

## Supplementary appendix

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## **Supplementary materials to the article: Vitamin D status and ill health: A systematic review**

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## **Webappendix 1: Factors associated with low vitamin D status as estimated by serum concentrations of 25-hydroxyvitamin D**

(the list includes best documented factors and is not exhaustive)

Age > 65.0 year\*  
Female gender  
Pregnancy  
High adiposity\*  
Physically inactive\*  
Absence of outdoor activities\*  
Smoking\*  
No sunbed use  
No recent holidays in sunny areas  
Being veiled, heavy dressed  
Winter season  
Diet poor in vitamin D  
Not taking vitamin D supplements  
Pigmented skin  
Institutionalized\*  
High latitude  
Acute disease involving marked inflammation, e.g., acute pancreatitis  
Presence of chronic diseases (e.g., kidney diseases, diabetes) \*  
Presence of chronic inflammatory condition\*,  
Congestive heart failure, colitis, periodontitis, tuberculosis  
High concentrations of serum makers of inflammation (eg, CRP, TNF- $\alpha$ )  
History of fracture after 50 years old  
Digestive malabsorption (eg, fat malabsorption)  
Nutritional patterns  
Variable or poor appetite  
Irregular meal pattern  
Leaving food on the plate  
Having oily fish less than once per month  
Having no natural teeth  
General health and functioning  
Having poor general health\*  
Frailty\*  
Disability\*  
Taking five or more medicines per day  
Not having social activities each week  
Unable to go shopping without help  
Unable to climb stairs without help  
Feeling sad some of the time in the past month, depression  
Cognitive disorders, dementia\*  
Low income

\*Condition often associated with low grade or with marked inflammation

## Webappendix 2: Revised calculation of the Nebraska randomised trial on vitamin D supplementation and cancer risk (Lappe et al, 2007).

A three-group randomised placebo controlled trial of vitamin D and calcium was conducted in Nebraska, USA, in 1,179 community-dwelling women aged 55 and over.<sup>1</sup> The primary endpoint was fracture incidence. Women were randomly assigned to receive each day 1.5 g supplemental elementary calcium alone (Ca-only), supplemental calcium plus 27.5 µg vitamin D3 (Ca + D), or placebo. The trial found a much reduced risk of cancer among women received vitamin D only supplementation (row (1) of the table). However, flaws in the design and conduct of this trial have been published.<sup>2-5</sup> Moreover, The statistical analysis of this trial reported in the published article (row (1) of the table) was not correct because authors compared the CA+D group to the placebo group, without considering that for evaluating the influence of vitamin D supplementation, the Ca-only group had to be merged with the placebo group.

Using data reported in the published article (1), we performed an intent-to-treat analysis we performed from (row (2) of the table) and obtained a statistically non-significant relative risk of cancer.<sup>1</sup>

Risk for all cancers	No. Women		No. Cancers			
Intervention	Intervention	Control	Intervention	Control	RR intervention vs. control	95% CI
(1) Vitamin D + Ca vs placebo (ignoring 445 women and 17 cancers in Ca only group)	446	288	13	20	0.40	0.20-0.82
(2) Vitamin D supplements vs. Ca or placebo	446	733	13	37	0.59	0.32-1.10

### References

- 1- Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;**85**:1586–91.
- 2 - Sood MM, Sood AR. Dietary vitamin D and decreases in cancer rates: Canada as the national experiment. *Am J Clin Nutr* 2007;**86**:1549.
- 3 - Ojha RP, Felini MJ, Fischbach LA. Vitamin D for cancer prevention: valid assertion or premature anointment? *Am J Clin Nutr* 2007;**86**:1804–5.
- 4- Bolland MJ, Reid IR. Calcium supplementation and cancer incidence. *Am J Clin Nutr* 2008;**87**:792–3.
- 5 - Schabas R. Artifact in the control group undermines the conclusions of a vitamin D and cancer study. *Am J Clin Nutr* 2008;**87**:792.

### Webappendix 3: Summary of randomised controlled trials on vitamin D supplementation and glucose metabolism endpoints.\*

First author	Year of publication	Ref.	No. Subjects	Type of subjects <sup>b</sup>	Dose (µg per day)	Duration (month)	baseline 25(OH) D (nmol/L)	25(OH) D during trial (nmol/L)	Calcium supplementation	Endpoint <sup>c</sup>							
										Newly diagnosed diabetes	Hb1AC	FPG	OGTT	SI <sup>g</sup>	FPI	FPC	HOMA
Nilas	1984	34	128	ND	50	24	NR	NR	no		Y						
Pittas	2007	19	222	ND/NGT	17.5	36	74.0	103.5	yes		Y						Y
Pittas	2007	19	92	ND/IGT	17.5	36	74.0	103.5	yes		Y**						Y**
de Boer <sup>a</sup>	2008	23	33951	ND	10	84	49.1 <sup>d</sup>	53.5 <sup>d</sup>	yes	Y	Y						
<b>Nagpal</b>	<b>2008</b>	<b>39</b>	<b>71</b>	<b>ND</b>	<b>214</b>	<b>1.5</b>	<b>36.0</b>	<b>70.5</b>	<b>no</b>								<b>Y</b>
<b>Sugden</b>	<b>2008</b>	<b>2</b>	<b>64</b>	<b>D</b>	<b>45</b>	<b>2</b>	<b>39.7</b>	<b>62.4</b>	<b>no</b>		<b>Y</b>						<b>Y</b>
Avenell	2009	24	5292	ND	20	43	NR	NR	yes	Y							
Jorde	2009	25	32	D	107	6	63.6	116.6	no		Y	Y			Y	Y	
<b>Zittermann</b>	<b>2009</b>	<b>26</b>	<b>165</b>	<b>ND</b>	<b>83</b>	<b>12</b>	<b>29.6</b>	<b>84.3</b>	<b>no</b>		<b>Y</b>	<b>Y</b>					
Jorde	2010	77	288	ND	71	12	56.0	100.1	yes		Y	Y	Y				Y
Jorde	2010	77	299	ND	143	12	57.9	134.1	yes		Y	Y	Y				Y
<b>Parekh</b>	<b>2010</b>	<b>27</b>	<b>28</b>	<b>D</b>	<b>268</b>	<b>1</b>	<b>36.7</b>	<b>102.5</b>	<b>no</b>		<b>Y</b>	<b>Y</b>	<b>Y</b>		<b>Y</b>		<b>Y</b>
Patel	2010	15	24	D	20	4	38.5	67.5	no		Y	Y		Y	Y		
<b>Von Hurst</b>	<b>2010</b>	<b>35</b>	<b>81</b>	<b>ND</b>	<b>100</b>	<b>6</b>	<b>20.7</b>	<b>78.9</b>	<b>no</b>			<b>Y*</b>			<b>Y</b>	<b>Y</b>	<b>Y**</b>
Witham	2010	28	40	D	22	4	40.4	58.2	no		Y						Y
<b>Witham</b>	<b>2010</b>	<b>28</b>	<b>37</b>	<b>D</b>	<b>45</b>	<b>4</b>	<b>47.3</b>	<b>74.9</b>	<b>no</b>		<b>Y</b>						<b>Y</b>
Bock	2011	36	59	ND	120	3	62.9	135.6	no			Y			Y	Y	
<b>Grimnes</b>	<b>2011</b>	<b>16</b>	<b>94</b>	<b>ND</b>	<b>140</b>	<b>6</b>	<b>41.6</b>	<b>140.7</b>	<b>no</b>		<b>Y</b>	<b>Y</b>		<b>Y</b>	<b>Y</b>		<b>Y</b>
<b>Kota</b>	<b>2011</b>	<b>30</b>	<b>30</b>	<b>D</b>	<b>220</b>	<b>3</b>	<b>31.6</b>	<b>62.6</b>	<b>no</b>		<b>Y</b>	<b>Y</b>					
Mitri	2011	29	47	D	50	4	65.3	80.9	yes		Y	Y	Y	Y	Y		
<b>Ardabili</b>	<b>2012</b>	<b>37</b>	<b>50</b>	<b>ND</b>	<b>60</b>	<b>2</b>	<b>17.0</b>	<b>57.7</b>	<b>no</b>			<b>Y</b>			<b>Y</b>		<b>Y</b>
Wood	2012	14	175	ND	10	12	32.8	63.8	no			Y			Y		Y
Wood	2012	14	182	ND	25	12	32.3	74.7	no			Y			Y		Y
Carrillo	2012	38	23	ND	100	3	51.3	82.3	yes			Y	Y		Y		Y

Davidson	2012	33	109	ND	317 <sup>c</sup>	12	54.2	172.6	no	Y <sup>f</sup>	Y	Y	Y			Y		
<b>Harris</b>	<b>2012</b>	<b>32</b>	<b>89</b>	<b>ND</b>	<b>100</b>	<b>3</b>	<b>39.0</b>	<b>78.4</b>	yes	Y	Y			Y	Y			
<b>Longenecker</b>	<b>2012</b>	<b>4</b>	<b>45</b>	<b>ND</b>	<b>100</b>	<b>3</b>	<b>22.2</b>	<b>34.5</b>	no		Y			Y		Y		
<b>Mozaffari-Khosravi</b>	<b>2012</b>	<b>31</b>	<b>45</b>	<b>D</b>	<b>85</b>	<b>3</b>	<b>24.0</b>	<b>61.2</b>	no	Y	Y					Y**		
Heshmat	2012	79	42	D	81	3	115.6	170.8	no		Y					Y		
<b>Simha</b>	<b>2012</b>	<b>80</b>	<b>12</b>	<b>ND</b>	<b>178</b>	<b>2</b>	<b>32.8</b>	<b>46.3</b>	no				Y					
Yiu	2013	8	100	D	125	3	54.0	144.4	no	Y	Y							
No RCTs with endpoint:											2	16	25	6	6	13	4	19

\* RCTs that included subjects with mean 25(OH)D <49 nmol/L and a supplementation of at least 50 µg per day are in bold.

FPC: fasting plasma c-peptide concentration; FPG: fasting plasma glucose concentration; FPI: fasting plasma insulin concentration; Hb1Ac: glycated haemoglobin; HOMA-IR: homeostasis model of assessment - insulin resistance.

NR: not reported; OGTT: oral glucose tolerance test; RCT: randomised trial; SI: sensitivity to insulin; 25(OH)D: serum 25-hydroxyvitamin D concentration.

<sup>a</sup> Women's Health Initiative (WHI) trial

<sup>b</sup> D: subjects with diabetes at baseline; ND: subjects without diabetes at baseline; NGT: normal glucose tolerance; IGT: impaired glucose tolerance

<sup>c</sup> Mean daily dose because doses were individually adapted in order to achieve 25(OH)D levels of 160-222 nmol/L.

<sup>d</sup> According to Autier et al, *J Clin Endo Metab* 2012; **97**(8):2606–13.

<sup>e</sup> Y means that the endpoint was examined by the trial; \* Statistically borderline; \*\* Statistically significant with p < 0.05 (two-sided test).

<sup>f</sup> At 12 months, the trial found 6.2% Hb1AC in intervention and 6% in control group (p=0.004). No data was reported (e.g., dispersion) allowing confirmation of the statistical significance of this small difference.

<sup>g</sup> Usually the glucose disposal rate (GDR).

## Webappendix 4: Meta-analysis of randomised controlled trials on vitamin D supplementation and glycohaemoglobin concentration (HbA1c) in subjects 18 years of age or more

Two methods were used to evaluate the impact of vitamin D supplementation on proportions of blood hemoglobin (Hb) that is glycosylated (i.e. % of HbA1c in all Hb). The first method was a comparison of changes in %HbA1c, intervention vs. control group. The second method was based on the difference in changes in %HbA1c between the intervention and control group.

For both methods, proportions of HbA1c were abstracted from the 16 intervention groups reported by 14 published trials retrieved by our literature searches (Webappendix 3). For each trial, we extracted for the intervention and control groups the %HbA1c at baseline and at trial end, as well as the difference (% at end minus % at baseline) with the corresponding standard deviation. We also extracted numbers of subjects, the diabetic status of subjects (ie, diabetic or non diabetic at baseline), the dose of vitamin D supplement and the duration of trial.

Some trials reported standard errors (SE). In this case, we computed standard deviations (SD) using the formula:  $SD = SE * \sqrt{N}$ , with N the number of subjects. Three trials did not report dispersion parameters for differences between baseline and trial end, we assigned to them the mean of standard deviations available for other trials <sup>(references 28,30,33 in the table 5 of the webappendix 5)</sup>.

In both methods, a meta-analysis was performed using a random effect model.<sup>1</sup> Heterogeneity across studies was evaluated by the I<sup>2</sup> statistics, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance.<sup>2</sup> Sensitivity analyses were carried out to evaluate the influence of each study on the overall estimate from the meta-analysis. Subgroup analyses examined whether the vitamin D dose (less than or equal and greater than the median 92.5 µg/day), the trial duration (less than or equal and greater than the median of 4 months) and the diabetic status of subjects at baseline influenced results. All statistical analyses were performed with R (version 2.14.1).

In method 1, a random effect model was applied to the difference in %HbA1c in each group, intervention and placebo.

Summary differences between intervention and control groups were very close. None of the Student t-tests applied on summary differences between intervention and control groups had a p value below 0.05.

### Method 1: one random effect model in each group, intervention and placebo.

<i>Intervention groups*</i>			
Included trials	Summary difference in %HbA1c between trial end and baseline	95% CI, lower bound	95% CI, upper bound
All 16	-0.18	-0.65	0.28
Dose ≤ 92.5µg/day	0.03	-0.21	0.28
Dose > 92.5µg/day	-0.45	-1.49	0.59
Duration ≤ 4 months	-0.28	-1.08	0.52
Duration > 4 months	0.00	-0.30	0.29
Diabetic	-0.30	-1.13	0.53
Non-diabetic	-0.01	-0.29	0.27

<sup>1</sup> van Houwelingen HC, Arends LR, Stijnen T (2002) Advanced methods in meta-analysis: multivariate approach and metaregression. Stat Med 21:589–624.

<sup>2</sup> Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558.

**Control groups\***

All 16	-0.19	-0.52	0.15
Dose $\leq$ 92.5 $\mu$ g/day	-0.01	-0.24	0.23
Dose > 92.5 $\mu$ g/day	-0.37	-1.14	0.40
Duration $\leq$ 4 months	-0.31	-0.89	0.27
Duration > 4 months	-0.01	-0.29	0.28
Diabetic	-0.33	-0.92	0.26
Non-diabetic	0.00	-0.28	0.27

\*Paired t-test for comparison between the intervention and control groups: p-value = 0.7902

In method 2, a preliminary investigation consisted in checking the hypothesis of equal baseline %Hb1Ac in the intervention and placebo groups. To this end, we applied a random effect model to differences in baseline %Hb1Ac between intervention and control group. The corresponding variances were computed using the delta method assuming the two variables independent ( $\text{var} = \text{var}(\text{intervention}) + \text{var}(\text{placebo})$ ). We found no significant difference between baselines values for the 15 trials considered together. We then applied a random effect model on differences between intervention and placebo groups in changes in %HbA1c observed during trials. The corresponding variances were also computed with the delta method. The following Table summarizes results obtained with Method 2.

All results were very close to zero, meaning an absence of impact of vitamin D supplementation on changes in the proportion of blood hemoglobin circulating under the form of Hb1Ac. Of note, there was no heterogeneity in results, meaning that all trials obtained very similar results. The similarity in results and the absence of heterogeneity in results is best illustrated with a Forrest plot (see below).

**Method 2: random effect applied to differences between intervention and placebo groups.**

Included trials	Summary difference between intervention and control groups in changes in %HbA1c during trials	95% CI, lower bound	95% CI, upper bound	I <sup>2</sup>
All 16	-0.01	-0.25	0.23	0
Dose $\leq$ 92.5 $\mu$ g/day	0.04	-0.30	0.38	0
Dose > 92.5 $\mu$ g/day	-0.08	-0.50	0.34	0
Duration $\leq$ 4 months	-0.01	-0.37	0.34	0
Duration > 4 months	0.00	-0.42	0.41	0
Diabetic	-0.02	-0.38	0.35	0
Non-diabetic	0.00	-0.40	0.39	0



## Webappendix 5: References of articles in Tables in the text and Tables in supplementary materials

References are listed by order of appearance in the Table.

**Table 1 - Meta- or pooled analyses of prospective cohort studies**

1. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. *Prev Med* 2010; **51**(3-4):228-33.
2. Sun Q, Pan A, Hu FB, Manson JE, Rexrode KM. 25-Hydroxyvitamin D levels and the risk of stroke: a prospective study and meta-analysis. *Stroke* 2012; **43**(6):1470-7.
3. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, Lichtenstein AH, Lau J, Balk EM. Systematic review: Vitamin D and cardiometabolic outcomes. *Ann Intern Med* 2010; **152**(5):307-14.
4. Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, Clarke A, Franco OH. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. *Maturitas* 2010; **65**(3):225-36.
5. Sokol SI, Tsang P, Aggarwal V, Melamed ML, Srinivas VS. Vitamin D status and risk of cardiovascular events: lessons learned via systematic review and meta-analysis. *Cardiol Rev* 2011; **19**(4):192-201.
6. Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal, SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes* 2012; **5**(6):819-29.
7. Chowdhury R, Stevens S, Ward H, Chowdhury S, Sajjad A, Franco OH. Circulating vitamin D, calcium and risk of cerebrovascular disease: a systematic review and meta-analysis. *Eur J Epidemiol* 2012; **27**(8):581-91.
8. Song GG, Bae SC, Lee YH. Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. *Clin Rheumatol* 2012; **31**(12):1733-9.
9. Afzal S, Bojesen SE, Nordestgaard BG. Low 25-Hydroxyvitamin D and Risk of Type 2 Diabetes: A Prospective Cohort Study and Meta-analysis. *Clin Chem* 2013; **59**(2):381-91.
10. Khan H, Kunutsor S, Franco OH, Chowdhury R. Vitamin D, type 2 diabetes and other metabolic outcomes: a systematic review and meta-analysis of prospective studies. *Proc Nutr Soc* 2012; **30**:1-9.
11. Gandini S, Boniol M, Haukka J, Byrnes G, Cox B, Sneyd MJ, Mullie P, Autier P. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer. *Int J Cancer* 2011; **128**(6):1414-24.
12. Lee DM, Tajar A, O'Neill TW, O'Connor DB, Bartfai G, Boonen S, Bouillon R, Casanueva FF, Finn JD, Forti G, Giwercman A, Han TS, Huhtaniemi IT, Kula K, Lean ME, Punab M, Silman AJ, Vanderschueren D, Wu FC, Pendleton N; EMAS study group. Lower vitamin D levels are associated with depression among community-dwelling European men. *J Psychopharmacol* 2011; **25**(10):1320-8.
13. Abnet CC, Chen Y, Chow WH, Gao YT, Helzlsouer KJ, Le Marchand L, McCullough ML, Shikany JM, Virtamo J, Weinstein SJ, Xiang YB, Yu K, Zheng W, Albanes D, Arslan AA, Campbell DS, Campbell PT, Hayes RB, Horst RL, Kolonel LN, Nomura AM, Purdue MP, Snyder K, Shu XO. Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; **172**(1):94-106.
14. Zheng W, Danforth KN, Tworoger SS, Goodman MT, Arslan AA, Patel AV, McCullough ML, Weinstein SJ, Kolonel LN, Purdue MP, Shu XO, Snyder K, Steplowski E, Visvanathan K, Yu K, Zeleniuch-Jacquotte A, Gao YT, Hankinson SE, Harvey C, Hayes RB, Henderson BE, Horst RL, Helzlsouer KJ. Circulating 25-hydroxyvitamin D and risk of epithelial ovarian cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; **172**(1):70-80.
15. Zeleniuch-Jacquotte A, Gallicchio L, Hartmuller V, Helzlsouer KJ, McCullough ML, Setiawan VW, Shu XO, Weinstein SJ, Weiss JM, Arslan AA, De Vivo I, Gao YT, Hayes RB, Henderson BE, Horst RL, Koenig KL, Patel AV, Purdue MP, Snyder K, Steplowski E, Yu K, Zheng W, Hankinson SE. Circulating 25-hydroxyvitamin D and risk of endometrial cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; **172**(1):36-46.
16. Purdue MP, Freedman DM, Gapstur SM, Helzlsouer KJ, Laden F, Lim U, Maskarinec G, Rothman N, Shu XO, Stevens VL, Zeleniuch-Jacquotte A, Albanes D, Bertrand K, Weinstein SJ, Yu K, Irish L, Horst RL, Hoffman-

- Bolton J, Giovannucci EL, Kolonel LN, Snyder K, Willett W, Arslan AA, Hayes RB, Zheng W, Xiang YB, Hartge P. Circulating 25-hydroxyvitamin D and risk of non-hodgkin lymphoma: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; **172**(1):58-69.
17. Gallicchio L, Moore LE, Stevens VL, Ahn J, Albanes D, Hartmuller V, Setiawan VW, Helzlsouer KJ, Yang G, Xiang YB, Shu XO, Snyder K, Weinstein SJ, Yu K, Zeleniuch-Jacquotte A, Zheng W, Cai Q, Campbell DS, Chen Y, Chow WH, Horst RL, Kolonel LN, McCullough ML, Purdue MP, Koenig KL. Circulating 25-hydroxyvitamin D and risk of kidney cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; **172**(1):47-57.
  18. Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, Qi D, Patel AV, Helzlsouer KJ, Weinstein SJ, McCullough ML, Purdue MP, Shu XO, Snyder K, Virtamo J, Wilkins LR, Yu K, Zeleniuch-Jacquotte A, Zheng W, Albanes D, Cai Q, Harvey C, Hayes R, Clipp S, Horst RL, Irish L, Koenig K, Le Marchand L, Kolonel LN. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; **172**(1):81-93.
  19. Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. *Am J Clin Nutr* 2012; **95**(1):91-100.
  20. Pilz S, Iodice S, Zittermann A, Grant WB, Gandini S. Vitamin D status and mortality risk in CKD: A meta-analysis of prospective studies. *Am J Kidney Dis* 2011; **58**(3):374-82.

**Table 2 - Prospective cohort studies not included in meta-analyses**

1. Karakas M, Thorand B, Zierer A, Huth C, Meisinger C, Roden M, Rottbauer W, Peters A, Koenig W, Herder C. Low Levels of Serum 25-Hydroxyvitamin D Are Associated with Increased Risk of Myocardial Infarction, Especially in Women: Results from the MONICA/KORA Augsburg Case-Cohort Study. *J Clin Endocrinol Metab* 2013; **98**(1):272-80.
2. Skaaby T, Husemoen LL, Pisinger C, Jørgensen T, Thuesen BH, Fenger M, Linneberg A. Vitamin D status and incident cardiovascular disease and all-cause mortality: a general population study. *Endocrine*. 2012 Sep 27. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. *Prev Med* 2010; **51**(3-4):228-33.
3. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. *Prev Med* 2010; **51**(3-4):228-33.
4. Bittner V, Wenger NK, Waters DD, DeMicco DA, Messig M, LaRosa JC. Vitamin D levels do not predict cardiovascular events in statin-treated patients with stable coronary disease. *Am Heart J* 2012; **164**(3):387-93.
5. Brøndum-Jacobsen P, Nordestgaard BG, Schnohr P, Benn M. 25-Hydroxyvitamin D and symptomatic ischemic stroke: An Original Study and Meta-Analysis. *Ann Neurol* 2013; **73**(1):38-47.
6. Sun Q, Pan A, Hu FB, Manson JE, Rexrode KM. 25-Hydroxyvitamin D levels and the risk of stroke: a prospective study and meta-analysis. *Stroke* 2012; **43**(6):1470-7.
7. Skaaby T, Husemoen LL, Pisinger C, Jørgensen T, Thuesen BH, Fenger M, Linneberg A. Vitamin D status and changes in cardiovascular risk factors: a prospective study of a general population. *Cardiology* 2012; **123**(1):62-70.
8. de Boer IH, Kestenbaum B, Shoben AB, Michos ED, Sarnak MJ, Siscovick DS. 25-hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification. *J Am Soc Nephrol* 2009; **20**(8):1805-12.
9. Welsh P, Doolin O, McConnachie A, Boulton E, McNeil G, Macdonald H, Hardcastle A, Hart C, Upton M, Watt G, Sattar N. Circulating 25OHD, dietary vitamin D, PTH, and calcium associations with incident cardiovascular disease and mortality: the MIDSPAN Family Study. *J Clin Endocrinol Metab* 2012; **97**(12):4578-87.
10. Zhao G, Ford ES, Li C, Croft JB. Serum 25-hydroxyvitamin D levels and all-cause and cardiovascular disease mortality among US adults with hypertension: the NHANES linked mortality study. *J Hypertens* 2012; **30**(2):284-9.
11. Lin SW, Chen W, Fan JH, Dawsey SM, Taylor PR, Qiao YL, Abnet CC. Prospective study of serum 25-hydroxyvitamin D concentration and mortality in a Chinese population. *Am J Epidemiol* 2012; **176**(11):1043-50.
12. Thomas GN, Ó Hartaigh B, Bosch JA, Pilz S, Loerbroks A, Kleber ME, Fischer JE, Grammer TB, Böhm BO, März W. Vitamin D levels predict all-cause and cardiovascular disease mortality in subjects with the metabolic

- syndrome: the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. *Diabetes Care* 2012; **35**(5):1158-64.
13. Signorello LB, Han X, Cai Q, Cohen SS, Cope EL, Zheng W, Blot WJ. A prospective study of serum 25-hydroxyvitamin D levels and mortality among African Americans and non-African Americans. *Am J Epidemiol* 2013; **177**(2):171-9.
  14. Agborsangaya CB, Surcel HM, Toriola AT, Pukkala E, Parkkila S, Tuohimaa P, Lukanova A, Lehtinen M. Serum 25-hydroxyvitamin D at pregnancy and risk of breast cancer in a prospective study. *Eur J Cancer* 2010; **46**(3):467-70.
  15. Almquist M, Bondeson AG, Bondeson L, Malm J, Manjer J. Serum levels of vitamin D, PTH and calcium and breast cancer risk—a prospective nested case-control study. *Int J Cancer* 2010; **127**(9):2159-68.
  16. Engel P, Fagherazzi G, Bouillon I, Dupré T, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Serum 25(OH) vitamin D and risk of breast cancer: a nested case-control study from the French E3N cohort. *Cancer Epidemiol Biomarkers Prev* 2010; **19**(9):2341-50.
  17. Eliassen AH, Spiegelman D, Hollis BW, Horst RL, Willett WC, Hankinson SE. Plasma 25-hydroxyvitamin D and risk of breast cancer in the Nurses' Health Study II. *Breast Cancer Res* 2011; **13**(3):R50.
  18. Amir E, Cecchini RS, Ganz PA, Costantino JP, Beddows S, Hood N, Goodwin PJ. 25-Hydroxy vitamin-D, obesity, and associated variables as predictors of breast cancer risk and tamoxifen benefit in NSABP-P1. *Breast Cancer Res Treat* 2012; **133**(3):1077-88. Erratum in: *Breast Cancer Res Treat* 2012; **135**(3):923.
  19. Weinstein SJ, Yu K, Horst RL, Ashby J, Virtamo J, Albanes D. Serum 25-hydroxyvitamin D and risks of colon and rectal cancer in Finnish men. *Am J Epidemiol* 2011; **173**(5):499-508.
  20. Park SY, Cooney RV, Wilkens LR, Murphy SP, Henderson BE, Kolonel LN. Plasma 25-hydroxyvitamin D and prostate cancer risk: the multiethnic cohort. *Eur J Cancer* 2010; **46**(5):932-6.
  21. Meyer HE, Rødsahl TE, Bjørge T, Brustad M, Blomhoff R. Vitamin D, season, and risk of prostate cancer: a nested case-control study within Norwegian health studies. *Am J Clin Nutr* 2013; **97**(1):147-54.
  22. Chen W, Dawsey SM, Qiao YL, Mark SD, Dong ZW, Taylor PR, Zhao P, Abnet CC. Prospective study of serum 25(OH)-vitamin D concentration and risk of oesophageal and gastric cancers. *Br J Cancer* 2007; **97**(1):123-8.
  23. Mondul AM, Weinstein SJ, Männistö S, Snyder K, Horst RL, Virtamo J, Albanes D. Serum vitamin D and risk of bladder cancer. *Cancer Res* 2010; **70**(22):9218-23.
  24. Arem H, Weinstein SJ, Horst RL, Virtamo J, Yu K, Albanes D, Abnet CC. Serum 25-hydroxyvitamin D and risk of oropharynx and larynx cancers in Finnish men. *Cancer Epidemiol Biomarkers Prev* 2011; **20**(6):1178-84.
  25. Tang JY, Parimi N, Wu A, Boscardin WJ, Shikany JM, Chren MM, Cummings SR, Epstein EH Jr, Bauer DC; Osteoporotic Fractures in Men (MrOS) Study Group. Inverse association between serum 25(OH) vitamin D levels and non-melanoma skin cancer in elderly men. *Cancer Causes Control* 2010; **21**(3):387-91.
  26. van der Pols JC, Russell A, Bauer U, Neale RE, Kimlin MG, Green AC. Vitamin D Status and Skin Cancer Risk Independent of Time Outdoors: 11-Year Prospective Study in an Australian Community. *J Invest Dermatol* 2013; **133**(3):637-41.
  27. Afzal S, Nordestgaard BG, Bojesen SE. Plasma 25-Hydroxyvitamin D and Risk of Non-Melanoma and Melanoma Skin Cancer: A Prospective Cohort Study. *J Invest Dermatol* 2013; **133**(3):629-36.
  28. Michaëlsson K, Baron JA, Snellman G, Gedeberg R, Byberg L, Sundström J, Berglund L, Arnlöv J, Hellman P, Blomhoff R, Wolk A, Garmo H, Holmberg L, Melhus H. Plasma vitamin D and mortality in older men: a community-based prospective cohort study. *Am J Clin Nutr* 2010; **92**(4):841-8.
  29. Bolland MJ, Bacon CJ, Horne AM, Mason BH, Ames RW, Wang TK, Grey AB, Gamble GD, Reid IR. Vitamin D insufficiency and health outcomes over 5 y in older women. *Am J Clin Nutr* 2010; **91**(1):82-9.
  30. Freedman DM, Looker AC, Chang SC, Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. *J Natl Cancer Inst* 2007; **99**(21):1594-602.
  31. Bodnar LM, Krohn MA, Simhan HN. Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. *J Nutr* 2009; **139**(6):1157-61.
  32. Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamäki H, Ylikomi T. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr* 2007; **86**(3):714-7.
  33. Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML. Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* 2010; **5**(6):e11088.
  34. Berry DJ, Hesketh K, Power C, Hyppönen E. Vitamin D status has a linear association with seasonal infections and lung function in British adults. *Br J Nutr* 2011; **106**(9):1433-40.

35. Quint JK, Donaldson GC, Wassef N, Hurst JR, Thomas M, Wedzicha JA. 25-hydroxyvitamin D deficiency, exacerbation frequency and human rhinovirus exacerbations in chronic obstructive pulmonary disease. *BMC Pulm Med* 2012;**12**:28.
36. Kunisaki KM, Niewoehner DE, Connett JE; COPD Clinical Research Network. Vitamin D levels and risk of acute exacerbations of chronic obstructive pulmonary disease: a prospective cohort study. *Am J Respir Crit Care Med* 2012; **185**(3):286-90.
37. Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psychiatry* 2008; **65**(5):508-12.
38. Milanesechi Y, Shardell M, Corsi AM, Vazzana R, Bandinelli S, Guralnik JM, Ferrucci L. Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. *J Clin Endocrinol Metab* 2010; **95**(7):3225-33.
39. Chan R, Chan D, Woo J, Ohlsson C, Mellström D, Kwok T, Leung P. Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. *J Affect Disord* 2011; **130**(1-2):251-9.
40. Lee DM, Tajar A, O'Neill TW, O'Connor DB, Bartfai G, Boonen S, Bouillon R, Casanueva FF, Finn JD, Forti G, Giwercman A, Han TS, Huhtaniemi IT, Kula K, Lean ME, Punab M, Silman AJ, Vanderschueren D, Wu FC, Pendleton N; EMAS study group. Lower vitamin D levels are associated with depression among community-dwelling European men. *J Psychopharmacol* 2011; **25**(10):1320-8.
41. May HT, Bair TL, Lappé DL, Anderson JL, Horne BD, Carlquist JF, Muhlestein JB. Association of vitamin D levels with incident depression among a general cardiovascular population. *Am Heart J* 2010; **159**(6):1037-43.
42. Knekt P, Kilkkinen A, Rissanen H, Marniemi J, Sääksjärvi K, Heliövaara M. Serum vitamin D and the risk of Parkinson disease. *Arch Neurol* 2010; **67**(7):808-11.
43. Llewellyn DJ, Lang IA, Langa KM, Muniz-Terrera G, Phillips CL, Cherubini A, Ferrucci L, Melzer D. Vitamin D and risk of cognitive decline in elderly persons. *Arch Intern Med* 2010; **170**(13):1135-41.
44. Slinin Y, Paudel ML, Taylor BC, Fink HA, Ishani A, Canales MT, Yaffe K, Barrett-Connor E, Orwoll ES, Shikany JM, Leblanc ES, Cauley JA, Ensrud KE; Osteoporotic Fractures in Men (MrOS) Study Research Group. 25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men. *Neurology* 2010; **74**(1):33-41.
45. Slinin Y, Paudel M, Taylor BC, Ishani A, Rossom R, Yaffe K, Blackwell T, Lui LY, Hochberg M, Ensrud KE; Study of Osteoporotic Fractures Research Group. Association between serum 25(OH) vitamin D and the risk of cognitive decline in older women. *J Gerontol A Biol Sci Med Sci* 2012; **67**(10):1092-8.
46. Breitling LP, Perna L, Müller H, Raum E, Kliegel M, Brenner H. Vitamin D and cognitive functioning in the elderly population in Germany. *Exp Gerontol* 2012; **47**(1):122-7.
47. Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, Beauchet O. Serum vitamin D deficiency as a predictor of incident non-Alzheimer dementias: a 7-year longitudinal study. *Dement Geriatr Cogn Disord* 2011; **32**(4):273-8.
48. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; **296**(23):2832-8.
49. Løken-Amsrud KI, Holmøy T, Bakke SJ, Beiske AG, Bjerve KS, Bjørnarå BT, Hovdal H, Lilleås F, Midgard R, Pedersen T, Benth JS, Sandvik L, Torkildsen O, Wergeland S, Myhr KM. Vitamin D and disease activity in multiple sclerosis before and during interferon- $\beta$  treatment. *Neurology* 2012; **79**(3):267-73.
50. Runia TF, Hop WC, de Rijke YB, Buljevac D, Hintzen RQ. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology* 2012; **79**(3):261-6.
51. Bates CJ, Hamer M, Mishra GD. A study of relationships between bone-related vitamins and minerals, related risk markers, and subsequent mortality in older British people: the National Diet and Nutrition Survey of People Aged 65 Years and Over. *Osteoporos Int* 2012; **23**(2):457-66.
52. Blicher TM, Jørgensen HL, Schwarz P, Wulf HC. Low levels of vitamin D are associated with increased mortality in patients attending a university hospital in Denmark. *Scand J Clin Lab Invest*. 2013 Feb;**73**(1):24-8.
53. Fang F, Kasperzyk JL, Shui I, Hendrickson W, Hollis BW, Fall K, Ma J, Gaziano JM, Stampfer MJ, Mucci LA, Giovannucci E. Prediagnostic plasma vitamin D metabolites and mortality among patients with prostate cancer. *PLoS One* 2011; **6**(4):e18625.
54. Fedirko V, Riboli E, Tjønneland A, Ferrari P, Olsen A, Bueno-de-Mesquita HB, van Duynhoven FJ, Norat T, Jansen EH, Dahm CC, Overvad K, Boutron-Ruault MC, Clavel-Chapelon F, Racine A, Lukanova A, Teucher B, Boeing H, Aleksandrova K, Trichopoulou A, Benetou V, Trichopoulos D, Grioni S, Vineis P, Panico S, Palli D, Tumino R, Siersema PD, Peeters PH, Skeie G, Brustad M, Chirlaque MD, Barricarte A, Ramón Quirós J,

- Sánchez MJ, Dorronsoro M, Bonet C, Palmqvist R, Hallmans G, Key TJ, Crowe F, Khaw KT, Wareham N, Romieu I, McKay J, Wark PA, Romaguera D, Jenab M. Prediagnostic 25-hydroxyvitamin D, VDR and CASR polymorphisms, and survival in patients with colorectal cancer in western European populations. *Cancer Epidemiol Biomarkers Prev* 2012; **21**(4):582-93.
55. Joergensen C, Gall MA, Schmedes A, Tarnow L, Parving HH, Rossing P. Vitamin D levels and mortality in type 2 diabetes. *Diabetes Care* 2010; **33**(10):2238-43.
  56. Joergensen C, Hovind P, Schmedes A, Parving HH, Rossing P. Vitamin D levels, microvascular complications, and mortality in type 1 diabetes. *Diabetes Care* 2011; **34**(5):1081-5.
  57. Remmelts HH, van de Garde EM, Meijvis SC, Peelen EL, Damoiseaux JG, Grutters JC, Biesma DH, Bos WJ, Rijkers GT. Addition of vitamin D status to prognostic scores improves the prediction of outcome in community-acquired pneumonia. *Clin Infect Dis* 2012; **55**(11):1488-94.
  58. Saliba W, Barnett O, Rennert HS, Rennert G. The risk of all-cause mortality is inversely related to serum 25(OH)D levels. *J Clin Endocrinol Metab* 2012; **97**(8):2792-8.
  59. Virtanen JK, Nurmi T, Voutilainen S, Mursu J, Tuomainen TP. Association of serum 25-hydroxyvitamin D with the risk of death in a general older population in Finland. *Eur J Nutr* 2011; **50**(5):305-12.
  60. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, Lappé DL, Muhlestein JB; Intermountain Heart Collaborative (IHC) Study Group. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol* 2010; **106**(7):963-8.
  61. de Boer IH, Levin G, Robinson-Cohen C, Biggs ML, Hoofnagle AN, Siscovick DS, Kestenbaum B. Serum 25-hydroxyvitamin D concentration and risk for major clinical disease events in a community-based population of older adults: a cohort study. *Ann Intern Med* 2012; **156**(9):627-34.
  62. Ensrud KE, Blackwell TL, Cauley JA, Cummings SR, Barrett-Connor E, Dam TT, Hoffman AR, Shikany JM, Lane NE, Stefanick ML, Orwoll ES, Cawthon PM. Osteoporotic Fractures in Men Study Group. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. *J Am Geriatr Soc* 2011; **59**(1):101-6.
  63. Puts MT, Visser M, Twisk JW, Deeg DJ, Lips P. Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol (Oxf)* 2005; **63**(4):403-11.
  64. Pilz S, Dobnig H, Winklhofer-Roob B, Riedmüller G, Fischer JE, Seelhorst U, Wellnitz B, Boehm BO, März W. Low serum levels of 25-hydroxyvitamin D predict fatal cancer in patients referred to coronary angiography. *Cancer Epidemiol Biomarkers Prev* 2008; **17**(5):1228-33.
  65. Albanes A, Mondul AM, Yu K, Parisi D, Horst H, Virtamo J, Weinstein SJ. Serum 25-Hydroxy Vitamin D and Prostate Cancer Risk in a Large Nested Case–Control Study. *Cancer Epidemiol Biomarkers Prev* 2011; **20**(9); 1850–60.
  66. Michael YL, Smit E, Seguin R, Curb JD, Phillips LS, Manson JE. Serum 25-hydroxyvitamin D and physical performance in postmenopausal women. *J Womens Health (Larchmt)* 2011; **20**(11):1603-8.
  67. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, Knol DL, Lips P. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 2007; **92**(6):2058-65.
  68. Verreault R, Semba RD, Volpato S, Ferrucci L, Fried LP, Guralnik JM. Low serum vitamin d does not predict new disability or loss of muscle strength in older women. *J Am Geriatr Soc* 2002; **50**(5):912-7.
  69. Chan R, Chan D, Woo J, Ohlsson C, Mellström D, Kwok T, Leung PC. Not all elderly people benefit from vitamin D supplementation with respect to physical function: results from the Osteoporotic Fractures in Men Study, Hong Kong. *J Am Geriatr Soc* 2012; **60**(2):290-5.
  70. Correia LC, Sodré F, Garcia G, Sabino M, Brito M, Kalil F, Barreto B, Lima JC, Noya-Rabelo MM. Relation of severe deficiency of vitamin D to cardiovascular mortality during acute coronary syndromes. *Am J Cardiol* 2013; **111**(3):324-7.
  71. Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, Køber L, Jensen JE. Vitamin D deficiency in postmenopausal, healthy women predicts increased cardiovascular events: a 16-year follow-up study. *Eur J Endocrinol* 2012; **167**(4):553-60.

**Table 3 - Cancer survival studies**

1. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N. Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. *J Clin Oncol* 2009; **27**(23):3757-63.
2. Yao S, Sucheston LE, Millen AE, Johnson CS, Trump DL, Nesline MK, Davis W, Hong CC, McCann SE, Hwang H, Kulkarni S, Edge SB, O'Connor TL, Ambrosone CB. Pretreatment serum concentrations of 25-

- hydroxyvitamin D and breast cancer prognostic characteristics: a case-control and a case-series study. *PLoS One* 2011; **6**(2):e17251.
3. Kim HJ, Lee YM, Ko BS, Lee JW, Yu JH, Son BH, Gong GY, Kim SB, Ahn SH. Vitamin D deficiency is correlated with poor outcomes in patients with luminal-type breast cancer. *Ann Surg Oncol* 2011; **18**(7):1830-6.
  4. Peppone LJ, Rickles AS, Janelsins MC, Insalaco MR, Skinner KA. The association between breast cancer prognostic indicators and serum 25-OH vitamin D levels. *Ann Surg Oncol* 2012; **19**(8):2590-9.
  5. Ng K, Meyerhardt JA, Wu K, Feskanich D, Hollis BW, Giovannucci EL, Fuchs CS. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. *J Clin Oncol* 2008; **26**(18):2984-91.
  6. Ng K, Sargent DJ, Goldberg RM, Meyerhardt JA, Green EM, Pitot HC, Hollis BW, Pollak MN, Fuchs CS. Vitamin D status in patients with stage IV colorectal cancer: findings from Intergroup trial N9741. *J Clin Oncol* 2011; **29**(12):1599-606.
  7. Fedirko V, Riboli E, Tjønneland A, Ferrari P, Olsen A, Bueno-de-Mesquita HB, van Duijnhoven FJ, Norat T, Jansen EH, Dahm CC, Overvad K, Boutron-Ruault MC, Clavel-Chapelon F, Racine A, Lukanova A, Teucher B, Boeing H, Aleksandrova K, Trichopoulou A, Benetou V, Trichopoulos D, Grioni S, Vineis P, Panico S, Palli D, Tumino R, Siersema PD, Peeters PH, Skeie G, Brustad M, Chirlaque MD, Barricarte A, Ramón Quirós J, Sánchez MJ, Dorronsoro M, Bonet C, Palmqvist R, Hallmans G, Key TJ, Crowe F, Khaw KT, Wareham N, Romieu I, McKay J, Wark PA, Romaguera D, Jenab M. Prediagnostic 25-hydroxyvitamin D, VDR and CASR polymorphisms, and survival in patients with colorectal cancer in western European populations. *Cancer Epidemiol Biomarkers Prev* 2012; **21**(4):582-93.
  8. Fang F, Kasperzyk JL, Shui I, Hendrickson W, Hollis BW, Fall K, Ma J, Gaziano JM, Stampfer MJ, Mucci LA, Giovannucci E. Prediagnostic plasma vitamin D metabolites and mortality among patients with prostate cancer. *PLoS One* 2011; **6**(4):e18625.
  9. Meyer F, Liu G, Douville P, Samson E, Xu W, Adjei A, Bairati I. Dietary vitamin D intake and serum 25-hydroxyvitamin D level in relation to disease outcomes in head and neck cancer patients. *Int J Cancer* 2011; **128**(7):1741-6.
  10. Zhou W, Heist RS, Liu G, Asomaning K, Neuberg DS, Hollis BW, Wain JC, Lynch TJ, Giovannucci E, Su L, Christiani DC. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. *J Clin Oncol* 2007; **25**(5):479-85.
  11. Newton-Bishop JA, Beswick S, Randerson-Moor J, Chang YM, Affleck P, Elliott F, Chan M, Leake S, Karpavicius B, Haynes S, Kukalich K, Whitaker L, Jackson S, Gerry E, Nolan C, Bertram C, Marsden J, Elder DE, Barrett JH, Bishop DT. Serum 25-hydroxyvitamin D3 levels are associated with breslow thickness at presentation and survival from melanoma. *J Clin Oncol* 2009; **27**(32):5439-44.

#### **Table 4 - Meta-analyses of randomised controlled trials**

1. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 2010; **152**(5):315-23.
2. Elamin MB, Abu Elnour NO, Elamin KB, Fatourehchi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Hazem A, Erwin PJ, Hensrud DD, Murad MH, Montori VM. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; **96**(7):1931-42.
3. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev* 2011; (7):CD007470.
4. Wang H, Xia N, Yang Y, Peng DQ. Influence of vitamin D supplementation on plasma lipid profiles: a meta-analysis of randomized controlled trials. *Lipids Health Dis* 2012; **11**:42.
5. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2011; **59**(12):2291-300.
6. Stockton KA, Kandiah DA, Paratz JD, Bennell KL. Fatigue, muscle strength and vitamin D status in women with systemic lupus erythematosus compared with healthy controls. *Lupus* 2012; **21**(3):271-8.
7. Rejnmark L, Avenell A, Masud T, Anderson F, Meyer HE, Sanders KM, Salovaara K, Cooper C, Smith HE, Jacobs ET, Torgerson D, Jackson RD, Manson JE, Brixen K, Mosekilde L, Robbins JA, Francis RM, Abrahamsen B. Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. *J Clin Endocrinol Metab* 2012; **97**(8):2670-81.
8. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, Lichtenstein AH, Lau J, Balk EM. Systematic review: Vitamin D and cardiometabolic outcomes. *Ann Intern Med* 2010; **152**(5):307-14.



**Table 5 - Randomised controlled trials not included in meta-analyses**

1. Manson JE, Allison MA, Carr JJ, Langer RD, Cochrane BB, Hendrix SL, Hsia J, Hunt JR, Lewis CE, Margolis KL, Robinson JG, Rodabough RJ, Thomas AM; Women's Health Initiative and Women's Health Initiative-Coronary Artery Calcium Study Investigators. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. *Menopause* 2010; **17**(4):683-91.
2. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. *Diabet Med* 2008; **25**(3):320-5.
3. Harris RA, Pedersen-White J, Guo DH, Stallmann-Jorgensen IS, Keeton D, Huang Y, Shah Y, Zhu H, Dong Y. Vitamin D3 supplementation for 16 weeks improves flow-mediated dilation in overweight African-American adults. *Am J Hypertens* 2011; **24**(5):557-62.
4. Longenecker CT, Hileman CO, Carman TL, Ross AC, Seydafkan S, Brown TT, Labbato DE, Storer N, Tangpricha V, McComsey GA. Vitamin D supplementation and endothelial function in vitamin D deficient HIV-infected patients: a randomized placebo-controlled trial. *Antivir Ther* 2012; **17**(4):613-21.
5. Dong Y, Stallmann-Jorgensen IS, Pollock NK, Harris RA, Keeton D, Huang Y, Li K, Bassali R, Guo DH, Thomas J, Pierce GL, White J, Holick MF, Zhu H. A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. *J Clin Endocrinol Metab* 2010; **95**(10):4584-91.
6. Sokol SI, Srinivas V, Crandall JP, Kim M, Tellides G, Lebastchi A, Yu Y, Gupta AK, Alderman MH. The effects of vitamin D repletion on endothelial function and inflammation in patients with coronary artery disease. *Vasc Med* 2012; **17**(6):394-404.
7. Stricker H, Tosi Bianda F, Guidicelli-Nicolosi S, Limoni C, Colucci G. Effect of a single, oral, high-dose vitamin D supplementation on endothelial function in patients with peripheral arterial disease: a randomised controlled pilot study. *Eur J Vasc Endovasc Surg* 2012; **44**(3):307-12.
8. Yiu YF, Yiu KH, Siu CW, Chan YH, Li SW, Wong LY, Lee SW, Tam S, Wong EW, Lau CP, Cheung BM, Tse HF. Randomized controlled trial of vitamin D supplement on endothelial function in patients with type 2 diabetes. *Atherosclerosis* 2013; **227**(1): 140-6.
9. Orwoll ES, Oviatt S. Relationship of mineral metabolism and long-term calcium and cholecalciferol supplementation to blood pressure in normotensive men. *Am J Clin Nutr* 1990; **52**(4):717-21.
10. Margolis KL, Ray RM, Van Horn L, Manson JE, Allison MA, Black HR, Beresford SA, Connelly SA, Curb JD, Grimm RH Jr, Kotchen TA, Kuller LH, Wassertheil-Smoller S, Thomson CA, Torner JC; Women's Health Initiative Investigators. Effect of calcium and vitamin D supplementation on blood pressure: the Women's Health Initiative Randomized Trial. *Hypertension* 2008; **52**(5):847-55.
11. Maki KC, Rubin MR, Wong LG, McManus JF, Jensen CD, Lawless A. Effects of vitamin D supplementation on 25-hydroxyvitamin D, high-density lipoprotein cholesterol, and other cardiovascular disease risk markers in subjects with elevated waist circumference. *Int J Food Sci Nutr* 2011; **62**(4):318-27.
12. Larsen T, Mose FH, Bech JN, Hansen AB, Pedersen EB. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. *Am J Hypertens* 2012; **25**(11):1215-22.
13. Gepner AD, Ramamurthy R, Krueger DC, Korcarz CE, Binkley N, Stein JH. A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. *PLoS One* 2012; **7**(5):e36617.
14. Wood AD, Secombes KR, Thies F, Aucott L, Black AJ, Mavroeidi A, Simpson WG, Fraser WD, Reid DM, Macdonald HM. Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. *J Clin Endocrinol Metab* 2012; **97**(10):3557-68.
15. Patel P, Poretsky L, Liao E. Lack of effect of subtherapeutic vitamin D treatment on glycemic and lipid parameters in Type 2 diabetes: A pilot prospective randomized trial. *J Diabetes* 2010; **2**(1):36-40.
16. Grimnes G, Figenschau Y, Almås B, Jorde R. Vitamin D, insulin secretion, sensitivity, and lipids: results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique. *Diabetes* 2011; **60**(11):2748-57.
17. Ponda MP, Dowd K, Finkelstein D, Holt PR, Breslow JL. The short-term effects of vitamin D repletion on cholesterol: a randomized, placebo-controlled trial. *Arterioscler Thromb Vasc Biol* 2012; **32**(10):2510-5.
18. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2006; **83**(4):754-9.
19. Pittas AG, Stark PC, Harris SS, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in non-diabetic adults. *Diab Care* 2007; **30**: 980-6.

20. Bjorkman MP, Sorva AJ, Tilvis RS. C-reactive protein and fibrinogen of bedridden older patients in a six-month vitamin D supplementation trial. *J Nutr Health Aging* 2009; **13**(5):435-9.
21. Jorde R, Sneve M, Torjesen PA, Figenschau Y, Gøransson LG, Omdal R. No effect of supplementation with cholecalciferol on cytokines and markers of inflammation in overweight and obese subjects. *Cytokine* 2010; **50**(2):175-80.
22. Yusupov E, Li-Ng M, Pollack S, Yeh JK, Mikhail M, Aloia JF. Vitamin d and serum cytokines in a randomized clinical trial. *Int J Endocrinol* 2010; 2010.
23. de Boer IH, Tinker LF, Connelly S, Curb JD, Howard BV, Kestenbaum B, Larson JC, Manson JE, Margolis KL, Siscovick DS, Weiss NS; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. *Diabetes Care* 2008; **31**(4):701-7.
24. Avenell A, Cook JA, MacLennan GS, McPherson GC; RECORD trial group. Vitamin D supplementation and type 2 diabetes: a substudy of a randomized placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing* 2009; **38**(5):606-9.
25. Jorde R, Figenschau Y. Supplementation with cholecalciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. *Eur J Nutr* 2009; **48**(6):349-54.
26. Zittermann A, Frisch S, Berthold HK, Götting C, Kuhn J, Kleesiek K, Stehle P, Koertke H, Koerfer R. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr* 2009; **89**(5):1321-7.
27. Parekh D, Sarathi V, Shivane VK, Bandgar TR, Menon PS, Shah NS. Pilot study to evaluate the effect of short-term improvement in vitamin D status on glucose tolerance in patients with type 2 diabetes mellitus. *Endocr Pract* 2010; **16**(4):600-8.
28. Witham MD, Crighton LJ, Gillespie ND, Struthers AD, McMurdo ME. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circ Heart Fail* 2010; **3**(2):195-201.
29. Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. *Eur J Clin Nutr* 2011; **65**(9):1005-15.
30. Kota SK, Jammula S, Kota SK, Tripathy PR, Panda S, Modi KD. Effect of vitamin D supplementation in type 2 diabetes patients with pulmonary tuberculosis. *Diabetes Metab Syndr* 2011; **5**(2):85-9.
31. Mozaffari-Khosravi H, Hosseinzadeh-Shamsi-Anar M, Salami MA, Hadinedoushan H, Mozayan MR. Effects of a single post-partum injection of a high dose of vitamin D on glucose tolerance and insulin resistance in mothers with first-time gestational diabetes mellitus. *Diabet Med* 2012; **29**(1):36-42.
32. Harris SS, Pittas AG, Palermo NJ. A randomized, placebo-controlled trial of vitamin D supplementation to improve glycaemia in overweight and obese African Americans. *Diabetes Obes Metab* 2012; **14**(9):789-94.
33. Davidson MB, Duran P, Lee ML, Friedman TC. High-Dose Vitamin D Supplementation in People With Prediabetes and Hypovitaminosis D. *Diabetes Care* 2013; **36**(2):260-6.
34. Nilas L, Christiansen C. Treatment with vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. *Int J Obes* 1984; **8**(5):407-11.
35. von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. *Br J Nutr* 2010; **103**(4):549-55.
36. Bock G, Prietl B, Mader JK, Höller E, Wolf M, Pilz S, Graninger WB, Obermayer-Pietsch BM, Pieber TR. The effect of vitamin D supplementation on peripheral regulatory T cells and  $\beta$  cell function in healthy humans: a randomized controlled trial. *Diabetes Metab Res Rev* 2011; **27**(8):942-5.
37. Ardabili HR, Gargari BP, Farzadi L. Vitamin D supplementation has no effect on insulin resistance assessment in women with polycystic ovary syndrome and vitamin D deficiency. *Nutr Res* 2012; **32**(3):195-201.
38. Carrillo AE, Flynn MG, Pinkston C, Markofski MM, Jiang Y, Donkin SS, Teegarden D. Impact of vitamin D supplementation during a resistance training intervention on body composition, muscle function, and glucose tolerance in overweight and obese adults. *Clin Nutr* 2013; **32**(3):375-81.
39. Nagpal J, Pande JN, Bhartia A. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. *Diabet Med* 2009; **26**(1):19-27.
40. Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawski-Wende J, Rohan T, Rossouw J, Lane D, O'Sullivan MJ, Yasmeen S, Hiatt RA, Shikany JM, Vitolins M, Khandekar J, Hubbell FA; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of breast cancer. *J Natl Cancer Inst* 2008; **100**(22):1581-91.



41. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003; **326**(7387):469.
42. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, Margolis KL, Ockene JK, Phillips L, Pottern L, Prentice RL, Robbins J, Rohan TE, Sarto GE, Sharma S, Stefanick ML, Van Horn L, Wallace RB, Whitlock E, Bassford T, Beresford SA, Black HR, Bonds DE, Brzyski RG, Caan B, Chlebowski RT, Cochrane B, Garland C, Gass M, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Judd H, Kooperberg CL, Kuller LH, LaCroix AZ, Lane DS, Langer RD, Lasser NL, Lewis CE, Limacher MC, Manson JE; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006; **354**(7):684-96.
43. Tang JY, Fu T, Leblanc E, Manson JE, Feldman D, Linos E, Vitolins MZ, Zeitouni NC, Larson J, Stefanick ML. Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: post hoc analyses of the women's health initiative randomized controlled trial. *J Clin Oncol* 2011; **29**(22):3078-84.
44. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007; **85**(6):1586-91.
45. Brunner RL, Wactawski-Wende J, Caan BJ, Cochrane BB, Chlebowski RT, Gass ML, Jacobs ET, LaCroix AZ, Lane D, Larson J, Margolis KL, Millen AE, Sarto GE, Vitolins MZ, Wallace RB. The effect of calcium plus vitamin D on risk for invasive cancer: results of the Women's Health Initiative (WHI) calcium plus vitamin D randomized clinical trial. *Nutr Cancer* 2011; **63**(6):827-41.
46. Hopkins MH, Owen J, Ahearn T, Fedirko V, Flanders WD, Jones DP, Bostick RM. Effects of supplemental vitamin D and calcium on biomarkers of inflammation in colorectal adenoma patients: a randomized, controlled clinical trial. *Cancer Prev Res (Phila)* 2011; **4**(10):1645-54.
47. Rohan TE, Negassa A, Chlebowski RT, Ceria-Ulep CD, Cochrane BB, Lane DS, Ginsberg M, Wassertheil-Smoller S, Page DL. A randomized controlled trial of calcium plus vitamin D supplementation and risk of benign proliferative breast disease. *Breast Cancer Res Treat* 2009; **116**(2):339-50.
48. Nursyam EW, Amin Z, Rumende CM. The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion. *Acta Med Indones* 2006; **38**(1):3-5.
49. Martineau AR, Timms PM, Bothamley GH, Hanifa Y, Islam K, Claxton AP, Packe GE, Moore-Gillon JC, Darmalingam M, Davidson RN, Milburn HJ, Baker LV, Barker RD, Woodward NJ, Venton TR, Barnes KE, Mullett CJ, Coussens AK, Rutterford CM, Mein CA, Davies GR, Wilkinson RJ, Nikolayevskyy V, Drobniewski FA, Eldridge SM, Griffiths CJ. High-dose vitamin D(3) during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. *Lancet* 2011; **377**(9761):242-50.
50. Martineau AR, Wilkinson RJ, Wilkinson KA, Newton SM, Kampmann B, Hall BM, Packe GE, Davidson RN, Eldridge SM, Maunsell ZJ, Rainbow SJ, Berry JL, Griffiths CJ. A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med* 2007; **176**(2):208-13.
51. Wejse C, Gomes VF, Rabna P, Gustafson P, Aaby P, Lisse IM, Andersen PL, Glerup H, Sodemann M. Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2009; **179**(9):843-50.
52. Ganmaa D, Giovannucci E, Bloom BR, Fawzi W, Burr W, Batbaatar D, Sumberzul N, Holick MF, Willett WC. Vitamin D, tuberculin skin test conversion, and latent tuberculosis in Mongolian school-age children: a randomized, double-blind, placebo-controlled feasibility trial. *Am J Clin Nutr* 2012; **96**(2):391-6.
53. Abu-Mouch S, Fireman Z, Jarchofsky J, Zeina AR, Assy N. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naïve patients. *World J Gastroenterol* 2011; **17**(47):5184-90.
54. Aloia JF, Li-Ng M. Re: epidemic influenza and vitamin D. *Epidemiol Infect* 2007; **135**(7):1095-6.
55. Avenell A, Cook JA, MacLennan GS, Macpherson GC. Vitamin D supplementation to prevent infections: a sub-study of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing* 2007; **36**(5):574-7.
56. Li-Ng M, Aloia JF, Pollack S, Cunha BA, Mikhail M, Yeh J, Berbari N. A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. *Epidemiol Infect* 2009; **137**(10):1396-404.
57. Laaksi I, Ruohola JP, Mattila V, Auvinen A, Ylikomi T, Pihlajamäki H. Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men. *J Infect Dis* 2010; **202**(5):809-14.

58. Murdoch DR, Slow S, Chambers ST, Jennings LC, Stewart AW, Priest PC, Florkowski CM, Livesey JH, Camargo CA, Scragg R. Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. *JAMA* 2012; **308**(13):1333-9.
59. Arpadi SM, McMahon D, Abrams EJ, Bamji M, Purswani M, Engelson ES, Horlick M, Shane E. Effect of bimonthly supplementation with oral cholecalciferol on serum 25-hydroxyvitamin D concentrations in HIV-infected children and adolescents. *Pediatrics* 2009; **123**(1):e121-6.
60. Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, Van Eldere J, Decallonne B, Bouillon R, Decramer M, Janssens W. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2012; **156**(2):105-14.
61. Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology (Berl)* 1998; **135**(4):319-23.
62. Dumville JC, Miles JN, Porthouse J, Cockayne S, Saxon L, King C. Can vitamin D supplementation prevent winter-time blues? A randomised trial among older women. *J Nutr Health Aging* 2006; **10**(2):151-3.
63. Dean AJ, Bellgrove MA, Hall T, Phan WM, Eyles DW, Kvaskoff D, McGrath JJ. Effects of vitamin D supplementation on cognitive and emotional functioning in young adults--a randomised controlled trial. *PLoS One* 2011; **6**(11):e25966.
64. Sanders KM, Stuart AL, Williamson EJ, Jacka FN, Dodd S, Nicholson G, Berk M. Annual high-dose vitamin D3 and mental well-being: randomised controlled trial. *Br J Psychiatry* 2011; **198**(5):357-64.
65. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med* 2008; **264**(6):599-609.
66. Bertone-Johnson ER, Powers SI, Spangler L, Larson J, Michael YL, Millen AE, Bueche MN, Salmoirago-Blotcher E, Wassertheil-Smoller S, Brunner RL, Ockene I, Ockene JK, Liu S, Manson JE. Vitamin D supplementation and depression in the women's health initiative calcium and vitamin D trial. *Am J Epidemiol* 2012; **176**(1):1-13.
67. Rossom RC, Espeland MA, Manson JE, Dysken MW, Johnson KC, Lane DS, Leblanc ES, Lederle FA, Masaki KH, Margolis KL. Calcium and Vitamin D Supplementation and Cognitive Impairment in the Women's Health Initiative. *J Am Geriatr Soc* 2012; **60**(12):2197-205.
68. Lips P, Binkley N, Pfeifer M, Recker R, Samanta S, Cohn DA, Chandler J, Rosenberg E, Papanicolaou DA. Once-weekly dose of 8400 IU vitamin D(3) compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. *Am J Clin Nutr* 2010; **91**(4):985-91.
69. Burton JM, Kimball S, Vieth R, Bar-Or A, Dosch HM, Cheung R, Gagne D, D'Souza C, Ursell M, O'Connor P. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. *Neurology* 2010; **74**(23):1852-9.
70. Stein MS, Liu Y, Gray OM, Baker JE, Kolbe SC, Ditchfield MR, Egan GF, Mitchell PJ, Harrison LC, Butzkueven H, Kilpatrick TJ. A randomized trial of high-dose vitamin D2 in relapsing-remitting multiple sclerosis. *Neurology* 2011; **77**(17):1611-8.
71. Mosayebi G, Ghazavi A, Ghasami K, Jand Y, Kokhaei P. Therapeutic effect of vitamin D3 in multiple sclerosis patients. *Immunol Invest* 2011; **40**(6):627-39.
72. Kimball S, Vieth R, Dosch HM, Bar-Or A, Cheung R, Gagne D, O'Connor P, D'Souza C, Ursell M, Burton JM. Cholecalciferol plus calcium suppresses abnormal PBMC reactivity in patients with multiple sclerosis. *J Clin Endocrinol Metab* 2011; **96**(9):2826-34.
73. Soilu-Hänninen M, Aivo J, Lindström BM, Elovaara I, Sumelahti ML, Färkkilä M, Tienari P, Atula S, Sarasoja T, Herrala L, Keskinarkaus I, Kruger J, Kallio T, Rocca MA, Filippi M. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon  $\beta$ -1b in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2012; **83**(5):565-71.
74. Heikkinen AM, Tuppurainen MT, Niskanen L, Komulainen M, Penttilä I, Saarikoski S. Long-term vitamin D3 supplementation may have adverse effects on serum lipids during postmenopausal hormone replacement therapy. *Eur J Endocrinol* 1997; **137**(5):495-502.
75. Caan B, Neuhauser M, Aragaki A, Lewis CB, Jackson R, LeBoff MS, Margolis KL, Powell L, Uwaifo G, Whitlock E, Wylie-Rosett J, LaCroix A. Calcium plus vitamin D supplementation and the risk of postmenopausal weight gain. *Arch Intern Med* 2007; **167**(9):893-902.
76. Sneve M, Figenschau Y, Jorde R. Supplementation with cholecalciferol does not result in weight reduction in overweight and obese subjects. *Eur J Endocrinol* 2008; **159**(6):675-84.
77. Jorde R, Sneve M, Torjesen P, Figenschau Y. No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year. *J Intern Med* 2010; **267**(5):462-72.

78. Kampman M, Steffensen LH, Mellgren SI, Jorgensen L. Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomized controlled trial. *Multiple Sclerosis Journal* 2012; **18**(8): 1144–1151.
79. Heshmat R, Tabatabaei-Malazy O, Abbaszadeh-Ahranjani S, Shahbazi S, Khooshehchin G, Bandarian F, Larijani B. Effect of vitamin D on insulin resistance and anthropometric parameters in Type 2 diabetes; a randomized double-blind clinical trial. *Daru* 2012; **20**(1):10.
80. Simha V, Mahmood M, Ansari M, Spellman CW, Shah P. Effect of vitamin D replacement on insulin sensitivity in subjects with vitamin D deficiency. *J Investig Med* 2012; **60**(8):1214-8.
81. Salesi M, Farajzadegan Z. Efficacy of vitamin D in patients with active rheumatoid arthritis receiving methotrexate therapy. *Rheumatol Int* 2012; **32**(7):2129-33.
82. Grossmann RE, Zughailer SM, Liu S, Lyles RH, Tangpricha V. Impact of vitamin D supplementation on markers of inflammation in adults with cystic fibrosis hospitalized for a pulmonary exacerbation. *Eur J Clin Nutr* 2012; **66**(9):1072-4.
83. Khoo AL, Koenen HJ, Michels M, Ooms S, Bosch M, Netea MG, Joosten I, van der Ven AJ. High-dose vitamin D(3) supplementation is a requisite for modulation of skin-homing markers on regulatory T cells in HIV-infected patients. *AIDS Res Hum Retroviruses* 2013; **29**(2):299-306.
84. Kjærgaard M, Waterloo K, Wang CE, Almås B, Figenschau Y, Hutchinson MS, Svartberg J, Jorde R. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial. *Br J Psychiatry* 2012; **201**(5):360-8.
85. Scragg R, Khaw KT, Murphy S. Effect of winter oral vitamin D3 supplementation on cardiovascular risk factors in elderly adults. *Eur J Clin Nutr* 1995; **49**(9):640-6.

## Webappendix 6: Selected articles that were excluded, with reason

1. Grossmann RE, Zughailer SM, Kumari M, Seydafkan S, Lyles RH, Liu S, Sueblinvong V, Schechter MS, Stecenko AA, Ziegler TR, Tangpricha V. Pilot study of vitamin D supplementation in adults with cystic fibrosis pulmonary exacerbation: A randomized, controlled trial. *Dermatoendocrinol* 2012; **4**(2):191-7. → **Inadequate adjustment for imbalances in baseline characteristics.**
2. Coussens AK, Wilkinson RJ, Hanifa Y, Nikolayevskyy V, Elkington PT, Islam K, Timms PM, Venton TR, Bothamley GH, Packe GE, Darmalingam M, Davidson RN, Milburn HJ, Baker LV, Barker RD, Mein CA, Bhaw-Rosun L, Nuamah R, Young DB, Drobniowski FA, Griffiths CJ, Martineau AR. Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. *Proc Natl Acad Sci USA* 2012; **109**(38):15449-54. → **Selection of patients from Martineau et al, 2011, ref.49 in Table 5.**
3. Tellioglu A, Basaran S, Guzel R, Seydaoglu G. Efficacy and safety of high dose intramuscular or oral cholecalciferol in vitamin D deficient/insufficient elderly. *Maturitas* 2012; **72**(4):332-8. → **Not a controlled randomized trial.**
4. Beilfuss J, Berg V, Sneve M, Jorde R, Kamycheva E. Effects of a 1-year supplementation with cholecalciferol on interleukin-6, tumor necrosis factor-alpha and insulin resistance in overweight and obese subjects. *Cytokine* 2012; **60**(3):870-4. → **Duplicate with Jorde et al, 2010, ref.21 in Table 5.**
5. Hornikx M, Van Remoortel H, Lehouck A, Mathieu C, Maes K, Gayan-Ramirez G, Decramer M, Troosters T, Janssens W. Vitamin D supplementation during rehabilitation in COPD: a secondary analysis of a randomized trial. *Respir Res* 2012; **13**:84. → **Selection of patients from Lehouck et al, 2012, ref.60 in Table 5.**

**Webappendix 7: Details of RCTs on vitamin D supplementation on selected conditions not included in meta-analyses.**

RCTs in bold are those that included subjects with baseline 25(OH)D less than 49 nmol/L and that tested supplementation with at least 50 µg per day of vitamin D.

Author, year	References of Table 5	RCT duration (months)	Total subjects included in RCT	Vitamin D dose (mcg/day)	Baseline 25(OH)D (nmol/L)	25(OH)D in intervention group during the study (nmol/L)	Marker	Significant (p<0.05) outcome (Y/N)
<b>Multiple outcomes related to arterial and endothelial function</b>								
Sugden, 2008	2	1.8	34	46	37.6	52.6	FMD response to hyperemia	Y
							FMD flow (%)	N
							FMD response to GTN	N
<b>Dong, 2010</b>	<b>5</b>	<b>3.6</b>	<b>49</b>	<b>50</b>	<b>32.5</b>	<b>84.4</b>	<b>carotid-femoral PWV</b>	<b>Y</b>
							<b>carotid-radial PWV</b>	<b>N</b>
							<b>carotid-distal PWV</b>	<b>N</b>
<b>Harris, 2011</b>	<b>3</b>	<b>3.6</b>	<b>45</b>	<b>50</b>	<b>33.7</b>	<b>99.4</b>	<b>FMD</b>	<b>Y</b>
<b>Longenecker, 2012</b>	<b>4</b>	<b>2.7</b>	<b>45</b>	<b>100</b>	<b>22.1</b>	<b>34.4</b>	<b>FMD</b>	<b>N</b>
<b>Sokol, 2012</b>	<b>6</b>	<b>2.7</b>	<b>90</b>	<b>179</b>	<b>32.0</b>	<b>98.4</b>	<b>RH-PAT score</b>	<b>N</b>
							<b>FRHI</b>	<b>N</b>
<b>Stricker, 2012</b>	<b>7</b>	<b>1</b>	<b>62</b>	<b>82</b>	<b>40.1</b>	<b>59.8</b>	<b>Alx</b>	<b>N</b>
							<b>Δ LDF</b>	<b>N</b>
Yiu, 2013	8	2.7	100	125	51.9	85.4	FMD	N
							NMD	N
							PWV	N
<b>Blood pressure</b>								
Orwoll & Oviatt, 1990	9	36	65	25	NR	NR	systolic	N
							diastolic	N
<b>Scragg, 1995</b>	<b>85(a)</b>	<b>1.2</b>	<b>189</b>	<b>71</b>	<b>35.4</b>	<b>53.1</b>	<b>systolic</b>	<b>N</b>
							<b>diastolic</b>	<b>N</b>
<b>Schleithoff, 2006</b>	<b>18</b>	<b>9</b>	<b>123</b>	<b>50</b>	<b>34.4</b>	<b>100.9</b>	<b>systolic</b>	<b>N</b>
							<b>diastolic</b>	<b>N</b>
Margolis, 2008	10	84	36 282	9	NR	NR	systolic	N
							diastolic	N
<b>Zittermann, 2009</b>	<b>26</b>	<b>12</b>	<b>200</b>	<b>83</b>	<b>29.5</b>	<b>83.6</b>	<b>systolic</b>	<b>N</b>
							<b>diastolic</b>	<b>N</b>

Maki, 2011	11	1.8	60	30	64.0	73.8	systolic	N
							diastolic	N
Larsen, 2012	12	4.4	130	75	56.6	108.2	systolic	N
							diastolic	N
Gepner, 2012	13	4	114	62	73.8	113.2	systolic	N
							diastolic	N
Wood, 2012	14	12	305	10 or 25	32.0 0.0	68.9 or 78.3	systolic	N
							diastolic	N
<b>Longenecker, 2012</b>	<b>4</b>	<b>2.7</b>	<b>45</b>	<b>100</b>	<b>22.1</b>	<b>34.4</b>	<b>systolic</b>	<b>N</b>
							<b>diastolic</b>	<b>N</b>
<b>Stricker, 2012</b>	<b>7</b>	<b>1</b>	<b>62</b>	<b>82</b>	<b>39.4</b>	<b>59.0</b>	<b>systolic</b>	<b>N</b>
							<b>diastolic</b>	<b>N</b>
Yiu, 2013	8	2.7	100	125	51.7	86.1	systolic	N
							diastolic	N

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GTN: glyceryl trinitrate; FMD: flow-mediated vasodilatation, NMD: nitroglycerin-mediated dilatation, AIX: aortic augmentation index,  $\Delta$  LDF: postischemic increase of laser Doppler flux, PWV: pulse wave velocity (a) RCT that was included in meta-analyses in Table 4: Scragg R, et al. *Eur J Clin Nutr* 1995; 49(9):640-6.

Author, year	References of Table 5	RCT duration (months)	Total subjects included in RCT	Vitamin D dose (mcg/day)	Baseline 25(OH)D (nmol/L)	25(OH)D in intervention group during the study (nmol/L)	Marker	Significant (p<0.05) outcome (Y/N)
<b>Inflammation marker: plasma C-reactive protein concentration</b>								
Schleithoff, 2006	18	9	123	50	34.4	100.9	CRP	N
Pittas, 2007	19	36	314	17	76.3	105.8	CRP	N
Bjorkman, 2009	20	6	218	10 or 30	22.1	59.0	CRP	N
<b>Zittermann, 2009</b>	<b>26</b>	<b>12</b>	<b>200</b>	<b>83</b>	<b>29.5</b>	<b>83.6</b>	<b>CRP</b>	<b>N</b>
Jorde, 2010	21	12	437	71 or 143	54.1	81.2	hs-CRP	N
<b>Grimmes, 2011</b>	<b>16</b>	<b>6</b>	<b>94</b>	<b>143</b>	<b>41.8</b>	<b>140.2</b>	<b>hs-CRP</b>	<b>N</b>
Hopkins, 2011	46	6	92	20	51.7	71.3	CRP	N
Gepner, 2012	13	4	114	62	73.8	113.2	CRP	N
<b>Longenecker, 2012</b>	<b>4</b>	<b>2.7</b>	<b>45</b>	<b>100</b>	<b>22.1</b>	<b>34.4</b>	<b>CRP</b>	<b>N</b>
<b>Ponda, 2012</b>	<b>17</b>	<b>1.8</b>	<b>151</b>	<b>179</b>	<b>32.0</b>	<b>105.8</b>	<b>hs-CRP</b>	<b>N</b>
<b>Sokol, 2012</b>	<b>6</b>	<b>2.7</b>	<b>90</b>	<b>179</b>	<b>32.0</b>	<b>98.4</b>	<b>hs-CRP</b>	<b>N</b>
<b>Stricker, 2012</b>	<b>7</b>	<b>1</b>	<b>62</b>	<b>83</b>	<b>39.4</b>	<b>59.0</b>	<b>hs-CRP</b>	<b>N</b>
Wood, 2012	14	12	305	10 or 25	32.0	64 or 73.8	hs-CRP	N
Yiu, 2013	8	2.7	1 000	125	51.7	145.1	hs-CRP	N
<b>Inflammation cytokines: plasma IL-6 or TNF-alpha concentration</b>								
Pittas, 2007	19	36	314	17	76.3	105.8	IL-6	N
<b>Zittermann, 2009</b>	<b>26</b>	<b>12</b>	<b>200</b>	<b>83</b>	<b>29.5</b>	<b>83.6</b>	<b>TNF-alpha</b>	<b>Y</b>
							<b>IL-6</b>	<b>N</b>
Yusupov, 2010	22	3	162	50	64.0	NR	IL-6	N
							TNF-alpha	N
Hopkins, 2011	46	6	92	20	51.7	71.3	IL-6	N
							TNF-alpha	N
Grossmann, 2012	82	2.7	30	74	73.8	90.3	IL-6	N
					0.0	0.0	TNF-alpha	Y
<b>Longenecker, 2012</b>	<b>4</b>	<b>2.7</b>	<b>45</b>	<b>100</b>	<b>22.1</b>	<b>34.4</b>	<b>IL-6</b>	<b>Y</b>
<b>Sokol, 2012</b>	<b>6</b>	<b>2.7</b>	<b>90</b>	<b>179</b>	<b>32.0</b>	<b>98.4</b>	<b>IL-6</b>	<b>N</b>
Wood, 2012	14	12	305	10 or 25	32.0	64 or 73.8	IL-6	N

\* From Grossmann et al. *Dermato-Endocrinol*, 2012; 4:191-7.

Author, year	References of Table 5	RCT duration (months)	Total subjects included in RCT	Vitamin D dose (mcg/day)	Baseline 25(OH)D (nmol/L)	25(OH)D in intervention group during the study (nmol/L)	Marker	Significant (p<0.05) outcome (Y/N)
<b>Infectious diseases</b>								
<i>Sputum conversion in TB patients</i>								
Nursyam, 2006	48	1.3	67	350	NR	NR	Sputum conversion	Y
Kota, 2011	30	2.7	45	214	32.0	61.5	Duration for sputum smear conversion	N
<b>Martineau, 2011</b>	<b>49</b>	<b>1.8</b>	<b>146</b>	<b>179</b>	<b>19.7</b>	<b>100.9</b>	<b>Time to sputum culture conversion</b>	<b>N</b>
<i>Tuberculosis score in TB patients</i>								
Wejse, 2009	51	12	365	21	76.3	100.9	Reduction in TB score	N
Ganmaa, 2012	52	6	120	20	17.2	49.2	Tuberculosis skin test conversion	N
<i>Viral response in hepatitis C patients</i>								
Abu-Mouch, 2011	53	5.3	72	50	49.2	91.0	Viral response in hepatitis C patients	Y
<i>Upper respiratory tract infections</i>								
Aloia, 2007	54	36	208	50	NR	NR	Reported cold and influenza	Y
RECORD, 2007	55	18	5292	20	NR	NR	Infection	N
							Antibiotic use	N
Ling, 2009	56	2.7	162	50	64.1	86.3	Incidence of upper tract respiratory infections	N
Laaksi, 2010	57	6	164	10	76.3	71.3	Number of days absent from duty due to respiratory tract infection	N
							No days absent from duty	Y
							Self reported symptoms of acute respiratory tract infections	N
							Number of upper respiratory tract infection (URTI) episodes	N
Murdoch, 2012	58	18	322	91	71.3	118.08	Duration of URTI	N



							Severity of URTI	N
							Number of days of missed work due to URTI	N
<b><i>CD4 count and skin Tregs in HIV patients</i></b>								
Arpadi, 2009	59	12	56	41	59.0	78.7	CD4 count	N
							CD4%	N
							Viral load log 10, copies	N
Khoo, 2013	83	3 or 2	16	20 or 90	24.6 to 29.5	36.9 to 135.5	CCR4	N
							CCR10	N
							CCR9	N
							integrin alpha5 beta7	N
<b><i>Chronic obstructive pulmonary disease</i></b>								
Lehouck, 2012	60	12	182	89	49.2	123.0	COPD	N

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