Supplement

Low vitamin D and risk of bacterial pneumonias: Mendelian randomisation studies in two population-based cohorts

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Table S1. Potential confounders according to concentrations of 25-hydroxyvitamin D in individuals in the general population.

	25-hydroxyvitamin D				
	≥50 nmol/L (n=17 762)	**25-49.9 nmol/L (n=13 102)**	**12.5-24.9 nmol/L (n=4081)**	**<12.5 nmol/L (n=888)**	**P-value[a]**
Age – years	58.9 (49.2-67.5)	57.6 (48.5-66.0)	57.0 (48.3-65.1)	57.8 (49.7-65.2)	4×10^{-13}
Men – no. (%)	7394 (42)	6255 (48)	2000 (49)	427 (48)	5×10^{-28}
BMI – kg/m^2	24.8 (22.7-27.5)	25.7 (23.3-28.7)	26.2 (23.4-29.4)	26.0 (22.8-29.4)	2×10^{-116}
Active smokers – no. (%)	4328 (24)	4334 (33)	2026 (50)	542 (61)	5×10^{-286}
Cumulative tobacco consumption – pack-years	17.9 (7.5-31.3)	20.0 (10.0-35.0)	25.2 (15.0-40.0)	30.0 (18.0-45.0)	2×10^{-98}
Alcohol – units/day	1.0 (0.4-2.0)	1.0 (0.3-2.0)	0.9 (0.0-2.0)	0.7 (0.0-2.3	0.002
eGFR – mL/min	78 (66-90)	76 (64-88)	74 (62-87)	72 (61-86)	9×10^{-43}
Chronic disease at baseline					
Diabetes – no. (%)	633 (4)	602 (5)	224 (5)	48 (5)	2×10^{-10}
Ischaemic heart disease	1030 (6)	658 (5)	192 (5)	45 (5)	0.001
COPD – no. (%)	343 (2)	259 (2)	94 (2)	29 (3)	0.02
Cancer – no. (%)	1142 (6)	705 (5)	205 (5)	39 (4)	2×10^{-6}

Data presented as median (25th and 75th percentiles), or number (percent). Based on the Copenhagen City Heart Study and the Copenhagen General Population Study. BMI = body mass index. COPD = chronic obstructive pulmonary disease. eGFR = estimated glomerular filtration rate.
[a]Calculated using linear or logistic regression, as appropriate.

Table S2. Association of potential confounders according to genetic variants in individuals in the general population.

	Association with *CYP2R1* rs117913124, P-value[a]	**Association with *CYP2R1* rs12794714, P-value[a]**	**Association with *CYP2R1* rs10741657, P-value[a]**	**Association with *DHCR7* rs7944926, P-value[a]**	**Association with *DHCR7* rs11234027, P-value[a]**	**Association with *GEMIN2* rs2277458, P-value[a]**	**Association with *HAL* rs3819817, P-value[a]**
Age – years	0.13	0.41	0.10	0.26	0.36	0.70	0.49
Men – no. (%)	0.22	0.07	0.03[b]	0.99	0.14	0.16	0.25
BMI – kg/m^2	0.34	0.09	0.08	0.38	0.20	0.50	0.52
Active smokers – no. (%)	0.12	0.66	0.69	0.16	0.04[b]	0.45	0.84
Cumulative tobacco consumption – pack-years[c]	0.45	0.18	0.28	0.58	0.79	0.48	0.31
Alcohol – units/day	0.92	0.46	0.14	0.81	0.88	0.33	0.75
eGFR – mL/min	0.88	0.65	0.67	0.13	0.07	0.94	0.21
Chronic disease at baseline							
Diabetes – no. (%)	0.67	0.37	0.62	0.81	0.67	0.59	0.22
Ischaemic heart disease	0.33	0.68	0.67	0.37	0.49	0.27	0.40
COPD – no. (%)	0.44	0.84	0.82	0.57	0.46	0.43	0.75
Cancer – no. (%)	0.59	0.37	0.54	0.14	0.61	0.23	0.61

Data presented as median (25th and 75th percentiles), or n (%). Based on the Copenhagen City Heart Study and the Copenhagen General Population Study. BMI = body mass index. COPD = chronic obstructive pulmonary disease. eGFR = estimated glomerular filtration rate.

[a]Calculated using linear or logistic regression, as appropriate.

[b]When P-value is adjusted for 11 individual analyses according to the Bonferroni method, a P=0.05/11=0.005 is required for statistical significance.

[c]Only calculated for former and current smokers.

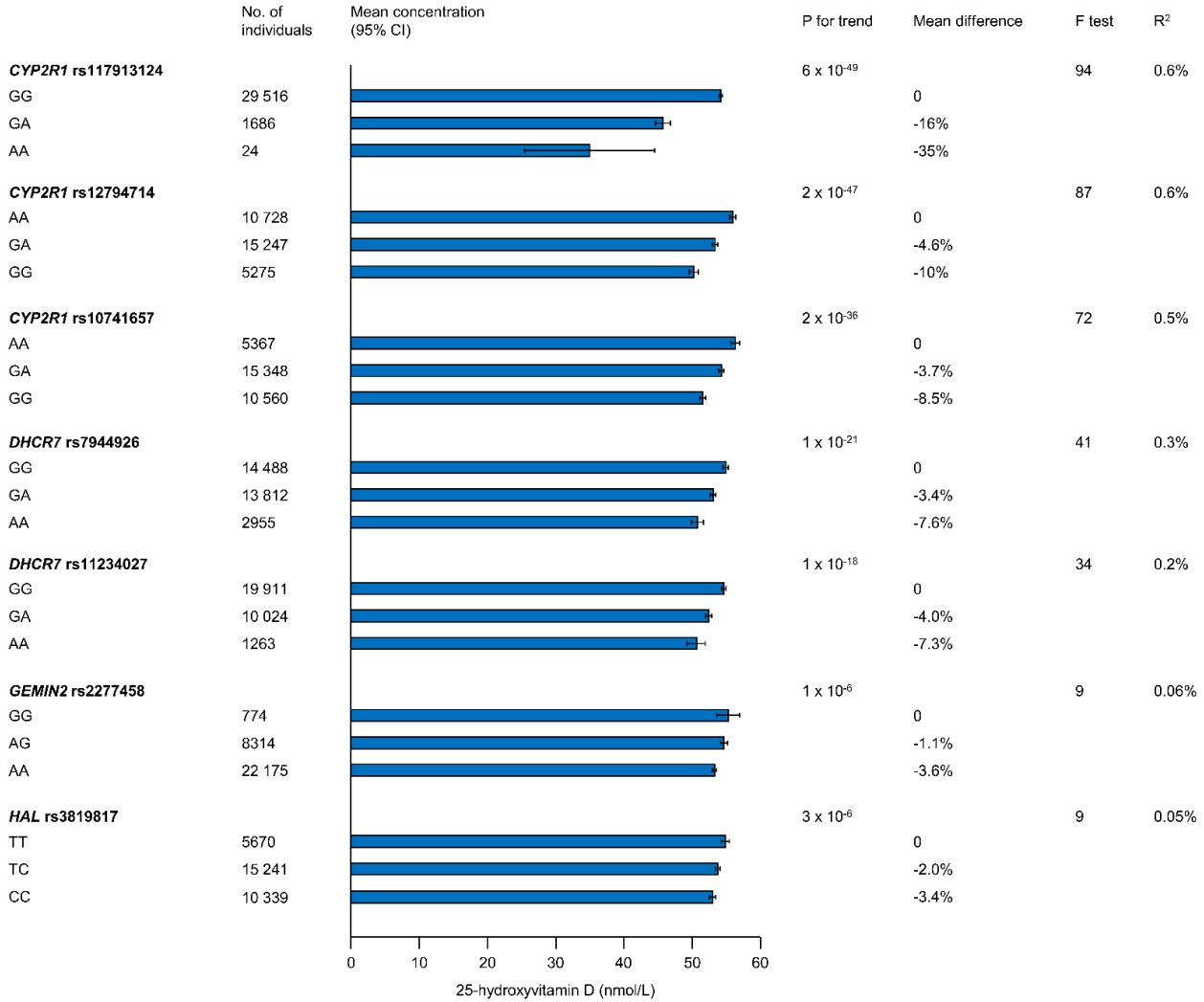

Figure S1. Association of genetic variants with plasma 25-hydroxyvitamin D concentration in individuals in the general population. Geometric mean plasma 25-hydroxyvitamin D concentration obtained from multiple linear regression models adjusted for age, sex, seasonal variation of 25-hydroxyvitamin D, birth year, and cohort. P-values for trend obtained from Wald's test. F test is for statistical strength of the genetic variants and R^2 is measure of explained variation, obtained from unadjusted models to avoid effect of other covariates. Based on the Copenhagen City Heart Study and the Copenhagen General Population Study. CI = confidence interval.

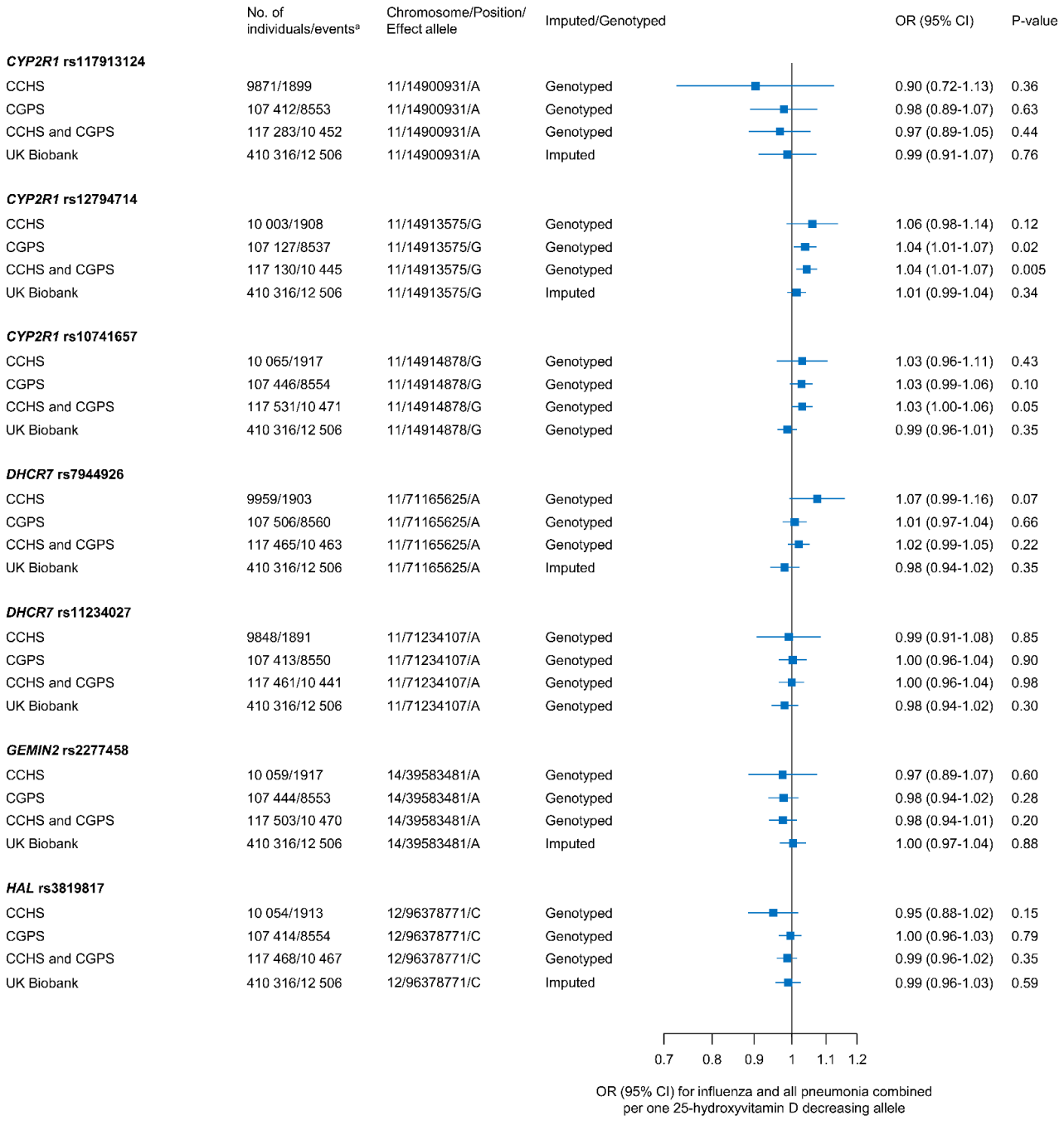

Figure S2. Risk of influenza and pneumonia according to 25-hydroxyvitamin D decreasing genotypes in individuals in the general population. Risk estimates for the Copenhagen City Heart Study (CCHS) and Copenhagen General Population Study (CGPS) obtained from logistic regression models adjusted for age, sex, birth year, and cohort. Risk estimates for the UK Biobank obtained from GeneATLAS. CI = confidence interval. OR = odds ratio.
[a]Number of individuals and events for UK Biobank may be lower than indicated, as this is based on summary data.

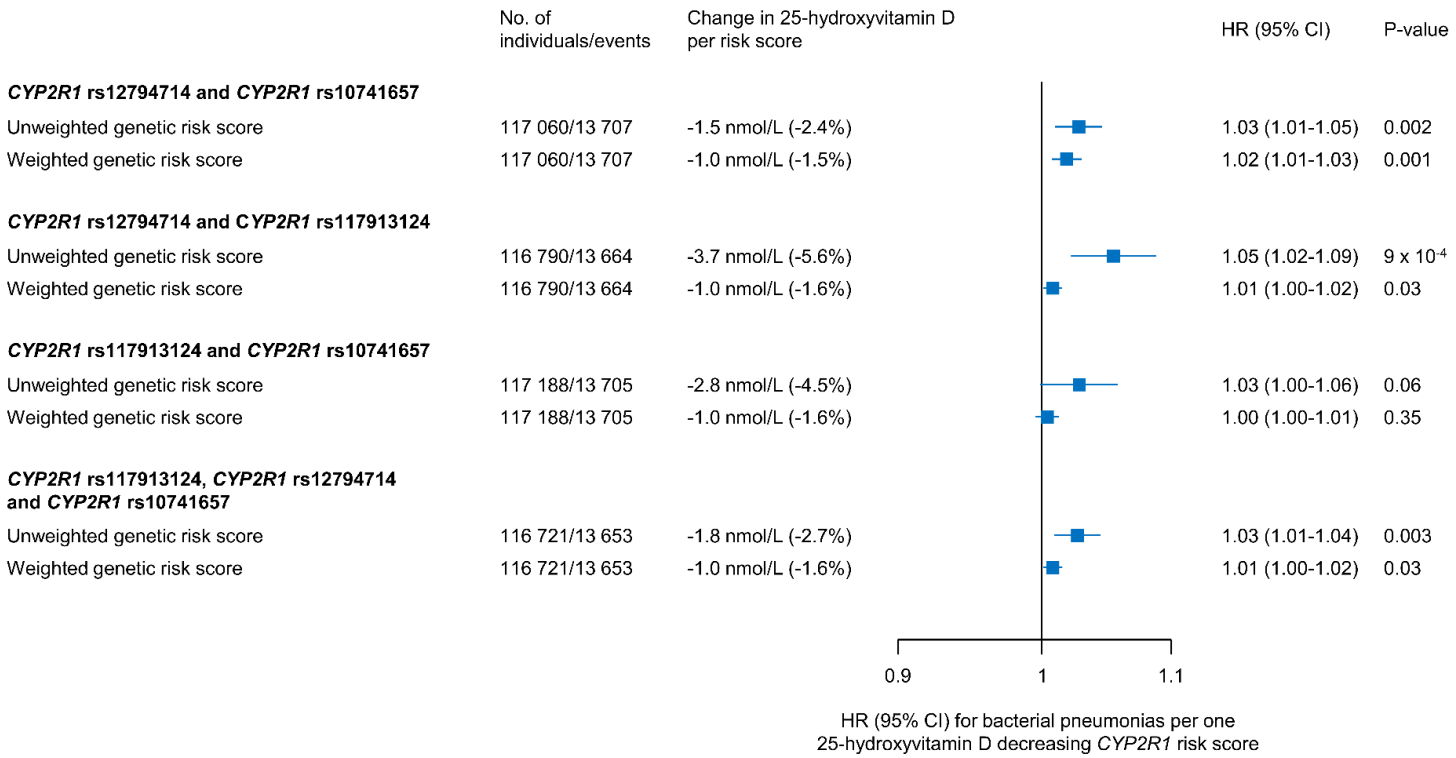

Figure S3. Risk of bacterial pneumonias according to 25-hydroxyvitamin D decreasing *CYP2R1* risk score in individuals in the general population. Risk estimates obtained from Cox regression models with multiple failure-time analysis according to Andersen and Gill adjusted for age (as timescale), sex, birth year, and cohort. Instrumental variable analysis not possible with Cox regression model with multiple-failure time analysis. Only internal weighted risk scores could be calculated as genome-wide association studies did not report necessary results so external weighted risk score could be calculated. Based on the Copenhagen City Heart Study and the Copenhagen General Population Study. CI = confidence interval. HR = hazard ratio.