Supplementary Data

Online-Only Supplemental Material

"Association of plasma vitamin D metabolites with incident type 2 diabetes: EPIC-InterAct case-cohort study across eight European countries"

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Supplemental Figure 7 Prospective association between plasma 25(OH)D_3 metabolites and type 2 diabetes stratified by BMI categories: EPIC-InterAct Study. Interaction of 25(OH)D metabolites with age, sex, BMI, physical activity, hormone therapy use (among women only) and menopausal status (among women only) for type 2 diabetes was examined, and only BMI showed significant interaction ($p<0.05$) with both non-epimeric 25(OH)D_3 and 3-epi-25(OH)D_3 (p-value < 0.001 for both). Hazard Ratios (HRs) and 95% confidence intervals (CI) are per 1-SD (calculated from the subcohort distributions) higher vitamin D metabolite, estimated using country-specific Prentice-weighted Cox regression models, stratified by three BMI subgroups. Country-specific estimates were combined using inverse variance-weighted random-effects meta-analysis. The adjusted covariates were age (as underlying timescale), sex, center, seasonality (sine and cosine function of the day of blood draw), smoking status, physical activity, education, alcohol drinking, total energy intake, Mediterranean diet score, circulating lipid biomarkers (HDL-C, LDL-C), BMI and the other 25(OH)D metabolites.

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Supplemental Table 1 Population characteristics at baseline by future case and non-case status: EPIC-InterAct Study*

	Non-cases (n=12980)		Cases (n=9671)	
	Mean/%	n/SD	Mean/%	n/SD
Total 25(OH)D†‡	41.3	17.3	37.2	16.2
Non-epimeric 25(OH)D_3, nmol/L†‡	40.9	17.3	36.9	16.3
3-epi-25(OH)D_3, nmol/L†‡	2.13	1.32	2.17	1.44
Ratio of 3-epi-25(OH)D_3 to non-epimeric 25(OH)D_3†‡	0.04	0.02	0.05	0.02
25(OH)D_2, nmol/L†‡	8.18	6.57	7.97	5.65
Age, y‡	51.5	9.10	54.9	7.60
BMI, kg/m^2‡	26.0	4.10	29.9	4.70
Sex, %				
Men	36.9	4784	49.9	4829
Women	63.1	8196	50.1	4842
Total energy intake, kcal/d‡	2126	636	2165	676
Alcohol consumption, %				
None	16.1	2085	17.9	1733
>0-<6g/d	34.3	4447	32.2	3117
6-<12g/d	14.5	1888	13.1	1266
12-<24g/d	15.5	2012	14.3	1381
≥24g/d	19.3	2502	21.8	2110
Mediterranean diet score, %				
Low (score 0-6)	22.5	2919	27.4	2652
Moderate (score 7-10)	43.5	5643	40.9	3953
High (score 11-18)	31.9	4135	28.3	2740
Physical activity, %				
Inactive	23.5	3044	29.9	2894
Moderately inactive	32.4	4206	31.5	3044
Moderately active	22.3	2901	19.9	1928
Active	20.3	2632	17.1	1653
Smoking status, %				
Never	47.5	6166	41.4	4008
Former	26.1	3392	29.4	2842
Current	25.1	3255	27.7	2683
Education level, %				
None	8.20	1069	11.3	1095
Primary	31.3	4060	39.7	3838
Technical or professional	22.0	2862	23.0	2221
Secondary	15.9	2062	11.0	1062
Higher education	20.4	2651	12.4	1195
Season of blood draw, %				
Winter (Dec-Feb)	24.3	3154	23.9	2310
Spring (Mar-May)	27.8	3606	27.9	2701
Summer (June-Aug)	19.9	2587	20.6	1992
Autumn (Sept-Nov)	27.8	3604	27.4	2646

*SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids.

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† Sample size was 12980 among non-cases and 9671 among cases for the measured non-epimeric 25(OH)D_3; 5292 among non-cases and 3694 among cases for measured 3-epi-25(OH)D_3; 615 among non-cases and 397 among non-cases for measured 25(OH)D_2. Total 25(OH)D: sum of non-epimeric 25(OH)D_3 + 25(OH)D_2.
‡ The variables were presented as mean and SD, and other variables were presented as % and number of participants (N).

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Supplemental Table 2 Population characteristics by quintiles of 3-epi-25(OH)D_3 to non-epimeric 25(OH)D_3 ratio, and 25(OH)D_2 in the subcohort of EPIC-InterAct Study*

	Quintiles of 3-epi-25(OH)D_3 to non-epimeric 25(OH)D_3 ratio						Quintiles of 25(OH)D_2					
	3-epi-25(OH)D_3 below LLQ † (n=8049)	Q1 (n=1102)	Q2 (n=1103)	Q3 (n=1102)	Q4 (n=1103)	Q5 (n=1103)	Below LLQ‡(n=12928)	Q1 (n=126)	Q2 (n=127)	Q3 (n=127)	Q4 (n=127)	Q5 (n=127)
Total 25(OH)D§	34.9 (14.5)	58.8 (13.1)	51.2 (14.2)	48.4 (15.5)	46.7 (17)	45.2 (20.2)	40.9 (17.3)	44.5 (16.3)	47.2 (17.9)	41 (16)	43.1 (14.9)	47.8 (15.9)
Non-epimeric 25(OH)D_3, nmol/L	34.4 (14.5)	58.6 (13.1)	51.0 (14.1)	48.1 (15.5)	46.4 (17)	44.8 (20.3)	40.9 (17.3)	41.2 (16.3)	42.9 (18)	34.8 (16.2)	34.2 (15)	30.3 (17.5)
3-epi-25(OH)D_3, nmol/L		1.3 (0.3)	1.6 (0.5)	1.9 (0.6)	2.4 (0.9)	3.5 (2.1)	2.1 (1.3)	2.1 (1.3)	2.3 (1.2)	2.0 (1.0)	2.0 (1.5)	2.5 (3.4)
3-epi-25(OH)D_3 to non-epimeric 25(OH)D_3 ratio		0.02 (0.003)	0.03 (0.002)	0.04 (0.003)	0.05 (0.004)	0.08 (0.02)	0.04 (0.02)	0.04 (0.02)	0.04 (0.02)	0.05 (0.02)	0.05 (0.03)	0.05 (0.02)
25(OH)D_2, nmol/L	8.7 (7.0)	6.2 (3.4)	6.2 (3.5)	7.4 (5.4)	6.6 (3.5)	8.8 (8.1)		3.4 (0.2)	4.3 (0.4)	6.2 (0.7)	8.9 (1)	18 (8.5)
Age, y	51.7 (9.0)	50.7 (9.7)	51.3 (9.3)	52 (9.2)	51.7 (8.7)	51.2 (8.9)	51.5 (9.1)	52.3 (8.9)	54.4 (9.1)	54.1 (7.5)	54.7 (8.2)	54.4 (7.7)
BMI, kg/m^2	26.3 (4.4)	25.2 (3.9)	25.5 (3.8)	25.9 (3.9)	26.2 (4.2)	26.5 (4.1)	26.2 (4.2)	24.8 (3.7)	25.3 (4.1)	25.4 (4)	25.8 (4.6)	25.1 (3.4)
Energy intake, kcal/d	2111 (633)	2093 (630)	2112 (643)	2126 (622)	2181 (658)	2235 (657)	2128 (641)	2100 (563)	2161 (588)	2098 (526)	2172 (566)	1966 (547)
Sex, %												
Men	34.3	32.3	37.9	39.7	46.1	52.3	37.4	28.6	40.9	38.6	44.1	26.8
Women	65.7	67.7	62.1	60.3	53.9	47.7	62.6	71.4	59.1	61.4	55.9	73.2
Alcohol consumption, %												
0 g/d	18.1	14.1	14	14.6	14.1	11.3	16.5	18.3	6.3	9.4	9.4	15.7
>0-<6 g/d	35.2	40.0	36.4	31.3	30.0	24.3	34.2	31.7	31.5	29.1	28.3	33.9
6-<12 g/d	14	17.7	15.5	15.1	14.8	12.3	14.2	16.7	21.3	17.3	18.9	23.6
12-<24 g/d	15.1	14.2	16.0	17.9	14.9	17.2	15.4	17.5	20.5	22.0	15.0	12.6
≥24 g/d	17.3	13.7	17.9	20.7	26.0	34.1	19.4	15.9	20.5	22.0	28.3	14.2
Mediterranean diet score, %												
Low (score 0-6)	21.9	27.1	25.2	22.1	21.1	21.0	22.4	22.2	24.4	27.6	26.8	16.5
Moderate (score 7-10)	43.2	42.8	45.5	43.2	43.2	43.4	43.1	50.8	45.7	46.5	48.0	55.1
High (score 11-18)	32.7	28	27	32.5	33.4	32.8	32.2	25.4	29.1	25.2	22.0	25.2
Physical activity, %												
Inactive	26.1	18.9	20.5	21.2	20.6	20.6	23.9	21.4	20.5	16.5	16.5	24.4

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Moderately inactive	33.0	29.4	31.7	32.4	32.0	32.4	32.4	29.4	33.9	34.6	31.5	33.9
Moderately active	21.6	25.3	23.8	21.5	22.8	22.0	22.1	26.2	23.6	24.4	26.8	18.1
Active	17.6	24.5	22.7	23.6	23.7	23.9	20.0	19.8	20.5	23.6	23.6	22.8
Smoking status, %												
Never	48.3	49.9	47.9	47.6	43.2	40.2	47.2	50.8	46.5	46.5	48.8	50.4
Former	24.5	27.9	26.7	26.8	30.2	32.0	26.2	28.6	34.6	26.0	25.2	20.5
Current	26.2	20.2	23.8	24.5	24.9	26.5	25.4	19.8	17.3	26.8	25.2	27.6
Educational level, %												
None	9.2	5.4	6.4	7.6	9.4	9.8	8.9	1.6	3.1	0	2.4	4.7
Primary	32.3	27.5	29.3	32.6	33.2	32.3	32	30.2	22.0	28.3	26.0	24.4
Technical or professional	21.4	24.8	24.2	23.2	21.2	22.1	21.8	23.8	26.0	29.9	32.3	26.0
Secondary	15.4	18.4	17.0	15.2	14.6	14.1	15.5	15.9	20.5	17.3	11.8	16.5
Higher education	19.8	21.3	20.8	19.0	20.0	20.1	19.7	25.4	26.8	22.0	25.2	28.3
Season of blood draw, %												
Winter (Dec-Feb)	29.1	16.4	18.3	16.9	19.1	16.5	24.4	23.0	16.5	25.2	29.1	28.3
Spring (Mar-May)	31.3	18.8	22.8	25.1	23.6	24.1	27.7	27.8	25.2	35.4	34.6	30.7
Summer (June-Aug)	14.7	24.5	24.2	26.5	28.1	33.7	19.9	27.0	21.3	18.9	13.4	17.3
Autumn (Sept-Nov)	24.7	40.0	34.7	31.0	28.8	25.7	27.8	21.4	36.2	20.5	22.8	23.6

*All values are expressed as mean (SD) or as percentage;
†This category represents that the ratio is missing because 3-epi-25(OH)D_3 is the below LLQ (1 nmol/L);
‡LLQ, lower limit of quantification. The LLQ for 25(OH)D_2 is 3 nmol/L.
§total 25(OH)D: sum of non-epimeric 25(OH)D_3 + 25(OH)D_2.

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Supplemental Table 3 Pairwise correlation of plasma 25(OH)D metabolites in the subchort of EPIC-InterAct Study*

	Non-epimeric 23(OH)D_3 and 3-epi-25(OH)D_3			Non-epimeric 23(OH)D_3 and 25(OH)D_2			3-epi-25(OH)D_3 and 25(OH)D_2		
	n	r	p	n	r	p	n	r	p
Total subcohort	5513	0.44	<0.001	634	-0.30	<0.001	222	-0.11	0.109
France	204	0.45	<0.001	49	-0.39	0.006	17	0.46	0.066
Italy	796	0.49	<0.001	46	-0.17	0.266	13	0.21	0.494
Spain	1292	0.47	<0.001	68	-0.18	0.135	25	-0.16	0.444
UK	508	0.42	<0.001	73	-0.10	0.421	25	0.04	0.864
Netherland	583	0.42	<0.001	45	-0.28	0.066	17	-0.07	0.779
Germany	838	0.42	<0.001	52	-0.39	0.004	16	-0.06	0.816
Sweden	477	0.43	<0.001	40	-0.37	0.019	19	-0.37	0.117
Denmark	815	0.50	<0.001	261	-0.34	<0.001	90	-0.35	<0.001

* EPIC-InterAct subcohort participants were used to calculate the statistics (Spearman's correlation coefficients) across the eight countries and in the total subcohort.

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Supplemental Table 4 Association of demographic, lifestyle, dietary factors or circulating biomarkers with plasma 25(OH)D metabolites in the EPIC-InterAct subcohort

25(OH)D metabolites	Factors evaluated as potential correlates with 25(OH)D metabolites	Complete case analysis				Analysis using multiple imputation		
		n	Beta*	95%CI	I^2, %	Beta	95%CI	I^2, %
Non-epimeric 25(OH)D_3, nmol/L (n=13562) †	**Demographic and lifestyle factors**							
	Sex (women vs men)	11369	-0.063	-0.158, 0.031	74.1	-0.060	-0.147, 0.026	80.9
	Age (per 5y)	11369	-0.007	-0.026, 0.012	57.7	-0.005	-0.024, 0.013	63.0
	BMI (per 5kg/m^2)	11369	-0.113	-0.135, -0.091	0	-0.118	-0.138, -0.098	0
	Alcohol (per 10g/d)	11369	0.026	-0.004, 0.055	80.9	0.017	-0.006, 0.041	76.4
	Former vs never smoker	11369	0.084	0.037, 0.131	22.9	0.078	0.032, 0.125	31.9
	Current vs never smoker	11369	-0.080	-0.135, -0.025	32.3	-0.088	-0.133, -0.042	19.8
	Moderate inactive vs inactive	11369	0.104	0.061, 0.147	0	0.122	0.076, 0.169	15.6
	Moderate active vs inactive	11369	0.191	0.107, 0.275	59.0	0.203	0.133, 0.273	50.3
	Active vs inactive	11369	0.301	0.246, 0.357	0	0.298	0.247, 0.350	0
	Middle vs low education level	11369	0.006	-0.036, 0.047	0	-0.010	-0.055, 0.035	21.6
	High vs low education level	11369	-0.003	-0.094, 0.088	64.3	0.002	-0.078, 0.081	60.9
	Latitudes (per 1000km)	11369	0.185	0.153, 0.217	NA‡	0.176	0.145, 0.206	NA
	Dietary vitamin D and supplements							
	Vitamin supplements (yes vs no)	11369	0.116	0.011, 0.221	86.9	0.115	0.016, 0.213	86.2
	Dietary vitamin D (per 10g/d)	11490	0.297	0.140, 0.454	62.7	0.325	0.170, 0.480	67.7
	Dietary food sources							
	Fish (per 100g/d)	11369	0.058	0.002, 0.113	0	0.102	0.021, 0.182	31.4
	Egg (per 100g/d)	11369	0.014	-0.089, 0.116	0	0.043	-0.055, 0.140	0
	Red meat (per 100g/d)	11369	0.022	-0.036, 0.079	0	0.021	-0.044, 0.085	22.4
	Dairy products (per 100g/d)	11369	0.007	-0.001, 0.015	0.60	0.007	-0.001, 0.015	0
	Total cereal (per 100g/d)	11369	-0.027	-0.048, -0.006	0	-0.03	-0.052, -0.008	16.8
	Poultry (per 100g/d)	11369	-0.077	-0.222, 0.067	51.2	-0.037	-0.160, 0.086	43.5
	Processed meat (per 100g/d)	11369	0.031	-0.075, 0.137	49.1	0.036	-0.035, 0.107	16.6
	Offal (per 10g/d)	11369	0.004	-0.027, 0.035	0	0.007	-0.023, 0.036	0

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25(OH)D metabolites	Factors evaluated as potential correlates with 25(OH)D metabolites	Complete case analysis				Analysis using multiple imputation		
		n	Beta*	95%CI	I^2, %	Beta	95%CI	I^2, %
	Margarine (per 10g/d)	11369	0.032	-0.001, 0.065	63	0.036	-0.001, 0.073	73.8
	Butter (per 10g/d)	11369	-0.042	-0.067, -0.017	0	-0.026	-0.049, -0.004	0
	Mushroom (per 10g/d)	11369	-0.004	-0.033, 0.025	0	-0.006	-0.034, 0.021	0
	Mediterranean diet score (per 1-category higher)	11490	0.024	-0.003, 0.051	0	0.029	0.003, 0.054	0
	Circulating biomarkers							
	SFA (per 1-SD)	11369	0.032	-0.007, 0.071	67.2	0.038	0.001, 0.074	69.1
	PUFA (per 1-SD)	11369	0.079	0.038, 0.120	70.5	0.08	0.042, 0.119	72.7
	HDL-cholesterol (per 1-SD)	11369	0.070	0.051, 0.089	0	0.072	0.054, 0.089	0
	LDL-cholesterol (per 1-SD)	11369	0.019	-0.002, 0.040	29.3	0.019	-0.002, 0.040	38.3
	Uric acid (per 1-SD)	11193	-0.002	-0.038, 0.033	52.9	-0.002	-0.033, 0.029	49.4
	Creatinine (per 1-SD)	11193	0.152	0.122, 0.183	46.9	0.149	0.122, 0.176	41
	AST (per 1-SD)	11193	-0.015	-0.043, 0.013	14.1	-0.011	-0.037, 0.016	17
	ALT (per 1-SD)	11193	0.005	-0.022, 0.033	0	0.005	-0.020, 0.03	0
	GGT (per 1-SD)	11193	-0.028	-0.051, -0.005	10.1	-0.03	-0.055, -0.005	27.7
3-epi-25(OH)D_3 (log-transformed) (n=13562) †	**Demographic and lifestyle factors**							
	Sex (women vs men)	11369	-0.297	-0.494, -0.1	68.8	-0.268	-0.445, -0.09	78.2
	Age (per 5y)	11369	-0.007	-0.044, 0.031	46.9	-0.011	-0.05, 0.029	60.9
	BMI (per 5kg/m^2)	11369	-0.131	-0.184, -0.079	0	-0.141	-0.188, -0.093	0
	Alcohol (per 10g/d)	11369	0.116	0.078, 0.154	45.4	0.102	0.069, 0.135	43.9
	Former vs never smoker	11369	0.108	0.014, 0.202	6.3	0.123	0.04, 0.207	0
	Current vs never smoker	11369	-0.169	-0.286, -0.053	24.2	-0.154	-0.252, -0.057	12
	Moderate inactive vs inactive	11369	0.166	0.047, 0.285	18.2	0.189	0.072, 0.305	25.8
	Moderate active vs inactive	11369	0.245	0.102, 0.388	29.9	0.275	0.152, 0.399	21.4
	Active vs inactive	11369	0.49	0.337, 0.644	28.1	0.486	0.369, 0.602	0
	Middle vs low education level	11369	-0.006	-0.115, 0.103	19.5	-0.048	-0.157, 0.062	33
	High vs low education level	11369	-0.011	-0.132, 0.109	5.3	-0.079	-0.186, 0.027	0

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25(OH)D metabolites	Factors evaluated as potential correlates with 25(OH)D metabolites	Complete case analysis				Analysis using multiple imputation		
		n	Beta*	95%CI	I^2, %	Beta	95%CI	I^2, %
	Latitudes (per 1000km)	11369	0.080	0.009, 0.152	NA	0.076	0.008, 0.144	NA
	Dietary vitamin D and supplements							
	Vitamin supplements (yes vs no)	11369	0.098	-0.032, 0.228	56.1	0.117	-0.009, 0.244	59.1
	Dietary vitamin D (per 10g/d)	11490	0.268	-0.101, 0.638	65.8	0.196	-0.16, 0.552	69.1
	Dietary food sources							
	Fish (per 100g/d)	11369	0.046	-0.2, 0.293	52.6	0.049	-0.201, 0.299	61.2
	Egg (per 100g/d)	11369	-0.054	-0.415, 0.308	40.3	0.043	-0.285, 0.371	40.7
	Red meat (per 100g/d)	11369	0.062	-0.078, 0.202	6.5	0.047	-0.081, 0.175	5.4
	Dairy products (per 100g/d)	11369	0.018	-0.006, 0.042	34	0.018	-0.002, 0.038	20.7
	Total cereal (per 100g/d)	11369	-0.003	-0.051, 0.045	0	-0.007	-0.051, 0.038	0
	Poultry (per 100g/d)	11369	0.034	-0.332, 0.399	61.6	0.034	-0.273, 0.342	54.4
	Processed meat (per 100g/d)	11369	0.146	-0.005, 0.298	0	0.137	0, 0.274	0
	Offal (per 10g/d)	11369	0.032	-0.046, 0.109	5.8	0.027	-0.043, 0.097	1.6
	Margarine (per 10g/d)	11369	0.032	-0.028, 0.091	47.7	0.021	-0.045, 0.086	61.3
	Butter (per 10g/d)	11369	-0.07	-0.136, -0.004	22.6	-0.063	-0.118, -0.007	12.8
	Mushroom (per 10g/d)	11369	0.035	-0.032, 0.102	0	0.024	-0.039, 0.087	0
	Mediterranean diet score (per 1-category higher)	11490	0.008	-0.055, 0.071	0	0.014	-0.044, 0.072	0
	Circulating biomarkers							
	SFA (per 1-SD)	11369	0.091	0.016, 0.165	56.5	0.107	0.037, 0.177	59.9
	PUFA (per 1-SD)	11369	0.022	-0.03, 0.073	16	0.012	-0.053, 0.077	53.4
	HDL-cholesterol (per 1-SD)	11369	0.08	0.037, 0.124	0	0.082	0.042, 0.122	0
	LDL-cholesterol (per 1-SD)	11369	-0.024	-0.079, 0.032	48.2	-0.023	-0.079, 0.033	57.4
	Uric acid (per 1-SD)	11193	0.091	0.039, 0.142	0	0.077	0.03, 0.125	0
	Creatinine (per 1-SD)	11193	0.11	0.063, 0.157	0	0.12	0.076, 0.165	0
	AST (per 1-SD)	11193	0.05	-0.023, 0.123	33.2	0.054	0.001, 0.108	0.4
	ALT (per 1-SD)	11193	-0.024	-0.126, 0.078	58.1	-0.033	-0.102, 0.035	25.9
	GGT (per 1-SD)	11193	0.054	-0.006, 0.115	25.9	0.047	-0.003, 0.096	14.2

Supplementary Data

25(OH)D metabolites	Factors evaluated as potential correlates with 25(OH)D metabolites	Complete case analysis				Analysis using multiple imputation		
		n	Beta*	95%CI	I^2, %	Beta	95%CI	I^2, %
Ratio of 3-epi-25(OH)D_3 to non-epimeric 25(OH)D_3 (log-transformed) (n=5513) †	**Demographic and lifestyle factors**							
	Sex (women vs men)	4612	-0.155	-0.246, -0.065	18.3	-0.117	-0.191, -0.043	19.9
	Age (per 5y)	4612	0.006	-0.025, 0.036	48.4	0	-0.023, 0.022	25.5
	BMI (per 5kg/m^2)	4612	0.037	-0.005, 0.079	0	0.046	0.008, 0.083	0
	Alcohol (per 10g/d)	4612	0.069	0.033, 0.106	63.7	0.060	0.034, 0.085	46.9
	Former vs never smoker	4612	0.046	-0.026, 0.117	0	0.050	-0.014, 0.114	0
	Current vs never smoker	4612	0	-0.076, 0.076	0	0.014	-0.056, 0.083	0
	Moderate inactive vs inactive	4612	-0.01	-0.118, 0.099	33	-0.012	-0.104, 0.081	24.8
	Moderate active vs inactive	4612	-0.059	-0.169, 0.051	23.8	-0.048	-0.132, 0.036	0
	Active vs inactive	4612	-0.007	-0.106, 0.091	0	0.003	-0.098, 0.105	17
	Middle vs low education level	4612	0.044	-0.031, 0.119	0	0.029	-0.039, 0.097	0
	High vs low education level	4612	-0.026	-0.117, 0.064	0	-0.042	-0.125, 0.040	0
	Latitudes (per 1000km)	4612	-0.139	-0.193, -0.086	NA	-0.139	-0.189, -0.089	NA
	Dietary vitamin D and supplements							
	Vitamin supplements (yes vs no)	4612	-0.046	-0.110, 0.018	0	-0.034	-0.094, 0.026	0
	Dietary vitamin D (per 10g/d)	4662	-0.043	-0.251, 0.165	39.9	-0.120	-0.347, 0.107	56.2
	Dietary food sources							
	Fish (per 100g/d)	4612	0.063	-0.090, 0.216	27.4	0.014	-0.152, 0.181	46.2
	Egg (per 100g/d)	4612	0.003	-0.181, 0.187	0	-0.061	-0.231, 0.109	0
	Red meat (per 100g/d)	4612	-0.035	-0.138, 0.067	0	-0.034	-0.130, 0.061	0
	Dairy products (per 100g/d)	4612	0.010	-0.008, 0.027	21.2	0.010	-0.004, 0.023	0
	Total cereal (per 100g/d)	4612	0.032	-0.006, 0.070	0	0.035	0, 0.070	0
	Poultry (per 100g/d)	4612	0.105	-0.042, 0.252	0	0.075	-0.117, 0.267	30.5
	Processed meat (per 100g/d)	4612	0.042	-0.074, 0.158	0	0.043	-0.061, 0.147	0
	Offal (per 10g/d)	4612	0.037	-0.019, 0.093	0	0.041	-0.012, 0.095	0
	Margarine (per 10g/d)	4612	-0.01	-0.060, 0.040	54.9	-0.009	-0.052, 0.034	48.2

Supplementary Data

25(OH)D metabolites	Factors evaluated as potential correlates with 25(OH)D metabolites	Complete case analysis				Analysis using multiple imputation		
		n	Beta*	95%CI	I^2, %	Beta	95%CI	I^2, %
	Butter (per 10g/d)	4612	-0.012	-0.074, 0.050	40.2	-0.006	-0.056, 0.043	27.4
	Mushroom (per 10g/d)	4612	0.043	-0.008, 0.094	0	0.044	-0.004, 0.092	0
	Mediterranean diet score (per 1-category higher)	4662	-0.028	-0.077, 0.021	0	-0.026	-0.07, 0.0190	0
	Circulating biomarkers							
	SFA (per 1-SD)	4612	0.019	-0.018, 0.056	0	0.013	-0.030, 0.056	34.3
	PUFA (per 1-SD)	4612	-0.078	-0.140, -0.017	60.4	-0.098	-0.167, -0.028	75.9
	HDL-cholesterol (per 1-SD)	4612	-0.023	-0.058, 0.012	0	-0.033	-0.065, -0.002	0
	LDL-cholesterol (per 1-SD)	4612	-0.034	-0.064, -0.003	0	-0.031	-0.059, -0.003	0
	Uric acid (per 1-SD)	4544	0.033	-0.045, 0.110	69.1	0.03	-0.026, 0.086	52.7
	Creatinine (per 1-SD)	4544	-0.075	-0.115, -0.034	15.8	-0.083	-0.116, -0.050	0
	AST (per 1-SD)	4544	0.016	-0.032, 0.064	11.6	0.018	-0.024, 0.059	4.8
	ALT (per 1-SD)	4544	-0.012	-0.101, 0.077	65.6	-0.018	-0.102, 0.066	68.4
	GGT (per 1-SD)	4544	0.071	0.001, 0.141	63.9	0.081	0.016, 0.146	66.3
$25(OH)D_2$ (log-transformed) (n=13562) †	**Demographic and lifestyle factors**							
	Sex (women vs men)	11369	-0.035	-0.228, 0.157	NA	-0.021	-0.201, 0.158	NA
	Age (per 5y)	11369	0.052	0.001, 0.103	NA	0.042	-0.005, 0.089	NA
	BMI (per 5kg/m^2)	11369	-0.052	-0.153, 0.049	NA	-0.091	-0.186, 0.003	NA
	Alcohol (per 10g/d)	11369	-0.041	-0.092, 0.01	NA	-0.023	-0.069, 0.023	NA
	Former vs never smoker	11369	-0.113	-0.286, 0.06	NA	-0.096	-0.257, 0.065	NA
	Current vs never smoker	11369	-0.119	-0.305, 0.067	NA	-0.153	-0.328, 0.021	NA
	Moderate inactive vs inactive	11369	-0.068	-0.267, 0.132	NA	-0.06	-0.248, 0.128	NA
	Moderate active vs inactive	11369	-0.082	-0.301, 0.137	NA	-0.062	-0.269, 0.144	NA
	Active vs inactive	11369	-0.133	-0.364, 0.097	NA	-0.124	-0.341, 0.094	NA
	Middle vs low education level	11369	0.165	-0.016, 0.345	NA	0.156	-0.013, 0.325	NA
	High vs low education level	11369	0.283	0.071, 0.495	NA	0.263	0.065, 0.461	NA
	Latitudes (per 1000km)	11369	0.234	0.098, 0.369	NA	0.19	0.061, 0.32	NA

Supplementary Data

25(OH)D metabolites	Factors evaluated as potential correlates with 25(OH)D metabolites	Complete case analysis				Analysis using multiple imputation		
		n	Beta*	95%CI	I^2, %	Beta	95%CI	I^2, %
	Dietary vitamin D and supplements							
	Vitamin supplements (yes vs no)	11369	1.095	0.918, 1.273	NA	1.038	0.87, 1.206	NA
	Dietary vitamin D (per 10g/d)	11490	0.192	-0.151, 0.535	NA	0.061	-0.273, 0.395	NA
	Dietary food sources							
	Fish (per 100g/d)	11369	0.061	-0.21, 0.333	NA	-0.025	-0.288, 0.238	NA
	Egg (per 100g/d)	11369	-0.164	-0.613, 0.284	NA	-0.139	-0.568, 0.289	NA
	Red meat (per 100g/d)	11369	0.07	-0.177, 0.317	NA	0.037	-0.196, 0.27	NA
	Dairy products (per 100g/d)	11369	-0.02	-0.052, 0.012	NA	-0.004	-0.035, 0.026	NA
	Total cereal (per 100g/d)	11369	-0.012	-0.106, 0.082	NA	-0.012	-0.1, 0.077	NA
	Poultry (per 100g/d)	11369	-0.035	-0.405, 0.335	NA	-0.107	-0.466, 0.251	NA
	Processed meat (per 100g/d)	11369	-0.034	-0.348, 0.281	NA	0.112	-0.17, 0.393	NA
	Offal (per 10g/d)	11369	0.003	-0.146, 0.153	NA	0	-0.145, 0.145	NA
	Margarine (per 10g/d)	11369	-0.025	-0.088, 0.037	NA	-0.031	-0.091, 0.029	NA
	Butter (per 10g/d)	11369	-0.088	-0.191, 0.014	NA	-0.071	-0.166, 0.024	NA
	Mushroom (per 10g/d)	11369	0.016	-0.087, 0.12	NA	0.037	-0.061, 0.135	NA
	Mediterranean diet score (per 1-category higher)	11490	0.083	-0.033, 0.199	NA	0.085	-0.026, 0.196	NA
	Circulating biomarkers							
	SFA (per 1-SD)	11369	-0.109	-0.199, -0.019	NA	-0.129	-0.213, -0.046	NA
	PUFA (per 1-SD)	11369	-0.02	-0.109, 0.069	NA	-0.017	-0.099, 0.065	NA
	HDL-cholesterol (per 1-SD)	11369	0.037	-0.042, 0.116	NA	0.024	-0.05, 0.098	NA
	LDL-cholesterol (per 1-SD)	11369	-0.044	-0.119, 0.031	NA	-0.004	-0.073, 0.065	NA
	Uric acid (per 1-SD)	11193	-0.013	-0.113, 0.086	NA	-0.025	-0.119, 0.069	NA
	Creatinine (per 1-SD)	11193	-0.041	-0.13, 0.049	NA	-0.019	-0.104, 0.067	NA
	AST (per 1-SD)	11193	0.035	-0.073, 0.144	NA	0.042	-0.06, 0.144	NA
	ALT (per 1-SD)	11193	0.082	-0.035, 0.199	NA	0.074	-0.036, 0.184	NA
	GGT (per 1-SD)	11193	-0.121	-0.214, -0.028	NA	-0.086	-0.167, -0.004	NA

*Beta and 95%CI represent standardized difference in individual 25(OH)D metabolite (in SD unit) per 1-standardised unit/category change in demographic, lifestyle, dietary factors or circulating biomarkers. For non-epimeric 25(OH)D_3 and ratio of 3-epi-25(OH)D_3 to non-epimeric 25(OH)D_3, linear regression was used to obtain the country-specific effect estimates, which

were combined across countries using random effects meta-analysis. For epimeric 25(OH)D_3 and 25(OH)D_2, the Tobit regression was used to obtain the effect estimate. For the multiple imputation analysis: linear/tobit regression with multiple imputations (10 imputed datasets) was used to obtained country-specific effect estimates [except for latitudes due to limited study center in some countries, or 25(OH)D_2 due to limited sample size], which were combined across countries using random effects meta-analysis. Low education level: none or primary school completed; middle education level: technical/professional or secondary school; high education level: Longer education (including university degree). Dietary factors were standardized into per 10g/d for alcohol, offal, margarine, butter, mushroom and dietary vitamin D, and per 100g/d for fish, egg, red meat, dairy products, cereal, poultry and processed meat intake. Mediterranean diet score was divided into three categories: low (0-6), middle (7-10) and high (11-18) and expressed as per 1-category higher for the estimate. Age and BMI were standardized into per 5y and per 5kg/m^2, respectively.

Covariates in the model include age, sex, center, seasonality (sine and cosine function of the day of blood draw), and the other covariates in this table (estimates for dietary vitamin D or Mediterranean diet score were not adjusted for food sources of vitamin D [red meat, dairy products, cereal, poultry, processed meat, offal, margarine, butter and mushroom], and vice versa; estimates for demographic, lifestyle, dietary factors or lipid markers (HDL-cholesterol, LDL-cholesterol, PUFA, SFA) were not adjusted for plasma hepatic [GGT, ALT or AST] or renal markers [creatinine, uric acid]). HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase.

†Sample sizes presented are that for the dataset in multiple imputation.

‡NA, not available; for latitudes (limited study center in some countries) and 25(OH)D_2 (limited sample size), the effect estimates were obtained combining all the countries and no meta-analysis was performed.

Supplementary Data

Supplemental Table 5 Association of total plasma 25(OH)D, as a sum of D_2, epimeric and non-epimeric D_3, with incident type 2 diabetes: EPIC-InterAct Study

	Hazard ratio (95% Confidence Intervals)*					
	Q1	Q2	Q3	Q4	Q5	Per 1-SD
Total 25(OH)D [sum of non-epimeric 25(OH)D_3, 3-epi-25(OH)D_3 and 25(OH)D_2], nmol/L						
Median (range)†	20.2 (5.68-<26.3)	31.2 (26.3-35.8)	40.1 (35.8-<44.7)	49.7 (44.7-<56.1)	65.4 (56.1-<132.1)	
N cases/ subcohort	2194/2465	1893/2473	1631/2493	1413/2472	1200/2442	
Model 1	1 (ref)	0.82 (0.71, 0.95)	0.64 (0.58, 0.71)	0.53 (0.46, 0.60)	0.43 (0.39, 0.48)	0.71 (0.69, 0.74)
Model 2	1 (ref)	0.81 (0.72, 0.91)	0.68 (0.60, 0.77)	0.59 (0.52, 0.67)	0.53 (0.47, 0.60)	0.77 (0.74, 0.81)
Model 3	1 (ref)	0.90 (0.76, 1.06)	0.79 (0.67, 0.94)	0.74 (0.60, 0.92)	0.73 (0.61, 0.88)	0.87 (0.82, 0.92)

* Hazard ratios (HRs) of type 2 diabetes comparing quintiles (Q2-Q5) of 25(OH)D metabolites with quintile 1 (Q1) or per 1-SD increase of 25(OH)D metabolites, estimated from country-specific Prentice-weighted Cox regression models; estimates were combined across countries using random-effects meta-analysis. The present analyses were based on complete case analyses excluding participants with missing covariates based on model 4.
Model 1: Adjusted for age (as underlying timescale), sex (men, women), center, and seasonality (continuous: sine and cosine function of the day of blood draw);
Model 2: Model 1 + smoking status (current, former, never), physical activity (inactive, moderately inactive, moderately active, active), education (none, primary, technical or professional, secondary, higher education), alcohol drinking (never, >0-<6 g/day, 6-<12 g/day, 12-<24 g/day, ≥24 g/day), total energy intake (continuous), Mediterranean diet score (low, moderate, high) and plasma lipid biomarkers (continuous: HDL-cholesterol, LDL-cholesterol);
Model 3: Model 2 + BMI (continuous);
†Median and range of the 25(OH)D metabolites in each quintile in the InterAct subcohort.

Supplementary Data

Supplemental Table 6 Association of the ratio of 3-epi-25(OH)D_3 to non-epimeric 25(OH)D_3 with incident type 2 diabetes: EPIC-InterAct Study

		Hazard ratio (95% Confidence Intervals)*						
Model	n	3-epi-25(OH)D_3 below LLQ †	Q1	Q2	Q3	Q4	Q5	Per 1-SD
Median (range)			0.02 (0.01-<0.03)	0.03 (0.03-<0.04)	0.04 (0.04-<0.05)	0.05 (0.05-<0.06)	0.07 (0.06-0.19)	
N cases/ subcohort		5143/ 7312	485/ 978	576/ 983	640/ 958	712/ 964	775/ 958	
Model 1	8029	1.42 (1.25, 1.60)	1 (ref)	1.16 (0.90, 1.48)	1.23 (1.05, 1.44)	1.35 (1.14, 1.60)	1.41 (1.20, 1.65)	1.15 (1.10, 1.21)
Model 2	8029	1.27 (1.11, 1.46)	1 (ref)	1.11 (0.90, 1.38)	1.16 (0.97, 1.38)	1.23 (1.02, 1.48)	1.37 (1.15, 1.63)	1.17 (1.11, 1.23)
Model 3	8029	1.13 (0.98, 1.32)	1 (ref)	1.09 (0.84, 1.41)	1.09 (0.90, 1.33)	1.19 (0.95, 1.47)	1.26 (1.04, 1.52)	1.14 (1.08, 1.21)
Model 4	8029	1.14 (0.98, 1.32)	1 (ref)	1.09 (0.84, 1.41)	1.10 (0.90, 1.33)	1.19 (0.96, 1.48)	1.26 (1.04, 1.53)	1.14 (1.08, 1.22)
Model 4, + dietary variables and supplements ‡	7357	1.12 (0.96, 1.31)	1 (ref)	1.07 (0.82, 1.40)	1.14 (0.91, 1.42)	1.27 (0.96, 1.67)	1.23 (1.00, 1.51)	1.13 (1.06, 1.20)
Model 4, excluding HbA1C≥6.5%	7431	1.11 (0.95, 1.30)	1 (ref)	1.05 (0.79, 1.39)	1.06 (0.85, 1.32)	1.13 (0.93, 1.38)	1.25 (1.02, 1.52)	1.14 (1.07, 1.21)
Model 4, excluding first 2 years' incident T2D	7764	1.14 (0.98, 1.33)	1 (ref)	1.09 (0.84, 1.42)	1.10 (0.91, 1.35)	1.20 (0.97, 1.48)	1.28 (1.05, 1.55)	1.15 (1.07, 1.22)
Model 4, + baseline HbA1c	7929	1.05 (0.89, 1.24)	1 (ref)	1.02 (0.77, 1.36)	1.14 (0.86, 1.50)	1.15 (0.94, 1.40)	1.18 (0.96, 1.45)	1.14 (1.07, 1.22)
Model 4, + hepatic and renal function markers §	7859	1.08 (0.92, 1.27)	1 (ref)	1.14 (0.85, 1.51)	1.07 (0.87, 1.30)	1.14 (0.93, 1.39)	1.11 (0.91, 1.37)	1.10 (1.02, 1.18)
Model 4, + plasma phospholipid SFA, PUFA	8005	1.09 (0.94, 1.27)	1 (ref)	1.05 (0.81, 1.36)	1.04 (0.86, 1.26)	1.13 (0.94, 1.37)	1.19 (0.99, 1.45)	1.12 (1.05, 1.19)
Model 4+ family history and disease prevalence ‖	3125	1.14 (0.91, 1.42)	1 (ref)	1.04 (0.77, 1.39)	1.18 (0.88, 1.59)	1.44 (0.97, 2.13)	1.07 (0.79, 1.46)	1.10 (0.96, 1.26)
Model 4, only including women	4309	1.12 (0.92, 1.37)	1 (ref)	1.06 (0.82, 1.39)	1.03 (0.79, 1.35)	1.39 (1.02, 1.89)	1.18 (0.89, 1.56)	1.12 (1.03, 1.23)
Model 4, hormone use and menopausal status in women	4126	1.13 (0.92, 1.39)	1 (ref)	1.05 (0.80, 1.39)	1.07 (0.82, 1.41)	1.42 (1.02, 1.97)	1.22 (0.91, 1.63)	1.15 (1.05, 1.26)

*Hazard ratios (HRs) of type 2 diabetes comparing quintiles (Q2-Q5) of 25(OH)D metabolites with quintile 1 (Q1) or per 1-SD increase of the ratio of 3-epi-25(OH)D_3 to non-epimeric 25(OH)D_3, estimated from country-specific Prentice-weighted Cox regression models; estimates were combined across countries using random-effects meta-analysis. Model 1-3 is the same as model 1-3 in the main analysis (Table 2), and the model 4 was model 3 + 25(OH)D_2 (categorical: below and above the LLQ). N cases/ subcohort in each category refers the sample size of model 1 to model 4.

†This category represents that the ratio is missing because 3-epi-25(OH)D_3 is the below LLQ (1 nmol/L);

‡Dietary variables and supplements include fish, egg, red meat, dairy products, cereal, poultry, processed meat, offal, margarine, butter, mushrooms and vitamin supplement use;

§Hepatic and renal function markers represent alanine transaminase, aspartate transaminase, and gamma-glutamyl transferase, and creatinine, uric acid, respectively.

‖Family history of diabetes and baseline prevalence of heart disease, stroke and cancer.

Supplementary Data

Supplemental Table 7 Sensitivity analysis for the association of plasma 25(OH)D metabolites with incident type 2 diabetes: EPIC-InterAct Study

Models	Hazard ratio (95% Confidence Intervals)*							
	n	Below LLQ	Q1	Q2	Q3	Q4	Q5	Per 1-SD
Non-epimeric 25(OH)D_3, nmol/L								
Model 4	20168		1 (ref)	0.88 (0.75, 1.04)	0.73 (0.61, 0.87)	0.74 (0.62, 0.88)	0.62 (0.54, 0.72)	0.81 (0.77, 0.86)
Model 4, + dietary variables and supplements†	18537		1 (ref)	0.87 (0.73, 1.03)	0.70 (0.57, 0.85)	0.72 (0.59, 0.88)	0.60 (0.51, 0.71)	0.81 (0.77, 0.86)
Model 4, excluding HbA1C≥6.5%	18555		1 (ref)	0.86 (0.72, 1.04)	0.75 (0.63, 0.88)	0.75 (0.62, 0.89)	0.62 (0.53, 0.72)	0.82 (0.78, 0.87)
Model 4, excluding first 2 years' incident T2D	19437		1 (ref)	0.88 (0.75, 1.03)	0.75 (0.63, 0.89)	0.75 (0.63, 0.88)	0.65 (0.56, 0.76)	0.82 (0.78, 0.87)
Model 4, + baseline HbA1c	19914		1 (ref)	0.88 (0.67, 1.16)	0.76 (0.61, 0.96)	0.75 (0.61, 0.93)	0.68 (0.56, 0.83)	0.84 (0.78, 0.90)
Model 4, + hepatic and renal function markers‡	19739		1 (ref)	0.94 (0.77, 1.13)	0.77 (0.61, 0.98)	0.83 (0.66, 1.04)	0.75 (0.62, 0.90)	0.87 (0.82, 0.93)
Model 4, + plasma phospholipid SFA, PUFA	20100		1 (ref)	0.87 (0.75, 1.01)	0.74 (0.62, 0.89)	0.75 (0.63, 0.89)	0.64 (0.55, 0.75)	0.83 (0.78, 0.87)
Model 4+ family history and disease prevalence§	7748		1 (ref)	0.77 (0.60, 0.99)	0.56 (0.43, 0.72)	0.61 (0.50, 0.76)	0.54 (0.42, 0.69)	0.78 (0.72, 0.85)
Model 4, only including women	11761		1 (ref)	0.82 (0.64, 1.04)	0.65 (0.46, 0.91)	0.77 (0.54, 1.10)	0.59 (0.48, 0.72)	0.83 (0.77, 0.89)
Model 4, hormone use and menopausal status in women	11334		1 (ref)	0.78 (0.60, 1.01)	0.63 (0.45, 0.88)	0.73 (0.50, 1.07)	0.56 (0.44, 0.71)	0.82 (0.76, 0.88)
3-epi-25(OH)D_3, nmol/L								
Model 4	8029	0.92 (0.79, 1.08)	1 (ref)	1.09 (0.85, 1.38)	0.99 (0.82, 1.19)	1.10 (0.92, 1.31)	1.36 (1.08, 1.71)	1.16 (1.09, 1.25)
Model 4, + dietary variables and supplements†	7357	0.88 (0.76, 1.02)	1 (ref)	1.02 (0.77, 1.36)	0.99 (0.79, 1.22)	1.09 (0.87, 1.37)	1.23 (1.00, 1.50)	1.15 (1.06, 1.24)
Model 4, excluding HbA1C≥6.5%	7431	0.93 (0.81, 1.08)	1 (ref)	1.08 (0.83, 1.42)	0.99 (0.81, 1.19)	1.06 (0.88, 1.28)	1.36 (1.08, 1.71)	1.16 (1.08, 1.24)
Model 4, excluding first 2 years' incident T2D	7764	0.93 (0.80, 1.08)	1 (ref)	1.08 (0.85, 1.38)	1.00 (0.83, 1.20)	1.13 (0.91, 1.40)	1.36 (1.09, 1.70)	1.16 (1.09, 1.25)
Model 4, + baseline HbA1c	7929	0.87 (0.75, 1.01)	1 (ref)	1.04 (0.75, 1.44)	0.93 (0.76, 1.13)	1.04 (0.86, 1.27)	1.46 (1.11, 1.92)	1.18 (1.10, 1.27)
Model 4, + hepatic and renal function markers‡	7859	0.94 (0.81, 1.10)	1 (ref)	1.14 (0.90, 1.45)	1.00 (0.82, 1.22)	1.04 (0.86, 1.27)	1.31 (1.02, 1.67)	1.12 (1.02, 1.22)
Model 4, + plasma phospholipid SFA, PUFA	8005	0.90 (0.76, 1.07)	1 (ref)	1.04 (0.81, 1.35)	0.97 (0.80, 1.17)	1.07 (0.88, 1.30)	1.26 (1.02, 1.56)	1.13 (1.05, 1.21)
Model 4+ family history and disease prevalence§	3125	0.80 (0.57, 1.11)	1 (ref)	0.95 (0.61, 1.47)	0.89 (0.55, 1.45)	1.08 (0.80, 1.46)	1.23 (0.82, 1.84)	1.12 (0.99, 1.26)
Model 4, only including women	4309	0.92 (0.72, 1.17)	1 (ref)	1.09 (0.75, 1.60)	0.96 (0.74, 1.25)	1.27 (0.98, 1.65)	1.51 (1.14, 2.00)	1.09 (0.98, 1.21)
Model 4, hormone use and menopausal status in women	4126	0.90 (0.69, 1.19)	1 (ref)	1.18 (0.73, 1.92)	0.93 (0.71, 1.22)	1.30 (1.00, 1.70)	1.53 (1.14, 2.05)	1.13 (0.99, 1.30)
25(OH)D_2, nmol/L								
Model 4	899	1.29 (0.86, 1.95)	1 (ref)	0.93 (0.52, 1.66)	1.15 (0.68, 1.96)	1.10 (0.62, 1.96)	1.00 (0.58, 1.73)	0.94 (0.76, 1.18)
Model 4, + dietary variables and supplements†	862	1.27 (0.83, 1.92)	1 (ref)	0.91 (0.50, 1.65)	1.09 (0.63, 1.88)	1.12 (0.63, 2.01)	1.05 (0.60, 1.83)	0.93 (0.72, 1.19)
Model 4, excluding HbA1C≥6.5%	843	1.32 (0.86, 2.02)	1 (ref)	0.96 (0.53, 1.72)	1.20 (0.69, 2.08)	1.11 (0.61, 2.00)	1.01 (0.57, 1.79)	0.98 (0.77, 1.23)
Model 4, excluding first 2 years' incident T2D	866	1.26 (0.83, 1.90)	1 (ref)	0.92 (0.51, 1.65)	1.05 (0.61, 1.81)	1.09 (0.61, 1.95)	0.94 (0.54, 1.65)	0.93 (0.74, 1.17)
Model 4, + baseline HbA1c	893	1.13 (0.75, 1.69)	1 (ref)	0.84 (0.47, 1.51)	1.07 (0.62, 1.82)	0.97 (0.55, 1.71)	0.93 (0.53, 1.62)	1.04 (0.83, 1.31)

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Model 4, + hepatic and renal function markers‡	883	1.27 (0.83, 1.94)	1 (ref)	0.93 (0.52, 1.67)	1.20 (0.69, 2.08)	1.09 (0.60, 2.00)	1.13 (0.65, 1.99)	0.96 (0.76, 1.22)
Model 4, + plasma phospholipid SFA, PUFA	896	1.22 (0.80, 1.84)	1 (ref)	0.93 (0.53, 1.64)	1.08 (0.63, 1.86)	1.02 (0.56, 1.84)	0.99 (0.57, 1.71)	0.95 (0.78, 1.17)
Model 4+ family history and disease prevalence§	576	1.84 (1.03, 3.28)	1 (ref)	0.95 (0.44, 2.07)	1.50 (0.71, 3.17)	1.36 (0.62, 2.97)	1.53 (0.73, 3.24)	1.21 (0.99, 1.48)
Model 4, only including women	549	1.52 (0.91, 2.55)	1 (ref)	1.43 (0.61, 3.35)	1.10 (0.53, 2.27)	1.22 (0.51, 2.91)	1.20 (0.60, 2.38)	0.99 (0.76, 1.28)
Model 4, hormone use and menopausal status in women	529	1.75 (1.02, 3.03)	1 (ref)	1.71 (0.73, 4.02)	1.27 (0.60, 2.69)	1.48 (0.62, 3.57)	1.58 (0.79, 3.16)	1.09 (0.82, 1.44)

* Hazard ratios (HRs) of type 2 diabetes comparing quintiles (Q2-Q5) of 25(OH)D metabolites with quintile 1 (Q1) or per 1-SD increase of 25(OH)D metabolites, estimated from country-specific Prentice-weighted Cox regression models; estimates were combined across countries using random-effects meta-analysis. Effect estimates for $25(OH)D_2$ were derived from analysis of the overall EPIC-InterAct data (i.e. not country-specific), due to limited sample size. 1-SD (calculated from the subcohort) was 17.3 nmol/L for non-epimeric $25(OH)D_3$, 1.31 nmol/L for 3-epi-$25(OH)D_3$, and 6.52 nmol/L for $25(OH)D_2$. Model 4 is the same as model 4 in the main analysis (Table 2), adjusted for age (as underlying timescale), sex, center, seasonality (sine and cosine function of the day of blood draw), smoking status, physical activity, education, alcohol drinking, total energy intake, Mediterranean diet score, circulating lipid biomarkers (HDL-C, LDL-C), BMI and the other two 25(OH)D metabolites.

†Dietary variables and supplements include fish, egg, red meat, dairy products, cereal, poultry, processed meat, offal, margarine, butter, mushrooms and vitamin supplement use.

‡Hepatic and renal function markers represent alanine transaminase, aspartate transaminase, and gamma-glutamyl transferase, and creatinine, uric acid, respectively.

§ Family history of diabetes and baseline prevalence of heart disease, stroke and cancer.

Supplementary Data

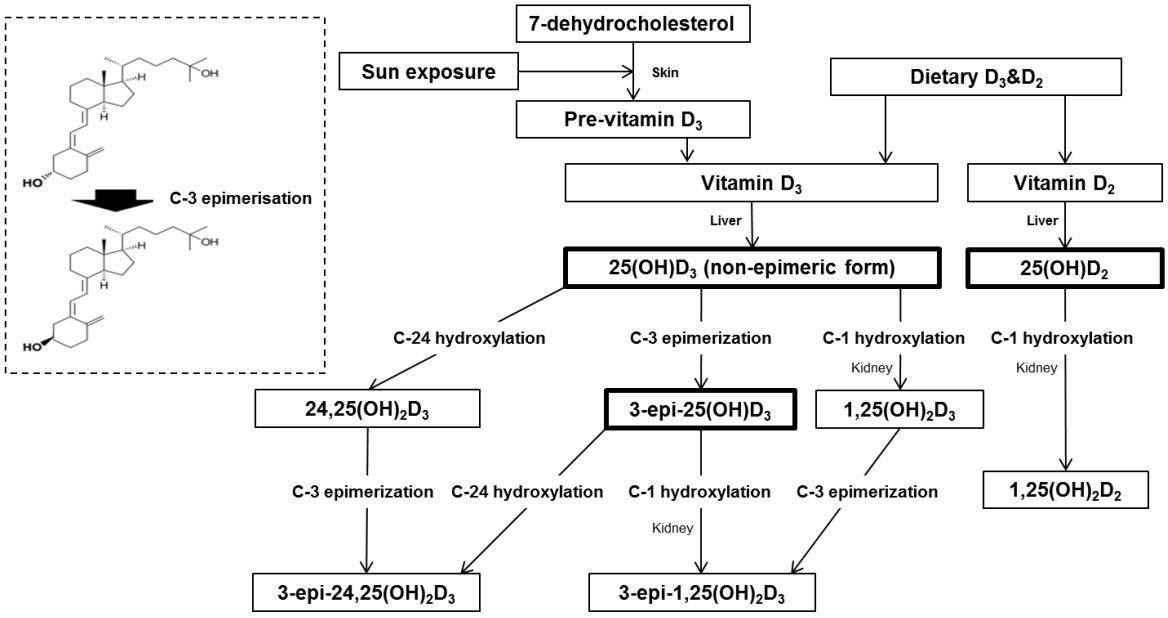
Supplemental Table 8 Association of plasma 25(OH)D metabolites (per 1 SD increase) with incident type 2 diabetes using complete case analysis and multiple imputation: EPIC-InterAct Study

		Complete case analysis		Multiple imputation	
	Model	HR (95%CI)	I^2, %	HR (95%CI)*	I^2, %
Non-epimeric $25(OH)D_3$, nmol/L	Cases/ subcohort	8331/ 12345		9671/ 13562	
	Model 1	0.71 (0.69, 0.74)	0	0.70 (0.68, 0.73)	0
	Model 2	0.77 (0.74, 0.80)	0	0.77 (0.74, 0.80)	0
	Model 3	0.86 (0.82, 0.91)	15.7	0.85 (0.81, 0.90)	36.7
	Model 4	0.81 (0.77, 0.86)	0	0.80 (0.76, 0.84)	0
3-epi-$25(OH)D_3$, nmol/L	Cases/ subcohort	3188/ 5033		3694/5513	
	Model 1	0.99 (0.94, 1.04)	0	0.99 (0.95, 1.04)	0
	Model 2	1.03 (0.97, 1.09)	0	1.03 (0.97, 1.10)	8
	Model 3	1.09 (1.02, 1.17)	18.1	1.08 (1.00, 1.17)	30.9
	Model 4	1.16 (1.09, 1.25)	0	1.17 (1.08, 1.26)	19.5
$25(OH)D_2$, nmol/L	Cases/ subcohort	343/ 572		397/634	
	Model 1	1.00 (0.85, 1.18)	NA‡	0.94 (0.79, 1.12)	NA‡
	Model 2	1.02 (0.84, 1.23)	NA	0.95 (0.78, 1.15)	NA
	Model 3	1.03 (0.84, 1.25)	NA	0.97 (0.79, 1.18)	NA
	Model 4	0.94 (0.76, 1.18)	NA	0.89 (0.72, 1.11)	NA

* Hazard Ratios (HRs) are per 1-standard deviation (study-specific) higher vitamin D metabolite [except for $25(OH)D_2$], estimated using country-specific Prentice-weighted Cox regression with multiple imputation (10 imputed datasets); estimates were then combined across countries using inverse variance-weighted random-effects meta-analysis. Effect estimates for $25(OH)D_2$ were derived from analysis of the overall EPIC-InterAct data (i.e. not country-specific), due to limited sample size. The sample size of cases/subcohort was 9671/13562 for epimeric $25(OH)D_3$, 3694/5513 for 3-epi-$25(OH)D_3$, and 397/634 for $25(OH)D_2$.
Model 1: Adjusted for age (as underlying timescale), sex, center, and seasonality (sine and cosine function of the day of blood draw);
Model 2: Model 1+smoking status, physical activity, education, alcohol drinking, total energy intake and Mediterranean diet score, and plasma lipid biomarkers (HDL-cholesterol, LDL-cholesterol);
Model 3: Model 2+BMI.
Model 4: Model 3 + mutual adjustment for the other two 25(OH)D metabolites [epimeric $25(OH)D_3$ (continuous), 3-epi-$25(OH)D_3$ (categorical: below LLQ, Q1, Q2, Q3, Q4, and Q5), or $25(OH)D_2$ (categorical: below and above LLQ)]. Results of the four models from the complete case analysis (already shown in the table 2) were also presented in the table as a comparison to the results from multiple imputation.
‡ NA, not available. Effect estimates for $25(OH)D_2$ were derived from analysis of the overall EPIC-InterAct data (i.e. not country-specific), therefore meta-analysis was not conducted and no I^2 was available.

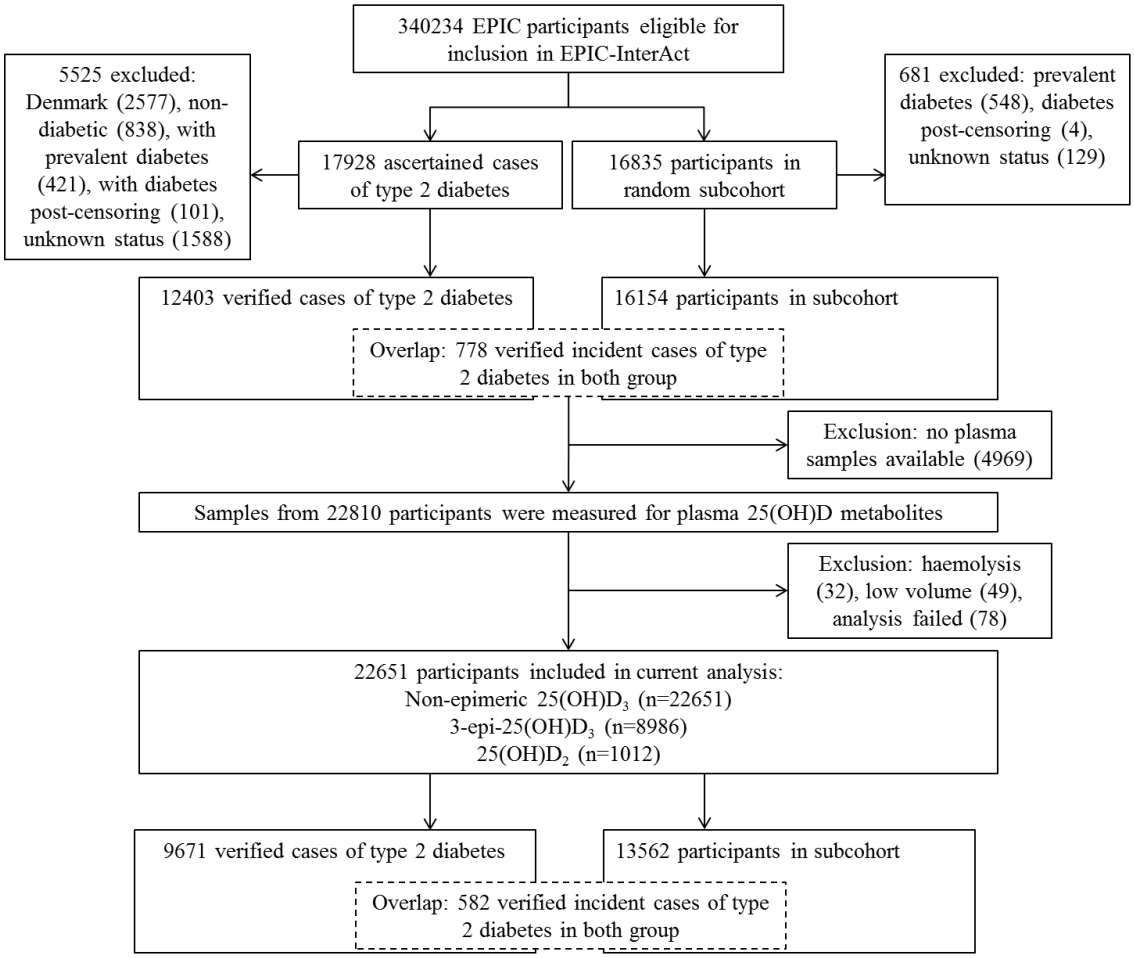
Supplementary Data

Supplemental Figure 1 Metabolic pathway of vitamin D metabolites. C-3-epimerisation means configuration of the hydroxyl bond at the C-3 position between vitamin D metabolites, as indicated in the molecular figure for the structure change (direction change of -OH group) from non-epimeric 25(OH)D3 to 3-epi-25(OH)D3 in the dashed rectangle. Metabolites assayed in the current study are highlighted by bold rectangles.



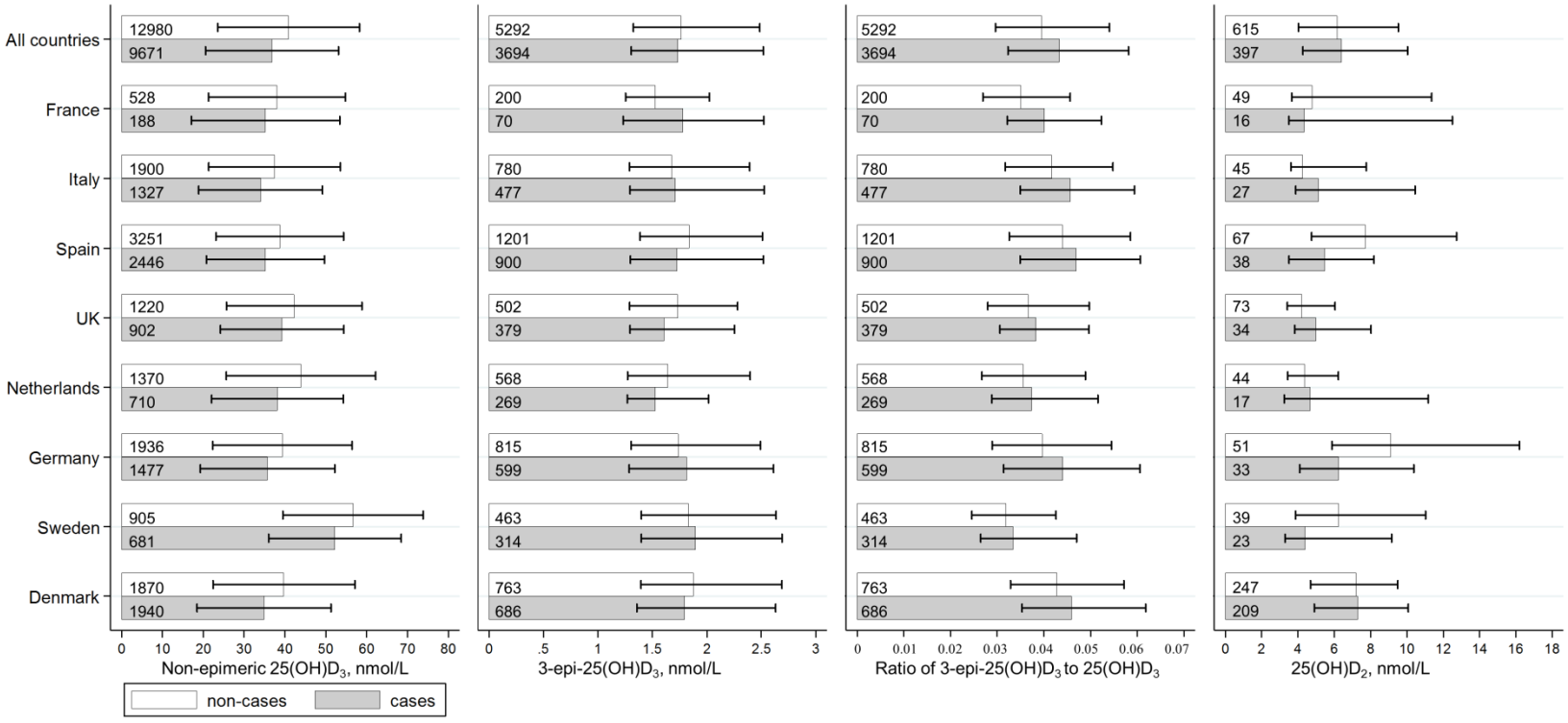
Supplementary Data

Supplemental Figure 2 EPIC-InterAct study design and participants included in the analysis

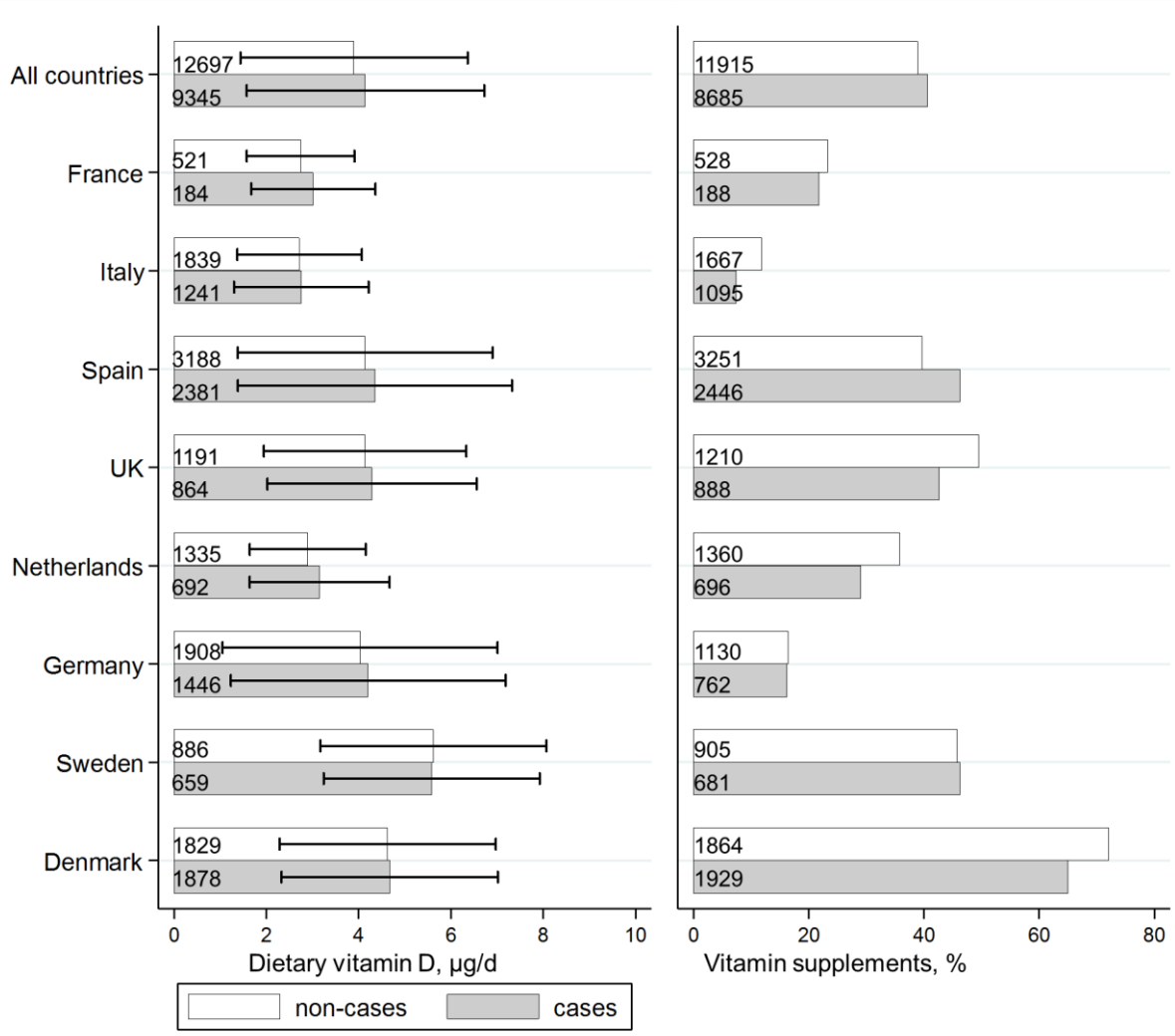


Supplementary Data

Supplemental Figure 3 Distribution of baseline plasma 25(OH)D metabolites, dietary vitamin D and vitamin supplement intake by future diabetes case status and country: EPIC-InterAct Study

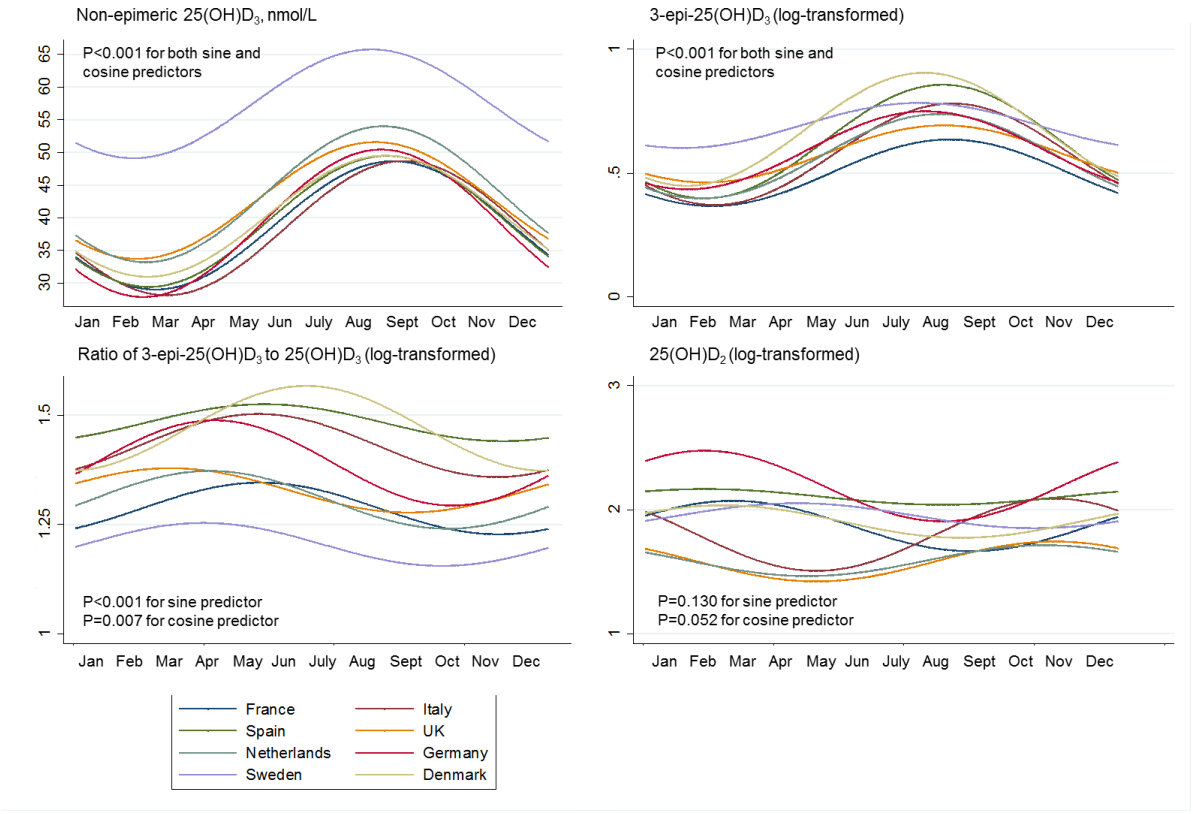


Supplementary Data



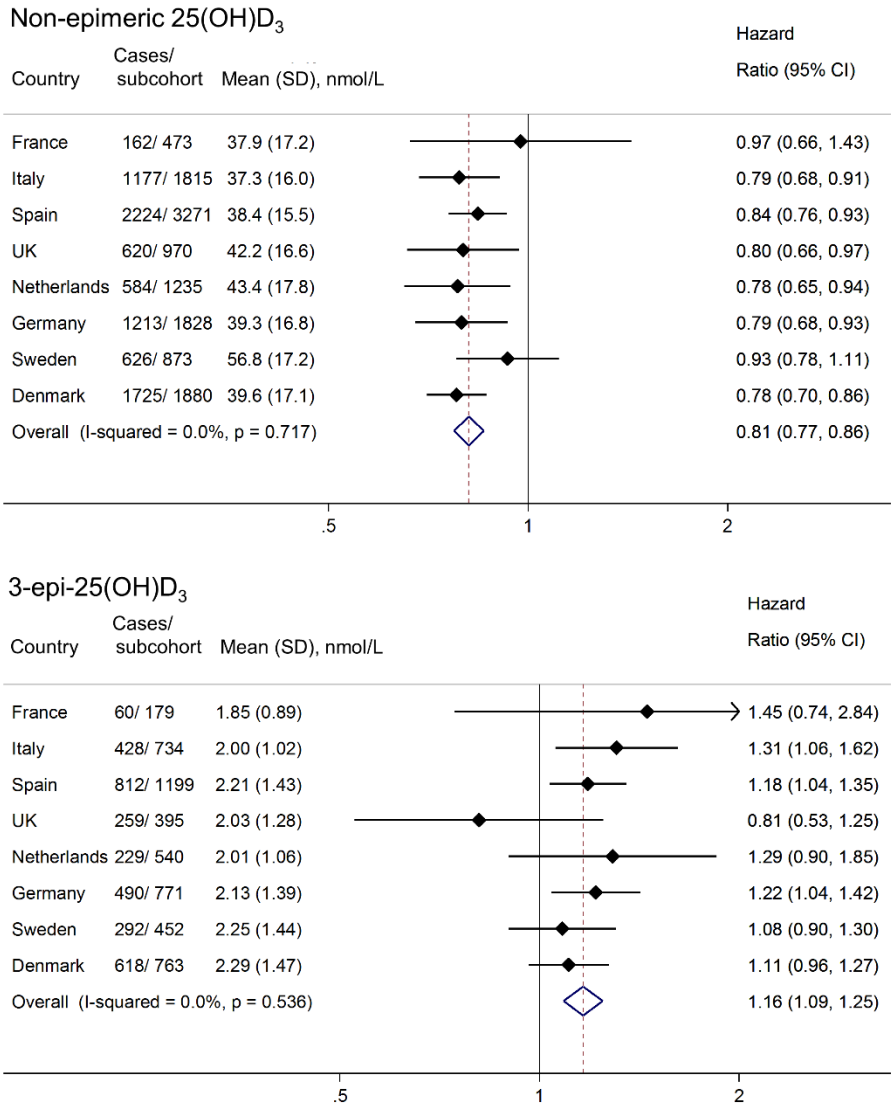
Supplementary Data

Supplemental Figure 4 Predicted levels of 25(OH)D metabolites by days of blood draw in the year: EPIC-InterAct Study



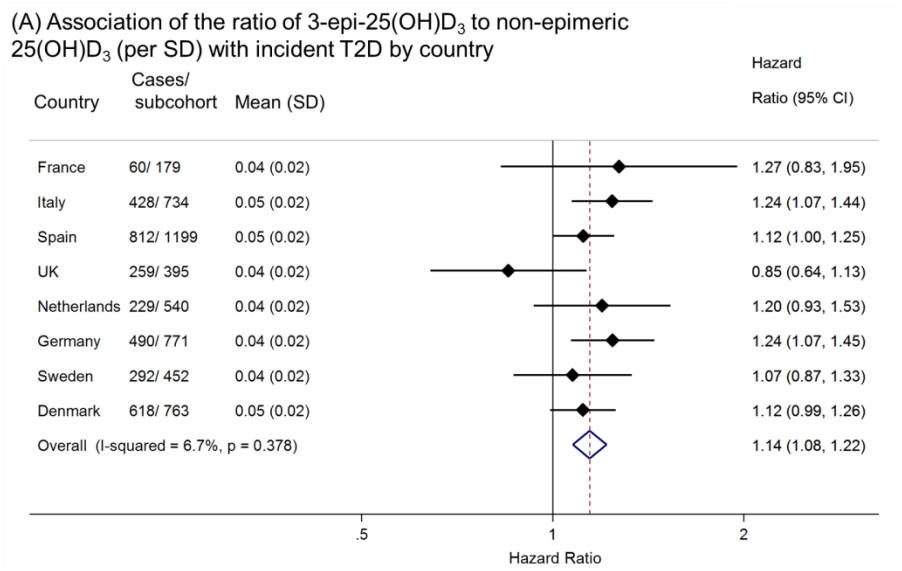
Supplementary Data

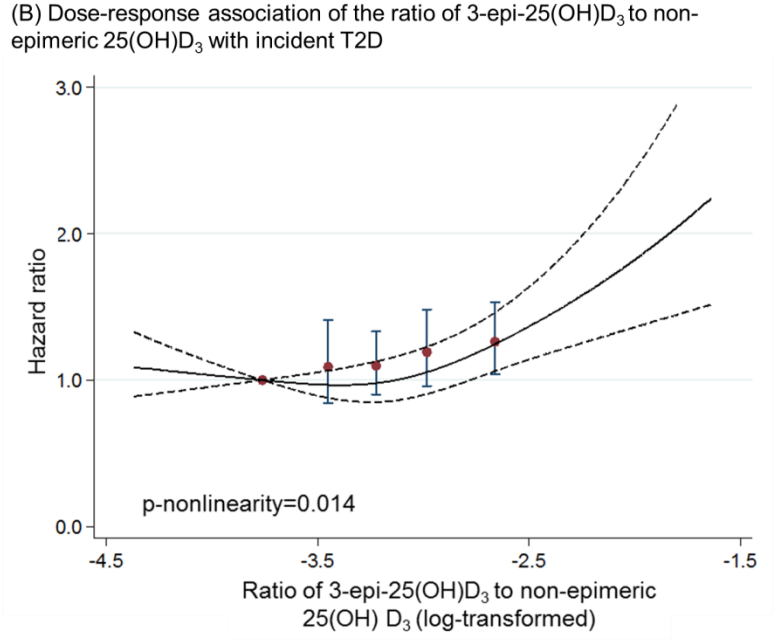
Supplemental Figure 5 Prospective associations of plasma 25(OH)D metabolites with incident type 2 diabetes by country: EPIC-InterAct Study



Supplementary Data

Supplemental Figure 6 Association of the ratio of 3-epi-25(OH)D_3 to non-epimeric 25(OH)D_3 with incident type 2 diabetes: EPIC-InterAct Study





Supplementary Data

Supplemental Figure S7 Prospective association between plasma 25(OH)D_3 metabolites and type 2 diabetes stratified by BMI categories: EPIC-InterAct Study