

**Clinical trial results:****Prevention of depression and poor physical function in older persons with vitamin D supplementation****Summary**

EudraCT number	2012-005332-29
Trial protocol	NL
Global end of trial date	09 May 2016

**Results information**

Result version number	v1 (current)
This version publication date	27 June 2022
First version publication date	27 June 2022
Summary attachment (see zip file)	Trial results paper (D-Vitaal AJCN pub.pdf)

**Trial information****Trial identification**

Sponsor protocol code	D-Vitaal protocol version 4.0
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	D-Vitaal: 12/354, Netherlands Trial Register: NTR3845

Notes:

**Sponsors**

Sponsor organisation name	VU University Medical Centre
Sponsor organisation address	P.O. Box 7057, Amsterdam, Netherlands, 1007 MB
Public contact	Trial Coordinator: N.M. van Schoor; Sponsor: P. Lips, VU University Medical Centre, 0031 (0)204448439, nm.vanschoor@amsterdamumc.nl
Scientific contact	Trial Coordinator: N.M. van Schoor; Sponsor: P. Lips, VU University Medical Centre, 0031 (0)204448439, nm.vanschoor@amsterdamumc.nl

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 May 2016
Global end of trial reached?	Yes
Global end of trial date	09 May 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the D-Vitaal trial is to answer the following two questions:

1. Does vitamin D supplementation decrease depressive symptoms in older persons?
2. Does vitamin D supplementation improve physical performance and decrease functional limitations in older persons?

Protection of trial subjects:

Careful health monitoring of participants during all follow-up moments (baseline, 2 weeks, 3 months, 6 months, 9 months, 12 months).

Background therapy:

Ensuring sufficient calcium intake by either advising to take at least 3 dairy products per day or prescribing calcium tablets 500 mg/day.

Evidence for comparator:

Not applicable, placebo was used as comparator.

Actual start date of recruitment	01 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 155
Worldwide total number of subjects	155
EEA total number of subjects	155

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	42

From 65 to 84 years	113
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment commenced in May 2013 and ended in April 2015. 19% of the participants were recruited through general practitioners; 81% of participants were recruited through municipality registries in and around Amsterdam.

### Pre-assignment

Screening details:

Recruitment:  $n \approx 56,000$

Screening questionnaire returned:  $n = 2312$ . Excluded:  $n = 1733$

Screening interview conducted:  $n = 579$ . Excluded:  $n = 424$

Randomized:  $n = 155$

Reasons for exclusion: please refer to the flow chart (Figure 1) publication of the trial results: de Koning et al. (2019) Am J Clin Nutr. 2019; 110(5): 1119-1130.

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Randomization was performed by an independent pharmacist. Only this pharmacist knew the key to the medication numbers for the participants (intervention group or placebo group).

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Intervention group
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Arm description:

3 daily tablets of 400 IU/day vitamin D3 (=1200 IU/day) for 12 months

Arm type	Experimental
Investigational medicinal product name	vitamin D3
Investigational medicinal product code	
Other name	cholecalciferol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 daily oral tablets of 400 IU vitamin D3 (cholecalciferol, Devaron) = 1200 IU/day.

<b>Arm title</b>	Placebo group
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Arm description:

3 daily tablets identical to intervention group for 12 months

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 daily oral placebo tablets, identical to tablets of intervention group but without vitamin D.

<b>Number of subjects in period 1</b>	Intervention group	Placebo group
Started	77	78
Completed	74	71
Not completed	3	7
Adverse event, serious fatal	1	-
perceived side effects by participant	2	3
no longer motivated / too burdensome	-	4

## Baseline characteristics

### Reporting groups

Reporting group title	Intervention group
Reporting group description: 3 daily tablets of 400 IU/day vitamin D3 (=1200 IU/day) for 12 months	
Reporting group title	Placebo group
Reporting group description: 3 daily tablets identical to intervention group for 12 months	

Reporting group values	Intervention group	Placebo group	Total
Number of subjects	77	78	155
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
study sample: 155 persons aged 60-80 years.			
Units: years			
median	67.8	67.3	
inter-quartile range (Q1-Q3)	65.4 to 71.7	63.4 to 72.0	-
Gender categorical			
Units: Subjects			
Female	45	44	89
Male	32	34	66

## End points

### End points reporting groups

Reporting group title	Intervention group
Reporting group description: 3 daily tablets of 400 IU/day vitamin D3 (=1200 IU/day) for 12 months	
Reporting group title	Placebo group
Reporting group description: 3 daily tablets identical to intervention group for 12 months	

### Primary: the difference in the 12-mo course of the depressive symptoms score between the 2 treatment groups

End point title	the difference in the 12-mo course of the depressive symptoms score between the 2 treatment groups
End point description:	
End point type	Primary
End point timeframe: Baseline - 6 months - 12 months (all three time points were included in the linear mixed models analysis).	

End point values	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: CES-D score				
arithmetic mean (standard error)	6.49 ( $\pm$ 7.62)	6.38 ( $\pm$ 6.43)		

<b>Attachments (see zip file)</b>	See Table 2/D-Vitaal AJCN pub.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	linear mixed models
Statistical analysis description: please refer to published paper on this trial: De Koning et al. (2019) Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial. Am J Cl Nutr 110(5): 1119-1130.	
Comparison groups	Intervention group v Placebo group

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.36
upper limit	2.08

Notes:

[1] - 2-sided tests to investigate the difference between the intervention (vitamin D) and placebo group.

<b>Statistical analysis title</b>	Copy of linear mixed models
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Statistical analysis description:

please refer to published paper on this trial: De Koning et al. (2019) Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial. Am J Cl Nutr 110(5): 1119-1130.

Comparison groups	Placebo group v Intervention group
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.36
upper limit	2.08

Notes:

[2] - 2-sided tests to investigate the difference between the intervention (vitamin D) and placebo group.

**Primary: the difference in the 12-mo course of the functional limitation scores between the 2 treatment groups**

End point title	the difference in the 12-mo course of the functional limitation scores between the 2 treatment groups
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End point description:

End point type	Primary
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End point timeframe:

Baseline - 6 months - 12 months (all three time points were included in the linear mixed models analysis).

<b>End point values</b>	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: LASA Functional Limitations Questionnaire				
arithmetic mean (standard deviation)	0.33 (± 1.19)	0.05 (± 1.16)		

<b>Attachments (see zip file)</b>	See Table 2/D-Vitaal AJCN pub.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	linear mixed models analysis
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Statistical analysis description:

Please refer to published paper on this trial: De Koning et al. (2019) Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial. Am J Cl Nutr 110(5): 1119-1130.

Comparison groups	Intervention group v Placebo group
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.2

Notes:

[3] - 2-sided tests to investigate the difference between the intervention (vitamin D) and placebo group.

### Primary: the difference in the 12-mo course of the physical performance score between the 2 treatment groups

End point title	the difference in the 12-mo course of the physical performance score between the 2 treatment groups
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End point description:

End point type	Primary
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End point timeframe:

Baseline - 6 months - 12 months (all three time points were included in the linear mixed models analysis).

<b>End point values</b>	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: SPPB score				
arithmetic mean (standard deviation)	-0.18 (± 1.86)	-0.20 (± 2.36)		

<b>Attachments (see zip file)</b>	See Table 2/D-Vitaal AJCN pub.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	linear mixed models analysis
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Statistical analysis description:

please refer to published paper on this trial: De Koning et al. (2019) Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial. Am J Cl Nutr 110(5): 1119-1130.

Comparison groups	Intervention group v Placebo group
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.38

Notes:

[4] - 2-sided tests to investigate the difference between the intervention (vitamin D) and placebo group.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

baseline - 12 months.

Adverse event reporting additional description:

Please refer to supplementary table 2 of the published paper on this trial. This table lists all (S)AEs, separately for the intervention and placebo group.

Assessment type	Systematic
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### Dictionary used

Dictionary name	see published paper
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Dictionary version	1
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### Reporting groups

Reporting group title	Intervention group
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Reporting group description:

vitamin D group

Reporting group title	placebo group
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Reporting group description:

placebo

<b>Serious adverse events</b>	Intervention group	placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 77 (7.79%)	10 / 78 (12.82%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 77 (2.60%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
stroke			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac disorder			
subjects affected / exposed	3 / 77 (3.90%)	5 / 78 (6.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorder			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Psychiatric decompensation			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.1 %

<b>Non-serious adverse events</b>	Intervention group	placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 77 (87.01%)	72 / 78 (92.31%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Precancerous disorder			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Vascular disorders			

Cardiovascular disorder subjects affected / exposed occurrences (all)	16 / 77 (20.78%) 16	18 / 78 (23.08%) 18	
Fluid retention subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 2	2 / 78 (2.56%) 2	
Immune system disorders Diabetes mellitus worsening subjects affected / exposed occurrences (all)	3 / 77 (3.90%) 3	1 / 78 (1.28%) 1	
Social circumstances Traffic accident subjects affected / exposed occurrences (all)	3 / 77 (3.90%) 3	2 / 78 (2.56%) 2	
Reproductive system and breast disorders Andrological disorder subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 2	2 / 78 (2.56%) 2	
Gynaecological disorder subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	1 / 78 (1.28%) 1	
Respiratory, thoracic and mediastinal disorders Pulmonary disease subjects affected / exposed occurrences (all)	12 / 77 (15.58%) 12	13 / 78 (16.67%) 13	
Psychiatric disorders Mental health problem subjects affected / exposed occurrences (all)	9 / 77 (11.69%) 9	12 / 78 (15.38%) 12	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	3 / 77 (3.90%) 3	2 / 78 (2.56%) 2	
Animal bite subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 2	0 / 78 (0.00%) 0	

Nervous system disorders			
Balance disorder			
subjects affected / exposed	5 / 77 (6.49%)	9 / 78 (11.54%)	
occurrences (all)	5	9	
Fatigue / malaise			
subjects affected / exposed	5 / 77 (6.49%)	11 / 78 (14.10%)	
occurrences (all)	5	11	
neurological disorder			
subjects affected / exposed	4 / 77 (5.19%)	9 / 78 (11.54%)	
occurrences (all)	4	9	
Sleep problem			
subjects affected / exposed	1 / 77 (1.30%)	5 / 78 (6.41%)	
occurrences (all)	1	5	
Headache			
subjects affected / exposed	2 / 77 (2.60%)	1 / 78 (1.28%)	
occurrences (all)	2	1	
Eye disorders			
Eye disorder			
subjects affected / exposed	3 / 77 (3.90%)	9 / 78 (11.54%)	
occurrences (all)	3	9	
Skin and subcutaneous tissue disorders			
Skin problem			
subjects affected / exposed	10 / 77 (12.99%)	9 / 78 (11.54%)	
occurrences (all)	10	9	
Hair loss			
subjects affected / exposed	2 / 77 (2.60%)	1 / 78 (1.28%)	
occurrences (all)	2	1	
Renal and urinary disorders			
Urinary tract disorder			
subjects affected / exposed	7 / 77 (9.09%)	9 / 78 (11.54%)	
occurrences (all)	7	9	
Endocrine disorders			
Vitamin B12 deficiency			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthritis / tendinitis / musculoskeletal disorder subjects affected / exposed occurrences (all)	45 / 77 (58.44%) 45	52 / 78 (66.67%) 52	
dental disorder subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	3 / 78 (3.85%) 3	
Fracture subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	1 / 78 (1.28%) 1	
Infections and infestations Ear/nose/throat disorder subjects affected / exposed occurrences (all)	5 / 77 (6.49%) 5	4 / 78 (5.13%) 4	
Infectious disease subjects affected / exposed occurrences (all)	23 / 77 (29.87%) 23	27 / 78 (34.62%) 27	
Metabolism and nutrition disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	18 / 77 (23.38%) 18	15 / 78 (19.23%) 15	
Thyroid disorder subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Weight loss/gain subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 2	1 / 78 (1.28%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2013	D-Vitaal Amendment 1.0, version: 1.0, date: 2013-12-17: This amendment contained changes to the study protocol that do not affect the safety of the participants or the investigational product. Main changes: 1. Addition of alternative recruitment strategies, due to disappointing inclusion results; 2. Two blood draws instead of three, to reduce the burden on respondents. This has no scientific consequences. 3. We moved questions from the interviews (baseline, 6 and 12 months) to a pre-fillable questionnaire to reduce interview time. 4. Addition of a short questionnaire on physical functioning to the screening, as the original questionnaire performs less well as a screening tool in this study population. 5. As an additional safeguard for respondent safety, we added a sentence to the informed consent form that the respondent gives permission for his/her primary care physician to be informed if any health problems come to light during the study.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

not applicable.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31340012>