**A randomised controlled trial of the effects of Vitamin D supplementation on knee osteoarthritis: the VIDEO study**

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**eTable 1: Additional baseline characteristics. Summary measures are mean(sd), median (range) or number (%).**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **N vitamin D /** **N Placebo** | **Vitamin D** | **Placebo**  |
| Age (yrs) | 237/237 | 64 (8) | 64 (8) |
| Sex: Female | 237/237 | 144 (61%) | 145 (61%) |
| Index knee: Right | 237/237 | 136 (57%) | 146 (62%) |
| Standing height (m) | 236/237 | 1.7 (0.1) | 1.7 (0.1) |
| Sitting height (m) | 145/146 | 0.85 (0.09) | 0.84 (0.09) |
| Weight (kg) | 236/237 | 83 (14) | 82 (16) |
| Birth weight (kg) | 67/69 | 3.3 (0.8) | 3.4 (0.9) |
| BMI(kg/m2) | 236/237 | 30 (5) | 29 (5) |
| Temperature (oC) | 234/237 | 36 (0.4) | 36 (0.4) |
| Systolic blood pressure (mm/Hg) | 234/236 | 135 (19) | 138 (20) |
| Diastolic blood pressure (mm/Hg) | 234/236 | 79 (12) | 78 (12) |
| Pulse (bpm) | 235/237 | 69 (12) | 69 (11) |
| Waist (cm) | 231/229 | 96 (12) | 95 (14) |
|  |  |  |  |
| Age at first period if female (yrs) | 142/145 | 13 (2) | 13 (2) |
| Age at menopause if female (yrs) | 136/136 | 48 (7) | 49 (6) |
| Hysterectomy if female | 137/141 | 57 (42%) | 41 (29%) |
| Any ovaries removed if female | 136/138 | 25 (18%) | 22 (16%) |
| Taking HRT if female | 142/145 | 12 (8%) | 12 (8%) |
| Oral contraceptive if female | 143/145 | 84 (59%) | 89 (61%) |
| Number of children if female | 143/145 | 2 (0 to 6) | 2 (0 to 5) |
|  |  |  |  |
| Family history of knee or hip OA | 236/235 | 113 (48%) | 109 (46%) |
| Alcohol consumption (units/wk) | 195/200 | 7 (2 to 14) | 6 (2 to 12) |
| Smoking status: Current | 237/237 | 16 (7%) | 9 (4%) |
|  Ex |  | 112 (47%) | 102 (43%) |
|  Never |  | 109 (46%) | 126 (53%) |
| Heberdens nodes | 237/237 | 145 (61%) | 165 (70%) |
| Bouchards nodes | 237/237 | 71 (30%) | 83 (35%) |
| CMC joint OA | 237/237 | 105 (44%) | 101 (43%) |
| Bilateral knee OA | 237/237 | 169 (71%) | 166 (70%) |
| Taking analgesics | 237/237 | 104 (44%) | 98 (41%) |
| Taking glucosamine or chondrotin | 237/237 | 109 (46%) | 104 (44%) |
| Taking cod liver oil | 236/236 | 73 (31%) | 78 (33%) |
| Total visits to any practitioner in last 6 months | 235/237 | 0 (0 to 6) | 0 (0 to 7) |
| WOMAC pain score | 236/232 | 33 (18) | 31 (19) |
| WOMAC function score | 236/232 | 36 (21) | 35 (20) |
| WOMAC stiffness score | 236/231 | 47 (24) | 43 (24) |
| WOMAC total score | 236/232 | 36 (19) | 35 (19) |
| WHOQOL-Bref physical | 237/231 | 64 (18) | 64 (15) |
| WHOQOL-Bref psychological | 237/231 | 72 (15) | 70 (14) |
| WHOQOL-Bref social | 237/231 | 73 (19) | 71 (19) |
| WHOQOL-Bref environment | 237/231 | 78 (13) | 77 (13) |
|  |  |  |  |
|  | **N vitamin D /** **N Placebo** | **Vitamin D** | **Placebo**  |
| Becks Depression Inventory (BDI) | 236/237 | 2 (3) | 2 (2) |
| None (BDI <4) |  | 191 (81%) | 180 (76%) |
| Mild (BDI 4-6) |  | 35 (15%) | 39 (17%) |
| Moderate (BDI 7-9) |  | 6 (2%) | 15 (6%) |
| Severe (BDI 10-14) |  | 4 (2%) | 3 (1%) |
| Mini Mental State Exam score | 236/237 | 29 (2) | 29 (2) |
| Number of physical activities  | 237/237 | 1 (0 to 4) | 1 (0 to 5) |
| Index knee varus | 227/229 | 62 (27%) | 75 (33%) |
| Index knee valgus | 228/223 | 54 (24%) | 45 (20%) |
| Index knee fixed flexion | 233/235 | 40 (17%) | 48 (20%) |
| Warmth index knee | 236/236 | 14 (6%) | 13 (6%) |
| Effusion (small to large) index knee | 237/237 | 96 (41%) | 90 (38%) |
| Crepitus (patellofemoral) index knee  | 237/236 | 213 (90%) | 211 (89%) |
| Crepitus (tibiofemoral) index knee | 124/120 | 30 (24%) | 23 (19%) |
| Quadriceps strength (kg, index knee) | 173/166 | 10 (6) | 11 (6) |
| Grip strength (kg, dominant hand) | 201/201 | 28 (11) | 28 (11) |
| Get up and Go Test | 197/195 |  |  |
| Grade 1 |  | 95 (48%) | 109 (55%) |
| Grade 2 |  | 91 (46%) | 75 (38%) |
| Grade 3 |  | 10 (5%) | 9 (5%) |
| Grade 4 |  | 1 (1%) | 1 (1%) |
| Grade 5 |  | 0 (0%) | 0 (0%) |
| Grade 6 |  | 0 (0%) | 1 (1%) |
| Timed Walk Test (time taken to walk 10m in seconds) | 197/195 | 9 (3) | 9 (3) |

WOMAC scores range from 0 to 100, 0 = no pain/disability, 100 = extreme pain/disability. WHOQOL-BREF domain scores range from 0 to 100, 0=worst, 100=best. BDI ranges from 0 to 63, 0 = minimal, 63=severe. Mini Mental State Exam score ranges from 0 to 30, scores >27 are considered normal.

**eTable 2: Multiple Imputation and Complete Case sensitivity analysis of the primary outcome**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **JSN (mm/year)** | **Vitamin D** | **Placebo** | **Difference [95% CI]** | **P-value** |
| Primary MI Analysis (N = 474)1 | -0.01 | -0.08 | 0.08 [-0.14 to 0.29] | 0.49 |
| Primary MI analysis restricted to individuals with baseline and ≥ 1 follow-up (N=380) 1 | -0.04 | -0.07 | 0.03 [-0.12 to 0.19] | 0.66 |
| Secondary outcomes with >25% missingness removed from MI model (N = 474) 2 | -0.03 | -0.08 | 0.05 [-0.08 to 0.18] | 0.48 |
| Secondary outcomes with >25% missingness removed from MI model restricted to individuals with baseline and ≥ 1 follow-up (N =380) 2 | -0.06 | -0.07 | 0.01 [-0.10 to 0.12] | 0.89 |
| MI model same as analysis model3 (N =474) | -0.08 | -0.08 | 0.00 [-0.09 to 0.09] | 0.98 |
| MI model same as analysis model restricted to individuals with baseline and ≥ 1 follow-up 3 (N =380) | -0.07 | -0.07 | 0.00 [-0.09 to 0.08] | 0.93 |
| Complete case analysis (N=242) (baseline, 1 year and 3 years JSW) | -0.09 | -0.08 | -0.01 [-0.10 to 0.07] | 0.77 |

1The primary imputation model included all primary and secondary outcomes, baseline covariates and predictors of missingness. Using all available information in the imputation model makes the MAR assumption more plausible and results in imputations with minimal bias. 2Secondary outcomes with greater than 25% missingness and a low correlation (r<0.20) with the primary outcome removed from the imputation model. 3Imputation model included primary outcome, centre, gender, glucosamine use, age and BMI. In each MI analysis the imputation model was fitted separately by treatment arm, the primary analysis model fitted to each of 50 imputed data sets and results were combined using Rubin’s rules.

**eFigure 1: Treatment effects from sensitivity analysis**

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Treatment effects from sensitivity analysis that assumes the rate of joint space narrowing is on average 25% (δJSW= -0.02 mm/year) to 500% (δJSW=-0.41 mm/year) quicker than the mean for the observed cases for all cases with missing outcome data. Missing outcomes were imputed under the varying assumptions for both arms and each arm separately.

**eTable 3: Treatment effect estimates for additional continuous secondary outcomes**

|  |  |  |  |
| --- | --- | --- | --- |
| **Rate of change per year** | **Vitamin D**  | **Placebo** | **Difference [95% CI]** |
| WHOQOL-Bref physical  | -0.48 | -0.79 | 0.31 [-1.01 to 1.61] |
| WHOQOL-Bref psychological  | -0.43 | -0.86 | 0.43 [-0.66 to 1.52] |
| WHOQOL-Bref social  | -0.29 | -1.26 | 0.97 [-0.22 to 2.17] |
| WHOQOL-Bref environment | -0.42 | -0.49 | 0.07 [-0.96 to 1.11] |
| Quadriceps strength (kg, index knee)  | -0.11 | -0.95 | 0.84 [-0.11 to 1.79] |
| Grip strength (kg, dominant hand) | -0.84 | -1.07 | 0.23 [-0.61 to 1.07] |
| Timed Walk Test (time taken to walk 10m in seconds) | 0.43 | 0.21 | 0.21 [-0.21 to 0.63] |
| Becks Depression Inventory | 0.03 | 0.03 | 0.01 [-0.19 to 0.21] |
| Mini Mental State Exam score | 0.09 | 0.17 | -0.08 [-0.23 to 0.06] |

Results generated from mixed models on the primary imputed data set (N=474) with adjustment for baseline value of the associated outcome, K&L grade, centre, gender, glucosamine use, age and BMI.WHOQOL-BREF domain scores range from 0 to 100, 0=worst, 100=best. Becks Depression Inventory ranges from 0 to 63, 0 = minimal, 63=severe. Mini Mental State Exam score ranges from 0 to 30, scores >27 are considered normal.

**eFigure 2: Mean WOMAC Pain Scores**



Mean WOMAC Pain Scores with 95% CI’s by treatment group

**eTable 4: Treatment effect estimates for ordinal and binary secondary outcomes**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Vitamin D** | **Placebo**  | **Difference [95% CI]** |
| Clinically significant progression (Medial index JSN>0.5mm) Unadjusted | N=92 (39%) | N=88 (37%) | 2% [-10% to 14%]1 |
| Adjusted |  |  | 3% [-10% to 16%]2 |
|  |  |  |  |
|  |  |  | Treatment x Time OR [95% CI] |
|  |  |  |  |
| Odds of higher grade in Get up and go test per year3,5 | 1.00 | 1.04 | 0.96 [0.73 to 1.27] |
| Patient specific Odds of knee warmth present per year (index knee)4,5 | 1.50  | 1.60  | 0.94 [0.65 to 1.35] |
| Patient specific Odds of knee effusion (small to large) present per year (index knee) 4,5 | 0.93 | 1.02 | 0.92 [0.73 to 1.15] |
|  |  |  |  |

1Corresponds to a relative risk of 1.05 [0.77 to 1.44]. 2Corresponds to an adjusted relative risk of 1.03 [0.76 to 1.40] with adjustment for baseline medial index JSW, centre, gender , glucosamine use, age and BMI.3 Result generated from an ordinal regression model with robust Huber-White sandwich estimators of SE’s. Odds ratio represents population-averaged effects for vitamin D patients versus placebo patients. 4 Results generated from a random intercept logistic model. 5Model fitted to the primary imputed data set (N=474) with adjustment for baseline value of the associated outcome, K&L grade, centre, gender, glucosamine use, age and BMI.

**eTable 5: Primary and Secondary Outcomes at 3 years**

|  |  |  |
| --- | --- | --- |
|  | **Vitamin D****N= 237** | **Placebo****N = 237** |
| Medial JSW index knee (mm) | 3.48 (2.13) | 3.33 (1.86) |
| Lateral JSW index knee (mm) | 4.94 (2.54) | 4.84 (2.61) |
| Medial JSW Contra-lateral knee (mm) | 3.30 (1.99) | 3.67 (1.99) |
| Lateral JSW Contra-lateral knee (mm) | 5.12 (2.32) | 5.00 (2.40) |
| Worst K&L grade (of medial/lateral)Index knee:  |  |  |
| 0 | 0 (0%) | 2 (1%) |
| 1 | 55 (23%) | 57 (24%) |
| 2 | 73 (31%) | 67 (28%) |
| 3 | 66 (28%) | 71 (30%) |
| 4 | 36 (15%) | 34 (14%) |
| TKR | 7 (3%) | 6 (3%) |
| Worst K&L grade (of medial/lateral)Contra-lateral knee:  |  |  |
| 0 | 7 (3%) | 14 (6%) |
| 1 | 62 (26%) | 57 (24%) |
| 2 | 64 (27%) | 71 (30%) |
| 3 | 54 (23%) | 55 (23%) |
| 4 | 36 (15%) | 24 (10%) |
| TKR | 14 (6%) | 16 (7%) |
| Clinically Significant Progression (Medial index JSN>0.5mm) | 92 (39%) | 88 (37%) |
| WOMAC pain score | 32 (25) | 32 (23) |
| WOMAC stiffness score | 39 (27) | 39 (26) |
| WOMAC function score | 36 (27) | 37 (26) |
| WOMAC total score | 35 (24) | 36 (23) |
| WHOQOL-Bref physical  | 63 (19) | 62 (18) |
| WHOQOL-Bref psychological  | 71 (17) | 68 (16) |
| WHOQOL-Bref social  | 72 (19) | 68 (21) |
| WHOQOL-Bref environment | 77 (15) | 76 (14) |
| Quadriceps strength (kg, index knee) | 10 (8) | 8 (6) |
| Grip strength (kg, dominant hand) | 26 (12) | 25 (11) |
| Get up and Go Test |  |  |
| Grade 1 | 135 (57%) | 126 (53%) |
| Grade 2 | 69 (29%) | 90 (38%) |
| Grade 3 | 21 (9%) | 19 (8%) |
| Grade 4 | 9 (4%) | 2 (1%) |
| Grade 5 | 3 (1%) | 0 (0%) |
| Grade 6 | 0 (0%) | 0 (0%) |
| Timed Walk Test (time taken to walk 10m) | 10 (5) | 10 (3) |
| Becks Depression Inventory (BDI) | 2 (3) | 2 (3) |
| None (BDI <4) | 180 (76%) | 178 (75%) |
| Mild (BDI 4-6) | 38 (16%) | 38 (16%) |
| Moderate (BDI 7-9) | 14 (6%) | 14 (6%) |
| Severe (BDI 10-14) | 5 (2%) | 7 (3%) |
| Mini Mental State Exam score | 29 (2) | 29 (1) |
| Warmth index knee |  40 (17%) | 38 (16%) |
| Effusion (small to large) index knee |  85 (36%) | 85 (36%) |

WHOQOL-BREF domain scores range from 0 to 100, 0=worst, 100=best. WOMAC scores range from 0 to 100, 0 = no pain/disability, 100 = extreme pain/disability. BDI ranges from 0 to 63, 0 = minimal, 63=severe. Mini Mental State Exam score ranges from 0 to 30, scores >27 are considered normal.