**Vitamin D receptor genotype influences risk of upper respiratory infection: supplementary material**

**Table S1:** Clinical trial dosing regimens, discovery cohort.

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| --- | --- | --- | --- |
| **Trial** | **Arm** | **Type of participant** | **One-year regimen** |
| ViDiAs (1) | Active | Adults with asthma | 6 x 3 mg (120,000 IU) vitamin D3 once every 2 months |
| Control | Adults with asthma | 6 x placebo once every 2 months |
| ViDiCO (2) | Active | Adults with COPD | 6 x 3 mg (120,000 IU) vitamin D3 once every 2 months |
| Control | Adults with COPD | 6 x placebo once every 2 months |
| ViDiFlu (3) | Active | Carers, , sheltered accommodation | 6 x 3 mg (120,000 IU) vitamin D3 once every 2 months |
| Residents, sheltered accommodation | 6 x 2.4 mg (96,000 IU) vitamin D3 once every 2 months + 10 µg (400 IU) vitamin D3 daily |
| Control | Carers, , sheltered accommodation | 6 x placebo once every 2 months |
| Residents, sheltered accommodation | 6 x placebo once every 2 months + 10 µg (400 IU) vitamin D3 daily |

**Table S2:** Baselineparticipant characteristics, discovery cohort: sub-group entering immunological analysis vs. all other participants.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Immunology sub-group (n=180) | | All other participants (n=545) |
| Sex, n (%) | Female | 91 (50.6) | | 303 (55.6) |
|  | Male | 89 (49.4) | | 242 (44.4) |
| Mean Age, years (SD) |  | 62.0 (13.2) | | 59.0 (15.4) |
| Mean BMI, kg/m2 (SD) |  | 28.0 (5.5) | | 28.2 (6.4) |
| Ethnicity, n (%) 1 | White | 163 (90.6) | | 450 (82.7) |
|  | Asian / Asian British | 8 (4.4) | | 23 (4.2) |
|  | Black / Black British | 6 (3.3) | | 56 (10.3) |
|  | Other | 2 (1.1) | | 15 (2.8) |
| Socio-economic position, n (%) 2 | Managerial/administrative/professional/intermediate professions | 100 (56.5) | | 308 (57.1) |
|  | Small employers/own account workers, supervisory/technical occupations, semi-routine/routine occupations | 75 (42.4) | | 218 (40.5) |
|  | Student | 0 | | 6 (1.1) |
|  | Unemployed | 2 (1.1) | | 7 (1.3) |
| Quarter of blood draw, n (%) | Q1 (January – March) | 51 (28.3) | | 178 (32.7) |
|  | Q2 (April – June) | 52 (28.9) | | 128 (23.5) |
|  | Q3 (July – September) | 37 (20.6) | | 101 (18.5) |
|  | Q4 (October – December) | 40 (22.2) | | 138 (25.3) |
| Smoking status, n (%) | Non-current | 141 (78.3) | | 427 (78.4) |
|  | Current | 39 (21.7) | | 118 (21.6) |
| Mean alcohol intake,  units/week (SD) 3 |  | 7.7 (11.7) | | 9.7 (15.8) |
| Influenza vaccination, n (%) | Yes | | 146 (81.1) | 446 (81.8) |
|  | No | | 34 (18.9) | 99 (18.2) |
| Respiratory comorbidity, n (%) | Asthma | | 43 (23.9) | 205 (37.6) |
|  | Chronic obstructive pulmonary disease | | 65 (36.1) | 174 (31.9) |
|  | None | | 72 (40.0) | 166 (30.5) |
| Baseline serum 25(OH)D, nmol/L (%) | <25 | 29 (16.1) | | 116 (21.3) |
|  | 25 – 49.9 | 75 (41.7) | | 222 (40.7) |
|  | 50 – 74.9 | 51 (28.3) | | 137 (25.1) |
|  | ≥ 75 | 25 (13.9) | | 70 (12.8) |
| Baseline mean serum 25(OH)D, nmol/L (SD) |  | 47.5 (24.4) | | 45.9 (24.8) |

***[1]*** *Ethnicity not reported in n=3 in immunology sub-group and n=1 in all other participants. Other ethnicities in immunology sub-group: n=1 White and Black Caribbean, n=1 preferred not to disclose. Other ethnicities in all other participants: n=6 White and Black Caribbean, n=2 White and Asian, n=2 White and Black African, n=1 Irish - Sri Lankan, n=1 Spanish – Filipino, n=1 Asian Caribbean, n=1 Mauritian, n=1 Preferred not to disclose.* ***[2]*** *Socio-economic position not reported in n=3 in immunology sub-group and n=6 in all other participants.* ***[3]*** *Alcohol consumption not reported in n=1 in immunology sub-group and n=12 in all other participants.One alcohol unit = 8g pure alcohol.*

**Table S3:** Baseline participant characteristics, replication cohort.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Replication cohort (n=737) | |
| Sex, n (%) | Female | 345 (46.8) | |
|  | Male | 392 (53.2) | |
| Mean Age, years (SD) |  | 11.5 (0.5) | |
| Mean BMI, kg/m2 (SD) |  | 19.3 (3.5) | |
| Ethnicity, n (%) | White | 737 (100) | |
|  | Asian / Asian British | 0 | |
|  | Black / Black British | 0 | |
|  | Other | 0 | |
| Respiratory comorbidity, n (%) | Asthma | | 131 (17.8) |
|  | Chronic obstructive pulmonary disease | | 0 |
|  | None | | 458 (62.1) |

**Table S4:** Genetic determinants of upper respiratory infection risk, discovery cohort: sensitivity analysis restricted to participants classifying their ethnic origin as ‘White European’.

| Gene | SNP | Genotype | N | No. of URIs per  person-year of follow-up (rate) | Adjusted  Incidence  Rate Ratio  (95% CI) 1 | P for trend |
| --- | --- | --- | --- | --- | --- | --- |
| *CYP3A4* | rs2740574 | AA | 552 | 843/516.6 (1.63) | 1.42 (1.00 to 2.00) | 0.048 |
|  |  | AG | 41 | 86/36.0 (2.39) |  |  |
|  |  | GG | 0 | \*0/0 (0.0) |  |  |
| *VDR* | rs4334089 | GG | 324 | 461/298.9 (1.54) | 1.18 (1.03 to 1.37) | 0.021 |
|  |  | AG | 219 | 372/204.7 (1.82) |  |  |
|  |  | AA | 50 | 95/49.0 (1.94) |  |  |
|  | rs11568820 | GG | 376 | 522/344.6 (1.51) | 1.31 (1.12 to 1.53) | 0.001 |
|  |  | GA | 183 | 318/173.9 (1.83) |  |  |
|  |  | AA | 28 | 75/27.5 (2.73) |  |  |
|  | rs7970314 | AA | 367 | 523/335.6 (1.56) | 1.23 (1.06 to 1.43) | 0.007 |
|  |  | AG | 197 | 339/188.8 (1.80) |  |  |
|  |  | GG | 32 | 72/30.1 (2.39) |  |  |

*[1] Adjusted for age, sex, smoking history, influenza vaccination history, allocation to vitamin D vs. placebo, respiratory comorbidity (asthma vs. COPD vs. none). \* URI rate could not be calculated due to 0 participants with the genotype or 0 URI events. Abbreviations: SNP: Single nucleotide polymorphism, URI: Upper Respiratory Infection, CI: Confidence interval, CYP-: Cytochrome P450 enzyme, VDR: Vitamin D receptor.*

**Table S5:** Genetic determinants of upper respiratory infection risk, discovery cohort: sensitivity analysis restricted to participants randomised to placebo

| Gene | SNP | Genotype | N | No. of URIs per  person-year of follow-up (rate) | Adjusted  Incidence  Rate Ratio  (95% CI) 1 | P for trend |
| --- | --- | --- | --- | --- | --- | --- |
| *CYP3A4* | rs2740574 | AA | 285 | 459/265.7 (1.73) | 1.46 (1.08 to 1.97) | 0.015 |
|  |  | AG | 35 | 74/30.5 (2.43) |  |  |
|  |  | GG | 21 | 25/17.5 (1.43) |  |  |
| *VDR* | rs4334089 | GG | 167 | 247/152.9 (1.62) | 1.22 (1.01 to 1.48) | 0.037 |
|  |  | AG | 124 | 234/114.3 (2.05) |  |  |
|  |  | AA | 50 | 76/46.4 (1.64) |  |  |
|  | rs11568820 | GG | 187 | 276/172.3 (1.60) | 1.37 (1.13 to 1.67) | 0.002 |
|  |  | GA | 104 | 202/96.1 (2.10) |  |  |
|  |  | AA | 45 | 74/39.9 (1.85) |  |  |
|  | rs7970314 | AA | 177 | 275/162.2 (1.70) | 1.23 (1.01 to 1.51) | 0.039 |
|  |  | AG | 110 | 210/102.3 (2.05) |  |  |
|  |  | GG | 53 | 73/47.6 (1.53) |  |  |

*[1] Adjusted for age, sex, ethnicity, smoking history, influenza vaccination history, respiratory comorbidity (asthma vs. COPD vs. none). Abbreviations: SNP: Single nucleotide polymorphism, URI: Upper Respiratory Infection, CI: Confidence interval, CYP-: Cytochrome P450 enzyme, VDR: Vitamin D receptor.*

**References**

1. Martineau AR, MacLaughlin BD, Hooper RL, Barnes NC, Jolliffe DA, Greiller CL, et al. Double-blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs). Thorax. 2015;70(5):451-7.

2. Martineau AR, James WY, Hooper RL, Barnes NC, Jolliffe DA, Greiller CL, et al. Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial. The Lancet Respiratory medicine. 2015;3(2):120-30.

3. Martineau AR, Hanifa Y, Witt KD, Barnes NC, Hooper RL, Patel M, et al. Double-blind randomised controlled trial of vitamin D3 supplementation for the prevention of acute respiratory infection in older adults and their carers (ViDiFlu). Thorax. 2015;70(10):953-60.