SUPPLEMENTARY DATA

Serum 25(OH)D assay

Serum levels of 25(OH)D were measured by LC-MS/MS. Liquid-liquid extraction of serum (80 µl) was performed as previously reported (1) on a Tecan Freedom Evo liquid handler (Männedorf, Switzerland). 25(OH) D_2 and D_3 were quantified using a Waters Acquity^{TM} *I*-class UPLC system with an autosampler and a binary solvent delivery system (Waters, Milford, MA) interfaced to Waters Xevo TQ-S benchtop tandem quadrupole mass spectrometer (Waters, Manchester, UK). The chromatography was performed on a 2.1 x 100 mm Waters Acquity HSS PFP Column, 100Å, 1.8 µm maintained at 50 °C. The column was eluted isocratically with 0.1% aqueous formic acid:methanol (23:77) at 0.45 mL. Sample injection volume was 3 µl and the injection interval was 2.7 min. The mass spectrometer was operated in positive electrospray ion mode (ESI+) and spray voltage was 1.3 kV; The system was controlled by MassLynx^{TM} version 4.1 software; desolvation gas temperature, 500 °C; source temperature 150 °C; desolvation gas flow 1000 L/h; cone gas flow, 150 L/h; collision gas pressure 3.5 x 10^{-3} mBar (argon); ion energies, 0.8 V for both quadrupoles. For quantitative analysis of 25(OH) D_3 and D_2, MRM transition *m/z* 383.3→257.2, 383.3→365.25 (QC) and 395.3→269.1, 395.3→377.2 (QC) were used respectively. For the internal standard (25(OH) D3-d6) MRM transition *m/z* 389.3→263.2 and 389.3→371.25 were used. The linear dynamic range (r^2>0.99) for 25(OH) D_2 and D_3 was from 4 nM to 280 nM and the limit of quantification (LOQ) was < 4 nmol/L for both.. Between-day coefficient of variation (% CV) for both was < 9 % at three different days (28 serum samples, MassCheck® level 1 and 2 for 25(OH) D_2 and D_3 serum controls from Chromsystems, (Chromsystems Instruments & Chemicals GmbH, Munchen, Germany) and Labquality vitamins 3/2012 and 4/2012 (Labquality eqas, Helsinki, Finland). Intraday precision values were calculated by assaying two serum samples 6 times on the same day. The CV for both was <2% at 34.3 and 58.6 nM. Accuracy for 25(OH) D_3 was 104.6 % (std 3.6) determined as a percentage of the mean concentration of MassCheck® level 1 and 2 and Labquality vitamins 3/2012 and 4/2012 assayed at three different days.

Reference.

1.Maunsell Z, Wright DJ, Rainbow SJ. Routine isotope-dilution liquid chromatography-tandem mass spectrometry assay for simultaneous measurement of the 25-hydroxy metabolites of vitamins D2 and D3. Clin Chem 2005 51:1683-90.

SUPPLEMENTARY DATA

Supplementary Table 1. Baseline values and change from baseline after 12 months (12 months value minus baseline value) in the vitamin D and the placebo groups in subjects with vitamin D levels at baseline < 50 mmol/L, and difference in change between the two groups (change in vitamin D group minus change in placebo group) adjusted for baseline level.

	Baseline values		Change from baseline after 12 month		Difference in change between the vitamin D and placebo groups, adjusted for baseline level (mean (2.5^{th}, 97.5^{th} percentiles)) ‖
	Vitamin D group (n = 87)	Placebo group (n = 83)	Vitamin D group (n = 80)	Placebo group (n = 74)	
Males, n (%) males	61 (70.1)	53 (63.9)			
Age (years)	60.5 ± 8.3	59.4 ± 10.1			
Body mass index (kg/m^2)	30.8 ± 4.6	30.5 ± 3.6	-0.0 ± 1.1	-0.3 ± 1.2	0.2 (-0.1, 0.6)
Systolic blood pressure (mmHg) ‡	133.5 ± 15.1	136.0 ± 15.3	-2.5 ± 13.2	-3.0 ± 13.7	-0.5 (-4,4, 3,5)
Diastolic blood pressure (mmHg) ‡	83.8 ± 12.0	84.3 ± 9.4	-4.5 ± 10.2	-4.1 ± 10.7	-0.7 (-3.5, 2.0)
Oral glucose tolerance test					
Fasting serum glucose (mmol/L)	6.20 ± 0.49	6.01 ± 0.43	-0.04 ± 0.56	0.05 ± 0.63	-0.07 (-0.25, 0.12)
2-h serum glucose (mmol/L)	7.45 ± 2.05	7.33 ± 1.88	0.74 ± 2.88	1.06 ± 2.43	-0.29 (-1.10, 0.52)
Fasting serum insulin (pmol/L)	106 (95, 118)	105 (89, 121)	11 (0, 22)	17 (4, 31)	-4 (-20, 11)
2-h serum insulin (pmol/L)	626 (514, 737)	643 (544, 743)	124 (-21, 269)	151 (32, 270)	-34 (-220, 152)
Fasting serum C-peptid (pmol/L)	1167 ± 352	1136 ± 380	25 ± 254	47 ± 280	-13 (-95, 69)
HbA_{1c} (%)	6.03 ± 0.27	6.02 ± 0.38	0.05 ± 0.30	0.12 ± 0.32	-0.07 (-0.17, 0.03)
HbA_{1c} (mmol/mol)	42.5 ± 2.9	42.3 ± 4.1	0.5 ± 3.2	1.3 ± 3.5	-0.7 (-1.8, 0.3)
HOMA IR	4.91 (4.35-5.47)	4.79 (4.00-5.58)	0.58 (-0.03-1.18)	0.87 (0.09-1.64)	-0.17 (-1.04, 0.71)
QUICKI	0.32 (0.31-0.32)	0.32 (0.31-0.32)	-0.00 (-0.01-0.00)	-0.01 (-0.01--0.00)	0.00 (-0.00, 0.01)
Serum 25(OH)D (nmol/L)	39.9 ± 7.8	39.4 ± 6.8	51.8 ± 22.4	6.6 ± 10.5	45.2 (39.7, 50.8) *
Serum calcium (mmol/L)	2.30 ± 0.07	2.30 ± 0.08	-0.03 ± 0.08	-0.04 ± 0.07	0.02 (-0.00, 0.04)
Serum parathyroid hormone (pmol/L)	6.0 (5.6-6.6)	6.6 (6.0-7.3)	-0.3 (-0.7-0.1)	0.2 (-0.2-0.6)	-0.7 (-1.2, -1.2)†
Serum creatinine (µmol/L)	68.9 ± 13.9	69.6 ± 12.5	1.2 ± 6.1	1.2 ± 6.4	-0.1 (-2.2, 1.9)
Serum hs-CRP (mg/L)	3.44 ± 5.31	4.56 ± 13.89	-0.70 ± 5.36	-0.15 ± 5.42	-0.53 (-1.71, 0.65)
Serum total cholesterol (mmol/L) §	5.49 ± 1.10	5.58 ± 1.08	-0.13 ± 0.84	-0.11 ± 0.82	-0.05 (-0.27, 0.17)
Serum LDL cholesterol (mmol/L) §	3.55 ± 1.00	3.54 ± 0.94	-0.12 ± 0.76	0.00 ± 0.70	-0.12 (-0.32, 0.08)
Serum HDL cholesterol (mmol/L) §	1.27 ± 0.26	1.30 ± 0.37	-0.06 ± 0.22	-0.03 ± 0.20	-0.04 (-0.11, 0.02)
Ratio total cholesterol/HDL cholesterol	4.5 ± 1.4	4.7 ± 1.6	0.3 ± 2.0	-0.1 ± 0.9	0.3 (-0.1, 0.8)
Triglycerides (mmol/L) §	1.71 (1.50-1.93)	1.87 (1.57-2.17)	0.07 (-0.11-0.25)	-0.25 (-0.47--0.03)	0.23 (-0.02, 0.49)
Apolipoprotein A1 (mmol/L) §	1.45 ± 0.20	1.51 ± 0.43	-0.10 ± 0.17	-0.13 ± 0.43	-0.05 (-0.12, 0.02)
Apolipoprotein B (mmol/L) §	1.05 ± 0.25	1.05 ± 0.25	-0.04 ± 0.20	-0.05 ± 0.17	0.01 (-0.04, 0.06)

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** $P < 0.001$. † $P < 0.05$*; general linear regression models adjusting for baseline value. ‡ 9 subjects with changes in antihypertensive medication during the 12 months were excluded from the analyses of changes in blood pressure and heart rate. § 8 subjects with changes in statin medication during the 12 months were excluded from the analyses of changes in lipids. || A positive value means there was an increase in the vitamin D group versus the placebo group.

Abbreviations: HbA_{1c}, glycated hemoglobin; HOMA IR, homeostatis model assessment; QUICKI, quantitative insulin sensitivity check index; 25(OH)D, 25-hydroxyvitamin D; LDL, low density lipoprotein; HDL, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein

Supplementary Table 2. Baseline values and change from baseline after 12 months (12 months value minus baseline value) in the vitamin D and the placebo groups, and difference in change between the two groups (change in vitamin D group minus change in placebo group) adjusted for baseline level. Included are subjects with baseline levels of 25(OH)D < 50 mmol/L and at 1 year 25(OH)D < 50 in the placebo group and 25(OH)D > 75 mmol/L in the intervention group.

	Baseline values		Change from baseline after 12 month		Difference in change between the vitamin D and placebo groups, adjusted for baseline level (mean (2.5^{th}, 97.5^{th} percentiles)) ‖
	Vitamin D group (n = 62)	Placebo group (n = 51)	Vitamin D group (n = 62)	Placebo group (n = 51)	
Males, n (%) males	43 (69.4)	35 (68.6)			
Age (years)	60.1 ± 8.5	60.0 ± 10.4			
Body mass index (kg/m^2)	30.2 ± 4.6	30.1 ± 3.9	0.0 ± 0.9	-0.3 ± 1.1	0.3 (-0.0, 0.7)
Systolic blood pressure (mmHg) ‡	133.9 ± 15.2	137.1 ± 15.2	-2.0 ± 13.3	-4.3 ± 12.7	1.4 (-3.4, 6.3)
Diastolic blood pressure (mmHg) ‡	83.9 ± 12.0	85.4 ± 9.1	-3.3 ± 9.5	-4.3 ± 9.7	-0.2 (-3.3, 3.0)
Oral glucose tolerance test					
Fasting serum glucose (mmol/L)	6.19 ± 0.52	6.13 ± 0.40	-0.05 ± 0.54	0.10 ± 0.68	0.11 (-0.36, 0.09)
2-h serum glucose (mmol/L)	7.50 ± 2.14	7.14 ± 1.99	7.95 ± 2.56	7.99 ± 2.71	0.46 (-1.13, 0.72)
Fasting serum insulin (pmol/L)	105 (89-120)	101 (78-123)	11 (-1-23)	15 (-3-34)	-3 (-21, 16)
2-h serum insulin (pmol/L)	641 (493-788)	641 (493-788)	47 (-65-158)	137 (-11-284)	-89 (-268, 90)
Fasting serum C-peptid (pmol/L)	1149 ± 376	1104 ± 384	17 ± 224	48 ± 310	-21 (-117, 76)
HbA_{1c} (%)	6.02 ± 0.26	6.02 ± 0.41	0.07 ± 0.30	0.12 ± 0.35	-0.05 (-0.17, 0.07)
HOMA IR	4.82 (4.10-5.55)	4.64 (3.48-5.80)	0.57 (-0.08-1.21)	0.84 (-0.22-1.90)	-.02 (-1.25, 0.85)

SUPPLEMENTARY DATA

QUICKI	0.32 (0.31-0.33)	0.32 (0.31-0.33)	-0.00 (-0.01-0.00)	-0.01 (-0.01--0.00)	0.00 (-0.00, 0.01)
25(OH)D levels (nmol/L)	40.7 ± 7.0	38.4 ± 7.5	57.9 ± 21.3	2.2 ± 8.1	57.7 (51.8, 63.5)*
Calcium (mmol/L)	2.31 ± 0.07	2.30 ± 0.08	-0.03 ± 0.08	-0.05 ± 0.07	0.02 (-0.00, 0.05)
PTH (pmol/L)	6.0 (5.4-6.7)	6.4 (5.6-7.2)	-0.4 (-0.8-0.0)	0.2 (-0.3-0.7)	-0.7 (-1.2, -0.2)†
Creatinine (µmol/L)	69.2 ± 14.3	69.4 ± 11.4	1.3 ± 6.5	2.5 ± 6.4	-1.2 (-3.6, 1.3)
Serum hs-CRP (mg/L)	3.74 ± 6.04	2.94 ± 3.86	-1.19 ± 5.54	-0.03 ± 5.58	-0.52 (-1.89, 0.85)
Cholesterol (mmol/L) §	5.45 ± 1.09	5.61 ± 1.12	-0.02 ± 0.71	-0.14 ± 0.70	0.08 (-0.17, 0.34)
LDL cholesterol (mmol/L) §	3.52 ± 1.01	3.53 ± 1.03	-0.04 ± 0.63	-0.02 ± 0.58	-0.01 (-0.23, 0.21)
HDL cholesterol (mmol/L) §	1.27 ± 0.28	1.34 ± 0.40	-0.03 ± 0.17	-0.02 ± 0.20	-0.02 (-0.09, 0.05)
Ratio total cholesterol/HDL cholesterol	4.5 ± 1.4	4.1 ± 1.6	0.1 ± 1.0	-0.1 ± 0.9	0.2 (-0.2, 0.5)
Triglycerides (mmol/L) §	1.68 (1.44-1.92)	1.83 (1.45-2.22)	0.06 (-0.16-0.28)	-0.27 (-0.56-0.01)	0.28 (-0.03, 0.59)
Apolipoprotein A1 (mmol/L) §	1.45 ± 0.21	1.58 ± 0.51	-0.10 ± 0.14	-0.15 ± 0.50	-0.04 (-0.12, 0.04)
Apolipoprotein B (mmol/L) §	1.04 ± 0.25	1.04 ± 0.27	-0.04 ± 0.16	-0.05 ± 0.15	0.03 (-0.04, 0.08)

* *P < 0.001*. † *P < 0.05*; general linear regression models adjusting for baseline value. ‡ 8 subjects with changes in antihypertensive medication during the 12 months were excluded from the analyses of changes in blood pressure and heart rate. §7 subjects with changes in statin medication during the 12 months were excluded from the analyses of changes in lipids. || A positive value means there was an increase in the vitamin D group versus the placebo group.

Abbreviations: HbA_{1c}, glycated hemoglobin; HOMA IR, homeostatis model assessment; QUICKI, quantitative insulin sensitivity check index; 25(OH)D, 25-hydroxyvitamin D; LDL, low density lipoprotein; HDL, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein

SUPPLEMENTARY DATA

Supplementary Table 3. Systolic and diastolic blood pressure at baseline in the vitamin D and placebo groups in subjects not using blood pressure medication, subjects on stable blood pressure medication and in subjects with hypertension not using or on stable blood pressure mediation.

	Subjects not using blood pressure medication		Subjects on stable blood pressure medication		Subjects with hypertension* not using or on stable blood pressure medication	
	Vitamin D group	Placebo group	Vitamin D group	Placebo group	Vitamin D group	Placebo group
Subjects regardless of baseline 25(OH)D	139	139	108	107	114	101
Systolic blood pressure (mmHg)	134.2 ± 17.2	133.2 ± 17.0	136.1 ± 15.7	138.9 ± 16.2	148.3 ± 12.5	150.8 ± 12.2
Diastolic blood pressure (mmHg)	82.9 ± 9.9	82.8 ± 9.3	84.6 ± 11.6	83.0 ± 9.9	90.4 ± 10.0	89.0 ± 9.4
Subjects with baseline 25(OH)D < 50 nmol/L	46	45	36	33	27	29
Systolic blood pressure (mmHg)	131.4 ± 13.2	134.8 ± 15.2	137.4 ± 16.2	137.5 ± 16.6	145.8 ± 11.5	151.3 ± 12.7
Diastolic blood pressure (mmHg)	82.6 ± 10.2	84.4 ±8.0	85.8 ± 13.8	84.5 ± 11.5	92.3 ± 11.1	91.8 ± 10.3

*Systolic blood pressure ≥ 140.0 mmHg and/or diastolic blood pressure ≥ 90.0 mmHg.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D

SUPPLEMENTARY DATA

Supplementary Table 4. Difference in change in blood pressure adjusted for baseline level between the vitamin D group and placebo group in relation to blood pressure medication and blood pressure status.

	Difference in change between the vitamin D and placebo groups, adjusted for baseline level (mean (2.5^{th}, 97.5^{th} percentile))		
	Subjects not using BP medication	Subjects on stable BP medication	Subjects with hypertension* not using or on stable BP medication
Subjects regardless of baseline 25(OH)D (n)	123/125	107/107	112/99
Systolic blood pressure (mmHg)	0.8 (-2.1, 3.7)	-2.1 (-5.7, 1.6)	2.4 (-1.5, 6.4)
Diastolic blood pressure (mmHg)	0.58 (-1.3, 2.5)	-0.71 (-2.8, 1.4)	1.66 (-0.8, 4.1)
Subjects with baseline 25(OH)D < 50 nmol/L	38/36	36/33	36/27
Systolic blood pressure (mmHg)	1.0 (-4.3, 6.4)	-2.4 (-8.5, 3.7)	3.8 (-3.3, 10.8)
Diastolic blood pressure (mmHg)	0.7 (-3.4, 4.7)	-1.55 (-5.3, 2.2)	1.48 (-3.1, 6.1)

* General linear regression models adjusting for baseline value. Systolic blood pressure ≥ 140.0 mmHg and/or diastolic blood pressure ≥ 90.0 mmHg. A positive value means there was an increase in the vitamin D group versus the placebo group.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D

SUPPLEMENTARY DATA

Supplementary Table 5. Lipid values at baseline in the vitamin D and placebo groups in subjects not using blood pressure medication, subjects on stable blood pressure medication and in subjects with hypertension not using or on stable blood pressure mediation.

	Subjects not using lipid medication		Subjects on stable lipid medication		Subjects not using or on stable lipid medication, subjects with baseline serum TC > 7.8 mmol/L and/or baseline serum LDL > 4.9 mmol/L	
	Vitamin D group	Placebo group	Vitamin D group	Placebo group	Vitamin D group	Placebo group
Subjects regardless of baseline 25(OH)D	186	193	62	54	27	22
Serum total cholesterol (mmol/L)	5.98 ± 0.96	5.98 ± 0.99	5.00 ± 0.92	5.24 ± 1.08	7.63 ± 0.59	7.65 ± 0.68
Serum LDL cholesterol (mmol/L)	3.98 ± 0.84	3.91 ± 0.87	3.04 ± 0.77	3.25 ± 0.86	5.43 ± 0.36	5.42 ± 0.37
Serum HDL cholesterol (mmol/L)	1.34 ± 0.33	1.37 ± 0.35	1.39 ± 0.36	1.39 ± 0.44	1.39 ±0.31	1.46 ± 0.28
Ratio cholesterol/HDL cholesterol	4.7 ± 1.3	4.6 ± 1.3	3.79 ± 1.09	4.06 ± 1.47	5.83 ± 1.20	5.37 ± 0.91
Serum triglycerides (mmol/L)	1.63 (1.51, 1.75)	1.64 (1.48, 1.79)	1.63 (1.40, 1.85)	1.63 (1.39, 1.88)	1.98 (1.66, 2.29)	1.60 (1.31, 1.89)
Serum apolipoprotein A1 (mmol/L)	1.52 ± 0.25	1.53 ± 0.32	1.57 ± 0.25	1.56 ± 0.33	1.57 ± 0.24	1.60 ± 0.19
Serum apolipoprotein B (mmol/L)	1.14 ± 0.22	1.13 ± 0.22	0.95 ± 0.23	1.00 ± 0.26	1.50 ± 0.14	1.50 ±0.12
Subjects with baseline 25(OH)D < 50 nmol/L (n)	59	56	23	24	8	5
Serum total cholesterol (mmol/L)	5.81 ± 0.96	5.83 ± 0.97	4.83 ± 1.01	5.12 ± 1.18	7.61 ± 0.46	7.88 ± 0.48
Serum LDL cholesterol (mmol/L)	3.87 ± 0.89	3.75 ± 0.90	2.88 ± 0.81	3.16 ±0.94	5.51 ± 0.32	5.70 ± 0.29
Serum HDL cholesterol (mmol/L)	1.27 ± 0.27	1.27 ± 0.37	1.27 ± 0.26	1.35 ± 0.39	1.21 ± 0.24	1.34 ± 0.26
Ratio total cholesterol/HDL cholesterol	4.8 ± 1.3	5.0 ± 1.6	3.98 ± 1.32	4.08 ± 1.69	6.48 ± 1.23	6.05 ± 1.14
Serum triglycerides (mmol/L)	1.70 (1.45, 1.94)	1.99 (1.57, 2.40)	1.86 (1.36, 2.36)	1.65 (1.26, 2.04)	2.15 (1.58, 2.72)	2.08 (1.11, 3.04)
Serum apolipoprotein A1 (mmol/L)	1.45 ± 0.21	1.51 ± 0.49	1.48 ± 0.19	1.52 ± 0.29	1.40 ± 0.18	1.54 ± 0.22
Serum apolipoprotein B (mmol/L)	1.11 ± 0.23	1.10 ± 0.24	0.92 ± 0.24	0.97 ± 0.28	1.52 ± 0.11	1.56 ± 0.14

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; LDL, low density lipoprotein; HDL, high density lipoprotein

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Supplementary Table 6. Difference in change in lipids adjusted for baseline level between the vitamin D group and placebo group in relation to lipid medication and lipid status.

	Difference in change between the vitamin D and placebo groups, adjusted for baseline level (mean (2.5^{th}, 97.5^{th} percentile))		
	Subjects not using lipid medication	Subjects on stable lipid medication	Subjects not using or on stable lipid medication, subjects with baseline serum TC > 7.8 mmol/L and/or baseline serum LDL > 4.9 mmol/L
Subjects regardless of baseline 25(OH)D (n)	165/175	62/54	25/22
Serum total cholesterol (mmol/L)	-0.20 (-0-33, -0.06)*	-0.08 (-3.73, 0.21)	-0.24 (-0.85, 0.38)
Serum LDL cholesterol (mmol/L)	-0.21 (-0.32, -0.09)*	-0.11 (-0.36, 0.14)	-0.18 (-0.72, 0.36)
Serum HDL cholesterol (mmol/L)	-0.03 (-0.07, 0.01)	-0.05 (-0.12, 0.02)	-0.08 (-0.18, 0.03)
Ratio total cholesterol/HDL cholesterol			0.09 (-0.41, 0.59)
Serum triglycerides (mmol/L)	0.10 (-0.07, 0.27)	0.13 (-0.08, 0.34)	0.40 (0.05, 0.76) *
Serum apolipoprotein A1 (mmol/L)	-0.02 (-0.07, 0.02)	-0.04 (-0.11, 0.02)	-0.05 (-0.13, 0.04)
Serum apolipoprotein B (mmol/L)	-0.03 (-0.06, -0.01)*	0.00 (-0.06, 0.07)	-0.04 (-0.16, 0.07)
Subjects with baseline 25(OH)D < 50 nmol/Lnmol/L (n)	51/46	23/24	5/5
Serum total cholesterol (mmol/L)	-0.14 (-0.37, 0.10)	0.07 (-0.39, 0.53)	†
Serum LDL cholesterol (mmol/L)	-0.23 (-0.44, -0.02)*	-0.01 (-0.42, 0.41)	†
Serum HDL cholesterol (mmol/L)	-0.02 (-0.09, 0.06)	-0.11 (-0.24, 0.02)	†
Ratio total cholesterol/HDL cholesterol			
Serum triglycerides (mmol/L)	0.20 (-0.14, 0.53)	0.30 (-0.09, 0.69)	†
Serum apolipoprotein A1 (mmol/L)	-0.03 (-1.12, 0.05)	-0.08 (-0.19, 0.03)	†
Serum apolipoprotein B (mmol/L)	-0.03 (-0.08, 0.02)	0.07 (-0.04, 0.19)	†

* $P < 0.05$; general linear regression models adjusting for baseline value. † Numbers to small to analyze. A positive value means there was an increase in the vitamin D group versus the placebo group.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; LDL, low density lipoprotein; HDL, high density lipoprotein

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3 and 4
	2b	Specific objectives or hypotheses	4 and 7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4 and 5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	na
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5 and 6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7 and 8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	na
Sample size	7a	How sample size was determined	7 and 8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5 - 6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5 - 6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5 - 6
	11b	If relevant, description of the similarity of interventions	na
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6 - 7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7

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Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4 and 8
	14b	Why the trial ended or was stopped	na
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	23
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	21 - 24
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	20 and 23
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	na
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10 - 11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13 - 14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12 - 14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11 - 14
Other information			
Registration	23	Registration number and name of trial registry	8
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15