, anti-atherogenic and anti-platelet phenotypes [54].

A mood-enhancing and hence quality of life enhancing effect of ultraviolet light has also been reported [55-58]. Modulation of mood triggered by ultraviolet light is possibly mediated through the skin and may involve three local systems: i) the skin analog of the hypothalamic-pituitary-adrenal (HPA) axis [59], ii) the serotoninergic/melatoninergic system [60], and iii) the immune system [61,62]. These pathways are assumed to inteact with systemic mechanisms of body homeostasis [61].

VITAMIN D, SUNLIGHT AND OLDER PEOPLE

With ageing, the production of vitamin D in the skin declines [63]. This is the combined effect of a decline in the ability of the kidney to synthesize $1,25(OH)_2D_3$ and an increase in catabolism of $1,25(OH)_2D_3$ by CYP24A1, which contributes to age-related bone loss [2]. Aging is also associated with a decrease in the concentration of the vitamin D receptor [2]. Vitamin D deficiency (serum 25(OH)D3 < 30 nmol/l) and insufficiency (serum 25(OH)D3 > 30 nmol/l<50 nmol/l) is common in older people, and is mediated by factors such as a reduction in mobility, greater time spent indoors, a lower intrinsic skin response to UV radiation and a reduced dietary vitamin D intake [64]. Almost all nursing home residents are vitamin D insufficient if vitamin D is not supplemented [65,66].

The Dutch Health Council (2012) advises standard daily vitamin D supplementation of 800 IU (20 mcg) for persons aged ≥ 70 years, with a target 25(OH)D serum concentration of ≥ 50 nmol/l [67]. This recommendation is in line with advice from the Institute of Medicine (IOM) (2011) [68,69] and the Expert Working Group on vitamin D (2012) [70]. While these guidelines are clear and easy to apply, a number of issues remain. The guidelines are possibly too general for a heterogeneous population of people aged 70 years and over, as this group often includes both the fit and active and the very frail. Is the recommended level of vitamin D supplementation appropriate for everyone in this heterogeneous group? Levels of 25(OH)D are known to be influenced by age [64], body mass index [71], medication use [67] and comorbidities [72]. How the medical doctors taking care of this population follow the guidelines, do they meet difficulties and what are they? And if there is good compliance to the guidelines, how do doctors regard sun exposure in the older population? Are they happy with vitamin D supplementation alone, assuming that it is the only significant effect of sun exposure? And once an adequate vitamin D level is achieved, do they feel that avoidance of sun exposure amounts to avoidance of its deleterious effects? The latter topic is quite controversial even in scientific literature. As already mentioned in the introduction, there is growing evidence that sun exposure may have positive effects on human health via mechanisms other than vitamin D synthesis alone, possibly providing protection against cancer, cardiovascular disease and autoimmune disease. It might also positively influence mood, depressive disorders and well-being. These data are predominantly derived from observational studies. A small number of RCTs have been conducted but using only small samples and with inconclusive findings. We formulated the goals of our study to specifically address these questions.

AIMS OF THIS THESIS

The overall aim of the studies described in this thesis was to investigate vitamin D supplementation strategies in older people and nursing home residents in the Netherlands, and to explore possible beneficial effects of ultraviolet light, over and above vitamin D synthesis, on the well-being and quality of life of nursing home residents with dementia. The detailed objectives of these studies:

Chapter 2 presents an observational study designed to investigate the efficacy of recommended dietary vitamin D supplementation in a population of frail nursing home residents. We investigated whether a sufficient serum 25(OH)D3 level was reached to ensure expected skeletal and non-skeletal effects.

Chapter 3 examines the vitamin D prescribing behaviour of elderly care physicians (ECPs) and general practitioners (GPs) in the Netherlands among people aged 70 years and over. We discuss controversial topics concerning vitamin D supplementation with the aim to clarifying and promoting vitamin D supplementation in older age groups.

Chapter 4 is a systematic review exploring and summarizing evidence obtained from clinical trials and observational studies on the effects of ultraviolet light. We discuss the effects of ultraviolet light applied to the skin or as a component of light therapy applied to the eyes, considering the impact on mood, depressive disorders and wellbeing.

Chapter 5 describes a randomized controlled trail that compared the effect of ultraviolet light to oral vitamin D supplementation on the well-being and quality of life of nursing home residents with advanced dementia.

Chapter 6 considers the impact of vitamin D supplementation and ultraviolet radiation on blood pressure changes in nursing home residents with dementia.

Chapter 7 is a general discussion of the main results of the studies, considers the clinical implications of our findings for the daily practice of physicians working with older people, and makes some recommendations for future research.

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Chapter 2

Efficacy of daily 800 IU vitamin D supplementation in reaching vitamin D sufficiency in nursing home residents: cross-sectional patient file study

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ABSTRACT

Background

The Dutch Health Council advises a standard daily vitamin D supplementation of 800 IU (20 mcg) for persons aged ≥ 70 years, with a target 25(OH)D serum concentration of ≥ 50 nmol/l. This recommendation is in line with advice from the Institute of Medicine (IOM) (2011) and the Expert Working Group on vitamin D (2012). A target 25(OH)D serum concentration of ≥ 75 nmol/l is also recommended in the literature. It is unknown whether this advice, initially designed for healthy adults/elderly, will lead to vitamin D sufficiency in the large majority of nursing home residents, taking into account the frailty of this population.

Methods

Cross-sectional patient file study. Participants were 71 psychogeriatric nursing home residents (25 males, 46 females) with a mean age of 83 (SD 7) years using cholecalciferol capsules (5600 IU) once a week, or cholecalciferol drops (50,000 IU/ml): 3 drops a week (7500 IU), for at least 3 months. Main outcome measure was serum 25(OH)D level after supplementation.

Results

Of all participants, 19 used cholecaliferol drops and 52 used cholecaliferol capsules. In total, mean serum 25(OH)D was 77 (SD 30) nmol/L and 55 residents (78%) were vitamin D sufficient. Among capsule users, mean serum 25(OH)D was 90 (SD 22) nmol/L and 49 (94%) were vitamin D sufficient. Among users of drops, mean serum 25(OH)D was 41 (SD 8) nmol/L and 6 (32%) were vitamin D sufficient.

Conclusion

In most of these residents, vitamin D supplementation once a week with cholecalciferol capsules containing 5600 IU (equivalent to 800 IU daily) resulted in vitamin D sufficiency (serum 25(OH)D ≥ 50 nmol/L). When choosing a vitamin D preparation for routine supplementation in nursing home residents it should be noted that major differences may exist in efficacy, even when the various preparations contain the same amount of vitamin D.

BACKGROUND

Vitamin D deficiency (serum 25(OH)D < 30 nmol/L) and insufficiency (serum 25(OH)D > 30 < 50 nmol/L) [1] is common among older people as a result of reduction in mobility, time spent outdoors with sun exposure, intrinsic skin response to ultraviolet radiation and dietary vitamin D intake [2,3]. In nursing home residents almost everyone is vitamin D insufficient if vitamin D is not supplemented [4,5].

The importance of vitamin D (especially among older persons) is growing with increasing knowledge on the numerous biological effects of vitamin D as a promoter of bone health [6], physical performance [7] and as a possible modulator in, e.g., cardiovascular disease [8,9], diabetes [10] and cancer [11]. In nursing homes, vitamin D supplementation is increasingly being considered as an indicator and standard for responsible care.

A consensus has not been reached yet among vitamin D researchers on the optimal 25(OH) D concentrations. The Endocrine Society clinical practice guidelines (2011)[12] recommend a target 25(OH)D serum concentration of ≥ 75 nmol/l with a daily vitamin D requirement of 1,500 -2,000 IU for persons aged ≥ 70 years.

The Dutch Health Council advises a standard daily vitamin D supplementation of 800 IU (20 mcg) for persons aged ≥ 70 years, with a target 25(OH)D serum concentration of ≥ 50 nmol/l [1]. This recommendation is in line with advice from the Institute of Medicine (IOM) (2011) [13] and the Expert Working Group on vitamin D (2012) [14].

However, it is unknown whether this advice, initially designed for healthy adults/elderly, will lead to vitamin D sufficiency in the large majority of nursing home residents, taking into account the frailty of this population with multiple comorbidities, polypharmacy, and dependency on basic activities of daily living. One study in Dutch nursing home residents, investigating the effect of equivalent oral doses of cholecalciferol 600 IU/day, 4200 IE/week and 18,000 IU/month on vitamin D status showed that, at 4 months, the percentage of patients with serum 25(OH)D < 50 nmol/L was 10.9% and 10.6% in the daily and weekly groups of vitamin D supplementation, respectively [5].

To our knowledge, no cross-sectional study in nursing home residents has investigated the efficacy of a daily vitamin D supplementation dose of 800 IU. Therefore, the present study investigates the prevalence of vitamin D sufficiency in a psychogeriatric nursing home population, after use of the recommended daily supplementation dose of 800 IU cholecalciferol.

METHODS

Participants and intervention

A cross-sectional study was carried out in 71 residents of dementia care units of the nursing home *Topaz Overduin* in Katwijk (the Netherlands), using cholecalciferol capsules, once a week 5600 IE or cholecalciferol drops (50,000 IU/ml), 3 drops a week (7500 IU). The capsules contained cholecalciferol 100 IE/mg, cellulose microcrystalline PH102, magnesium stearate en lactose monohydrate (180). Drops were a watery mixture composed of cholecalciferol concentrate in oil, citric acid monohydrate, star anise oil, potassium sorbates, polysorbatum 80 (polyoxyethylene sorbitan monooleat), sugar syrup, and purified water.

The only exclusion criterion was the use of vitamin D for less than 3 months. All blood samples were drawn on the same day.

The best parameter for vitamin D status, 25-hydroxyvitamin D [25(OH)D], was measured by a radioimmunoassay (25-OH-vitamin D RIA, Diasorin, Stillwater, MN, USA). The assay has 100% cross reactivity with 25(OH)D2 and 25(OH)D3. Total imprecision (Interassay coefficient of variation) is 9.4% at 22 nmol/l. SCAL Medical Diagnostics (Foundation central primary care laboratory) is certified by the Dutch Board for Accreditation and participates in external quality assessment schemes organized by the Foundation Quality Control Medical Laboratory Diagnostics.

Ethical approval

Ethical approval was not necessary under Dutch regulations since this study was a retrospective patient file study. Among all elderly care physicians in the participating nursing home, drawing blood samples, in order to check the effects of vitamin D supplementation on individual serum 25(OH)D levels, is considered to be a quality of care standard and therefore part of good medical practice. Therefore, the drawing of blood samples was for clinical purposes and complied with The Dutch Law of Agreement to Medical Treatment (WGBO), and not as research that has to comply with the Dutch law on Medical Research in Humans (WMO), for which ethical approval is required. Informed consent however is also necessary for all diagnostic and clinical work under the WGBO, so patients who did not want their blood samples taken, could refuse.

Potential factors that influence 25(OH)D concentration

From the patient files, data were collected on factors possibly influencing a rise in serum 25(OH)D: age, comorbidity, number and sort of medication use (anticonvulsant medication and corticosteroids were taken into account because these increase catabolism of 25(OH)D [1]), body mass index (BMI), sun exposure, Modification of Diet in Renal Disease (MDRD) as an estimate of the renal function, and Functional Ambulation Classification (FAC) scores as an

assessment of the mobility, performed by physiotherapists and physicians. The FAC consists of five items. Scores range from 0–5 (0 = Nonfunctional ambulation; 1 = Ambulator-dependent for physical assistance level II; 2 = Ambulator-dependent for physical assistance – level I; 3 = Ambulator-dependent for supervision; 4 = Ambulator- independent level surfaces only; and 5 = Ambulator independent) [15].

Comorbidity was expressed as the number of chronic diseases, taking into account 7 major conditions [16], i.e. chronic obstructive pulmonary disease, cardiac disease, peripheral arterial disease, diabetes mellitus, stroke, cancer and rheumatoid arthritis/osteoarthritis, and measured by review of the patients' medical files. BMI was calculated as body weight in kg divided by height in m^2 and subsequently categorized into three groups: underweight (BMI < 20 kg/m^2), normal weight (BMI > 20 kg/m^2) and overweight (BMI > 25 kg/m^2).

Adequate compliance was defined to exist when more than 80% of the vitamin D medication was ingested.

STATISTICAL ANALYSIS

Main outcome measure was serum 25(OH)D level after supplementation. We express continuous variables as means ± standard deviation and categorical variables as percentages. We used Student's T for comparisons, as well as Chi-squared test. A logistic regression analysis was used to assess the possible predictors of 25(OH)D insufficiency. P-values were considered significant at a p-value < 0.05. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to estimate the strength of the association when the p-value was significant. All analyses were conducted with SPSS 21 software.

RESULTS

Of the 71 participants with at least 3 months supplementation, 19 used cholecaliferol drops (3 males/16 females) and 52 used cholecaliferol capsules (14 males/38 females). In total, mean serum 25(OH)D was 77 (SD 30) nmol/L and 55 residents (78%) were vitamin D sufficient (Table 1).

Of the 52 capsule users, mean age was 83 (SD 7) years and mean serum 25(OH)D was 90 (SD 22) nmol/L. None of this group was vitamin D deficient [25(OH)D < 30 nmol/L], whereas 3 (6%) were vitamin D insufficient [25(OH)D <50 nmol/L], 49 (94%) were vitamin D sufficient [25(OH)D ≥ 50 nmol/L] and 42 of this group (80%) had serum 25(OH)D levels > 75 nmol/L.

Table 1 Characteristics of 71 patients with vitamin D supplementation

	Total group	Supplementation by capsules	Supplementation by drops	P
Subjects (females/males), n	71 (46/25)	52 (38/14)	19 (16/3)	0.5
Age in years, mean (SD)	83 (7)	83 (7)	82 (8)	0.4
Serum 25(OH)D[1] nmol/L, mean (SD)	77 (30)	90 (22)	41 (18)	<0.001
Ser. 25(OH)D in residents, % (n)				
≥75	61 (43)	80 (42)	5 (1)	
≥50-74.9	17 (12)	14 (7)	26 (5)	
30-49.9 nmol/L	14 (10)	6 (3)	37 (7)	
< 30 nmol/L	8 (6)	0 (0)	32 (6)	
Duration supplementation% (n)				
3-6 months	24 (17)	33 (17)	0 (0)	<0.001
12-18 months	45 (32)	60 (31)	5 (1)	
>18 months	31 (22)	7 (4)	95 (18)	
Subjects with sunlight exposure >1 x week% (n)	61 (43)	44 (23)	74 (14)	0.2
Number of medications% (n)				
<5	73 (52)	73 (38)	74 (14)	0.9
>5	27 (19)	27 (14)	26 (5)	
Medication influencing 25(OH)D	15 (11)	15 (8)	15 (3)	
- anticonvulsants	1 (1)	2 (1)	0	0.8
- corticosteroids	14 (10)	13 (7)	15 (3)	
FAC[2], % (n)				
0	39 (27)	43 (23)	21 (4)	
1	11 (8)	10 (5)	16 (3)	
2	11 (8)	10 (5)	16 (3)	0.3
3	14 (10)	10 (5)	26 (5)	
4	21 (15)	23 (12)	16 (3)	
5	4 (3)	4 (2)	5 (1)	
BMI[3], % (n)				
<20 underweight	55 (39)	60 (31)	42 (8)	0.01
20-25 healthy weight	34 (24)	34 (18)	32 (6)	
>25 overweight	11 (8)	6 (3)	26 (5)	
MDRD[4], % (n)				
<60	31 (22)	33 (17)	26 (5)	0.7
>60	69 (49)	67 (35)	74 (14)	
Chronic disease[5], % (n)				
≤2	73 (52)	73 (38)	74 (14)	0.6
>2	27 (19)	27 (14)	26 (5)	

Values are mean (SD) or number (percentage).

Of the 19 drop users, mean age was 82 (SD 8) years and mean serum 25(OH)D level was 41 (SD 18) nmol/L. In this group, 6 (32%) were vitamin D deficient [25(OH)D < 30 nmol/L], 7 (37%) were vitamin D insufficient [25(OH)D <50 nmol/L], 6 (31%) were vitamin D sufficient [25(OH)D ≥50 nmol/L], and 1 (5%) had serum 25(OH)D levels > 75 nmol/L. Among drops user, all 19 (100%) participants were compliant. Among capsule users 50 (96%) were compliant and 2 (4%) were not.

Because of the lower serum concentration of 25(OH)D in the group of drop users we used Student's T for comparisons as well as Chi-squared test to compare the basic characteristics of the two groups that can influence the 25(OH)D concentration. A significant difference was established in the BMI between the two groups (p 0.01) with a higher number of persons with overweight in the group of the drop users. Subsequently we carried out a bivariate analysis with the serum vitamin D concentration (patients divided in two groups 25(OH)D < 50 nmol/l and 25(OH)D ≥ 50 nmol/l) as dependent variable to control for potential confounders that can influence vitamin D concentration. The use of cholecalciferol drops was a strong predictor of 25(OH)D insufficiency (OR 35.3; p < 0.0001; 95% CI 7.7-160.9) (Table 2).

In the total study population, residents with 25(OH)D serum levels ≥50 nmol/L were more likely to have less comorbidity: i.e. ≤ 2 chronic somatic diseases registered (p = 0.02; OR 4.0; CI 1.2-13.0). However, this correlation was not significant among drop users. Among capsule users, the number of vitamin D insufficient subjects was too low (<5) to examine this correlation.

In both groups, no association was found between the other possible confounders (gender, age, BMI, renal function, sun exposure, number and kind of medication and mobility status) and vitamin D insufficiency.

DISCUSSION

Vitamin D supplementation that may be needed to achieve optimal concentration of 25(OH) D in all populations is not established. Studies suggest that 700 to 1000 IU vitamin D per day may be enough to bring 50% of the younger and older adults up to 75–100 nmol/l [17-19]. In our study a supplementation of 5600 IU vitamin D once a week by capsules brings 80% of the older adults to serum 25(OH)D higher than 75 nmol/l.

A strength of the present study is that it is the first to demonstrate that a population-based approach in vitamin D supplementation strategy is feasible, even in a population of fragile institutionalized older people.

Table 2 Predictors of vitamin D insufficiency in patients with dementia with Vitamin D supplementation: binary logistic regression analyses

	25(OH)D[1] < 50 nmol/L	25(OH)D ≥50 nmol/L	P-value	OR	95% CI
N	16	55			
Gender, % (n)			0.9		
Male	25 (12)	23 (13)			
Female	75 (4)	76 (42)			
Age in years, mean (SD)	83 (SD 8)	83 (SD 7)	0.9		
Subjects with sunlight exposure >1x/week, % (n)	25 (4)	44 (24)	0.1		
Drops/capsules, % (n)					
- drop users	81 (13)	11 (6)	<0.0001	35.3	7.7-160.9
- capsule users	19 (3)	89 (49)			
No. of medications, % (n)					
<5	75 (12)	72 (40)	0.8		
>5	25 (4)	27 (15)			
FAC[2], % (n)					
0	25 (4)	42 (23)			
1	6 (1)	13 (7)			
2	19 (3)	9 (5)	0.3		
3	31 (5)	9 (5)			
4	13 (2)	24 (13)			
5	6 (1)	4 (2)			
BMI[3], (n)					
<20 underweight	56 (9)	55 (30)	0.3		
20-25 healthy weight	25 (4)	36 (20)			
>25 overweight	19 (3)	9 (5)			
MDRD[4], % (n)					
<60	37 (6)	29 (16)	0.6		
>60	62 (10)	71 (39)			
Comorbidity[5], % (n)					
≤ 2 diseases	50 (8)	80 (44)	0.02	0.2	0.07-0.8
>2 diseases	50 (8)	20 (11)			

[1] 25(OH)D –25-hydroxyvitamin D

[2] FAC - Functional Ambulation Classification

[3] BMI - Body Mass Index

[4] MDRD - Modification of Diet in Renal Disease

[5]Chronic diseases from seven majors: chronic obstructive pulmonary disease, cardiac disease, peripheral arterial disease, stroke, diabetes mellitus, rheumatoid arthritis/osteoarthritis and cancer.

However, because it is a single-site study with a relatively small number of patients the external validity is limited. The study was conducted in Dutch nursing home residents and recommendations are for this population. Reproduction of the study in multiple sites and countries is therefore warranted.

The present study reveals a striking difference between the efficacy of drops and capsules in reaching vitamin D sufficiency in a psychogeriatric nursing home population.

In capsules users only 3 of 52 subjects (6%) were vitamin D insufficient; 2 of these participants had low medication compliance because of unwillingness to take the medication (presumably related to their cognitive decline). The third insufficient resident had a history of recurrent bladder carcinoma, long carcinoma and radiotherapy, cardiac disease and chronic renal failure. Among users of drops, no less than 13 of 19 subjects (69%) had insufficient 25(OH) serum levels. Possible reasons for this discrepancy were further investigated.

Indeed we didn't have the baseline 25(OH)D levels of our patients before the supplementation. In a previous study conducted in Netherlands, vitamin D baseline level was found to be insufficient in 98% of the nursing home residents [5]. It is also obvious in our study that the drop users have a longer duration of vitamin D supplementation than capsule users ($p < 0.0001$) and no one of the drop users receives the supplementation shorter than one year.

Compliance with the ingestion of drops was 100% in all participants; drops were administered by spoon with apple sauce, or in a small quantity of tea or water. In no case did drops exceeded the maximum shelf life and all were stored as specified by the pharmacist; the pharmacist also confirmed that 3 drops do in fact contain 7500 IU of cholecalciferol. Drops were a watery mixture composed of cholecalciferol concentrate in oil, citric acid monohydrate, star anise oil, potassium sorbates, polysorbatum 80 (polyoxyethylene sorbitan monooleat), sugar syrup, and purified water, which appears to have better bioavailability than oily formulations [20]. In the nursing home *Topaz Overduin* the method used for supplementing vitamin D has changed over time from drops to capsules; this means that there was no specific reason why any resident should still be using drops.

The nursing staff was asked about the way drops were administered. They reported this occurred in 3 ways, depending on the nurse's personal choice: 1) 3 drops were administered directly from the drop container, 2) 3 drops were given using a 1-ml syringe (delivered standard by the pharmacist with the drop container and the instruction that 0.11 ml be taken in case of syringe use), or 3) 0.11 ml was administrated with the 1-ml syringe. Over time, each resident received the drops in these different ways, implying that there was no set procedure of administration for any particular group.

A literature search for confounders in attaining accuracy and precision of delivery from containers with oral drops, yielded several pediatric and ophthalmologic studies [21-23]. Interestingly one of these studies, assessing the dose uniformity of samples delivered from pediatric oral droppers, discovered that the key factor in achieving satisfactory dispensing is the position of the dropper - which has to be held vertically[21].

In our nursing home, the two other routes of administration of drops are also susceptible to dosage errors, i.e. accurate titration of 0.11 ml cholecalciferol with a 1-ml syringe is practically impossible; also, drops given via a syringe have a different volume than drops given with the container. Since the nursing staff of our nursing home received no instructions concerning the administration of drops, this might be an explanation for the discrepancy found. Because dosage errors are possible when administering small volumes of solutions, nursing staff should be guided on the correct method of delivery.

CONCLUSION

Vitamin D supplementation using cholecalciferol capsules containing 5600 IU, once a week (equal to 800 IU daily) will result in vitamin D sufficiency (serum 25(OH)D ≥ 50 nmol/L), regardless of gender, age, BMI, renal function, sun exposure, comorbidity, medication and mobility status. When choosing a vitamin D preparation for routine supplementation for nursing home residents, it is important to note that major differences in efficacy may exist between various types of preparations, even when they apparently contain the same amount of vitamin D. This raises the issue of standardization of drops administration for the purpose of avoiding failure in the meeting of recommended daily needs of vitamin D.

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Chapter 3

Vitamin D Supplementation in Older Persons: Guidelines versus Practice. Letter to the Editor

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TO THE EDITOR:

Older individuals are particularly susceptible to vitamin D deficiency due to: an age-related reduction of cholecalciferol production in the skin, limited exposure to direct sunlight, co-morbidity, polypharmacy, and inadequate nutritional intake.[1] A survey in Europe (SENECA) among community-dwelling older people (aged ≥80 years) without vitamin D-supplementation showed that 36% of older men and 47% of older women had serum 25(OH)D concentration levels ≤ 30 nmol/l. [2] In nursing home residents, the prevalence of vitamin D deficiency can rise to 98-100%.[3]

In 2008, the Dutch Health Council recommended vitamin D supplementation in nursing home residents, and for older persons with a dark skin.[4] In 2012 this advice was renewed, targeting all people aged ≥ 70 years to use supplementation of 800 IU vitamin D per day. [5]

The aim of this study was to explore vitamin D prescribing behavior of elderly care physicians (ECPs; who are specialized as a primary care expert in geriatric medicine, usually working in nursing homes) and of general practitioners (GPs) in persons aged 70 years and over and to examine a possible trend in this behavior.

A survey was administered between 15 December 2017 and 30 January 2018 to all (1685) ECPs and 310 GPs in the Netherlands. The ECPs were asked to participate in the survey using the Survey Monkey platform. They were invited to participate via a newsletter of the national professional association for elderly care physicians (Verenso), the Dutch Academic Networks Elderly Care (SANO), or via a general information letter sent to their working locations. At a continuing vocational training day for GPs (15 December 2017), 310 physicians were approached by the investigator to complete the survey (which was part of the program). The survey was completed by 414 ECPs and 310 GPSs. The questions of the survey covered three domains: 1) knowledge of the 2012 vitamin D supplementation advice of the Dutch Health Council and their attitude towards it, 2) active vitamin D prescription behavior and dosage prescribed, 3) attitude towards monitoring 25(OH)D before and after supplementation.The results of the survey were analyzed as absolute and relative frequencies, and they were compared with a similar survey conducted in 2010 among a group of 648 ECPs and 40 GPs in the Netherlands (table 1).

The present survey among physicians in the Netherlands who practice in nursing homes (ECPs) and in the community (GPs) shows an increasing awareness of the importance of vitamin D supplementation in older people. Most ECPs (94.2%) and over a third of GPs (34.0%) prescribed vitamin D systematically (consistent with the guidelines) for patients aged ≥ 70 years; a comparison with 2010 showed a trend of an increase in the prescribing of vitamin D supplementation.

Table 1 Results from physician surveys concerning vitamin D prescribing behavior in people aged 70 years and over

	ECPs				GPs			
	2010 (n=648)		2017 (n=414)		2010 (n=42)		2017 (n=310)	
	n	%	n	%	n	%	n	%
Is familiar with advice of the Dutch Health Council	419	64.7	326	78.7	28	66.7	220	71.0
Nursing home has policy regarding routine vitamin D supplementation	344	53.1	395	95.4	N/A	N/A	N/A	N/A
Usually forgets to think about vitamin D supplementation	---	---	---	---	22	52.4	99	31.8
Finds vitamin D supplementation useful	487	75.2	337	81.4	---	---	198	63.9
Prescribes vitamin D systematically (consistent with Dutch guidelines) to people aged over 70 years	323	49.8	390	94.2	---	---	105	34.0
Prescribes vitamin D to people aged over 70 years:								
20 µg (800 IE) per day	294	45.4	350	84.5	21	52.5	272	87.7
10 µg (400 IE) per day	303	46.7	7	1.7	13	31.0	16	5.1
other dose	52	7.9	57	14.0	2	4.8	22	7.4
Does routine laboratory testing for serum 25(OH)D								
before supplementation begins	38	5.9	52	12.6	---	---	155	49.5
monitoring with special conditions (medication, obesity, malabsorption)	---	---	41	9.9	---	---	56	18.4
monitoring serum 25(OH)D after supplementation	---	---	4	1.0	---	---	37	11.7
no routine testing	---	---	317	76.5	---	---	166	20.4

N/A, not applicable, ---not asked

Differences in the prescribing behavior of ECPs and GPs might be explained by differences in the populations taken care of by these physicians. It is no longer questioned whether all nursing home residents should receive vitamin D supplementation,[6] but rather it is regarded a standard of good care. On the other hand, GPs may need to overcome some practical problems: the population of the community-dwelling people is very heterogeneous, ranging from vulnerable older people to very vital and active older persons. There is uncertainty in the prescribing behavior of the GPs: 49.5 % always performs blood tests to assess serum 25(OH)D before starting supplementation and 36.1% find the supplementation in the people aged 70 years and over not useful.

A scoping review of the existing literature concerning the clinical management of low vitamin D in community-dwelling people concluded that "broad variability in physicians' knowledge, attitude and behaviors related to vitamin D testing are reflective of the landscape of uncertainty in research findings, recommendations, and guidelines".[7] A survey conducted in 2015 among general practitioners in Belgium showed uncertainty in vitamin D prescribing behaviors even though in the population of nursing home residents.[8]

Worldwide, there is lack of consensus between the guidelines for vitamin D supplementation in community-dwelling older people, e.g. prescribing vitamin D titrated to the degree of deficiency, or standard supplementation in this group at risk. The present literature concerning the topic of vitamin D supplementation is ambiguous with regard to guidance.

An umbrella review stated that there is no convincing data from clinical trials for the benefits of vitamin D supplementation overall.[9] However, another umbrella review concluded that most randomized controlled trials are carried out in populations that are not vitamin D deficient.[10] Further, there is an increasing body of evidence from observational and clinical studies that support the presence of thresholds in vitamin D status below which health risks increase, and vitamin D supplementation has beneficial effects.[11]

Future studies may elucidate specific groups of community-dwelling older people who are more likely to benefit from vitamin D supplementation and this might reduce the apparent uncertainty of GPs regarding their vitamin D supplementation strategies. While awaiting the results of well-designed randomized clinical trials, GPs should consider vitamin D supplementation in persons aged ≥ 70 years (patients with osteoporosis, malabsorption, hyperthyroidism, chronic kidney disease or liver failure) and always prescribe vitamin D supplementation for their most vulnerable patients.[12]

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Chapter 4

Effect of Ultraviolet Light on Mood, Depressive Disorders and Well-being

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ABSTRACT

Background

Human and animal studies have shown that exposure to ultraviolet light can incite a chain of endocrine, immunologic and neurohumoral reactions that might affect mood. This review focuses on the evidence from clinical trials and observational studies on the effect of ultraviolet light on mood, depressive disorders, and wellbeing.

Methods

A search was made in PubMed, Embase, Web of Science, Cochrane, Psychinfo, CINAHL, Academic Search Premier and Science Direct, and the references of key papers, for clinical trials and observational studies describing the effect of ultraviolet light applied to skin or eyes on mood, depressive disorders, and wellbeing.

Results

Of the seven studies eligible for this review, the effect of ultraviolet light on mood, depressive symptoms and seasonal affective disorders was positive in six of them

Conclusions

Of the seven studies, six demonstrated benefit of exposure to ultraviolet radiation and improvement in mood which supports a positive effect of ultraviolet light on mood. Because of the small number of the studies and their heterogeneity more research is warranted to confirm and document this correlation.

INTRODUCTION

Depressive disorders are an important clinical problem as they can decrease the quality of life of the patient and caregiver [1]. Depressive disorders are associated with functional impairment, cognitive changes, and increased morbidity and mortality [2-4]; unfortunately, their prevention and treatment remain a challenge. Despite the relative effectiveness of antidepressant medication and psychological treatment, major depression in older persons over longer follow-up periods shows a chronic remitting course or, in some patients, has a chronic character [4]. This implies the need for alternative methods to treat depressive disorders in the elderly.

Sunlight has long been used to treat different medical conditions. For example, Niels Ryberg Finsen demonstrated that ultraviolet (UV) light can have a curative effect in lupus vulgaris (a skin variant of tuberculosis); in 1903, he was awarded the Noble Prize for Medicine and Physiology. Nowadays, UV light is an important treatment option for several skin diseases including psoriasis, atopic dermatitis, morphea, scleroderma, vitiligo, and mycosis fungoides[5].

A mood-enhancing effect of UV light has also been reported [6-9]. This effect might be accomplished via two target organs working as receptors for UV light: i.e. skin and eyes.

A possible mood-modulating effect of UV light via the skin is through the vitamin D pathway. The major source of vitamin D for humans is exposure of the skin to sunlight (UVB 280-315nm) resulting in the conversion of 7-dehydrocholesterol to pre-vitamin D3. The recent discovery that the human brain also possesses vitamin D receptors [10,11] indicates that mood and depressive disorders might be influenced by vitamin D deficiency directly, by acting on brain cells.

Other pathways that may be triggered by UV light to modulate mood and act through skin exposure involve three local systems: i) the skin analog of the hypothalamic-pituitary-adrenal (HPA) axis [12], ii) the serotoninergic/melatoninergic system [13], and iii) the immune system [14,15]. These pathways are assumed to interplay with systemic mechanisms of body homeostasis [14].

Using eyes as a target, bright light therapy is applied for the treatment of seasonal affective disorders (SAD); it is thought that bright light can help suppress melatonin production in the pineal gland, thereby attenuating many of the symptoms associated with SAD [16]. However, it remains unclear whether UV light has an additional value in the therapeutic light spectrum, or whether it exercises only a deleterious effect on the eyes.

Bearing in mind the theoretical points mentioned above, this review explores and summarizes the evidence obtained from clinical trials and observational studies on the effect of UV light applied to the skin or as a component of light therapy applied to the eyes on mood, depressive disorders, and wellbeing.

METHODS

Protocol and registration

This systematic review was designed according to the PRISMA method [17,18]. The protocol is registered and published in the PROSPERO database (PROSPERO 2017: CRD42017059971).

Eligibility criteria

A PICO (population, intervention, control, outcome)-based search strategy was conducted on 22 March 2017. Eligible for this review were studies in the general population in which: i) exposure to UV light or sunlight was used as an intervention, and ii) the effect on mood, depressive disorders, and wellbeing was measured as an outcome. Included were clinical trials and observational studies on sunlight, in which exposure to sunlight occurred outdoors and the number of exposure hours was recorded.

Search strategy

With the assistance of an experienced librarian the following bibliographic databases were searched: PubMed, Embase, Web of Science, Cochrane, Psychinfo, CINAHL, Academic Search Premier and Science Direct. Also, the references of key papers and of the included studies were explored. The search strategy included terms related to UV light, mood, affective disorders, and wellbeing (for the PubMed search strategy see Appendix A). Although no restriction was made regarding the date of publication, articles had to be in English, Dutch, German or Russian.

Study selection

Of the identified studies, the titles and abstracts were screened by the first author (BV) and categorized on exclusion criteria. The categories were reviewed by the second author (RvB) by randomly assessing the titles and abstracts in the different categories; differences were discussed until consensus was reached. References from the included studies and from key articles were also assessed. The full-text articles derived from this process were independently assessed by the first and second author; any differences were discussed until consensus was reached.

Data Extraction

Information extracted from the selected studies included: year of publication, study design, study population (characteristics of chronic disease, if any), setting (community, or hospitalized), intervention and control conditions, outcome measures on mood and results, and information for assessment of risk of bias. The first and second author extracted data from the studies independently from each other; any discrepancies were resolved by discussion.

Risk of bias

Risk of bias of the individual studies was evaluated on outcome level by the first and second author independently, using Cochrane Collaboration's tool for assessing risk of bias [19]. Risk of bias assessment comprised evaluation of sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective outcome reporting, and other bias. Disagreements were resolved through discussion and consensus, or by consulting the last author (MC).

Data synthesis and analysis

All outcomes on mood, depressive disorders and wellbeing reported in the studies were extracted. For each study, characteristics including study size, population, intervention, control group, main outcome measures, and follow-up period were described. Synthesis and analysis were done in a narrative manner and structured according to the site of action of UV light: skin or eyes.

RESULTS

Study selection

After removing duplicates from the 702 articles yielded by the search, 677 records remained (Figure 1). After screening on title (no UV light, sunshine, mood, mood disorders or wellbeing) and language, 532 publications were excluded and 145 publications remained. After evaluating these 145 papers on abstract, another 126 were excluded for the following reasons: 9 were ideas, editorials or theoretical reviews, 17 concerned vitamin D and depression but no intervention with UV light, 96 examined the effect of light therapy on depression but UV light was not used as a therapeutic fraction of light spectrum, and 4 explored the relation between vitamin D and sunlight but not in connection with mood, mood disorders, or wellbeing.

Following assessment of the remaining 19 full-text articles for eligibility, 12 studies were excluded: 3 RCT's that had no control group without UV light, 4 examined the effect of sunlight on mood on subjects while staying indoors (no direct contact of ultraviolet light to skin or eyes), 4 did not measure mood variables but preference for UV light as the only psychological parameter, and 1 was a systematic review.

Finally, 7 studies were regarded eligible for this systematic review. All examined the effect of UV light or sunlight on mood, wellbeing or depressive disorders, applied directly to skin or eyes as an intervention in a group of healthy people, or patients diagnosed with a chronic disease. In 6 of these 7 studies, a control group was used for comparison, and one of the studies was observational.

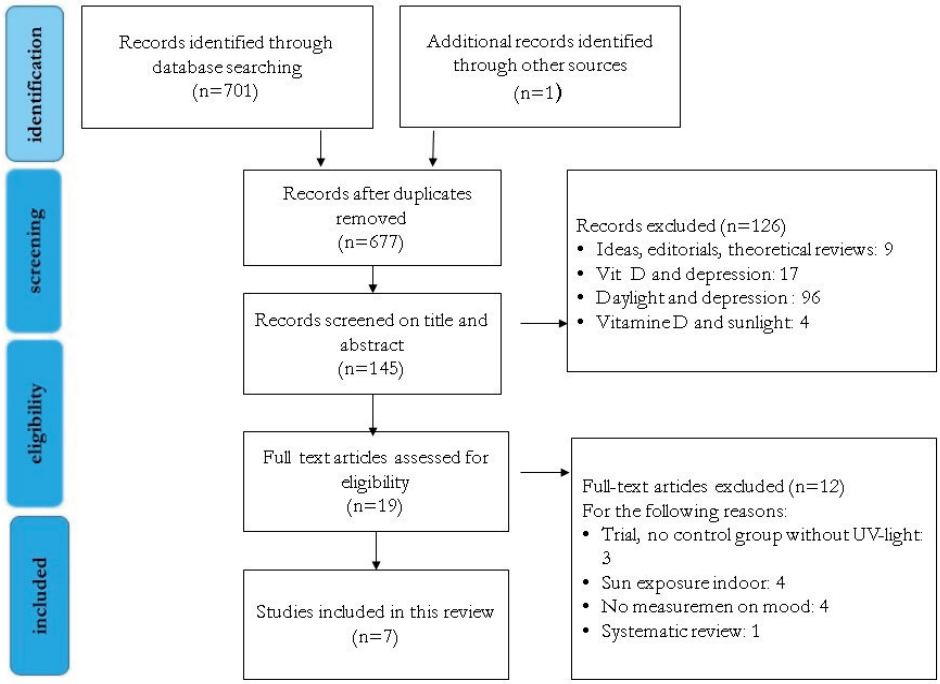

Figure 1 Prisma-based flowchart of the literature search, selection, and review process

Study characteristics

Seven studies were assessed in this review [5,16,20-24], i.e. 6 clinical trials of which 2 randomized controlled trials (RCTs), 2 cross-over studies, 1 prospective clinical trial, 1 study with a randomized parallel design, and 1 observational study. The characteristics of these studies are presented in Table 1.

Participants

Participants in the selected studies were healthy volunteers [22], and patients with fibromyalgia syndrome [20], dermatological conditions [5], multiple sclerosis (MS) [21], and SAD [16,23,24]. The numbers of participants per study ranged from 13 [23] to 198 [21].

Methods of selected studies

All studies included a control group, except the observational study [21]. The control groups consisted of: i) patients belonging to the same cohort but not receiving the intervention [20,22,24], ii) two control groups of which one of the same cohort having the intervention applied on a smaller surface of the body and one composed of healthy volunteers (receiving or not receiving the intervention) [5], or iii) the study had a cross-over design [16,24].

Table 1 Data extraction sheet and study characteristics

Study	Intervention	Site of action	Outcome measures	Results
Mood				
Gambichler et al., 2002 RCT not blinded; N=53; Volunteers	Group 1: UVA whole body Group 2: No UVA	Skin (2x/week, 10-15 min)	1. BBS 2. FKB-20 T1 (baseline), T2 after first exposure, T3 end of study	1. UVA exposed volunteers were more balanced (p=0.01), less nervous (p=0.03), more strengthened (p=0.009) at T3 in comparison to T1 2 UVA exposed volunteers showed more robustness and strength (p=0.011) and more satisfaction with their own appearance (p=0.04) at T3 in comparison to T1
Taylor et al., 2009 RCT, partly blinded, a pilot, N=19, Patients with fibromyalgia syndrome	Group 1: UV (4% UVB, 96% UVA) Group 2: No UV	Skin, A. Acclimation phase: 6 sessions non UV bed, followed by UV bed B. RCT phase: 18 sessions, 3 x week, 10 min each	1. PANAS (positive affect) 2. PANAS (negative affect)	A. Acclimation phase: 1. Increased positive affect (p=0.003) as measured by: -tanning bed preference (p <0.0001) -well-being (p = 0.001) -relaxation (p <0.0001) 2. Decreased negative affect (p <0.018) as represented by: -tension (p = 0.02) -distress (p = 0.03) -nervousness (p = 0.026) Changes in being active, enthusiastic, alert, attentive or sad were not significant before and after UV -exposure B. RCT phase: No data
Depression scores and depression				
Edstrom et al.,2010, Prospective clinical trial, N=77 Patients with dermatological conditions and healthy volunteers	Patients -Group 1: WBI (Whole body irradiation) UVA/UVAB/PUVA) -Group 2: PUVA on hands/feet Volunteers Group 3: WBI (UVB/UVA) Group 4: Placebo	Skin, 2 a 3/ week	MADRS	- No significant difference between groups in the baseline MADRS. -Highly significant improvement in MADRS score in patients with WBI (p < 0.001), tendency towards improvement in the healthy group with WBI (p = 0.08) -Both patients and volunteers divided in groups: UVA, UVB, UVAB: Significant improvement in UVB and UVAB group in MADRS (p<0.001 and p<0.01, respectively)
Knippenberg et al., 2014, Prospective longitudinal cohort study, N=198, Duration of 2.5 years Patients with MS	No	Skin and possibly eyes	-Depressive symptoms and anxiety measured with HADS (0-21) - Sun exposure, quantified in time spent in the sun - Serum 25(OH) D	- Personal reported sun exposure was inversely associated with depression scores ((β-0.26 (95% CI -0.40, -0.12), p≤0.001 When both 25 (OH) D and sun exposure were included in de model, the magnitude of sun exposure remained stable (β: -0.26 (95% CI-0.40, -0.11)) p=0.001, 25 (OH) D remained non-significant P=0.667

Table 1 Data extraction sheet and study characteristics (continued)

Study	Intervention	Site of action	Outcome measures	Results
Lam et al., 1991 Triple crossover study, pilot, N=13, Patients with recurrent major depression, Seasonal pattern	A. 1 week: 2500 lux cool-white fluorescent light with UVA By non-response/ relapse: B.1 week: 2500 lux cool-white fluorescent light By non-response/ relapse: C. 500 lux cool-white fluorescent light	Eyes (three 1-week intervals, 2 hours per day)	1.SIGH-SAD 2. BDI	A.. Dim light (500 Lux) had a small, not statistically significant effect on HAM-D, BDI and ATYP scores B. UV-light condition produced a statistically significant effect on HAM-D, BDI, ATYP compared with other two conditions, resp. p<0.003, p<0.02, p<0.008 C.. The UV-blocked condition produced significant improvement only in atypical symptoms of depression p<0.02
Pudikov et al., 2012 Crossover clinical trial, N=24, Patients with seasonal depression	24 patients were examined in different years. Group 1: Phototherapy in the optical range Group 2: Same as group 1 but enriched in UVA	Eyes (25 days, 2 sessions of 60 min. with interval between sessions increasing each day)	1. HDRS-SAD, Based on the opinion of the attending physician 2. BDI, based on the assessment of patient.	1. Tendency to unidirectional changes in the results on HDRS-SAD and BDI scales during both therapy's (p<0.05) 2. The patient's state is most markedly improved in the first week of phototherapy irrespective of the method used. 3. In week 3 and 4 of therapy the maximum efficiency was observed in the group with combined optical and UV radiation which was statistically significant only with respect to HDRS-SAD (p =0.03 and p=0.01 respectively)
Lam et al, 1992, Randomized parallel design N=35, patients with recurrent major depression, seasonal pattern	Light therapy with full spectrum lenses Group 1: UV-blocked condition Group 2: UVA condition	Eye (2 weeks, 2 hours per day)	1. SIGH-SAD 2. BDI	1. The analysis of SIGH-SAD scores did not find significant effect of condition (p<0.70), nor condition-by-time (p<0.70). 2. Analysis of BDI didn't find significant effects of condition (p<0.25), nor condition –by-time (p<0.20). 3. Both analysis have found only a significant effect of time (p<0.0001)

BBS = Basler Befindlichkeits- Scala, FKB -20 = Fragebogen zum Körperbild, PANAS = Positive and Negative Affect Scale, MADRS = Montgomery-Asberg Depression Rating Scale, HADS = Hospital Anxiety and Depression Scale, HDRS-SAD = Hamilton Depression Rating Scale-Seasonal Affective Disorders Version, BDI = Beck Depression Inventory, SIGH-SAD = Structured Interview Guide for the HAM-D, SAD version

All studies used a repeated measure design for evaluation of the effect of the intervention.

Interventions

The studies can be categorized into two groups according to the target site of the intervention: in one group the targeted organ was the skin [5,20-22], whereas in the other the intervention was applied to the eyes (with the retina as target) [16,23,24].

The intervention used in the selected studies was UV light [5,20,22], optical light combined with UV light ([16,23,24], or outdoor exposure to sunlight [21]. In five of the studies, UV light was explicitly defined as UVA light (315-400 nm) [16,20,22-24] and in one study different groups were specifically receiving UVA, UVB (280-315 nm) or UVA+UVB light [5].

In the 4 studies in which skin was the target, UV light was applied either to the whole body [5,22], to smaller body areas [5], or was not specified [20]. The duration of UV light exposure to the skin ranged from 3-6 weeks (2-3 times a week for 10-15 min). In the study with sun exposure, the duration of sun exposure was calculated in hours spent in the sun during the weekends and holidays between summer 2002 and summer 2005 [21].

Phototherapy in studies targeting the retina was applied for 1, 2 or 3 weeks. Duration of the interventions per day was either 2 sessions of 60 min in the morning and afternoon [16], or 1 session of 2 h in the morning [23,24].

Outcome measures

This systematic review focuses on the outcome measures mood, depressive disorders, and wellbeing.

Mood

Mood was assessed in two studies. In the study with patients with fibromyalgia, mood was evaluated with the PANAS (Positive and Negative Affect Scale) [20]. In the study with healthy volunteers, emotional state and physical awareness were assessed with the BBS (Basler Befindlichkeits- Scala) and the FKB-20 (Fragebogen zum Körperbild), respectively [22].

Depression

Depression was assessed in five studies. Depression was evaluated with the CPRS-S-A (Comprehensive Psychopathological Self-Rating Scale for Affective Syndromes) which had been transformed to correspond to the MADRS (Montgomery-Asberg Depression Rating Scale) in patients with dermatological conditions and healthy volunteers as a control group [5].

Depression symptoms and anxiety were measured with the HADS (Hospital Anxiety and Depression Scale) in patients with MS [21]. HDRS-SAD (Hamilton Depression Rating Scale-Seasonal Affective Disorders Version) and the BDI (Beck Depression Inventory) were used in

all studies comparing phototherapy in the optical range, with phototherapy in the optical range enriched in UV light in patients with SAD [16,23,24].

Well-being

Although wellbeing was frequently mentioned in two studies [5,20], none of these studies used a measurement scale specified for wellbeing.

Risk of bias

The results of the risk of bias evaluation are summarized in Table 2; in some cases a narrative explanation is given for further clarification.

Table 2 Risk of bias criteria in individual studies

Study, first author	Sequence generation	Allocation concealment	Blinding participants and outcome assessors	Incomplete outcome data	Selective outcomes reporting	Other or bias
Gambichler et al., 2002	LR	?	HR	LR	HR	Competing Interests
Taylor et al., 2009	?	LR	LR	LR	HR	LR
Edstrom et al., 2010	?	?	HR	LR	?	LR
Knippenberg et al., 2014	Observational study	Observational study	LR	LR	LR	High risk, related to study design
Lam et al.,1991	LR	LR	LR	LR	LR	Order effect Small number participants
Lam et al., 1992	?	LR	LR	LR	LR	Compliance to treatment not guaranteed
Pudikov et al., 2012	?	?	HR	LR	LR	LR

LR – Low risk, HR – High risk,? - Not clearly reported, unclear risk of bias

All studies gave little or no information on the sequence generation and allocation concealment. Significant bias was found in all studies as a consequence of study design. None of the studies met all the criteria of a double-blinded randomized control study with a good statistical power. Both studies by Lam et al. had a low risk bias according to the Cochrane Collaboration's tool of bias [23,24]. However, the first study had little power because of the small number of participants and a possible order effect that can confound multiple cross-over designs [23]; the second study raises questions about the compliance of patients who performed the intervention at home [24]. Although Knippenberg et al. performed a study with long duration and many participants, the observational character of the study was a limiting factor [21]. Gambichler et al. mentioned that not blinding their participants may have influenced their results [22]. Edstrom et al. performed a study creating groups with different UV light exposure, different spectrum

of the UV light, and a two-control group design, but with limited possibility to blind the participants and assessors because of the different interventions [5]. Taylor et al., apart from not blinding the assessors, provided no information on mood changes in the second (randomized control) phase of their study [20]. These authors focused on improvement of mood after each UV session in the acclimation phase when each participant underwent 6 tanning sessions at which they were exposed to two beds: a non-UV control bed and a UV treatment bed, which might simply be a consequence of an order effect, determined by the preference for a UV bed.

Results of individual studies

Results of the individual studies are presented in Table 1.

Mood

Both studies using UV light targeted to skin and examining the psychological parameters showed a significant improvement in mood. Gambichler et al. concluded that UVA exposed volunteers were more balanced, less nervous, more strengthened and robust, and more satisfied with their own appearance after 3 weekly sessions of whole body UVA exposure [22].

Taylor et al. showed increased positive affect and decreased negative affect after UV stimuli in the acclimation phase of their study (6 sessions non UV, followed by a UV bed) as measured by tanning preference, tanning expectations, increased wellbeing, relaxation, and decreased tension, stress and nervousness [20]. The adjusted mean for the PANAS negative affect (10 low-50 high) after UV exposure in patients with fibromyalgia was 13.5 (SE 0.84) compared to 13.8 (SE 1.00) after the control session (p=0.019). The adjusted mean for the PANAS positive affect (10 low-50 high) after UV exposure was 29.3 (SE 1.84) compared to 28.3 (SE 1.75) after the control sessions (p=0.030).

Depression scores

Four out of the 5 studies that investigated the effect of UV light reported a positive effect of UV radiation on depression scores in the examined populations. Both studies that applied UV exposure to the skin reported positive effects (Edstrom et al. 2010; Knippenberg et al. 2014), two studies that applied UV exposure to the eye reported positive effects (Lam et al. 1991, Pudikov et al. 2012), and one study that applied UV exposure to the eye reported no positive effect on depression (Lam et al. 1992).

Edstrom et al. demonstrated a significant improvement in MADRS in both dermatological patients and volunteers after 6 weeks (2-3 sessions weekly) UVB exposure of the whole body and significant improvement of MADRS in dermatologic patients who received whole body irradiation with UVA or combined UVA/UVB irradiation with the same duration [5]. The median of the MADRS score in the group of the dermatological patients with whole body

UV-irradiation was 8 (IQR 4-13) before the treatment, and 4 (IQR 2-7) after the treatment. The median of the MADRS score in the group of the volunteers receiving whole body UV irradiation was 5 (IQR 4-10) before the treatment, and 4 (IQR 0-5) after the treatment. However, because a MADRS score below 20 is considered non-pathological, these data do not describe the effect of UV light on depression, but only on depressive scores. The authors stated that wellbeing improved as the MADRS score decreased.

Knippenberg et al. showed that higher levels of reported sun exposure were associated with lower depression scores in an observational cohort study of 198 MS patients with a follow-up of 2.5 years [21]. Of the 198 observed patients, 38 patients had the diagnosis depression. The association between sun exposure and HADS depression score in patients with MS was β = -0.44 (95% CI 0.89, 0.01, p=0.056) with 1.5 h/day sun exposure and β = -0.79 (95% CI -1.34, -0.25, p=0.005) with 3.5 h/day sun exposure.

Three studies examined the effect of phototherapy enriched in UVA light exposed to the eye on depressive episodes of patients with SAD. Two of these three studies concluded that maximum efficiency of phototherapy on depression was observed in the groups receiving combined optical and UVA light [16,23]. In the first study, the UVA light condition was the only treatment in which the traditional measures of depression and the HAM-D scores ($p < 0.003$) and BDI scores ($p < 0.02$) were significantly reduced ([23] after 1-week treatment periods, one hour per day with different light spectrum and intensity. In the second study in week 3 and 4 of the treatment, the maximum efficiency of 4-week treatment two hours per day was observed in the group with combined optical and UVA radiation which was significant only with respect to HDRS-SAD ($p = 0.03$ and $p=0.01$, respectively), but not to the BDI score [16]. The third study found that addition of UV light to the optical spectrum in the phototherapy was not beneficial for alleviation symptoms of SAD during 2-week light treatment [24].

Area exposed to UV light

One of the studies proposed that UV light exposure of the whole body (rather than one part of the body) may be superior in influencing mood in a positive manner [5]; however, no other studies examined this aspect.

Benefits of UV spectrum

In most of the studies, the fraction of UV light used was UVA light. In the study of Edstrom, however, it was shown that UVB light was superior to UVA light in improving depressive symptoms [5].

DISCUSSION

Main findings

After an extensive search in multiple bibliographic databases, 145 papers were screened on title and abstract and 19 publications were assessed for eligibility. Of these publications, 7 met the inclusion criteria and are discussed in this systematic review.

The selected studies with skin as the target organ for UV light [5,20-22] were relatively heterogeneous. There was diversity in the population examined, in the psychological instruments used to assess mood and depressive disorders, and in the spectrum of the UV light that was applied. Although mood and depressive symptoms were analyzed in all these studies, they were not always the primary outcome. Other outcomes of UV light treatment were also investigated, e.g. effect on pain, fatigue, and dermatological conditions. However, the effect of UV light on mood and depressive symptoms was consistently corrected for these other conditions.

The overall effect of UV light intervention on mood was positive in the two studies that examined this effect. [20,22]. However, the bias present in them made the results inconclusive. None of the two studies using depression scales as a measurement for depressive symptoms conducted a separate analysis in a subgroup of depressed participants [5,21]. The study population was a combination of people with depression, depressive symptoms and people without depression. Anyway both of them showed improvement of depressive scores after treatment with UV-light or sunlight. In the study observing the effect of sun exposure on depressive symptoms in patients with MS two mechanisms are discussed as possibly involved in the improvement of the depressive scores : the immunologic and endocrine mechanisms of UV light and the effect of bright light [21].

The trials targeting the retina with optical light enriched with the UV fraction were performed with a homogenous population of patients with SAD [16,23,24]. The UV light used in the studies was UVA light fraction added to the optical range. The studies had depression as their main outcome and the psychological instruments used to measure depression were comparable. Despite the homogenous populations and the comparable instruments used, the effects of UV light on SAD were variable. Duration and intensity of the light treatment in those studies was different and all of them had some degree of risk of bias.

Strengths and limitations

For this review an extensive search was made in major electronic databases and the references in key and selected articles were checked. All of the selected studies, apart from one that was observational [21], used a control group, assessed mood and depressive disorders with more than one psychological instrument, and performed repeated measurements. The one observational

study was of longer duration and had good statistical power. The effects in the observational study and the controlled studies (although relatively heterogeneous in character) concurred with each other.

Most RCTs had problems with allocation concealment and blinding. In the trials with UV light intervention affecting the skin, tanning can be a confounder and, if not blinded, can disturb the results. In one of the studies, the participants were blinded for the tanning and the lamps whereas the assessors were not [20].

In one of the studies, the number of participants was too low to have any statistical power [23]. In two of the studies, a per-protocol analysis was performed that could have influenced evaluation of the effect of the intervention [5,22]; on the other hand, this may have provided a better picture of the effect of the treatment.

Finally, because of the small number of studies which met the inclusion criteria and the small amount of dispersion in the sample size, publication bias cannot be excluded.

Comparison with other studies

Research on the beneficial effects of UV light on mood and depression is still in its infancy [25]. The effect of UV light on skin as a target organ in improving mood and depressive disorders has not yet been examined by systematically reviewing the existing literature. To our knowledge this is the first review to focus on this effect. An interesting prospective controlled study of Meffert et al. [26], not included in our review because a double intervention was used (UV and infra-red (IR) light), reports on the effect of 10 low-dose UV and infrared (IR) irradiations of elderly people with inflammatory degenerative muscle and bone disease. Under controlled conditions, suberytemal amounts of UV and IR resulted in some favorable and continual effects like increase in serum 25(OH) D level, decrease of pain, and improvement of wellbeing and training state. It may be useful to reproduce this study in separate groups with UV light and IR light only, and a control group.

To study the effect of UV light applied to the retina in the treatment of SAD, Lee et al. [27] performed a meta-analysis on spectral properties of phototherapy in these disorders. They found no difference in the treatment efficacy between full spectrum light with UV component, full spectrum light without UV component, and green-yellow light in SAD. However, due to insufficient information on the search strategy and eligible articles, no meaningful conclusions can be drawn.

A possible mood-modulating effect of UV light via the skin is through the vitamin D pathway. Many observational studies found a significant negative correlation between 25(OH)D levels

and depression in people ≥60 years [28-33]. In a recent meta-analysis, however, no evidence was found for a reductive effect of vitamin D supplementation on depression in adults [34].

Similarly, a recent prospective observational study of Knippenberg et al, included in our review, reported that sun exposure, rather than 25(OH)D levels, was associated with fewer symptoms of depression and fatigue in patients with multiple sclerosis [21]. The relation between vitamin D, UVB and mood is still not well understood and possibly not all beneficial effects of UV radiation exposure occur through UVB induced vitamin D synthesis [25], as we already discussed in the introduction.

CONCLUSIONS AND IMPLICATIONS

Of the 7 included studies, 6 showed a positive effect of UV light on mood, depressive scores or SAD which supports a positive correlation between ultraviolet light exposure and mood improvement. However, the small number of studies, their heterogeneity and the small number of participants in some studies, the existing bias, and the suboptimal study designs make it difficult to draw general conclusions about the effect of UV light on mood and depressive disorders.

Dating from ancient times, researchers have suggested that sunshine, apart from its deleterious effects, also has curative effects. Because of the seasonal and meteorological changes, we cannot use sunshine in an unlimited way. This has triggered research to determine the components in sunshine that may have a beneficial effect on health, as well as their artificial reproduction. The administration of bright white visible light is considered to be the treatment of choice for patients with SAD [35,36]. We have concentrated on the UV component of sunshine and its effect on mood and depressive disorders. The results of the reviewed studies, the available knowledge on UV light mechanisms, and the neural, endocrine and immune regulation of mood provide sufficient information to warrant further research in this area. First of all, appropriate UV exposure schedules need to be established to predict and control DNA damage [37]. Second, a good design of future studies (double-blind, RCTs with sufficient power) are required. In addition, studies in the general population, as well as in cohorts of people with depressive disorders, are needed. Important aspects in this are a good definition and differentiation of the light spectrum, determination of the therapeutic range of the intervention, and the duration of the effect which can be ensured by repeated measurements.

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Chapter 5

The Effect of Ultraviolet B Irradiation Compared with Oral Vitamin D Supplementation on the Well-being of Nursing Home Residents with Dementia: A Randomized Controlled Trial

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ABSTRACT

There are indications that ultraviolet B (UVB) exposure has beneficial effects on well-being through mechanisms other than vitamin D synthesis alone. We conducted a randomized controlled multicenter trial to compare the effects of UVB light and vitamin D supplementation (VD) in terms of the well-being of nursing home (NH) residents with dementia. Participants were randomly assigned to the intervention group (UVB group, n = 41; half-body UVB irradiation, twice weekly over 6 months, with 1 standard erythema dose (SED)) or to the control group (VD group, n = 37; 5600 International units (IU) cholecalciferol supplementation once a week). The main outcome was well-being, measured by the Cohen-Mansfield Agitation Inventory (CMAI) and the Cornell scale for depression in dementia at 0, 3, and 6 months. Secondary outcomes were QUALIDEM quality of life domains and biochemical parameters of bone homeostasis. Intention-to-treat analysis with linear mixed modeling showed no significant between-group differences on agitation (p = 0.431) or depressive symptoms (p = 0.982). At six months, the UVB group showed less restless/tense behavior compared to the VD group (mean difference of the mean change scores 2.2, 95% CI 0.8 to 3.6; p = 0.003 for group x time interaction) and lower serum 25(OH)D3 concentration (estimated mean difference - 21.9, 95% CI -32,6, -11.2; p = 0.003 for group difference). The exposure of nursing home residents with dementia to UVB light showed no positive benefits in terms of wellbeing. UVB treatment may have a positive effect on the restless/tense behavior characteristic of advanced dementia but more research is needed to confirm this finding.

INTRODUCTION

Observational studies indicate that low sun exposure increases the risk of cardiovascular disease [1,2] and that there is a strong inverse relationship between all-cause mortality and sun exposure [1]. Therapy using ultraviolet (UV) light is an important treatment option for several skin diseases [3]. A mood-enhancing effect of UV light has also been reported [4-9]. UV light acting on the skin is absorbed by 7-dehydrocholesterol in the plasma membrane of epidermal cells, resulting in production of previtamin D3 [10], the major source (90%–95%) of vitamin D for most vertebrates, including humans [2].

Inadequate sun exposure leads to vitamin D deficiency and insufficiency [11,12]. Supplementation of vitamin D in old age is an important field of study in geriatrics. The nursing home population is at particular risk of sun-deprivation because of disease and disability, the limited resources and staffing in nursing homes, and a lack of organizational modalities [13-15]. A pilot trial of an eight-week course of weekly, frontal half body irradiation with ultraviolet B (UVB) of nursing home residents in a Dutch nursing home showed a significant increase in 25(OH) D3 [11].

Induction of cutaneous vitamin D production by using UVB exposure may be preferable to oral supplementation amongst older nursing home residents because it cannot induce toxic levels, it helps prevent polypharmacy and it is plausible that vitamin D synthesis is not the sole mechanism by which sunlight or UVB light exerts its beneficial effects on human health and well-being. Getting older is inevitably accompanied by perceiving a continuous loss in functioning, healthy state and social engagements, and this process is strongly delineated and progressive in persons with dementia [16]. Improving wellbeing (feeling of happiness, sadness, stress and pain) empowers adaption abilities [17], and this can be especially meaningful in the population with advanced dementia where agitation is a persistent and most common symptom and often requires intensive pharmacological management [18].

Therefore, the aim of this study is to compare the effect of UVB irradiation to oral vitamin D supplementation on well-being in nursing home residents with advanced dementia.

MATERIALS AND METHODS

This study had a randomized controlled multicenter trial design. Written informed consent was obtained from the legal representatives of all participants. The study was conducted in accordance with the declaration of Helsinki, and protocol was approved by the Medical Ethical

Committee of Leiden University Medical Center (Registration No P16.010) on 11 April, 2016 and was registered in the Dutch Trial Register (NL5704).

Participants were recruited from three nursing homes connected to the University Network for the Care sector South Holland (UNC-ZH). Team leaders of the NHs sent information letters with an informed consent form to all nursing home residents and their families. An independent physician with a specialty in internal medicine was assigned to answer the questions of the participants and their families.

Inclusion criteria were a diagnosis of dementia and an age exceeding 70 years, while exclusion criteria were (1) actinic keratosis, (2) skin cancer, (3) porphyria, (4) sun allergy, (5) use of drugs that may induce photodermatosis, (6) hypercalcemia, (7) use of vitamin D fortified food, (8) anxiety, agitation or resistance to bodily contact. Examination of the participants for actinic and cancer skin lesions, as well as skin type according to the Fitzpatrick scale [19], was performed by a dermatologist.

The participants were randomized in blocks of four and assigned to either receive the intervention (UVB light; UVB group) or standard vitamin D treatment (control; VD group). The group assignment files were placed in sequentially numbered opaque sealed envelopes to conceal the sequence until individual interventions were assigned. Intervention delivery and outcome assessment was not blinded. Nursing staff administered the medication, intervention and questionnaires to avoid disturbance of the daily routine.

The sample size was calculated on the basis of the Cohen-Mansfield Agitation Inventory (CMAI), an instrument measuring agitation and covering 29 behavioral items, each rated on a 7-point Likert scale of frequency (varying from never to several times an hour). Summed scores ranged from 29 to 203. Assuming a standard deviation (SD) of 13 points, an α of 0.05 and an estimated drop-out of 40%, a sample of 80 patients would provide an 80% probability of detecting a mean between group differences of 10 points.

The intervention consisted of half body UVB-irradiation with 1 standard erythema dose (SED). The procedure was carried out twice a week with a portable, tilting sunbed canopy (Topaz 10 V, VDL Hapro Laboratory, Kapelle, the Netherlands) positioned at a fixed distance of 75 cm above a bed. The standard tanning lamps were replaced with UVB spectrum lamps (F71T12 100W Preheat-Bipin, Cosmedico, Stuttgart, Germany). Lamp light emission consisted of UVB-5.013 Wm^{-2}, ultraviolet A (UVA)-4.650 W m^{-2}, ultraviolet C (UVC)-0.00001Wm^{-2}, with UVB accounting for 54.6% of the spectrum. The exposure time was set at eight minutes a session, which was safeguarded by an electronic timer to prevent unintended longer exposure. Protective glasses were worn during treatment. The total treatment time over 6 months was

432 min. UVB treatment was discontinued when participants clearly objected or showed signs of discomfort on two consecutive sessions. They were then removed from the UVB exposure group and started again on vitamin D capsules. The control group received vitamin D capsules, 5600 IU cholecalciferol supplementation once a week, which is the standard treatment dose for all older persons >70 years according to the Dutch Health Council [20]. All nursing home residents in the Netherlands receive this standard supplementation. In the UVB group, vitamin D supplementation was stopped one week after drawing blood for the baseline biochemical parameters and one week before starting the intervention.

The primary outcome was well-being, monitored with the CMAI and the Cornell scale for depression in dementia at 0, 3 and 6 months. Higher CMAI scores indicate a more frequent display of agitated behavior [21,22]. The Cornell scale for depression in dementia was used to assess mood. It consists of 19 questions classified in 5 categories: mood-related signs, behavioral disturbance, physical signs, cyclic functions and ideational disturbances. Scores higher than twelve indicate probable major depression [23]. Secondary outcome measures were quality of life (QoL), serum 25(OH)D3 concentration and biochemical parameters of bone homeostasis. The QUALIDEM (shortened version) was used to assess QoL [24] and consists of 18 items covering 6 domains of QoL, including care relationship, positive affect, negative affect, restless tense behavior, social relations and social isolation. The higher the score on a subscale, the better the person does on this particular QoL domain. Serum levels of 25(OH)D3 were measured using an electrochemiluminescence immunoassay (ECLSA, Roche diagnostics, Basel, Switzerland). Serum creatinine, parathyroid hormone (PTH), calcium and phosphate were measured at 0 and 6 months. The assessments were performed by the nursing staff, and at least two experienced nurses discussed them and completed the forms. Bone homeostasis parameters were measured at the biochemical laboratory of Leiden University Medical Center.

Information on participant's sociodemographic characteristics (gender, age and skin type) and dementia severity were obtained at the baseline. Dementia severity was assessed using the Bedford Alzheimer Nursing Severity Scale (BANS-S), which is composed of 7 items, scaled 7–28, and a score of 17 or higher indicates severe dementia.

Statistical analyses were performed in SPSS 23.0 (IBM Corp. Released 2015,Armonk, N.Y., USA) in accordance with the intention-to-treat principle. Descriptive statistics were used to outline the basic characteristics of the study population. The results are reported using the mean and standard deviation (SD) for normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. Pearson's chi-square test, student's t-test and Mann-Whitney U-tests were used to test differences between the baseline measurements in the intervention and control groups. A p-value <0.05 was considered statistically significant. Analysis of treatment effects was conducted using linear mixed models that

accounted for repeated measurements in the subjects, estimated using restricted maximum likelihood (Brady T.West, 2009) [25]. Time was treated as a categorical variable. As fixed effects, we entered randomization, time, randomization-by-time interaction and the baseline of the outcome measure. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality. The following effects were estimated for the outcome variable: the main effect of the intervention, the main effect of time (at three time points) and the interaction between group and time. The treatment effect was presented at each time point as an estimated difference between the mean change score per group (95% CI) with the VD group as a reference. If the missing items on the Cornell depression scale were up to five, they were imputed as a mean item score.

RESULTS

Participants

This study was carried out between October 2016 and April 2017 in two nursing homes, and between October 2017 and April 2018 in a third nursing home. We started with the trial at the third location later because the number of persons who gave informed consent from the first two locations were not enough to reach the calculated power of the study and finding a new location prepared to participate in the trial needed more time. The legal representatives of seventy-nine nursing home residents gave informed consent to participate in the study (Figure 1).

Table 1 shows the baseline characteristics of the study participants in the VD and UVB groups. There was no significant difference between the two groups concerning the primary outcome well-being (agitation and depression) or on QoL measures determined using QUALIDEM. Regarding baseline data on biochemical markers of bone homeostasis, 18 measurements were missing (8 in the VD group and 10 in the UVB group) due to logistical problems at the laboratory. Linking laboratory patient's numbers with trial numbers failed and therefore the source of the samples could not be identified. The baseline serum concentration of 25(OH)D3 in the 78 nursing home residents was significantly lower in the UVB group, with a median of 66.4 (IQR, 53.6–78.7), versus 86.4 (IQR, 65.1–99.7) in the VD group.

Adherence of Nursing Home Residents to the Intervention

Twelve of the participants (30%) in the UVB group refused to adhere to the intervention procedure following initial sessions for a variety of reasons, including an unwillingness to remove clothes or to wear protective glasses, feeling cold or anxious, not understanding the purpose of the procedure or being unable to lie quietly on a bed during UVB exposure. The other participants (70%) showed variable adherence to the UVB treatment regime or died

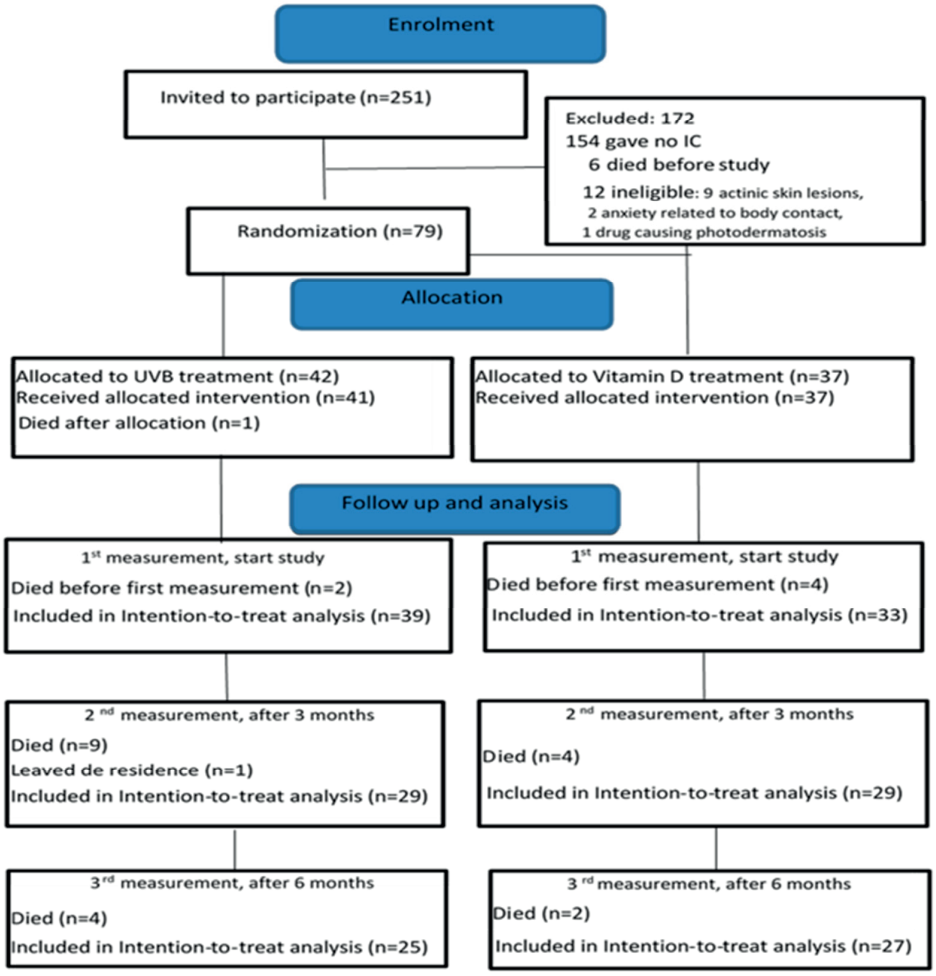

Figure 1. Enrolment illustrated in a CONSORT 2010 flow diagram.
IC: informed consent, UVB: ultraviolet B

before the end of the treatment period, which resulted in the following duration of the UVB exposure: 8 of the participants (19%) completed UVB sessions of between 24 and 100 min in total, 3 (7%) between 100 and 200, 14 (34%) between 200 and 300 min and 4 (10%) between 300 and 400 min (when participants clearly objected to the UVB session it was discontinued). Eleven (28%) of the participants experienced the sessions as being pleasant and reinforcing, as observed by the nursing staff.

Effect of UVB on the Outcome Variables

Table 2 shows the results of multilevel analyses of effects on the primary and secondary outcomes.

Table 1 Characteristics of the participants at baseline by study group.

Variable	UVB	Vitamin D	*p*-Value
Gender %,(n)			0.20 [a]
male	24 (10)	38 (14)	
Female	76 (31)	62 (23)	
Age in years, mean (SD)	84.2 (79.5–87.5)	83.6 (77.5–88.5)	0.74 [b]
Fitzpatrick skin scale %,(n)			0.90 [c]
1. always burns easily, never tans	0	3 (1)	
2. always burns easily, tans slightly	66 (27)	62 (23)	
3. burns moderately, tans gradually	30 (12)	32 (12)	
4. burns minimally, tans moderately	0	0	
5. rarely burns, tans profusely	5 (2)	0	
6. never burns, tans profusely	0	3 (1)	
Dementia severity, mean BANS-S (SD)	15.1 (4.3)	16.6 (5.7)	0.20 [b]
Agitation (median CMAI, IQR)	40.0 (30.3–62.5)	41.0 (30.5–61.0)	0.82 [d]
Cornell Scale For Depression (Median, IQR)	9.5 (4.9–13.0)	9.5 (5.0–12.0)	0.88 [d]
QUALIDEM (Median, IQR)			
A. Care relationship	6.0 (4.0–8.0)	7.0 (5.0–8.5)	0.28 [d]
B. Positive affect	10.0 (7.5–12.0)	9.0 (8.0–11.5)	0.63
C. Negative affect	3.0 (3.0–4.0)	4.0 (3.0–4.0)	0.98
D. Restless/tense behavior	6.0 (2.5–8.0)	6.0 (3.0–8.0)	0.91
E. Social relations	6.0 (4.5–8.0)	6.0 (4.0–7.0)	0.45
G. Social isolation	6.5 (4.0–9.0)	8.0 (5.0–9.0)	0.52
Blood tests (Median, IQR)) [#]			
Creatinine (µmol/L)	73.0 (61.0–82.0)	72.5 (56.0–88.2)	0.82 [d]
Calcium (mmol/L)	2.3 (2.3–2.5)	2.3 (2.3–2.4)	0.81
Phosphate (mmol/L)	1.1 (1.0–1.1)	1.1 (0.9–1.3)	0.60
Alkaline phosphatase (U/I)	86.4 (65.3–116.6)	82.4 (70.0–97.9)	0.96
25(OH)D3 (nmo/L)	66.4 (53.6–78.7)	86.4 (65.1–99.7)	0.04
Parathyroid hormone (pmol/L)	5.7 (3.0–7.6)	3.5 (2.7–6.5)	0.24

[a] Pearson's Chi-squared test used for gender; [b] Students t-test for age and BANS-S; [c] Kruskal-Wallis test for skin type; [d] Mann-Whitney test for the other parameters. [#] Missing: Vitamin D, *n* = 11; UVB, *n* = 14, IQR—Interquartile range, CMAI—Cohen-Mansfield Agitation Inventory, BANS-S—Bedford Alzheimer Nursing Severity Scale, 25(OH)D3: serum 25-hydroxyvitamin D.

Effect of UVB Treatment on Well-Being

No significant between-group differences were observed for the primary outcome measures. With the VD group as a reference, the CMAI estimated difference between mean change scores was 4.4 (95% CI −2.3 to 11.2, $p = 0.194$) at three months and −0.2 (95% CI −6.8 to 7.2, $p = 0.953$) at six months. The Cornell estimated difference was 1.3 (95% CI −1.9 to 4.6, $p = 0.412$) at three months and −1.3 (95% CI −4.5 to 1.9, $p = 0.427$) at six months.

Effect of UVB Treatment on Secondary Outcomes

Quality of life as measured by QUALIDEM showed a significant difference between groups and over time on the subscale "restless/tense behavior". With the VD group as a reference, the estimated difference between mean change scores on restless/tense behavior was −1.1 (95% CI −2.1 to −0.1, p = 0.025) at three months and 1.1 (95% CI 0.1 to 2.1, p = 0.042) at six months. The linear mixed model analysis showed a significant time x group interaction effect (p = 0.003), with less restless/tense behavior at six months in the UVB group with the VD group as a reference, compared to the three months outcomes (estimated difference between mean change scores 2.2, 95% CI 0.8 to 3.6).

The 25(OH)D3 serum concentrations in the UVB group at six months was lower in comparison to the VD group, with an estimated difference between mean scores of −9.3 (95% CI −19.4 to 1.0, p = 0.073) at three months and -21.9 (95% CI −32.6 to −11.2, p < 0.001) at six months.

No significant between-group differences were observed for the remaining biochemical parameters of bone homeostasis (data not shown).

Harmful or Adverse Events

Transitional redness of the skin was observed in 3 participants in the UVB group, although this disappeared after 24 h.

Additional (Sensitivity) Analysis

Because of the variability in duration of UVB exposure in the intervention group, we performed an additional analysis, keeping those who maintained any duration of UVB exposure as "UVB-exposed" and moving those who refused the intervention to the control group (12 participants) [Appendix Table A1]. No significant between-group difference was observed for the primary outcome measures. Quality of life as measured by QUALIDEM showed a difference between groups and over time on the subscale "restless/tense behavior", p = 0.012. With the VD group as a reference, the estimated difference between mean change scores on restless/tense behavior was −0.6 (95% CI −1.7 to 0.4, p = 0.207) at three months and 1.2 (95% CI 0.2 to 2.3, p = 0.025) at six months.

DISCUSSION

In this study, the first randomized control trial to assess the effect of UVB on agitation and depression in people with dementia, we found no significant effect of UVB light on the well-being of nursing home residents. By comparison, in a population of dermatological patients and healthy volunteers, Edstrom et al. reported a significant improvement in scores on the

Table 2 Estimated marginal group means and *p*-values, based on mixed model analysis*.

	3 Months (*n* = 58)			6 Months (*n* = 52)			*p*-Value		
	Estimated Mean Score	Adjusted MD	*p*-Value	Estimated Mean Score	Adjusted MD	*p*-Value	Pg	Pt	Pgt
	(95% CI)	(95% CI)		(95% CI)	(95% CI)				
CMAI total score							0.431	0.076	0.258
UVB	49.4 (44.7, 54.0)	4.4 (–2.3, 11.2)	0.194	50.6 (45.7, 55.5)	–0.2 (–6.8, 7.2)	0.953			
VD	45.0 (41.0, 49.8)			50.4 (45.4, 55.5)					
Cornell scale for depression							0.982	0.014	0.246
UVB	8.5 (6.4, 10.7)	1.3 (–1.9, 4.6)	0.412	10.1 (8.0, 12.2)	–1.3 (–4.5, 1.9,)	0.427			
VD	7.2 (4.8, 9.7)			11.4 (9.0, 13.8)					
Care relationship (QUAL)							0.776	0.421	0.307
UVB	6.2 (5.8, 7.0)	–0.2 (–1.0, 0.6)	0.684	6.3 (5.7, 6.7)	0.3 (–0.5, 1.2)	0.402			
VD	6.4 (5.4, 6.5)			6.3 (5.7, 6.7)					
Positive affect (QUAL.)							0.698	0.363	0.646
UVB	8.8 (7.9, 9.7)	0.4 (–0.9, 1.6)	0.555	8.9 (8.0, 9.9)	0.0 (–1.3, 1.3)	0.947			
VD	8.4 (7.5, 9.3)			8.9 (8.0, 9.8)					
Negative affect (QUAL.)							0.303	0.507	0.866
UVB	3.4 (3.0, 3.7)	–0.2 (–0.7, 0.3)	0.483	3.3 (3.0, 3.7)	–0.2 (–0.7, 0.3)	0.377			
VD	3.6 (3.2, 3.9)			3.5 (3.1, 3.8)					
Restless/Tense (QUAL.)							0.937	0.520	0.003
UVB	4.6 (3.9, 5.1)	–1.1 (–2.1, –0.1,)	0.025	5.5 (4.8, 6.2)	1.1 (0.1, 2.1,)	0.042			
VD	5.7 (5.0, 6.4)			4.4 (3.7, 5.1)					
Social relations (QUAL.)							0.960	0.920	0.763
UVB	5.7 (5.1, 6.3)	–0.1 (–1.0, 0.8)	0.813	5.8 (5.1, 6.5)	0.1 (–0.8, 1.0)	0.879			
VD	5.8 (5.1, 6.4)			5.7 (5.1, 6.4)					
Social isolation (QUAL.)							0.329	0.441	0.158
UVB	5.9 (5.3, 6.6)	–0.8 (–1.7, 0.2)	0.104	6.2 (5.5,6.8)	0.0 (–1.0, 1.0)	0.988			
VD	6.7 (6.1, 7.4)			6.2 (5.5, 6.8)					
25(OH)D3							0.003	0.141	0.001
UVB	66.3 (59.1, 73.5)	–9.3 (–19.4, 1.0)	0.073	62.7 (54.9, 70.5)	–21.9 (–32.6, –11.2)	0.000			
VD	75.6 (69.0, 82.1)			84.6 (77.9, 91.3)					

CMAI (Cohen-Mansfield agitation inventory): higher scores indicate a higher level of agitation; Cornell scale for depression: higher scores indicate more depressive symptoms; QUALIDEM: higher scores indicate higher QoL; 25(OH)D3: serum 25-hydroxyvita-

min D3; * The mixed model analysis adjusted for the baseline of the outcome measures shows the *p*-values for the intervention (UVB) versus control (VD) condition (Pg), the overall time effect (Pt) and the interaction effect of group and time (Pgt). The treatment effect is presented as adjusted mean difference (MD) between the VD and UVB groups for each time point with the VD group as a reference

Montgomery Asberg Depression Rating Scale (MADRS) after six weeks (2–3 sessions weekly) of whole body UVB exposure [3]. The difference in results may be attributable to lower treatment adherence and a smaller body area exposed to UVB light amongst our participants.

Our study showed an increase in restless/tense behavior in the UVB group in the first three months and less restless/tense behavior in the same group in the second three-month period compared to the control group. The additional analysis showed no difference between two groups in the first three months and the same results in the second three months. A similar effect was found in a study by Gambichler et al., where healthy volunteers reported feeling more balanced and less nervous after three weekly sessions of whole-body UVA exposure [26]. A positive effect of UVB light on restless/tense behavior in this study population was observed after six months. This could be due to an adaptation period in which participants with advanced dementia became accustomed to a change in their daily routine, late response to the treatment or dose response to the treatment. To look at the normal progression of the restless behavior in people with dementia in NH homes, we referred to the study of Mjorud et al., a 10 months follow up of persons with dementia living in nursing homes [27]. The authors observed that 19.6% of the participants improved in the course of 10 months on the tension scale of the QUALID, 35.7% remained stable and 44.5% worsened. This variance of 34.6% was associated with changes in the clinical dementia rating, NPI scores and baseline tension score. The mechanisms that can be triggered by UV light to modulate positive psychological effects are: (A) through the vitamin D receptors in the brain [28,29] and (B) through the skin affecting three local systems: (i) the skin analog of the hypothalamic-pituitary-adrenal (HPA) axis [30], (ii) the serotoninergic/melatoninergic system [31] and (iii) the immune system [32]. The effect of UV light exerted through skin is a process assumed to interplay with systemic mechanisms of body homeostasis, involving the paraventricular and arcuate nuclei of hypothalamus and triggering rapid stimulation of the brain [33].

Serum concentrations of 25(OH)D3 increased significantly in the VD group in the last three month period in comparison to the UVB group. This was not in line with the pilot study of Chel et al. which showed a significant increase in 25(OH)D3 in persons with dementia after 8 weeks of UVB exposure and this was not the case in our study. This could be due to differences in adherence to the prescribed regime, an inability of older skin to synthesize 25(OH)D3 over a longer period or to 25(OH)D3 reaching a plateau (81.5% of our participants in the UVB

group were VD sufficient (25(OH)D >50 nmol/L [34]) in comparison with the pilot study where the participants were VD deficient or insufficient [35,36].

A major strength of our study was the multicenter RCT design, which included a six-month follow-up period. We also carried out an intention-to-treat analysis that provides not only an estimation of the effect of treatment but also the applicability of the procedure in this specific population.

The main limitations of our study were the lack of blinding and the low adherence to the intervention by nursing home residents with dementia. To partially reduce the last limitation, we performed a sensitivity analysis comparing the participants who actually were UVB exposed with participants who were not UVB exposed. The additional analysis showed the same results as the intention-to-treat analysis for the main outcomes of the study.

There are strategic lessons to be learned from this study, especially for researchers dedicated to the population of people with dementia. In terms of adherence, it was really difficult to have all the participants stick with the intervention. For ethical reasons, UVB treatment was discontinued when participants clearly objected or showed signs of discomfort on two consecutive sessions. The use of sunbeds by nursing home residents with dementia also highlighted certain practical problems underlying the low adherence, including feeling cold, anxious, being unable to lie still or being unable to understand the purpose of the procedure. Future research efforts in this field should first attempt to find more comfortable approaches to administering UVB light.

The effect of UVB light on wellbeing has not yet been examined in this population. In our study, the amount of the UVB light administered was calculated on the base of the UVB light needed to sustain a sufficient 25(OH)D3 serum concentration. The exposure needed to achieve any effect on agitation, depression or quality of life is not yet known. It is possible that a better adherence to the prescribed regime or a more intensive treatment than the treatment our participants actually received might present other results on the effect of UVB on wellbeing and quality of life.

CONCLUSIONS

The exposure of nursing home residents with dementia to UVB light showed no positive benefits in terms of wellbeing. UVB treatment may have a positive effect on the restless/tense behavior characteristic of advanced dementia, but more research is needed to confirm this finding.

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Appendix A Table A1. Estimated marginal group means and p-values, based on mixed model analysis, additional analysis*.

	3 Months (n = 58)			6 Months (n = 52)			p-Value		
	Estimated Mean Score (95% CI)	Adjusted MD (95% CI)	p-Value	Estimated Mean Score (95% CI)	Adjusted MD (95% CI)	p-Value	Pg	Pt	Pgt
CMAI total score							0.847	0.175	0.155
UVB	49.3 (43.9, 54.7)	3.3 (–3.6, 10.2)	0.343	49.2 (43.5–54.8)	–2.2 (–9.4, 5.0)	0.554			
VD	46.0 (41.7, 50.3)			51.3 (46.7–55.8)					
Cornell scale for depression							0.483	0.032	0.260
UVB	8.5 (6.4, 10.7)	2.1 (–1.9, 4.6)	0.200	10.1 (8.0–12.2)	–0.5 (–2.7, 3.6)	0.775			
VD	7.1 (5.0, 9.1)			11.0 (8.8, 12.9)					
Care relationship (QUAL)							0.575	0.617	0.285
UVB	6.0 (5.4, 6.7)	–0.5 (– 1.3, 1.3)	0.259	6.2 (5.5, 6.8)	0.3 (–0.5, 1.2)	0.820			
VD	6.5 (6.0, 7.0)			6.1 (5.6, 6.7)					
Positive affect (QUAL.)							0.827	0.602	0.171
UVB	8.8 (7.8, 9.9)	0.4 (–0.9, 1.6)	0.561	8.5 (7.5, 9.6)	0.0 (–1.3, 1.3)	0.354			
VD	8.5 (7.7, 9.3)			9.1 (8.3, 9.9)					
Negative affect (QUAL.)							0.945	0.337	0.218
UVB	3.6 (3.2, 4.0)	0.2 (–0.3, 0.7)	0.452	3.3 (2.8,3.7)	–0.2 (–0.7, 0.3)	0.406			
VD	3.4 (3.1, 3.7)			3.5 (3.2, 3.8)					
Restless/Tense (QUAL.)							0.969	0.462	0.012
UVB	4.8 (4.0, 5.6)	–0.6 (–1.7, 0.4,)	0.207	5.7 (4.8, 6.5)	1.2 (0.2, 2.3,)	0.025			
VD	5.4 (4.8, 6.0)			4.5 (3.7, 5.1)					
Social relations (QUAL.)							0.939	0.857	0.324
UVB	5.9 (5.2, 6.7)	0.3 (–0.6, 1.2)	0.484	5.6 (4.9, 6.4)	–0.3 (–1.2, 0.7)	0.573			
VD	5.6 (5.1, 6.2)			5.9 (5.3, 6.5)					
Social isolation (QUAL.)							0.292	0.557	0.546
UVB	6.0 (5.2, 6.8)	–0.6 (–1.6, 0.4)	0.223	6.0 (5.2, 6.8)	–0.3 (–1.3, 0.7)	0.596			
VD	6.6 (6.0, 7.2)			6.2 (5.6, 6.7)					
25(OH)D3							0.039	0.237	0.005
UVB	67.6 (59.1, 76.0)	–5.1 (–15.8, 5.6)	0.344	64.1 (54.9, 73.3)	–16.8 (–28.0, –5.5)	0.004			
VD	72.7 (66.5, 78.9)			80.7 (74.5, 87.1)					

CMAI (Cohen-Mansfield agitation inventory): higher scores indicate a higher level of agitation; Cornell scale for depression: higher scores indicate more depressive symptoms; QUALIDEM: higher scores indicate higher QoL; 25(OH)D3: serum 25-hydroxyvitamin D3. * The mixed model analysis adjusted for the baseline of the outcome measures shows the p-values for the intervention (UVB) versus control (VD) condition (Pg), the overall time effect (Pt) and the interaction effect of group and time (Pgt). The treatment effect is presented as adjusted mean difference (MD) between the VD and UVB group for each time point with VD group as reference category

Chapter 6

The Effect of Ultraviolet Irradiation Compared to Oral Vitamin D Supplementation on Blood Pressure of Nursing Home Residents with Dementia

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ABSTRACT

Background: Observational studies have reported an inverse association between ultraviolet (UV) radiation and hypertension. The aim of this study was to assess differences in blood pressure changes between persons with dementia receiving UV light versus vitamin D (VD) supplementation.

Methods: Post-hoc analysis of randomized controlled trial data concerning nursing home residents with dementia (N=61; 41 women, mean age 84.8 years). The participants received half-body UV irradiation, twice weekly over 6 months, at one standard erythema dose (UV group, n=22) or 5600 international units of cholecalciferol once a week (VD group, n=39). Short-term effects were evaluated after 1 month and long-term effects after 3 and 6 months. Differences in blood pressure changes were assessed using linear mixed models.

Results: With the VD group as a reference, the estimated difference in mean change of systolic blood pressure was -26.0 mm Hg [95% confidence interval (CI) -39.9, -12.1, p=.000] at 1 month, 4.5 mmHg (95% CI -6.8, 15.9, p=0.432) at 3 months, and 0.1 (95% CI -14.1, 14.3, p=0.83) at 6 months. The estimated difference in diastolic blood pressure was -10.0 mmHg (95% CI -19.2, -0.7, p=0.035) at 1 month, 3.6 mmHg (95% CI -4.1, 11.2, p=0.358) at 3 months, and 2.7 (95% CI -6.8, 12.1, p=0.580) at 6 months.

Conclusions: UV light had only a short-term effect but not a long-term effect on blood pressure reduction compared to VD use in this sample of normotensive to mild hypertensive nursing home residents with dementia. Future studies will be needed to determine the effect of UV light in different samples of the population and especially in a population with hypertension.

BACKGROUND

Hypertension is a major risk factor for cardiovascular disease (CVD) (1). Its prevalence increases with older age, reaching 80% in people above the age of 75 (2). Older people with CVD usually have multiple chronic conditions which are often addressed by guidelines that focus on a single disease, an approach that can increase the risk of inappropriate polypharmacy (3). In order to reduce the medication burden it may be worthwhile examining readily modifiable risk factors such as insufficient sun exposure and vitamin D (VD) deficiency, both of which play a role in blood pressure homeostasis.

Epidemiological studies have shown that blood pressure correlates with geographical latitude (4), and that sunlight exposure might reduce both blood pressure and CVD (5, 6). Possible modulators of this effect include VD (7-10), temperature (11), ultraviolet A (UVA) radiation (12, 13) and ultraviolet B (UVB) light radiation (14). VD (which production in the skin is triggered by UVB) corrects abnormalities in calcium homeostasis and regulates the renin-angiotensin system, both of which play a role in the development of hypertension (15, 16). It has been proposed that UV light, in addition to its role in the production of VD in the skin, may have a blood pressure regulatory effect that is independent of VD: UVA mediates mobilisation of cutaneous nitric oxide stores to the systemic circulation which works as an endothelial relaxant factor and causes vascular relaxation and vasodilatation (12, 13).

Observational studies suggest an inverse association between sun or UV exposure and blood pressure, an effect that remains even after correcting for temperature, demographic and lifestyle variables and serum 25(OH)D3 concentration (17-19). There is also some evidence from intervention studies suggesting that UV light might reduce arterial blood pressure but these results are inconsistent (12, 13, 20-24), possibly due to inclusion of different target populations (people with or without hypertension, patients on haemodialysis or healthy volunteers), the UV light spectrum used and the follow-up time. An early effect of UV light exposure on blood pressure was reported by Oplander et al. and Liu et al (12, 13). In these two studies healthy volunteers were exposed to a single dose of whole body UVA ($20J/m^2$) for 15 and 22 minutes, respectively. In the first study, the authors observed a reduction of both systolic and diastolic blood pressure 15 minutes after the intervention, while in the second study mean diastolic pressure decreased during the intervention and persisted at a lower level for 30 minutes after the UVA intervention. A randomised trial reported by Krause et al. included 18 patients, aged 26 to 66 years, who were assigned to receive either full-body UVA or UVB irradiation for 6 weeks (22). UVA had no effect on blood pressure but UVB caused a reduction in both systolic and diastolic blood pressure. Some of these studies attributed the observed effect to the production of VD via UVB light (21, 22), and others to the effect of UVA light on peripheral arterial resistance.

The most consistent body of evidence supporting the effects of VD supplementation, including effects on CVD, is found for older persons with very low serum 25(OH)D3 levels, a finding that supports recommendations for VD supplementation in this population (25-27). Supplementation of VD is common in nursing home residents with dementia because this group is especially at risk of sun deprivation. Nursing home residents with dementia spend most of their time indoors, and a study by Cutler and Kane showed that of those who are physically able, only 22% actually go outside daily(28). Whether VD supplementation can completely replace the effect of sun light exposure in maintaining blood pressure homeostasis in nursing home residents with dementia is still not firmly established. Therefore the objectives of this study are:

1. To compare the effect of UV exposure and VD supplementation on blood pressure over time.
2. To compare the effect of UV exposure and VD supplementation on serum 25(OH)D3 levels over time.

METHODS

Study population and intervention

We conducted a post-hoc analysis of blood pressure data from participants in a multicentre randomized control trial (RCT) that ran for 6 months. The trail was designed to compare the effects of UV light and VD supplementation in terms of well-being of nursing home residents with dementia.

The study population, RCT design and interventions have been described in detail elsewhere (29). Briefly, participants were recruited from three nursing homes affiliated with the University Network for the Care sector South Holland (UNC-ZH). The RCT was carried out between October 2016 and April 2017 in two nursing homes, and between October 2017 and April 2018 in a third nursing home. Seventy-nine nursing home residents met the inclusion criteria were randomized to the intervention group (UV light, UV group) or standard VD treatment group (control, VD group), which involved supplementation with 5600 International units (IU) cholecalciferol once a week. The intervention consisted of half body UV irradiation with 1 standard erythema dose (SED) two times a week for 8 minutes. Lamp light emission consisted of UVB-5.013 Wm^{-2}, ultraviolet A (UVA)-4.650 W m^{-2}, ultraviolet C (UVC)-0.00001Wm^{-2}, with UVB accounting for 54.6% of the spectrum. UV treatment was discontinued when participants clearly objected or showed signs of discomfort on two consecutive sessions. They were then removed from the UV exposure group and started on VD capsules. The protocol for the RCT was approved by the Medical Ethical Committee of Leiden University Medical Center (Registration No P16.010) and the study was registered in the Dutch Trial Register (NL5704).

For the post-hoc analyses, blood pressure data were obtained from the medical records of the nursing home residents participating in the RCT. Blood pressure was routinely measured in the first week of each month in the morning after 5 minutes of quiet rest using an automatic (Omron I-C10/M6, Omron Healthcare Co. Ltd, Kyoto, Japan) sphygmomanometer as a part of standard care. The routine measurements were taken when the nursing home residents were not sick and had no complaints. Serum levels of 25(OH)D3 measured using an electrochemiluminescence immunoassay (ECLIA, Roche diagnostics, Basel, Switzerland) were obtained from the medical records.

Outcome measures

The primary outcome measure of the post-hoc analysis was the difference in change of systolic and diastolic blood pressure over time between the intervention and control groups and the within group changes over time. Time points of one month, three months and six months after starting the intervention were chosen at which to monitor short-term and long-term effects. Because of variability in adherence to the intervention in a study population of subjects with dementia, in this post-hoc analysis we created two test situations: 1) a main analysis :all participants exposed to any UV irradiation [UV(all), intervention group] versus VD1 [control group, people randomized to the VD group plus the participants from the UV group who refused irradiation], and 2) an additional analysis concerning all participants exposed to UV for longer than 3 months [UV (exposure>3months) group] versus VD2 [control group, people randomized to the VD group plus the participants from the UV group who were exposed to irradiation for less than 3 months]. Differences in the change of serum level of 25(OH)D3 in the intervention versus the control group was a secondary outcome measure. Changes were measured at 3 and 6 months.

Measurements at baseline

Information on participant's sociodemographic characteristics (gender, age and skin type) and dementia severity were obtained at baseline. The skin type of each participant was assessed by a dermatologist using the ordinal Fitzpatrick scale which represents a classification of the skin phototypes, based on six categories according to the amount of melanin pigment in the skin, and validated for estimation of the response of different types of skin to UV light. (30). Dementia severity was assessed using the Bedford Alzheimer Nursing Severity-Scale (BANS-S) (31) which comprises 7 items, scaled 7-28, with a score of 17 or higher indicating severe dementia (32). For each participant, we took the blood pressure measurement of the month before the start of the intervention as a baseline measurement. The VD status of the participants was estimated based on 25(OH)D3 serum concentrations in nmol/l before starting the intervention.

Statistical analysis

Statistical analyses were performed with SPSS 23.0 (IBM Corp. Released 2015, Armonk, N.Y., USA). To test differences in basic characteristics between the intervention and control group, we used Pearson's chi-square test for categorical variables, the unpaired t-test for continuous normally distributed variables and the linear trend test for ordinal variables. A p-value <0.05 was considered statistically significant. Within group differences were measured by a paired t-test and the mean change was determined between baseline and one month, three months and six months. Analysis of the effects of UV light and VD treatments on blood pressure was conducted using linear mixed models for between group differences. In the linear mixed model analyses, time was treated as a categorical variable. Blood pressure was defined as a dependent variable, independent variables were the study groups (control and intervention) and time. Control variables (covariates) were baseline blood pressure for the main outcome and baseline vitamin D for the secondary outcome and for both main and secondary outcome: all baseline characteristics that were significantly different between the intervention and control group. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality. The following effects were estimated for the outcome variable: the main effect of the intervention, the main effect of time (at six time points) and the interaction between group and time. The treatment effects were presented at three time points for the systolic and diastolic blood pressure (after one month, three and six months of treatment) and two time points for 25(OH)D3 (after three and six months of treatment) respectively, as estimated mean scores with 95% confidence interval (CI) and a p-value for the adjusted estimated difference between the mean change score (95% CI), with the VD group as reference.

RESULTS

Participants

Of the 79 participants included in the RCT, we had blood pressure measurements of 61 participants (33 randomized in the UV group and 28 randomized in the VD group) and we included those 61 participants in the post-hoc analysis. Due to refusal of UV-treatment, we transferred 10 of the participants of the UV-group to the VD group which resulted in the assignment of 23 participants to the UV(all) group and 38 to the VD1 group for the main analysis . On the baseline characteristics between the UV (all) and VD1 groups only a difference in skin type was found (p=0.03) (Table 1).

For the additional analysis we transferred 10 more patients to the VD (all) group, because they had UV treatment for 3 months or shorter (6 passed away and 4 refused UV treatment and started on VD capsules), so we finally assigned 13 participants to the UV(>3 months) group and 48 patients to the VD2 group. The baseline characteristics of the participants in the additional analysis showed no difference with exception of the serum 25(OH)D3 concentration

Table 1. Characteristics of the participants at baseline by study group

Variable	UV (all) (n=23)	VD1 (n=38)	p-value
Gender %, (n)			
male	26.1 (6)	36.8 (14)	0.39 [a]
female	73.9 (17)	63.2 (24)	
Age in years, mean (SD)	84.8 (6.8)	83.5 (7.0)	0.46 [b]
Fitzpatrick skin scale %,(n)			
1.always burns easily, never tans	0	2.6 (1)	0.03 [c]
2.always burns easily, tans slightly	56.5 (13)	73.7 (28)	
3.burns moderately, tans gradually	34.8 (8)	23.7 (9)	
4.burns minimally, tans moderately	0	0	
5.rarely burns, tans profusely	8.7 (2)	0	
6.never burns, tans profusely	0	0	
Dementia severity, mean BANS-S (SD)	16.0 (4.0)	15.6 (5.1)	0.75 [b]
Baseline blood pressure, mmHg			
Systolic, mean (SD)	140.5 (25.4)	130.0 (21.7)	0.09 [b]
Diastolic, mean (SD)	76.6 (9.9)	74.1 (14.5)	0.48 [b]
Using antihypertensive medication %,(n)	43.5 (10)	31.6 (12)	0.35 [a]
Serum 25(OH)D3 levels, nmol/l, mean (SD)	71.6 (24.9)	77.4 (31.9)	0.22 [b]

SD, Standard deviation
BANS-S, Bedford Alzheimer Nursing Severity-Scale
25(OH)D3, 25-hydroxyvitamin D3
a - Pearson's Chi-squared test used for gender, medication
b - Unpaired T-test for age, BANS-S, blood pressure and 25(OH)D3
c –Linear trend test
Mean systolic and diastolic blood pressures were 140.5 mmHg (SD 26.0) and 76.6 mmHg (SD 10.1) in de UV group versus 130.3 mmHg (SD 21.5) and 74.1 mmHg (SD 14.2) in the VD1 group (p=0.11).). The use of
antihypertensive medication was comparable (45.4% in the UV (all) group vs. 30.8 % in the VD1 group, p=0.25).
The 25(OH)D3 serum concentration did not differ between the groups (69.6 mmol/l, SD 24.0 in the UV (all) group vs. 78.3 mmol/l, SD 31.9, p=0.32 in the VD1 group). Of the participants in the UV(all) group, 88.9% were VD sufficient (25(OH)D >50 nmol/L compared to 79.4% in the VD1 group. We adjusted for skin type in the linear mixed model of the main analysis.

which was significantly lower in the UV(>3 months) group, p=0.04 (Additional file 1). We adjusted for this in the linear mixed model of the additional analysis.

Effect of UVB treatment on systolic blood pressure

After one month of treatment, the mean systolic blood pressure in the UV(all) group was 24.5 mmHg lower (95% CI 7.6, 41.3, p=0.008) than at baseline(table 2). By contrast, mean systolic blood pressure in the VD1 group did not change significantly, with a mean change of 6.2 mmHg (95% CI -10.1, 22.7, p=0.416). The adjusted mean change difference between the two groups, with the VD1 group as a reference, after one month of treatment, was -26.0 mmHg (95% CI -39.9, -12.1, p=.000) (table 3). At 3 and 6 months there was neither within group difference nor between group difference in systolic blood pressure of the control and intervention group.

Table 2. Within group differences between baseline and 1, 3 and 6 months: Paired T-test

Group	Period	Outcome variable	Mean Change	95% CI of the difference		p-value
				Lower	Upper	
VD1	1-0 month, n=11	Systolic BP	6,2	-10,1	22.7	,416
	3-0 month, n=30	Systolic BP	-3,8	-11.3	3,6	,300
	6-0 month, n=17	Systolic BP	-4,9	-18,2	8.4	,444
	1-0 month, n=11	Diastolic BP	3,8	-7,1	14.7	,455
	3-0 month, n=30	Diastolic BP	-1,2	-7,5	5.1	,702
	6-0 month, n=17	Diastolic BP	-4,6	-13,4	4.1	,278
	3-0 month, n=24	25(OH)D3	-4,6	-11,4	2.2	,172
	6-0 month, n=21	25(OH)D3	4,9	-2,9	12,8	,208
UV(all)	1-0 month, n=13	Systolic BP	-24,4	-41,9	-7,6	,008
	3-0 month, n=13	Systolic BP	-7,1	-22,9	8.6	,342
	6-0 month, n=8	Systolic BP	-7,7	-26,7	11,2	,366
	1-0 month, n=13	Diastolic BP	-7,1	-15,0	0.9	,076
	3-0 month, n=13	Diastolic BP	0,4	-6,0	6,8	,898
	6-0 month, n=8	Diastolic BP	2,7	-5.1	10.6	,437
	3-0 month, n=13	25(OH)D3	-6,3	-15,4	2.9	,163
	6-0 month, n=9	25(OH)D3	-11,5	-23.0	-0,02	,050

95% CI: 95% Confidence interval

Systolic BP: Systolic blood pressure, Diastolic BP: Diastolic blood pressure, 25(OH)D3: serum 25-hydroxyvitamin D3

UV (all): the group of the people, received any UVB radiation, VD1 group: people randomized in VD group plus the participants from the UV group who have refused irradiation

Effect of UVB treatment on diastolic blood pressure

After one month of treatment, the mean diastolic blood pressure in the UV(all) group was 7.1 mmHg (95% CI -15.0, 0.9, p=0.076) lower than baseline versus 3.8 mmHg (95% CI -7.1, 14.7, p=0.455) higher than baseline in the VD1 group, but neither change was statistically significant. The adjusted mean change difference between the two groups, with the VD1 group as a reference, was -10.0 mm Hg (95% CI -19.2, -0.7, p=0.035). At 3 and 6 months, there was no statistically significant within and between group differences in diastolic blood pressure.

Additional analysis

In an additional analysis restricted to participants who were exposed to UV for longer than 3 months the results were similar [UV (exposure >3 months), n=13, VD2, n=48] (Table 3). The adjusted difference in the change in systolic blood pressure between the groups, with the VD2 group as reference, was -22.3 mmHg (95% CI -38.7, -5.9, p=0.008) after one month, -3.1 mmHg (95% CI -15.7, 9.6, p=0.632) at 3 months and -7.0 (95% CI -23.5, 9.4, p=0.400) at six months. The adjusted difference in the change in diastolic blood pressure between the groups, with the VD2 group as reference, was not significant at all time points.

Table 3. Estimated marginal group means and p-values, based on mixed model analysis

	1 month			3 months			6 months			p-value		
	Estimated mean score (95%CI)	Adjusted MD (95%CI)	p-value	Estimated mean score (95%CI)	Adjusted MD (95%CI)	p-value	Estimated mean score (95%CI)	Adjusted MD (95%CI)	p-value	Pg	Pt	Pgt
Systolic BP												
Main analysis										0.612	0.811	0.002
UV (all), n=23	117.4 (107.9, 126.8)	-26.0 (-39.9, -12.1)	.000	132.1 (122.8, 141.5)	4.5 (-6.8, 15.9)	0.432	128.3 (116.6, 139.9)	0.1 (-14.1, 14.3)	0.832			
VD1, n=38	143.4 (133.6, 153.2)			127.6 (121.4, 133,6)			128.2 (120.2, 136.2)					
Additional analysis										0.256	0.642	0.064
UV (>3months), n=13	116.8(103.5, 130.1)	-22.3 (-38.7, -5.9)	0.008	127.6 (117.0, 138.3)	-3.1 (-15.7, 9.6)	0.632	123.3 (109.2, 137.4)	-7.0 (-23.5, 9.4)	0.400			
VD2, n=48	139.1 (129.5, 148.7)			130.7 (124.1, 137.4)			130.3 (121.9, 138.7)					
Diastolic BP												
Main analysis										0.692	0.738	0.106
UV (all), n=23	69.4 (63.0, 75.7)	-10.0 (-19.2, -0.7)	0.035	77.3 (71.2, 83.7)	3.6 (-4.1, 11.2)	0.358	76.4 (68.7, 84.2)	2.7 (-6.8, 12.1)	0.580			
VD1, n=38	79.3 (72.8, 85.9)			73.8 (69.6, 78.0)			73.8 (68.4, 79.1)					
Additional analysis										0.580	0.802	0.712
UV (>3months), n=13	70.0 (61.3, 78.7)	-6.6 (-17.4, 4.2)	0.227	75.7 (68.6, 82.8)	0.9 (-7.5, 9.3)	0.834	74.6. (65.3, 83.9)	0.9 (-10.0, 11.7)	0.878			
VD2, n=48	76.6 (70.3, 82.9)			74.8 (70.3, 79.1)			73.7 (68.2, 79.3)					
25(OH)D3												
Main analysis										0.037	0.230	0.006
UV (all), n=23				67.3 (58.3, 76.3)	- 5.9 (-17.3, 5.4)	0.299	64.0 (54.3, 73.5)	- 17.5 (-29.3, -5.7)	0.004			
VD1,n=38				73.2 (66.8, 79.6)			81.4 (74.8, 87.9)					
Additional analysis										0.076	0.395	0.04
UV (>3months), n=13				67.5 (57.7, 77.2)	-5.3 (-16.9, 6.4)	0.368	64.6 (53.9, 75.3)	-15.0 (-27.4., -2.5)	0.019			
VD2, n=48				72.7 (66.6, 78.9)			79.6 (73.3, 85.8)					

Systolic BP: Systolic blood pressure, Diastolic BP: Diastolic blood pressure, 25(OH)D3: serum 25-hydroxyvitamin D3

*The mixed model analysis adjusted for the baseline of the outcome measures shows the p-values for the intervention (UVB) versus control (VD) condition UV (all): the group of the people, received any UVB radiation, VD1 group: people randomized in VD group plus the participants from the UV group who have refused irradiation UV (>3months): all participants having had UV exposure longer than 3 months, VD2 group: people randomized in the VD group plus all the participants from the UV group having had irradiation shorter than 3 months. Main analysis: VD1 - control group and UV (all) -intervention group, adjusted for the baseline of the outcome measures and skin type. Additional analysis: VD2 – control group and UV (>3months)) - intervention group, adjusted for the baseline of the outcome measures (Pg), the overall time effect (Pt) and the interaction effect of group and time (Pgt). The treatment effect is presented as adjusted mean difference (MD) between the VD and UV group for each time point with VD group as reference category.

Secondary outcomes

At three months, there were no within or between group differences in serum concentrations of 25(OH)D3 in the intervention or control group in either the main or additional analysis (Table 2 and 3). At six months, however, the serum concentration of 25(OH)D3 in both UV groups [UV(all) estimated mean 64.0 nmol/l (95% CI 54.3, 73.5) and UV (>3 months) estimated mean 64.6 (95% CI 57.7, 77.2)] was lower than in the VD groups [VD1 estimated mean 81.4 nmol/l (95% CI 74.8, 87.9) and VD2 estimated mean 79.6 nmol/l (95% CI 73.3, 85.8)]. The estimated difference between the mean scores was -17.5 nmol/l (95% CI -29.3, -5.7, p=0.004) and -15.0 nmol/l (95% CI -27.4, -2.5, p=0.019), respectively. The overall group effect estimating for the change in the difference between the two groups over the whole period was significant in the main analysis (p=0.037) but not significant in the additional analysis (p=0.076).

DISCUSSION

This post hoc analysis found no sustained effect of UV light compared to VD supplementation on blood pressure in nursing home residents with dementia aged 70 years and older. A reduction of blood pressure was seen in the UV group in the first month of treatment but was no longer observed at three and six months.

There are two frequently mentioned hypotheses regarding how UV light might influence blood pressure: the Vitamin D (VD) hypothesis and Nitric Oxide (NO) hypothesis. The VD hypothesis assumes that UVB light triggers the production of VD, which then exerts antihypertensive and vasculoprotective effects (33). Possibly this is an indirect mechanism which is a part of a complex process in maintaining blood pressure homeostasis. In our study the baseline levels of the serum 25(OH)D3 in the intervention and control group were comparable. After three months there was also not a significant change in serum 25(OH)D3 concentration in either groups. The reduction of blood pressure in the first month of the intervention in the UV(all) group cannot be explained with the VD-hypothesis. The NO hypothesis assumes that UVA mobilizes cutaneous NO stores (12) or NO from intracutaneous photolabile nitric oxide derivatives (13) to the systemic circulation, resulting in a rapid and direct effect of endothelial relaxation and subsequent vascular relaxation and vasodilatation. Mobilisation of NO stores from the skin to the circulation when irradiated by UV light might explain the reduction of blood pressure in the UV group during the first month of our study. However, the fact that this effect was not sustained in the following months of our study might be explained by the hypotheses underlying the mechanisms of development of tolerance to nitrates: the "metabolic" theory which suggests decreased activity of the NO released in the NO-induced vasodilatation (end-organ tolerance) and the "functional" theory highlighting the counter-

regulatory mechanisms marked by neurohumoral activation, increased catecholamine release, sodium retention and intravascular volume expansion. (34, 35). Moreover, the old and frail condition of the nursing home residents in our study may have also influenced the depletion-repletion kinetics of the cutaneous NO pool. Our study population was also normotensive to mildly hypertensive (according to the definition of the European Society of Cardiology (36)), with 45.4% of the participants in the UV group and 30.8 % in the VD group using antihypertensive medication, which can trigger cardiovascular and central regulatory mechanisms that further limit blood pressure reduction.

We only hypothesize but we do not know why the effect of UV light on blood pressure reduction in our study was of a short duration. People with hypertension have frequently endothelial dysfunction and decreased NO synthesized from the vascular endothelium (37). Using the cutaneous release of NO in controlling blood pressure is an attractive option. NO is a multipotent molecule which stimulates a cascade of reactions which result in vasodilatation of vascular smooth muscle cells, prevention of platelet adhesion and aggregation and a range of anti-inflammatory and anti- proliferative reactions preventing atherosclerosis (38) . Having in mind the above mentioned mechanisms which might have determined the short duration of UV effect on blood pressure, it is interesting to replicate the study in a group of younger (better depletion-repletion kinetics) and hypertensive patient's not using medication (to possibly avoid the counterregulation). For old people with dementia using antihypertensive medication and going outside more frequently, it might be relevant to check blood pressure in the summer months and eventually consider to stop or reduce the medication. Although patients with dementia have no increased vulnerability to blood pressure lowering treatment (39) and a good control of blood pressure may prevent disability from stroke (40, 41), maintaining the 150-130 mmHg on-treatment systolic blood pressure values are the safety range for optimal physical and cognitive functioning (42-44).

A major strength of this post hoc analysis was the use of repeated measurements for the outcome variables of participants. We had a control group and the participants were randomized at random initially. The randomisation that we used in the test situations created in the post-hoc analysis was not based on selection on the outcome variables. We used mixed linear model analysis which provides the flexibility of modelling not only the means of the data but their variances and covariances as well. We have also corrected for the baseline measurements. With the linear mixed modelling we looked at the difference in the changes between the control and intervention group, but we used also the parametric test for controlling for the within group changes.

This post-hoc analysis has some limitations. We used data of our RCT for a secondary data analysis. Blood pressure measurements were taken from patients' files and not measured

according to a standardized protocol, a single measurement was performed per time point. We had also missing data which was partially mitigated carrying out a linear mixed model analysis, corrected for baseline blood pressure. The number of the participants was small (wide confidence intervals for the findings) and the study may have had limited power to detect a clinically important difference between the intervention and control group. We had no data on the natural UV exposure time and dietary vitamin D.

CONCLUSION

This post hoc analysis found a short-term effect (at one month) but not a long term effect (at three and six months) of UV regarding systolic and diastolic blood pressure reduction in a VD-sufficient population of nursing home residents with dementia. Future larger studies with an RCT design should investigate the effect of UV in both the short and long-term and also in different populations (VD-sufficient vs. VD-insufficient, hypertensive vs. normotensive). This will contribute to understand better the association between ultraviolet light and hypertension and the role of sun exposure as a modulator in CVD risk management which is of crucial importance for the population of frail older people who are particularly deprived of sun exposure.

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Table A1 Characteristics of the participants at baseline by study group (additional analysis)

Variable	UV (>3 months) (n=13)	VD2 (n=48)	p-value
Gender %, (n)			
male	15.4 (2)	37.5 (18)	0.13 [a]
female	84.6 (11)	62.5 (30)	
Age in years, mean (SD)	84.6 (6.5)	83.8 (7.1)	0.75 [b]
Fitzpatrick skin scale %,(n)			
1.always burns easily, never tans	0	2.1 (1)	0.13 [c]
2.always burns easily, tans slightly	53.8 (7)	70.8 (34)	
3.burns moderately, tans gradually	38.5 (3)	25 (12)	
4.burns minimally, tans moderately	0	0	
5.rarely burns, tans profusely	7.7 (1)	2.1 (1)	
6.never burns, tans profusely	0	0	
Dementia severity, mean BANS-S (SD)	14.9 (4.5)	15.9 (4.8)	0.50 [b]
Baseline blood pressure, mmHg			
Systolic, mean (SD)	143.4 (26.1)	131.4 (22.4)	0.32 [b]
Diastolic, mean (SD)	75.5 (10.5)	74.9 (13.5)	0.56 [b]
Using antihypertensive medication %,(n)	46.2 (6)	33.3 (16)	0.39 [a]
Serum 25(OH)d3 levels, nmol/l, mean (SD)	65.2 (17.4)	78.3 (31.8)	0.04 [b]

Chapter 7

General discussion

Observational studies have found associations between low vitamin D levels and a wide range of serious outcomes, including cardiovascular disease, malignancies, diabetes, autoimmune diseases and higher mortality [1-8]. Furthermore, randomized control trials, meta-analyses and Mendelian studies have confirmed the effects of vitamin D supplementation on bone health, hypertension risk, acute respiratory infections and mortality in populations with very low vitamin D levels [9-16]. However, there is increasing evidence that sun exposure may exert its positive effects on human health via mechanisms other than vitamin D synthesis alone. Sunshine appears to protect against several types of cancer, cardiovascular disease and autoimmune diseases [17-19], as well as positively influencing mood, depressive disorders and well-being [20]. As many people aged 70 years and over are both vitamin D deficient and sun-deprived, the potential for health problems is obvious [21, 22]. In this thesis we therefore explore the utility of vitamin D in older people, focusing on supplementation strategies and the possible additional effects of ultraviolet light beyond vitamin D synthesis, with the aim of improving the well-being and quality of life of nursing home residents with dementia

MAIN FINDINGS OF THE STUDIES PRESENTED IN THIS THESIS:

1) Of the 71 participants in a cross-sectional study (all nursing home residents with dementia, mean age of 83), 19 used cholecalciferol drops and 52 used cholecalciferol capsules. Mean serum 25(OH)D was 77 (SD 30) nmol/L and 55 residents (78%) were vitamin D sufficient. Among capsule users, mean serum 25(OH)D was 90 (SD 22) nmol/L (considerably higher than the expected 50 nmol/l), and 49 (94%) were vitamin D sufficient. Among users of drops, mean serum 25(OH)D was 41 (SD 8) nmol/L and only 6 (32%) were vitamin D sufficient (Chapter 2).
2) Our survey of the vitamin D prescribing behaviour of elderly care physicians (ECPs) and general practitioners (GPs) in the Netherlands for persons aged 70 years and over shows that most ECPs (94.2%) and more than a third of GPs (34.0%) prescribed vitamin D systematically (consistent with the guidelines) to their patients aged ≥70 years; a comparison with 2010 showed an increasing trend towards prescribing vitamin D supplements (Chapter 3).
3) Our systematic review of clinical trial and observational study evidence on the effects of ultraviolet light on mood, depressive disorders and well-being found that of the seven studies included, six showed a positive effect of UV light on domains of psychological health, suggesting a positive correlation between ultraviolet light and an improvement of mood (Chapter 4).
4) Half-body ultraviolet irradiation for six months in nursing home residents with dementia is not superior to oral vitamin D supplementation as regards well-being measured with the

Cornell depression scale and Cohen-Mansfield agitation inventory. However, ultraviolet light has a positive effect on restless/tense behaviour after six months of intervention (Chapter 5).

5) Compared to vitamin D supplementation, ultraviolet light has a short-term effect on blood pressure (evident at one month but not at three and six months) in a normotensive to mildly hypertensive population of nursing home residents (Chapter 6).

Vitamin D supplementation in older people: treatment or prevention of vitamin D deficiency?

Dietary reference values for vitamin D

Dutch dietary reference values for vitamin D were published in 2000 and then again in 2008, and set adequate vitamin D intake for people 70 years and over at 10 µg per day (400IE) [23]. In 2012, a committee of experts at the Dutch Health Council issued a re-evaluation of the 2008 dietary reference values on the basis of the most recent scientific evidence. For those aged 70 years and over, the committee concluded that previous recommendations may have been too low [24]. This may be related to inadequate sun exposure. It is generally assumed that two-thirds of vitamin D is derived from production in the skin following sun exposure and one third from dietary intake [24]. In the Netherlands, sunlight-induced vitamin D production in the skin is only possible in the period March to November, and requires exposing (bare) hands and face to the sun for 15-30 minutes between the hours of 11.00 and 15.00.

Foodstuffs rich in vitamin D include oily fish, liver, meat, eggs and dairy products. Owing to limited mobility and co-morbidities, the amount of sun exposure and dietary intake of vitamin D amongst older people are both often insufficient. As a consequence the Dutch Health Council now advises supplementation in this particular group, with dietary reference values set at 20 µg (800IE). These dietary reference values encompass total theoretical vitamin D supply from both diet and sunlight to help ensure that (almost) all persons aged 70 and over achieve the target value. The target value for serum 25(OH)D is a concentration of 50 nmol/l, which in older people is regarded as protective with regard to bone health and falls among the very frail.

Dietary reference values are a screening instrument designed to prevent vitamin D deficiency rather than treat it, and the values apply to healthy individuals. Vitamin D metabolism and its conversion to the active form are dependent on the correct functioning of several organs and on the availability of a number of enzymes and active substances. Impairment in the functioning of skin, intestines, liver, kidneys or cells of the immune system, as is frequently the case in older people, can lead to vitamin D deficiency, and it is not clear that supplementation at vitamin D levels suitable for healthy people actually improves the health of older persons. Older people are also likelier to use medications that can potentially influence the production

of 25(OH)D in the liver, such as antiepileptics (carbamazepine, oxcarbazepine, phenytoin, phenobarbital), immunosuppressants (corticosteroids) or diuretics (thiazides).

Dietary vitamin D reference values applied to frail people

In **chapter 2** we describe a cross-sectional study in nursing home residents. In this study we investigated the efficacy of daily vitamin D supplementation for at least three months, at a dose of 20 µg (800 IE) in the form of capsules or drops. We also collected data on various factors that may influence serum 25(OH)D levels, including age, co-morbidity, number and sort of medication use, body mass index (BMI), sun exposure, modification of diet in renal disease (MDRD) and Functional Ambulation Classification (FAC) scores as an assessment of mobility. We found that in most residents (94% of residents had a mean serum 25(OH)D concentration of 90 nmol/l, SD 22) vitamin D supplementation once a week with cholecalciferol capsules containing 5600 IU (equivalent to 800 IU daily) resulted in vitamin D sufficiency (serum 25(OH)D ≥ 50 nmol/L). Our results show that Dutch Health Council advice concerning vitamin D supplementation in people 70 years and older is adequate to maintain vitamin D sufficiency and is also applicable to the most frail people if cholecalciferol capsules are used.

The baseline concentration of serum 25(OH)D in our research population was not determined, but from literature we know that nursing home residents are almost universally vitamin D insufficient without vitamin D supplementation [21, 22]. The results of our study show that the supplementation strategy proposed by the Dutch Health Council for maintenance of vitamin D sufficiency in older people can also be used effectively in the treatment of vitamin D deficiency (serum 25(OH)D < 30 nmol/L) and insufficiency (serum 25(OH)D > 30 < 50 nmol/L) in this population. Endocrine Society clinical practice guidelines recommend a dose of 50 000 IU of vitamin D once a week for eight weeks followed by 800-1000 IU/day maintenance therapy for treatment of vitamin D deficiency and insufficiency [25]. In obese patients and patients on medications that affect vitamin D metabolism, the American Geriatrics Society and the Endocrine Society suggest use of even higher doses of vitamin D [25, 26]. However, in our study we found no association between BMI, renal function, number and kind of medication and 25(OH)D status. It seems possible that a daily dose of 800 IE vitamin D, the dietary reference value defined by the Dutch Health Council, is enough to both prevent and treat vitamin D deficiency and insufficiency in all patients aged 70 years and above, independent of any health condition (excluding patients with malabsorption syndromes. Similarly, in a study by Chel et al. [22], recommended preventive supplementation of vitamin D (600 IE or 800 IE daily, or 4200 IE or 5600 IE weekly) achieved vitamin D sufficiency in 90-94 % of deficient or insufficient older people after 3-4 months. More research in larger groups of patients is needed to confirm this finding. An accepted standard for supplementation doses of vitamin D in this population subgroup would make implementation easier and cheaper.

Towards an adequate intake of vitamin D

In **chapter 3** we explored the vitamin D prescribing behaviour of elderly care physicians (ECPs) and general practitioners (GPs) in the Netherlands using a survey approach. The study found increased awareness in these two physician groups of the importance of vitamin D supplementation in older people when compared to the results of a similar study carried out in 2010 [27]. In our study 94.2% of the ECPs and 34% of the GPs prescribed vitamin D systematically (consistent with guidelines) to their patients aged 70 years and over. In nursing homes in the Netherlands vitamin D supplementation is regarded as the standard of care because it is widely appreciated that almost all nursing home residents are vitamin D insufficient without supplementation. The prescribing behaviour of GPs is less consistent, which is possibly related to the heterogeneity of their specific older patient population, which ranges from fit and active to very vulnerable people. GPs frequently order blood tests (49.5%) to assess serum 25(OH) D before they start supplementation or when they are unsure of the utility of vitamin D supplementation (36%). This is likely related to current ambiguity of the literature concerning guidance of vitamin D supplementation.

Untreated vitamin D deficiency in older people can have serious health consequences [10, 23, 28, 29]. There are two approaches to the prevention and treatment of vitamin D deficiency and insufficiency: population or individual. The population approach entails vitamin D supplementation in an entire group of people vulnerable for vitamin D deficiency or insufficiency. An individual-based approach targets individuals with vitamin D deficiency or insufficiency. Choosing a population-based approach in the 70 years or older group is supported by solid evidence from observational studies and clinical trials, and many studies point to a vitamin D threshold below which disease risks increase and vitamin D supplementation shows beneficial effects [30].

As already mentioned, vitamin D deficiency has a high prevalence in older people. In the Longitudinal Aging Study Amsterdam (LASA), of the 1311 community-dwelling older persons tested for serum 25(OH)D levels, 48.4 % were vitamin D insufficient (25(OH)D < 50 nmol/l) and 11.3% were vitamin D deficient (25(OH)D < 25 nmol/l) [31]. In a German study of 1418 community-dwelling older people aged ≥65 years, the proportions of vitamin D deficiency, insufficiency and sufficiency were respectively 78.8, 19.2 and 1.9% in March, compared to 16.1, 63.4 and 20.5% in Augustus [32]. Vitamin D insufficiency is very common in community-dwelling older people and shows a strong seasonal pattern. This public health issue in this specific risk group argues for a population-based approach, and the proposed solution is in line with Dutch Health Council advice [24] and has a favourable cost-benefit ratio [30]. Concerns related to exceeding the tolerable upper level intake limit are unfounded, as the recommended levels of supplementation are significantly lower than tolerable upper intake levels for adults (100 µg per day per person). International research data and data from the National Institute

for Public Health and Environment (RIVM) suggest that sunlight exposure in the Netherlands leads to the production an average of 6-7 µg of vitamin D per day. In an evaluation report of dietary reference values for vitamin D, the Dutch Health Council stated that the mean vitamin D intake from foods in the age group between 7 and 70 years is 2.3 to 4.1 µg for men and 2.3 to 3.2 µg for women in the Netherlands. In conclusion, even in the case of people with a good vitamin D intake, sufficient sun exposure and vitamin D supplementation, the daily intake would still be much lower than the tolerable upper level. For older people with sufficient sun exposure and vitamin D intake, an estimated average requirement of 10 µg (400 IE) per day will ensure that the target level of 50 nmol/l serum 25(OH)D is reached independently of any medication used, BMI, co-morbidity, kidney or liver function [24].

With an average primary care visit only lasting 13-16 minutes, time to adequately address topics such as vitamin D supplementation may be limited, particularly in complex cases. To reduce costs and lengthy visits, a useful addition to the GP's electronic dossier may be a computer-aided reminder for when a patient turns 70 and an automatic message that includes a prescription and patient information leaflet covering the use of vitamin D. Special care should be taken regarding patients suffering from granuloma-forming disorders such as sarcoidosis, tuberculosis, chronic fungal infections or primary hyperthyroidism, as these patients should be monitored for serum calcium levels [25]. Another possible option is to assign the vitamin D supplementation program to the Municipal Health Services.

Effect of ultraviolet light and vitamin D on well-being and quality of life in people with dementia

Following the discovery by Niels Ryberg of the curative effect of ultraviolet (UV) light on lupus vulgaris (a skin variant of tuberculosis), additional beneficial effects of sunlight have been documented in the scientific literature. Human and animal studies have shown that exposure to ultraviolet light can incite a chain of endocrine, immunologic and neurohumoral reactions that affect mood and hence quality of life [33-36]. To collate evidence from observational studies and clinical trials concerning the effect of ultraviolet light on mood, depressive disorders and well-being, we carried out a systematic review **(chapter 4)**. Of the seven studies included, six showed a positive effect of UV light on domains of psychological health. Extrapolating from this review, we suggest that ultraviolet light and mood show a positive correlation. However, due to the small number and heterogeneity of studies more research will be needed to confirm and further document this correlation.

Consequently, we conducted a multicentre randomized controlled trial **(chapter 5)** focused on the effect of ultraviolet light and vitamin D supplementation on the well-being and quality of life of nursing home residents with dementia. We considered well-being as the personal aspect of the multidimensional concept 'quality of life', as recent research has shown that mood and

behavioural problems are important predictors of quality of life among nursing home residents with moderate to severe dementia [37]. During the observation period of six months, our study showed no significant between-group differences regarding agitation or symptoms of depression. However, at six months the group receiving ultraviolet light showed less restless/tense behaviour compared to the vitamin D group. Discussing possible explanations for these results, we highlight potential mechanisms through which ultraviolet light affects mood and well-being.

A possible mood-modulating effect of UV light via the skin is mediated by the vitamin D pathway

The major source of vitamin D for humans is exposure of the skin to sunlight (UVB 280-315 nm), resulting in the conversion of 7-dehydrocholesterol to previtamin D3. The recent discovery that the human brain also possesses vitamin D receptors indicates that mood and depressive disorders might be directly influenced by vitamin D deficiency [38, 39]. Indeed, many observational studies have reported a significant negative correlation between 25(OH)D levels and depression in people ≥60 years [29, 40-44].

In our RCT **(chapter 5)**, both the vitamin D group and the UV group were vitamin D-sufficient, which may explain the lack of an additional effect of the interventions on mood and well-being. However, a recent meta-analysis found no evidence of an effect on depression in adults with vitamin D supplementation [45]. In a study by Knipperberg et al., participants with multiple sclerosis reported their levels of sun exposure and that was inversely correlated with depression, the magnitude of the effect of sun exposure on depression remained also stable when 25(OH)D3 was included in the model [46].

A possible mood-modulating effect of UV light via the skin is mediated by the other pathway than vitamin D synthesis alone

Other pathways that may be triggered by UV light to modulate mood and act through skin exposure involve three local systems: (i) the skin analogue of the hypothalamic-pituitary-adrenal (HPA) axis,[33] (ii) the serotoninergic/melatoninergic system [34], and (iii) the immune system [35, 36]. These pathways are assumed to interact with systemic mechanisms of body homeostasis [35]. There is an increasing literature on molecular mechanisms that may play a role in depression [47]. Depression is characterized by slightly increased cerebrospinal fluid (CSF) concentrations of several pro-inflammatory cytokines [48], and pro-inflammatory cytokines in turn enhance the activity of indoleamine 2,3-dioxygenase, the first rate-limiting enzyme of tryptophan degradation. Increased tryptophan degradation can induce serotonin depletion and depression. The above mentioned mechanisms of UV action on the skin, immune and nervous system may impact the systems underlying depression and help establish a new balance. This was indeed observed in studies by Edstrom et al. [49], Knippenberg et al.

[46] and Pudikov et al. [50], in which the mean age [interquartile range (IQR)] of participants was 54 (48-59), 48 (37-59) and 36 (24-42), respectively. However, this was not the case in our study **(chapter 5)**. One possible explanation for this inconsistency is the very different age and co-morbidity of the participants in our study: people with dementia and a mean age 84 (IQR80-88). Overall, late-life depression has distinctive features that differentiate it from depressive disorders occurring at younger ages, and it is accompanied by subcortical vascular changes and hippocampal atrophy [51]. Thus depression in old age, and especially in dementia, is characterized by not only molecular changes in comparison to younger age depression but also structural changes in the brain. Confirmation of this difference came when well-controlled studies, systematic reviews and meta-analyses found no reliable or convincing efficacy for antidepressants in patients with dementia and co-occurring depressive disorders [52, 53].

The lack of an observed effect on agitation in our study, in either group, may also be associated with the multifactorial character of the agitation experienced by people with dementia. Agitation often occurs in the cognitively impaired and is a collection of symptoms that may reflect an organic psychiatric disorder (e.g. dementia), a medical illness, an adverse effect of medication or it may be secondary to insecurity, frustration, fears or misperceptions produced by impaired hearing, sight or aphasia. For the treatment of this multifactorial problem a more complex approach is likely needed

In our study, the participants allocated to the UV group showed a decrease in restless/tense behaviour after six months of treatment. This may be due to the effects of UV on the skin and the local production of serotonin, cytokines and beta-endorphin which together promote a feeling of well-being, boost the immune system, relieve pain and improve relaxation [33, 34, 54]. In a study by Gamblichler et al., UVA-exposed volunteers felt significantly more balanced, less nervous and strengthened after three weeks of UVA exposure twice a week. Following the first UVA exposure, serum serotonin was significantly higher and serum melatonin significantly lower compared to before exposure.

In reference to methodological considerations, discussed in details later in this thesis, there were some practical problems during our randomized controlled trial in terms of the variable adherence of nursing home residents to UV treatment. If this could be solved by finding a more satisfactory manner of administering UV light treatment, this intervention might be a good complementary therapy for restless/tense behaviour and improve the quality of life of older people with dementia. A replication of this RCT is warranted to confirm these findings.

Effect of ultraviolet (UV) light and vitamin D supplementation on blood pressure in people with dementia

UV type A from sun exposure is known to increase circulating nitric oxide, which in turn decreases peripheral resistance [55, 56]. Vitamin D may also influence blood pressure by correcting abnormalities in calcium homeostasis and regulating the renin-angiotensin system [2, 9]. In **chapter 6** we focused on the comparative effects of UV light versus vitamin D supplementation in relation to blood pressure reduction. The light emissions used in our study consisted of UV light A and B, which ensured production of vitamin D, allowing us to estimate additional effects of ultraviolet light on blood pressure over and above the effect of vitamin D.

We conducted a post-hoc analysis of a randomized controlled trial to assess differences in blood pressure changes between persons with dementia receiving UV light versus vitamin D supplementation. This post-hoc analysis showed only a short-term (at one month) effect of UV light on blood pressure reduction compared to vitamin D use in a vitamin D sufficient population of nursing home residents. This might be due to regulatory and counterregulatory mechanisms or to the depletion-repletion kinetics of active substances in the skin, or to increased resistance of the end target organs to these substances. In addition to these biological mechanisms, the small sample size in our study could have influenced the results. This is discussed further in the section on methodology.

Our results are in line with most other studies carried out to examine the effect of UV light on blood pressure [55-57], but none of these studies were designed to observe the long-term effects of this intervention. Future studies should investigate the effect of UV light on blood pressure in larger groups of people, over longer timeframes and in different populations (vitamin D sufficient vs. vitamin D insufficient, hypertensive vs. normotensive, young vs. old). A range of different ultraviolet light exposure regimes should be studied, including UV type A, UV type B and a combination of both in order to assess if this treatment is likely to be beneficial.

Thus far, solid evidence from large observational studies indicates that sun exposure can be a potentially beneficial environmental factor in the maintenance and regulation of blood pressure [18, 58, 59]. These observational studies had large sample sizes, long follow-up and community-based sampling, which together increases their external validity. However, the studies also had limitations regarding measurement error in the determination of sun exposure, as the hours of sun exposure were not always documented. Based on studies with adequate documentation of daily hours of sun exposure, it appears that insufficient exposure to UV radiation and/or active avoidance of sunlight may be a new risk factor for hypertension.

Amongst community-dwelling frail older people who may be particularly deprived of sun exposure, it is important to implement public health care programs that encourage people to go

outdoors and carry out outside activities. Besides environmental factors such as sun exposure, time outdoors has other positive effects that can influence blood pressure such as decreased stress, greater physical activity and a greater likelihood of social contact [60].

For nursing home residents with dementia, the passive and active use of green gardens can be a feasible and applicable option when caregivers, disciplines, managers, relatives and volunteers are involved, motivated and well-trained [61].

Methodological considerations of the randomized controlled trial

Blinding of the trial

Even while writing the protocol for the RCT "The Effect of Ultraviolet B Irradiation Compared with Oral Vitamin D Supplementation on the Well-being of Nursing Home Residents with Dementia", we were aware that blinding of the trial was impossible. We also choose not to use cluster randomisation because each nursing home included in the trial had its own program for improving resident's quality of life, a factor that might have negatively influenced the results. Excepting exposure to the intervention, we aimed to ensure that all other circumstances remained the same.

Blinding participants to the treatment was logistically difficult. The nursing home residents who participated in the trial received an explanation of the aims of the trial and expectations of the treatment. As all participants had dementia, it was not possible to be certain that they understood and remembered this information by the time of the UV light sessions.

Nursing staff were not blinded, as they administered the medication and intervention, and completed the questionnaires.

Adherence of Nursing Home Residents to the Intervention

Neglecting to examine adherence and its impact on outcome can compromise the interpretation of research finding and lead to inappropriate recommendations and decisions regarding the use and implementation of an intervention. In our study we therefore analysed the adherence of nursing home residents to the UV intervention, the methods used to partially solve problems of adherence and how adherence was related to outcomes.

A recognizable problem in our study was the variable adherence of nursing home residents to UV light treatment. Twelve of the participants (30%) in the UV group refused to adhere to the intervention procedure for a variety of reasons, including an unwillingness to remove clothes or to wear protective glasses, feeling cold or anxious, not understanding the purpose of the procedure or being unable to lie quietly on a bed during UV exposure. Furthermore, 19% of the participants joined the sessions only for the first three months and 41% continued for more

than 3 months, while 28% seemed to find the sessions pleasant and reinforcing according to nursing staff. Given the marked difficulties in adherence, and particularly the fact that those who disliked UV treatment were started on vitamin D supplementation, per protocol analysis results were also interesting. In view of the variable duration of exposure and keeping in mind sample size, we considered participants as "treated" following any duration of UV exposure, only allocating participants to the vitamin D control arm when they refused treatment. This additional analysis showed the same results for the main outcomes as the intention-to-treat analysis.

Missing data

As some participants inevitably passed away due to dementia during the course of the study, we had some missing data. When designing the study, we calculated that 56 participants would be needed to provide an 80% probability of detecting a mean between-group difference of 10 points on the CMAI. Taking into account the vulnerability and high mortality rates in this population, we chose to recruit 78 participants. Ultimately, 52 of the participants could be included in the analysis at the 6-month time point, equating to 93% of our original power estimate (5256*100% = 93%). Furthermore, we chose a linear mixed model as a bias-reducing analysis. The alternative was a complete case analysis, but this has drawbacks such as substantial loss of information and adverse effects on precision and power [62, 63]. In the linear mixed model, using direct likelihood analysis, we used the observed data without deletion or imputation. In doing so, appropriate adjustments valid under MAR (missing at random) were made to parameters at times when data were incomplete due to within-patient correlations. We did not use multiple imputations because this has advantages when both outcomes and covariates are missing and in our case only outcome data were missing.

Methodological considerations of the post-hoc analysis

We carried out a post-hoc analysis of the randomized controlled trial data with the aim of assessing differences in blood pressure change between persons with dementia receiving ultraviolet light versus vitamin D supplementation. One of the limitations of this post-hoc analysis was the technique of blood pressure measurement. Data obtained from the medical records of the nursing home residents were monthly pragmatic blood pressure measurements (1 measurement per time) rather than the standardized method for automated blood pressure measurement (the average of 3 measurements taken after 5 minute breaks) [64]. Another source of uncertainty was the power of the post-hoc analysis. The sample size of the RCT, which data were used for the post-hoc analysis, was calculated on the basis of Cohen-Mansfield Agitation Inventory. We did not calculated the power of the post-hoc analysis which primary outcome was the difference in blood pressure between intervention and control group. Power analysis used to indicate power for outcomes already observed does not provide sensible results

[65]. In addition, the lack of a statistical difference in blood pressure between the vitamin D and UV groups might have been due to the small size of our study.

CONCLUSIONS:

1. Vitamin D supplementation using cholecalciferol capsules containing 5600 IU once a week (equal to 800 IU daily) results in vitamin D sufficiency (serum 25(OH)D ≥50 nmol/l) in a population of nursing home residents regardless of gender, age, BMI, renal function, sun exposure, comorbidity, medication or mobility status.
2. Vitamin D prescribing behaviour of elderly care physicians and general practitioners in the Netherlands in relation to persons aged 70 years and over indicates an increasing awareness of the importance of vitamin D supplementation in older people.

General practitioners need more guidance regarding their prescribing behaviour due both to their often heterogeneous patient population and contradictions in international guidelines.

3. Compared to vitamin D supplementation, the effect of ultraviolet light showed no improvement of the well-being in general after UV irradiation in nursing home residents but improvement of some aspects of quality of life such as restless /tense behaviour.
4. Ultraviolet light has a short-term effect, reducing systolic and diastolic blood pressure in a vitamin D sufficient population of normotensive to lightly hypertensive nursing home residents with dementia.

RECOMMENDATIONS

1. In nursing homes residents, vitamin D supplementation with capsules (800 IE per day or 5600IE per week) is sufficient to reach a serum concentration of 50 nmol/l 25(OH)D3.
2. The data presented in this thesis and a solid evidence from large observational studies indicate that ultraviolet light may have effects beyond the synthesis of vitamin D in nursing home residents who are especially sun-deprived.

a. We recommend implementation of a public health care program that encourages outdoor activities by older people, even for (very) frail older people. Balanced sun exposure can ensure the production of vitamin D, promote relaxation of stress and improve cardiovascular and neuroendocrine regulation, all of which contribute to health and well-being. Technically approved sunbeds with appropriate ultraviolet exposure schedules can be used in the winter months and for very frail people who cannot go outdoors. The use of sunbeds by nursing home residents with dementia highlighted certain practical problems, including feeling cold, anxious, being unable to lie still or being unable to understand the purpose

of the procedure. Future research efforts in this field should first attempt to find more satisfactory approaches to administering ultraviolet light.

b. It will be interesting to reproduce our trial on the effect of ultraviolet light compared with oral vitamin D supplementation on the well-being of nursing home residents without cognitive impairment.
c. Checking up blood pressure and adjusting medication in de summer by older people with antihypertensive medication and going outside more frequently might be relevant because the possible reducing effect of UV on blood pressure
d. Further research is needed on the effect of ultraviolet light on blood pressure in a larger population sample that includes hypertensive older people, to evaluate if a more sustained effect can be reached using this intervention.

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Chapter 8

Summary

Vitamin D is a regulating hormone that modulates multifactorial processes, helping to ensure the balance and maintenance of human health. Just a few of these processes include sustaining bone mineral homeostasis, body balance, anticancer activity, blood pressure and the regulation of immunity. Most cells and organs in the human body express vitamin D receptors, but below a certain threshold (25(OH)D3 - the vitamin D metabolite that best reflects vitamin D serum concentration) vitamin D is unable to exert its effects. In general, a serum concentration of 50 nmol/l is accepted as vitamin D sufficiency, although it is unclear whether this figure can be generalized to all clinical outcomes. Factors such as age, liver and kidney function, medication and body mass index (BMI) all influence vitamin D serum concentrations in the human body.

Vitamin D deficiency (serum 25(OH)D3 < 30 nmol/l) and insufficiency (serum 25(OH)D3 > 30 nmol/l<50 nmol/l) are both common in older people and are mediated by factors such as a reduction in mobility, more time spent indoors, a lower intrinsic skin response to UV radiation and a reduced dietary vitamin D intake. Almost all nursing home residents are vitamin D insufficient if vitamin D is not supplemented.

In addition to being a risk factor for dermatologic malignancies, observational and epidemiological studies suggest that sunlight may have positive effects on human health via mechanisms other than vitamin D synthesis alone. These effects may include prevention of some types of cancers, cardiovascular disease, autoimmune diseases and the improvement of mood disorders.

The aims of this thesis were to examine whether recommended vitamin D supplementation strategies are applicable to the most vulnerable population of people aged 70 years and over, and whether ultraviolet light has additional benefits (other than vitamin D synthesis alone) for the well-being, quality of life and blood pressure of vitamin D sufficient but particularly sun-deprived nursing home residents with dementia.

In **chapter 2**, we present a cross-sectional study designed to evaluate the efficacy of vitamin D supplementation in achieving vitamin D sufficiency. As advised by the Dutch Health Council, vitamin D sufficiency was defined as serum25(OH)D ≥50 nmol/l in vulnerable people 70 years and over, and the supplementation regime consisted of cholecalciferol capsules 5600 IE once a week or cholecalciferol drops, 3 drops (7500 IU) once a week.

The mean serum 25(OH)D concentration of capsule users was 90 nmol/l, and while no one in this group was vitamin D deficient (serum25(OH)D <30nmol/l), 6% was vitamin insufficient (serum25(OH)D<50 nmo/l> 30 nmol/l). The mean serum 25(OH)D concentration of those receiving drops was 41 nmol/l, 32% of whom were vitamin D deficient and 37% were vitamin D insufficient. Analysis of the baseline characteristics of those receiving capsules versus drops showed a significant difference in BMI between the two groups, with a higher number

of persons with overweight amongst those receiving drops. To search for predictors of low vitamin D concentrations (lower than 50nmol/l) we applied logistic regression analysis to the whole group of nursing home residents, but could not identify a significant trend for possible predictors of vitamin D insufficiency and deficiency apart from the use of vitamin D drops.

This study showed that weekly vitamin D supplementation with 5600 IU cholecalciferol capsules (equal to 800 IU daily) results in vitamin D sufficiency, regardless of gender, age, BMI, renal function, sun exposure, comorbidity, medication or mobility status.

In **Chapter 3**, we looked at the vitamin D prescribing behaviour of general practitioners (GPs) and elderly care physicians (ECPs) caring for people 70 years old and over, encompassing both community dwelling older persons and nursing home residents in the Netherlands.

Today, international guidelines and expert societies recognize the vitamin D deficiency pandemic in older people and the consequent health risks. However, their recommendations concerning vitamin D supplementation differ due to a lack of consensus in the scientific literature regarding the optimal serum vitamin D concentration and the most efficient approach to vitamin D supplementation: population-based or individual-based. In the Netherlands, the Dutch Health Council has chosen an unambiguous, population-based approach to vitamin D supplementation for people 70 years and older: daily supplementation with vitamin D 800 IU for everyone in this group.

We carried out a Netherlands-based survey using either the Survey Monkey Platform or a general information letter sent to 1685 ECPs. In addition, we approached 310 GPs with the same questions during a vocational training day. To identify a possible trend in vitamin D prescription we compared these results to a survey carried out in 2010. Analysis showed that 79% of ECPs and 71% of GPs had a good understanding of the vitamin D guidelines. In comparison to the earlier survey, there was an increasing awareness of the importance of vitamin D supplementation in older people, with 94% of ECPs and 34% of GPs systematically prescribing vitamin D to their patients aged 70 years and older. Uncertainty in the prescribing behaviour of GPs was attributed to the heterogeneity of their patient population, ranging from the healthy and active to frail people with significant comorbidity. Half of all GPs claimed to regularly monitor serum 25(OH)D before starting supplementation.

In **chapter 4**, we describe our systematic review of literature on the effect of ultraviolet (UV) light, when applied to the skin or eyes, on mood, depression and well-being. A PICO (population, intervention, control, and outcome)-based search strategy was carried out in the following bibliographic databases: PubMed, Embase, Web of Science, Cochrane, Psychinfo, CINAHL, Academic Search Premier and Science Direct. Finally, seven studies were selected as eligible

for this literature review: one observational study and six clinical trials. Participants in the selected studies were healthy volunteers, patients with fibromyalgia syndrome, dermatological conditions, multiple sclerosis or seasonal affective disorders.

Two of the studies examined the effect of UV light applied to the skin on mental state, finding significant improvements in mood. Five of the studies investigated the effect of UV light applied to the skin or eyes on depressive symptoms and seasonal affective disorders in participants with or without depressive disorders. Four of the five studies showed a positive effect on depressive symptoms.

Though the overall effect of UV light intervention on mood and depressive symptoms was positive, the small number of studies and certain methodological problems make drawing general conclusions difficult.

In **Chapter 5**, we present the results of our randomized multicentre controlled trial on the effect of ultraviolet B (UVB) irradiation versus vitamin D (VD) supplementation on the well-being of nursing home residents with dementia. Participants were recruited from three nursing homes in the Netherlands connected to the University Network for the Care sector South Holland (UNC-ZH), and the intervention consisted of half-body UVB irradiation with 1 standard erythema dose of 8 minutes, twice a week. The control group received VD capsules (5600 IU cholecalciferol weekly). At baseline and after three and six months, the participants in both arms were evaluated on the primary outcome, wellbeing, monitored with the CMAI (Cohen-Mansfield agitation inventory) scale and Cornell scale for depression in dementia. Secondary outcomes were quality of life monitored with QUALIDEM (shortened version) and biochemical parameters of bone homeostasis such as VD serum concentration, creatinine, parathyroid hormone (PTH), calcium and phosphate.

Seventy-nine nursing home residents participated in the study. There were no significant differences between baseline characteristics of the intervention and control groups, apart from VD concentration which was higher in the vitamin D group (p=0.04). No significant between-group differences were found regarding agitated behaviours or depressive symptoms for the UVB and VD groups, either at 3 months or 6 months from the start of treatment. Interestingly, at six months the UVB group showed less restless/tense behaviour (maximal score on the scale 9) compared to the VD group. The difference in estimated means (adjusted for other variables in the model) over time was 2.2 (95% CI 0.8 to 3.6). There was no difference in biochemical parameters at three months between the two groups, although at six months VD serum concentration was higher in the VD group (difference in means -21.9; 95% CI –32.6 to –11.2). We concluded that the exposure of nursing home residents with dementia to UVB light showed no positive benefits in terms of wellbeing. UVB treatment may have a positive

effect on the restless/tense behavioural characteristics of advanced dementia, but more research is needed to confirm this finding.

In **chapter 6**, we examined the effect of ultraviolet (UV) irradiation versus vitamin D (VD) supplementation on blood pressure in a particularly sun-deprived population, nursing home residents with dementia.

Cardiac output and peripheral resistance are the determinants of arterial blood pressure. Ultraviolet A light from sun exposure is known to increase circulating nitric oxide, which results in a decrease in peripheral resistance. VD may also effect blood pressure through the correction of abnormalities in calcium homeostasis and regulation of the renin-angiotensin system.

This study consisted of a post-hoc analysis of medical records detailing the blood pressure measurements of participants in the randomized control trial described in chapter 5. The participants (N=61, 41 women, mean age 84.8 years) received half-body UV irradiation for 8 minutes twice weekly or 5600 IU of cholecalciferol once a week over 6 months. Short-term effects were evaluated after 1 month and long-term effects after 3 and 6 months. Differences in blood pressure changes were assessed using linear mixed models. The baseline characteristics of both groups did not differ significantly. After one month of treatment the participants in the UV group had a lower blood pressure, with a difference between the two groups of – 23 mmHg (95% CI -37.1, -10.1, p=0.001) in estimated mean systolic blood pressure and – 9.5 mmHg (95% CI -9.8, -4.4, p=0.001) in diastolic blood pressure, with VD group as reference. At three and six months there were no significant between-group differences in either systolic or diastolic blood pressure.

We concluded that UV light has only a short-term effect on blood pressure reduction compared to VD supplementation in this sample of normotensive to mild hypertensive nursing home residents with dementia.

The general discussion in **chapter 7** outlines the main findings of this thesis. We deliberate on the topic of vitamin D supplementation in older people in light of the current guidelines and on the possible additional effects of ultraviolet light beyond vitamin D synthesis on nursing home residents. The most recent guidelines advise more research on the cut-off that defines vitamin D deficiency and whether it varies by specific clinical outcome. Nevertheless, it is well known that the physiology of aging makes older people particularly susceptible to vitamin D deficiency and that, if untreated, it can have serious health consequences. We also discuss the different supplementation strategies for nursing home residents and community dwelling persons aged 70 years and older.

We then elaborate on the effects of ultraviolet light on the well-being of nursing home residents. Our findings showed no improvement in the general well-being of nursing home residents after UV irradiation but some aspects of quality of life such as restless/tense behaviour showed improvement. We assume that reduced well-being in dementia is a multifactorial problem that requires a broader approach.

Our findings regarding decreased blood pressure in the first month of UV light treatment in normotensive to mildly hypertensive nursing home residents with dementia raise three issues for future research: 1) our study might have lacked sufficient power to detect more subtle changes in blood pressure at three and six months, 2) older people on hypertensive medication may need adjustment of medication during the summer months, and 3) UV light might have a positive effect on the regulation of blood pressure in hypertensive patients.

Excessive sun exposure has long been a staple of health campaigns but there is now increasing evidence that insufficient sun exposure may also be a significant public health problem. Older people with dementia are particularly sun-deprived due to disability and spending insufficient time outside. In our study, the use of sunbeds in this population presented practical problems that led to low adherence. In comparison, spending time outside is less problematic for people with dementia and should be stimulated and incorporated into daily activities as a part of a healthy lifestyle program.

Chapter 9

Samenvatting

Vitamin D is een regulerend hormoon dat multifactoriële processen moduleert die zorgen voor evenwicht en behoud van de menselijke gezondheid. Vitamine D speelt een rol bij het reguleren van o.a. botmineraalhomeostase, lichaamsbalans, immuunrespons en bloeddruk: de meeste cellen en organen in het menselijk lichaam hebben vitamine D-receptoren. Er zijn drempelwaardes van 25(OH)D3 (alhoewel biologisch inert, de belangrijkste determinant van de vitamine D-status) waaronder vitamine D niet in staat is om zijn effecten uit te oefenen. Over het algemeen worden serumconcentraties boven de 50 nmol/l als normaal beschouwd. Er is echter onvoldoende bewijs om die grens met zekerheid vast te stellen. Factoren zoals leeftijd, lever- en nierfuncties, medicatie, body mass index (BMI) kunnen de vitamine D serumconcentratie in het menselijk lichaam beïnvloeden.

Vitamine D-deficiëntie (serum 25(OH)D3 < 30 nmol/l) en insufficiëntie (serum 25(OH)D3 > 30 nmol/l<50 nmol/l) komen vaak voor bij ouderen en worden gemedieerd door factoren zoals een vermindering van de mobiliteit, meer tijd binnenshuis doorbrengen, een lagere intrinsieke huidrespons op UV-straling en een verminderde vitamine D-inname via de voeding. Bijna alle verpleeghuisbewoners zijn vitamine D-deficiënt als vitamine D niet wordt gesuppleerd.

Uit observationele en epidemiologische studies blijkt dat zonlicht, afgezien van het feit dat het een risicofactor is voor dermatologische maligniteiten, een positief effect kan hebben op de menselijke gezondheid via andere mechanismen dan alleen vitamine D-synthese. Deze effecten kunnen worden gespecificeerd als preventie tegen sommige soorten kanker, hart- en vaatziekten, auto-immuunziekten en verbetering van stemmingsstoornissen en dus het bevorderen van het welzijn.

Het doel van dit proefschrift was om te onderzoeken of de aanbevolen vitamine D-suppletiestrategieën effectief zijn bij kwetsbare ouderen van 70 jaar en ouder en of er een extra effect is van ultraviolet licht (anders dan vitamine D-synthese) op het welbevinden, de kwaliteit van leven en de bloeddruk van verpleeghuisbewoners met dementie die voldoende vitamine D gesuppleerd zijn maar weinig buiten in de zon komen.

In **hoofdstuk 2** presenteren we een cross-sectionele studie die tot doel had de werkzaamheid van vitamine D suppletie, zoals geadviseerd door de Gezondheidsraad, op het bereiken van adequate vitamine D-spiegels bij verpleeghuisbewoners (70 jaar en ouder) te onderzoeken. Vitamine D suppletie vond plaats met cholecalciferolcapsules 5600 IE eenmaal per week of cholecalciferol druppels, 3 druppels (7500 IE) eenmaal per week.

De gemiddelde serumconcentratie van 25(OH)D van de capsulegebruikers was 90 nmol/l; niemand in deze groep was vitamine D-deficiënt; 6% was vitamine D-insufficient. De gemiddelde 25(OH)D serumconcentratie van de druppelgebruikers was 41 nmol/l: 32 % was vitamine

D-deficient; 37 % vitamine D insufficient. Analyse van de basis kenmerken van de capsule-en druppelgebruikers toonde een significant verschil in de BMI tussen de twee groepen met meer overgewicht in de groep van de druppelgebruikers. Logistische regressieanalyse werd toegepast op de totale groep verpleeghuisbewoners om te zoeken naar voorspellers van een lage vitamine D-concentratie (lager dan 50nmol/l). We vonden geen trend voor mogelijke voorspellers van vitamine D-insufficiëntie en deficiëntie, afgezien van het gebruik van vitamine D-druppels.

Onze studie toonde aan dat vitamine D-suppletie met cholecalciferolcapsules met 5600 IE, eenmaal per week (gelijk aan 800 IE per dag) resulteerde in een toereikende vitamine D status, ongeacht geslacht, leeftijd, BMI, nierfunctie, blootstelling aan de zon, comorbiditeit, medicatie en mobiliteitsstatus.

In **hoofdstuk 3** hebben we gekeken naar het vitamine D-voorschrijfgedrag van Nederlandse huisartsen en specialisten ouderengeneeskunde bij 70-plussers, zowel thuiswonend als geïnstitutionaliseerd

Tegenwoordig zijn de internationale richtlijnen en expertverenigingen zich vooral bewust van de vitamine D-tekort "pandemie" bij ouderen, met alle gezondheidsrisico's van dien. Er is echter een verschil in hun aanbevelingen voor vitamine D-suppletie die voortvloeit uit een gebrek aan consensus in de wetenschappelijke literatuur over de meest efficiënte serum vitamine D-concentratie en de meest efficiënte aanpak van vitamine D-suppletie: populatie- of individueel-gericht. In Nederland heeft de Gezondheidsraad gekozen voor een populatiegericht, eenduidige suppletieadvies van 800 IE vitamine D per dag, voor alle ouderen van 70 jaar en ouder

Wij hebben een enquête afgenomen via het Survey Monkey Platform bij huisartsen en een algemene informatiebrief naar 1685 specialisten ouderen geneeskunde (Elderly Care Physicians, ECP's) gestuurd. We benaderden 310 huisartsen met dezelfde vragen die we de ECP's schriftelijk stelden, op een dag van medische nascholing. Om een mogelijke trend in het voorschrijven van vitamine D te schetsen, vergeleken we de resultaten met een enquête uit 2010. De analyse toonde een goede kennis van de vitamine D-richtlijnen bij 79% van de ECP's en 71% van de huisartsen. In vergelijking met 2010 was er een toenemend bewustzijn van het belang van vitamine D-suppletie bij ouderen: 94% van de ECP's en 34% van de huisartsen schreef vitamine D systematisch voor aan hun patiënten van 70 jaar en ouder. De onzekerheid in het voorschrijfgedrag van de huisartsen kwam voort uit de heterogeniteit van hun populatie: van gezonde en actieve mensen tot kwetsbare mensen met veel comorbiditeit. 50% van de huisartsen controleerde regelmatig 25(OH)D serumspiegels voordat met suppletie werd begonnen.

In **hoofdstuk 4** wordt een review van de literatuur beschreven over het effect van ultraviolet (UV) licht op stemming, depressie en welbevinden. Een PICO (population, intervention, control, and outcome)-gebaseerde zoek strategie werd uitgevoerd in de volgende bibliografische databases: PubMed, Embase, Web of Science, Cochrane, Psychinfo, CINAHL, Academic Search Premier en Science Direct. Ten slotte werden zeven studies geselecteerd die in aanmerking kwamen voor opname in deze review: zes klinische studies waarvan twee gerandomiseerde gecontroleerde studies (RCT's), twee cross-over studies, één prospectieve klinische studie, één studie met een gerandomiseerd parallel design en één observationele studie. Deelnemers aan de geselecteerde studies waren gezonde vrijwilligers, patiënten met fibromyalgiesyndroom, dermatologische aandoeningen, multiple sclerose en seizoensgebonden affectieve aandoeningen.

Twee van de studies onderzochten het effect van UV-licht via de huid op de gemoedstoestand en toonden een significante verbetering van de stemming. Vijf van de studies onderzochten het effect van UV-licht via de huid of ogen op depressieve symptomen en seizoensgebonden affectieve stoornissen bij deelnemers met of zonder depressieve stoornissen. Vier van de vijf studies toonden een positief effect op depressieve symptomen.

Hoewel het algehele effect van een UV-lichtinterventie op stemmings- en depressieve symptomen positief was, is het moeilijk om algemene conclusies te trekken vanwege het kleine aantal studies over dit onderwerp en de methodologische problemen bij enkele van deze studies,.

In **hoofdstuk 5** worden de resultaten gepresenteerd van onze multicenter gerandomiseerde gecontroleerde studie naar het effect van ultraviolette B (UVB) bestraling in vergelijking met vitamine D (VD) suppletie op het welbevinden van verpleeghuisbewoners met dementie. Deelnemers werden gerekruteerd uit drie verpleeghuizen in Nederland verbonden aan het Universitair Netwerk voor de Care sector Zuid-Holland (UNC-ZH). De interventie bestond uit UV-bestraling op de gehele voorzijde van het lichaam met 1 standaard erytheem doses 8 minuten lang, 2 keer per week. De controlegroep ontving VD-capsules, 5600 IE cholecalciferol eenmaal per week. Bij aanvang en na drie en zes maanden werden de deelnemers in beide armen geëvalueerd op de primaire uitkomst – welbevinden, gemonitord met de CMAI -schaal (Cohen-Mansfield Agitation Inventory) en Cornell schaal voor depressie bij dementie en op de secundaire resultaten - kwaliteit van leven gemonitord met QUALIDEM (verkorte versie) en biochemische parameters van bothomeostase, zoals VD-serumconcentratie, creatinine, bijschildklierhormoon (PTH), calcium en fosfaat.

Negenenzeventig verpleeghuisbewoners namen deel aan het onderzoek. Er was geen verschil in de uitgangskenmerken van de interventie- en controlegroep, afgezien van de VD-concentratie die hoger was in de vitamine D interventiegroep (p=0,04).Wij deden een intention-to-treat analyse. Wanneer de verpleeghuisbewoners de interventie met UV licht weigerden, werd

opnieuw gestart met VD-capsules, maar zij bleven in de interventiegroep gevolgd worden. Aan het begin van de studie weigerden 12 bewoners (30%) de interventie.

Er werd geen verschil gevonden in de agitatie- en depressiescores van beide groepen, noch na 3 maanden noch na 6 maanden van de start van de behandeling. Interessant is dat de UVB-groep na een half jaar minder rusteloos/gespannen gedrag vertoonde (maximale score op de QUALIDEM schaal is 9) in vergelijking met de VD-groep. Het verschil in de geschatte gemiddelde scores (gecorrigeerd voor andere variabelen in het model) bedroeg in de loop van de tijd 2,2 (95% CI 0,8 tot 3,6). Er was geen verschil in de biochemische parameters na drie maanden tussen de twee groepen, na zes maanden was de VD-serumconcentratie hoger in de VD-groep, het verschil in de geschatte gemiddelde concentraties was -21,9 (95% BI –32,6 tot –11,2). Wij concludeerden dat voor het bevorderen van welbevinden UVB geen duidelijk toegevoegde waarde heeft ten opzichte van orale vitamine D suppletie. UVB-behandeling kan een positief effect hebben op het rusteloze/ gespannen gedrag dat kenmerkend is voor gevorderde dementie, maar er is meer onderzoek nodig om deze bevinding te bevestigen.

In **hoofdstuk 6** onderzochten wij het effect van ultraviolette (UV) bestraling in vergelijking met vitamine D (VD)-suppletie op de bloeddruk van verpleeghuisbewoners met dementie. Wij hebben ons gericht op de oudere mensen met dementie omdat deze populatie weinig buiten in de zon komt en een tekort aan zonlicht heeft.

Cardiale output en perifere weerstand zijn de determinanten van arteriële bloeddruk. Het is bekend dat ultraviolet A-licht als component van het zonlicht het circulerende stikstofmonoxide verhoogt, hetgeen effect heeft op het afnemen van de weerstand van de perifere bloedvaten. VD heeft ook een potentieel effect op de bloeddruk door het corrigeren van afwijkingen in calciumhomeostase en het reguleren van het renine-angiotensinesysteem.

Deze studie was een post-hoc analyse van de bloeddrukmetingen geregistreerd in de medische dossiers van de deelnemers aan de gerandomiseerde controlestudie beschreven in hoofdstuk 5. De deelnemers (N=61, 41 vrouwen, gemiddelde leeftijd 84,8 jaar) kregen 8 minuten tweemaal per week UV-bestraling op de gehele voorzijde van het lichaam of 5600 IE cholecalciferol eenmaal per week gedurende 6 maanden. Korte termijneffecten werden geëvalueerd na 1 maand en lange termijneffecten na 3 en 6 maanden. Verschillen in bloeddrukveranderingen werden beoordeeld met behulp van linear mixed models. De basiskenmerken van beide groepen verschilden niet. Na een maand behandeling hadden de deelnemers van de UV-groep een lagere bloeddruk, het verschil in de verandering van de geschatte gemiddelde systolische bloeddruk tussen de twee groepen was – 23 mmHg (95% BI -37,1, -10,1, p=0,001) en van de geschatte gemiddelde diastolische bloeddruk was – 9,5 mmHg (95% BI -9,8, -4,4). Na drie en zes maanden was er geen groepsverschil in zowel systolische als diastolische bloeddruk.

We concludeerden dat UV-bestralingen slechts een kortdurend effect had op bloeddrukverlaging in vergelijking met orale VD-suppletie in deze groep van normotensieve tot milde hypertensieve verpleeghuisbewoners met dementie.

De algemene bespreking in **hoofdstuk 7** schetst de belangrijkste bevindingen van dit proefschrift. Besproken worden de vitamine D-suppletie bij ouderen in het licht van de huidige richtlijnen en de effecten van ultraviolet licht op het welbevinden en bloeddruk van verpleeghuisbewoners.

De meest recente richtlijnen adviseren meer onderzoek naar de drempelwaarde voor het definieren van vitamine D-deficiëntie en naar de vraag of deze waarde hetzelfde is voor de verschillende klinische uitkomsten. Het is wel bekend dat de fysiologie van veroudering de oudere mensen bijzonder kwetsbaar maakt voor vitamine D-tekort en dat als het onbehandeld is, het ernstige gevolgen voor de gezondheid kan hebben. We bespreken de verschillende suppletiestrategieën bij verpleeghuisbewoners en thuiswonende ouderen van 70 jaar en ouder.

Bestralingen met UV-licht leiden in vergelijking met vitamine D suppletie niet tot een verbetering van het welbevinden in het algemeen bij de verpleeghuisbewoners, maar wel tot verbetering van sommige aspecten van de kwaliteit van leven zoals rusteloos / gespannen gedrag. We gaan ervan uit dat een slecht welbevinden bij dementie een multifactorieel probleem is dat een bredere aanpak vereist.

Ten aanzien van het effect van UV licht op de bloeddruk in normotensieve tot milde hypertensieve verpleeghuisbewoners met dementie worden drie aspecten geschetst voor toekomstig onderzoek: 1) onze studie had mogelijk niet genoeg statistische power om subtielere veranderingen in de bloeddruk te detecteren na drie en zes maanden, 2) oudere mensen met bloeddrukverlagende medicatie zouden mogelijk een aanpassing in de medicaties in de zomer moeten krijgen 3) UV-licht zou een positief effect kunnen hebben op de regulering van de bloeddruk bij hypertensieve patiënten.

Er zijn aanwijzingen dat onvoldoende blootstelling aan zonlicht kan leiden tot gezondheidsrisicos's. Vooral verpleeghuisbewoners met dementie hebben last van zondeprivatie door beperkingen in de mobiliteit en weinig buiten komen. De toepassing van kunstmatig zonlicht met behulp van zonnebanken liet in deze populatie praktische problemen zien. Behalve eventuele vitamine D-deficientie, zijn er andere redenen om buiten komen bij mensen met dementie te stimuleren en het op te nemen in de dagelijkse activiteiten als onderdeel van de gezonde leefstijl programma's.

Chapter 10

Резюме

Витамин D се образува в кожата от 7-дехидрохолестерол под влиянието на ултравиолетовата светлина. Витамин D е регулаторен хормон, който модулира многофакторни процеси, осигуряващи баланс и поддържане на човешкото здраве. Витамин D играе роля в регулирането на хомеостазата на костните минерали, баланса на организма, имунния отговор и кръвното налягане, наред с много други процеси: повечето клетки и органи в човешкото тяло имат рецептори за витамин D. Съществуват прагови стойности на 25(OH)D3 (въпреки че е биологично инертен, най-важният показател за серумната концентрация на витамин D), под които витамин D не може да оказва своето въздействие. По принцип серумните концентрации над 50 nmol/l се считат за нормални. Въпреки това няма достатъчно данни, за да се определи със сигурност тази граница. Фактори като възраст, чернодробни и бъбречни функции, медикаменти, индексът на телесна маса (ИТМ) могат да повлияят на серумната концентрация на витамин D в човешкия организъм.

Дефицитът на витамин D (серумен 25(OH)D3 < 30 nmol/l) и недостатъчността (серумен 25(OH)D3 > 30 nmol/l<50 nmol/l) са често срещани при възрастните хора и се дължат на фактори като намалена подвижност, увеличено време, прекарано в затворени помещения, по-ниска вътрешна реакция на кожата към ултравиолетовите лъчи и намален прием на витамин D с храната. Почти всички стари хора, настанени в домове за дългосрочни грижи имат недостиг на витамин D, ако не се приема допълнително.

Наблюденията и епидемиологичните проучвания показват, че слънчевата светлина, освен че е рисков фактор за дерматологични злокачествени заболявания, може да има положителен ефект върху човешкото здраве чрез механизми, различни от синтеза на витамин D. Тези ефекти могат да се определят като превенция на някои видове рак, сърдечносъдови заболявания, автоимунни заболявания и подобряване на нарушенията на настроението, като по този начин се насърчава благосъстоянието.

Целта на тази дисертация е да се проучи дали препоръчаните стратегии за добавяне на витамин D са ефективни при възрастни хора на 70 и повече години, с много и комплексни заболявания и дали ултравиолетовата светлина има допълнителен ефект (различен от синтеза на витамин D) върху благосъстоянието, качеството на живот и кръвното налягане на стари хора с деменция, настанени в домове за дългосрочни грижи, които имат адекватна серумна концентрация на витамин D, но получават малко слънчева светлина на открито.

В **глава 2** представяме крос-секционален анализ, което имаше за цел да изследва ефикасността на суплементирането с витамин D, както препоръчва Съветът по здравеопазване на Нидерландия, за постигане на адекватни нива на витамин D при

стари хора с деменция, настанени в домове за дългосрочни грижи. Суплементирането на витамин D се извършваше с капсули холекалциферол 5600 IU веднъж седмично или капки холекалциферол, 3 капки (7500 IU) веднъж седмично.

Средната серумна концентрация на 25(OH)D при потребителите на капсули беше 90 nmol/l; никой от тази група нямаше дефицит на витамин D; 6% имаха недостиг на витамин D. Средната серумна концентрация на 25(OH)D при употребяващите капки беше 41 nmol/l: 32 % бяха с дефицит на витамин D, а 37 % - с недостиг на витамин D. Анализът на основните характеристики на потребителите на капсули и на капки показаха значителна разлика в ИТМ между двете групи, като в групата на потребителите на капки имаше повече хора с наднормено тегло. Логистичният регресионен анализ, приложен към цялата група възрастни хора не откри тенденция за възможни предиктори на недостатъчност и дефицит на витамин D.

Нашето проучване показа, че суплементирането на витамин D с капсули с холекалциферол, съдържащи 5600 IU веднъж седмично (еквивалентно на 800 IU дневно), води до статус на достатъчно количество на витамин D независимо от пола, възрастта, ИТМ, бъбречната функция, излагането на слънце, съпътстващите заболявания, медикаментите и състоянието на физическа активност.

В **глава 3** са описани тенденциите в поведението на общопрактикуващите лекари и специалисти по гериатрия в Нидерландия по отношение на предписването на витамин D на хора на възраст над 70 години, живеещи както у дома, така и в институции за дългосрочни грижи.

Към ден днешен международните ръководства и експертните асоциации са наясно най-вече с „пандемията“ от недостиг на витамин D при възрастните хора, с всички произтичащи от това рискове за здравето. Въпреки това са налице различия в препоръките им за суплементирането на витамин D, които се дължат на липсата на консенсус в научната литература относно най-ефективната серумна концентрация на витамин D и най-ефективния подход за добавяне на витамин D: популационен или индивидуален. В Нидерландия Съветът по здравеопазване е избрал недвусмислената препоръка за добавяне на 800 IU витамин D на ден при всички възрастни хора на възраст над 70 години.

За да очертаем възможна тенденция в предписването на витамин D, направихме анкета сред 1685 лекари, полагащи грижи за възрастни хора (Elderly Care Physicians, ECP's) чрез платформата Survey Monkey или общо информационно писмо. Обърнахме се към 310 общопрактикуващи лекари със същите въпроси, които зададохме писмено по

време на continuing medical education (CME). Резултатите сравнихме с подобна анкета от 2010 г. Анализът показа добро познаване на насоките за витамин D сред 79% от лекарите, полагащи грижи за възрастни хора, и 71% от общопрактикуващите лекари. В сравнение с 2010 г. се е увеличила осведомеността за значението на суплементирането на витамин D при възрастните хора: 94% от лекарите, полагащи грижи за възрастни хора, и 34% от общопрактикуващите лекари системно предписват витамин D на своите пациенти на възраст над 70 години. Разликата в практиката на общопрактикуващите лекари при предписване на витамин D на възрастните хора се дължи на разнородността на населението за което те полагат грижа: от здрави и активни хора до фрагилни хора с много съпътстващи заболявания. 50% от общопрактикуващите лекари редовно проверяват серумните нива на 25(OH)D преди да предпишат суплементирането.

В **глава 4** е направен преглед на литературата относно ефекта на ултравиолетовата (UV) светлина върху настроението, депресията и благосъстоянието. Стратегията за търсене, основана на PICO (население, интервенция, контрол и резултат), беше извършена в следните библиографски бази данни: PubMed, Embase, Web of Science, Cochrane, Psychinfo, CINAHL, Academic Search Premier и Science Direct. В крайна сметка за включване в настоящия преглед бяха избрани седем проучвания: шест клинични проучвания, включително две рандомизирани контролирани проучвания (РКП), две кръстосани проучвания, едно проспективно клинично проучване, едно проучване с паралелен рандомизиран дизайн и едно наблюдение. Участниците в избраните проучвания са били здрави доброволци, пациенти със синдром на фибромиалгия, дерматологични заболявания, множествена склероза и сезонно афективно разстройство.

Две от проучванията изследват ефекта на ултравиолетовата светлина през кожата върху настроението и показват значително подобрение на настроението. Пет от проучванията изследват ефекта на ултравиолетовата светлина през кожата или очите върху симптомите на депресия и сезонно афективно разстройство. Четири от петте проучвания показват положителен ефект върху депресивните симптоми.

Въпреки че общият ефект от интервенцията с ултравиолетова светлина върху настроението и депресивните симптоми е положителен, трудно е да се направят общи заключения поради малкия брой проучвания по тази тема и методологичните проблеми в някои от тях.

В **глава 5** са представени резултатите от нашето многоцентрово рандомизирано контролирано проучване върху ефекта от облъчването с ултравиолетови лъчи B (UVB) в сравнение със суплецията на витамин D (VD) върху благосъстоянието на стари хора с деменция, настанени в домове за дългосрочни грижи.

Участниците бяха набрани от три домове за дългосрочни грижи за стари хора с деменция в Нидерландия, свързани с университетската мрежа в сектора на здравеопазването в Южна Холандия (UNC-ZH). Интервенцията се състоеше в облъчване с UV лъчи на цялата предна част на тялото с 1 стандартна еритемна доза в продължение на 8 минути 2 пъти седмично. Контролната група приемаше капсули с витамин D, 5600 IU холекалциферол веднъж седмично. Психичното благосъстояние на участниците в проучването беше евалюирано, в началото и след три и шест месеца, на базата на скалата за оценка на агитираното поведение според Коен-Мансфийлд (CMAI) (неадекватно вербално, вокално или моторно поведение с неясен произход при хора с деменция) и скалата на Корнел за депресия при деменция. Като вторични резултати бяха проследени качество на живот, оценено с QUALIDEM (съкратена версия), и биохимичните параметри на костната хомеостаза, като серумна концентрация на витамин D, креатинин, паратиреоиден хормон (PTH), калций и фосфат.

В проучването участваха седемдесет и девет стари хора с деменция (средна възраст 84 години). Нямаше разлика в изходните характеристики между интервенционната и контролната група, с изключение на по-високата концентрация на витамин D в контролната група (p=0,04). Анализът беше извършен на базата на "intention-to-treat"принципа. Когато участниците в проучването откажеха интервенцията с UV светлина, отново започваха да приемат витамин D на капсули, но продължаваха да бъдат наблюдавани в интервенционната група. В началото на проучването 12 участници (30%) отказаха интервенцията.

Не се установи разлика в показателите между двете групи, измерени според скалата на Коен-Мансфийлд за неадекватно поведение и скалата на Корнел за депресия при деменция нито след 3 месеца, нито след 6 месеца от началото на лечението. Интересно е, че след шест месеца групата с UVB показа по-малко неспокойно/напрегнато поведение (максималната оценка по скалата QUALIDEM е 9) в сравнение с групата с VD. Разликата в изчислените средни резултати (коригирани за другите променливи в модела) във времето беше 2,2 (95% CI 0,8-3,6). Нямаше разлика в биохимичните параметри след три месеца между двете групи, след шест месеца серумната концентрация на витамин D беше по-висока в групата на VD, като разликата в оценените средни концентрации беше -21,9 (95% BI -32,6 до -11,2). Стигнахме до заключението, че за подобряване на благосъстоянието UVB няма ясна добавена стойност в сравнение с перорално приемане на витамин D. Лечението с UVB може да има положителен ефект върху неспокойното/напрегнато поведение, характерно за напредналата деменция, но са необходими допълнителни изследвания, за да се потвърди тази констатация.

В **глава 6** изследвахме ефекта на ултравиолетовото (UV) облъчване в сравнение със суплементирането на витамин D (VD) върху кръвното налягане при стари хора с деменция, настанени в домове за дългосрочни грижи. Фокусирахме се върху възрастните хора с деменция, тъй като тази група от населението излиза малко на открито и има недостиг на слънчева светлина.

Сърдечният дебит и периферното съдово съпротивление са определящи за артериалното налягане. Известно е, че ултравиолетовата светлина А, като компонент на слънчевата светлина, увеличава циркулиращия азотен оксид, който оказва влияние върху намаляването на периферното съдово съпротивление. Витамин D е също известен с потенциалния си ефект върху кръвното налягане чрез коригиране на нарушенията в калциевата хомеостаза и регулирането на системата ренин-ангиотензин.

Това проучване представлява post-hoc анализ на измерванията на кръвното налягане, записани в медицинските досиета на участниците в рандомизираното контролно проучване, описано в глава 5. Участниците (N=61, 41 жени, средна възраст 84,8 години) са получавали 8 минути UV облъчване на цялата предна част на тялото два пъти седмично или 5600 IU холекалциферол веднъж седмично в продължение на 6 месеца. Краткосрочните ефекти бяха оценени след 1 месец, а дългосрочните - след 3 и 6 месеца. Разликите в промените на кръвното налягане бяха оценени с помощта на линейни смесени модели. Основните характеристики на двете групи не се различаваха. След едномесечно лечение участниците в групата с UV облъчване имаха по-ниско кръвно налягане, като разликата в промяната на очакваното средно систолично кръвно налягане между двете групи беше - 23 mmHg (95% BI -37,1, -10,1, p=0,001), а на очакваното средно диастолично кръвно налягане - 9,5 mmHg (95% BI -9,8, -4,4), като VD групата беше разглеждана като референция . След три и шест месеца не се установи разлика между групите нито в систоличното, нито в диастоличното кръвно налягане.

Стигнахме до заключението, че ултравиолетовата светлина има само краткосрочен ефект върху намаляването на кръвното налягане в сравнение с перорално приемане на витамин D в тази определена група от възрастните хора с деменция, които бяха с нормално или леко повишено кръвно налягане1

Общата дискусия в **глава 7** очертава най-важните констатации на тази дисертация. Обсъждат се суплементирането на витамин D при по-възрастните хора в светлината на настоящите насоки и ефектите на ултравиолетовата светлина върху благосъстоянието и кръвното налягане на стари хора с деменция, настанени в домове за дългосрочни грижи.

Най-новите насоки препоръчват повече изследвания върху праговата стойност за определяне на дефицита на витамин D и върху ефекта на тази стойност върху различните клинични резултати. Добре известно е, че физиологията на стареенето прави по-възрастните хора особено уязвими към недостиг на витамин D и че ако не се лекува, той може да има сериозни последици за здравето.

В сравнение с приема на витамин D, облъчването с UV светлина не подобрява като цяло благосъстоянието на стари хора с деменция, настанени в домове за дългосрочни грижи, но подобрява някои аспекти на качеството на живот, като например неспокойното/напрегнато поведение, характерно за напредналата деменция. Нашата хипотеза е че лошото благосъстояние при хората с деменция е многофакторен проблем, който изисква по-широк подход.

Що се отнася до ефекта на ултравиолетовата светлина върху кръвното налягане при нормално и леко хипертонични пациенти с деменция, на базата на тази дисертация се очертават три аспекта за бъдещи изследвания: 1) Необходимо е проучване с по-голяма статистическа сила, за да открие по-незначителни промени в кръвното налягане, нашето проучване беше post-hoc анализ, чиято статистическа сила беше изчислена за друг първичен резултат; 2) По-възрастните хора, които приемат лекарства за понижаване на кръвното налягане, може да се нуждаят от корекция на лекарствата през лятото; 3) Ултравиолетовата светлина може да има положителен ефект върху регулирането на кръвното налягане при пациенти с хипертония.

Налице са данни, че недостатъчното излагане на слънчева светлина може да доведе до рискове за здравето. По-специално, старите хора с деменция, настанени в домове за дългосрочни грижи страдат от недостиг на слънчева светлина поради ограниченията в мобилността и малкото време, прекарано на открито. Прилагането на изкуствена слънчева светлина показва практически проблеми при тази популация. Освен възможния недостиг на витамин D, има и други здравни аспекти, определящи необходимостта да се насърчават дейностите на открито при хората с деменция и да се включват в ежедневните дейности като част от програмите за здравословен начин на живот.

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CURRICULUM VITAE

Bistra Veleva was born on April 27th, 1969 in Sofia, Bulgaria. After graduating from the secondary school at English Language Gymnasium, Sofia in 1991, she started her medical training at the Sofia Medical University. Thereafter she worked as a junior resident in Pediatrics at Private Medical Center "Mediva", Sofia.

In 2002 Bistra came to the Netherlands and she entered the Master Oncology Programme at the VU University Medical Center. She did two major internships by the Department of Pharmacology and Department of Medical Oncology where she did translational research on the treatment and screening of colon cancer and the role of Human papilloma virus in cervical cancer under the supervision of Prof. dr. Frits Peters, Prof. dr. Peter Snijders and Prof. dr. Gerrit Meijer. After this, she entered the two-year Dutch internship programme (coschap) of the VUMC Medical School in Amsterdam and having completed this, she could practice as a physician in the Netherlands. Then she worked as a resident (ANIOS) at the Department of Internal Medicine at Haaglanden Medical Center.

In 2011, Bistra entered into three-year specialist medical training to become an elderly care physician at the Leiden University Medical Center. And in November 2015 she started the PhD-trajectory at the Leiden University Medical Center, Department of Public Health and Primary Care. She did the research described in this thesis under the supervision of Prof. dr. Mattijs Numans, dr. Victor Chel and dr. Monique Caljouw. This research was a part of the theme "Quality of life in dementia", initiated from the University Network for the Care Sector South Holland (UNC-ZH), a collaboration between the Leiden University Medical Center and twelve care institutions in the province of South Holland. Bistra combined her PhD-training with her work as an elderly care physician at WoonZorgcentra Haaglanden, a member of the UNC-ZH and funder of her research.