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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-α)
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.[1] 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.[2-5] 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. [1]

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

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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 [b]	Dose (µg per day)	Duration (month)	baseline 25(OH) D (nmol/L)	25(OH) D during trial (nmol/L)	Calcium supple-mentation	Endpoint [e]							
										Newly diagnosed diabetes	Hb1AC	FPG	OGTT	SI [g]	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 [a]	2008	23	33951	ND	10	84	49.1 [d]	53.5 [d]	yes	Y		Y					
Nagpal	**2008**	**39**	**71**	**ND**	**214**	**1.5**	**36.0**	**70.5**	**no**								**Y**
Sugden	**2008**	**2**	**64**	**D**	**45**	**2**	**39.7**	**62.4**	**no**		**Y**						**Y**
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	
Zittermann	**2009**	**26**	**165**	**ND**	**83**	**12**	**29.6**	**84.3**	**no**		**Y**	**Y**					
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
Parekh	**2010**	**27**	**28**	**D**	**268**	**1**	**36.7**	**102.5**	**no**		**Y**	**Y**	**Y**		**Y**		**Y**
Patel	2010	15	24	D	20	4	38.5	67.5	no		Y	Y		Y	Y		
Von Hurst	**2010**	**35**	**81**	**ND**	**100**	**6**	**20.7**	**78.9**	**no**			**Y***			**Y**	**Y**	**Y****
Witham	2010	28	40	D	22	4	40.4	58.2	no		Y						Y
Witham	**2010**	**28**	**37**	**D**	**45**	**4**	**47.3**	**74.9**	**no**		**Y**						**Y**
Bock	2011	36	59	ND	120	3	62.9	135.6	no			Y			Y	Y	
Grimnes	**2011**	**16**	**94**	**ND**	**140**	**6**	**41.6**	**140.7**	**no**		**Y**	**Y**		**Y**	**Y**		**Y**
Kota	**2011**	**30**	**30**	**D**	**220**	**3**	**31.6**	**62.6**	**no**		**Y**	**Y**					
Mitri	2011	29	47	D	50	4	65.3	80.9	yes		Y	Y	Y	Y	Y		
Ardabili	**2012**	**37**	**50**	**ND**	**60**	**2**	**17.0**	**57.7**	**no**			**Y**			**Y**		**Y**
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 [c]	12	54.2	172.6	no		Y [f]	Y	Y	Y				Y
Harris	**2012**	**32**	**89**	**ND**	**100**	**3**	**39.0**	**78.4**	**yes**		**Y**	**Y**			**Y**	**Y**		
Longenecker	**2012**	**4**	**45**	**ND**	**100**	**3**	**22.2**	**34.5**	**no**			**Y**			**Y**			**Y**
Mozaffari-Khosravi	**2012**	**31**	**45**	**D**	**85**	**3**	**24.0**	**61.2**	**no**		**Y**	**Y**						**Y****
Heshmat	2012	79	42	D	81	3	115.6	170.8	no			Y						Y
Simha	**2012**	**80**	**12**	**ND**	**178**	**2**	**32.8**	**46.3**	**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.
[a] Women's Health Initiative (WHI) trial
[b] D: subjects with diabetes at baseline; ND: subjects without diabetes at baseline; NGT: normal glucose tolerance; IGT: impaired glucose tolerance
[c] Mean daily dose because doses were individually adapted in order to achieve 25(OH)D levels of 160-222 nmol/L.
[d] According to Autier et al, *J Clin Endo Metab* 2012; **97**(8):2606–13.
[e] Y means that the endpoint was examined by the trial; * Statistically borderline; ** Statistically significant with $p < 0.05$ (two-sided test).
[f] 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.
[g] 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 glycated (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 en 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 (references 28,30,33 in the table 5 of the webappendix 5).

In both methods, a meta-analysis was performed using a random effect model.[1] Heterogeneity across studies was evaluated by the I^2 statistics, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance.[2] 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.

Intervention groups*

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

[1] van Houwelingen HC, Arends LR, Stijnen T (2002) Advanced methods in meta-analysis: multivariate approach and metaregression. Stat Med 21:589–624.
[2] 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 ≤ 92.5µg/day	-0.01	-0.24	0.23
Dose > 92.5µg/day	-0.37	-1.14	0.40
Duration ≤ 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 (var = var(intervention) + var(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^2**
All 16	-0.01	-0.25	0.23	0
Dose ≤ 92.5µg/day	0.04	-0.30	0.38	0
Dose > 92.5µg/day	-0.08	-0.50	0.34	0
Duration ≤ 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

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

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Table 3 - Cancer survival studies

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Table 4 - Meta-analyses of randomised controlled trials

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Webappendix 6: Selected articles that were excluded, with reason

1. Grossmann RE, Zughaier 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.**
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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)
Multiple outcomes related to arterial and endothelial function								
Sugden, 2008	2	1.8	34	46	37.6	52.6	FMD response to hyperemia	Y
							FMD flow (%)	N
							FMD response to GTN	N
Dong, 2010	**5**	**3.6**	**49**	**50**	**32.5**	**84.4**	**carotid-femoral PWV**	**Y**
							carotid-radial PWV	**N**
							carotid-distal PWV	**N**
Harris, 2011	**3**	**3.6**	**45**	**50**	**33.7**	**99.4**	**FMD**	**Y**
Longenecker, 2012	**4**	**2.7**	**45**	**100**	**22.1**	**34.4**	**FMD**	**N**
Sokol, 2012	**6**	**2.7**	**90**	**179**	**32.0**	**98.4**	**RH-PAT score**	**N**
							FRHI	**N**
Stricker, 2012	**7**	**1**	**62**	**82**	**40.1**	**59.8**	**Alx**	**N**
							Δ LDF	**N**
Yiu, 2013	8	2.7	100	125	51.9	85.4	FMD	N
							NMD	N
							PWV	N
Blood pressure								
Orwoll & Oviatt, 1990	9	36	65	25	NR	NR	systolic	N
							diastolic	N
Scragg, 1995	**85(a)**	**1.2**	**189**	**71**	**35.4**	**53.1**	**systolic**	**N**
							diastolic	**N**
Schleithoff, 2006	**18**	**9**	**123**	**50**	**34.4**	**100.9**	**systolic**	**N**
							diastolic	**N**
Margolis, 2008	10	84	36 282	9	NR	NR	systolic	N
							diastolic	N
Zittermann, 2009	**26**	**12**	**200**	**83**	**29.5**	**83.6**	**systolic**	**N**
							diastolic	**N**

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
Longenecker, 2012	**4**	**2.7**	**45**	**100**	**22.1**	**34.4**	**systolic**	**N**
							diastolic	**N**
Stricker, 2012	**7**	**1**	**62**	**82**	**39.4**	**59.0**	**systolic**	**N**
							diastolic	**N**
Yiu, 2013	8	2.7	100	125	51.7	86.1	systolic	N
							diastolic	N

GTN: glyceryl trinitrate; FMD: flow-mediated vasodilatation, NMD: nitroglycerin-mediated dilatation, Alx: aortic augmentation index, Δ 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)
Inflammation marker: plasma C-reactive protein concentration								
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
Zittermann, 2009	**26**	**12**	**200**	**83**	**29.5**	**83.6**	**CRP**	**N**
Jorde, 2010	21	12	437	71 or 143	54.1	81.2	hs-CRP	N
Grimnes, 2011	**16**	**6**	**94**	**143**	**41.8**	**140.2**	**hs-CRP**	**N**
Hopkins, 2011	46	6	92	20	51.7	71.3	CRP	N
Gepner, 2012	13	4	114	62	73.8	113.2	CRP	N
Longenecker, 2012	**4**	**2.7**	**45**	**100**	**22.1**	**34.4**	**CRP**	**N**
Ponda, 2012	**17**	**1.8**	**151**	**179**	**32.0**	**105.8**	**hs-CRP**	**N**
Sokol, 2012	**6**	**2.7**	**90**	**179**	**32.0**	**98.4**	**hs-CRP**	**N**
Stricker, 2012	**7**	**1**	**62**	**83**	**39.4**	**59.0**	**hs-CRP**	**N**
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
Inflammation cytokines: plasma IL-6 or TNF-alpha concentration								
Pittas, 2007	19	36	314	17	76.3	105.8	IL-6	N
Zittermann, 2009	**26**	**12**	**200**	**83**	**29.5**	**83.6**	**TNF-alpha**	**Y**
							IL-6	**N**
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
Longenecker, 2012	**4**	2.7	45	100	22.1	34.4	IL-6	Y
Sokol, 2012	**6**	2.7	90	179	32.0	98.4	IL-6	N
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)
Infectious diseases								
Sputum conversion in TB patients								
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
Martineau, 2011	**49**	**1.8**	**146**	**179**	**19.7**	**100.9**	**Time to sputum culture conversion**	**N**
Tuberculosis score in TB patients								
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
Viral response in hepatitis C patients								
Abu-Mouch, 2011	53	5.3	72	50	49.2	91.0	Viral response in hepatitis C patients	Y
Upper respiratory tract infections								
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
CD4 count and skin Tregs in HIV patients								
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
Chronic obstructive pulmonary disease								
Lehouck, 2012	**60**	**12**	**182**	**89**	**49.2**	**123.0**	**COPD**	**N**