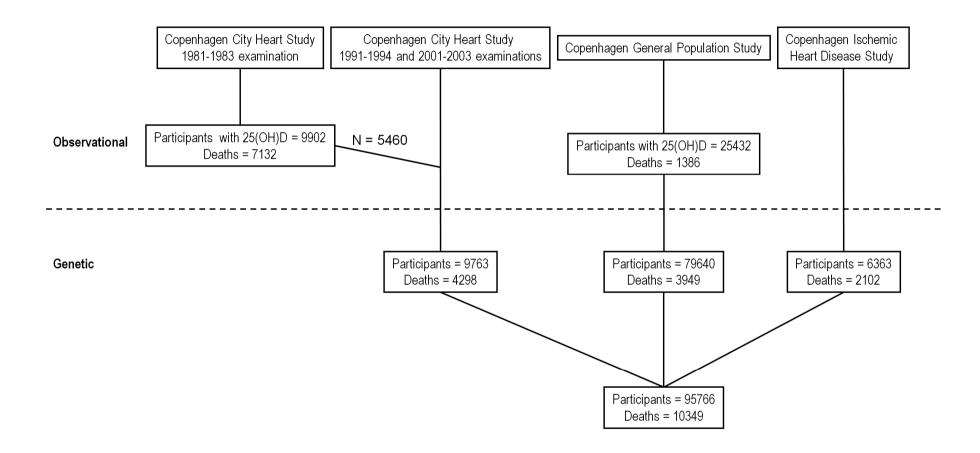
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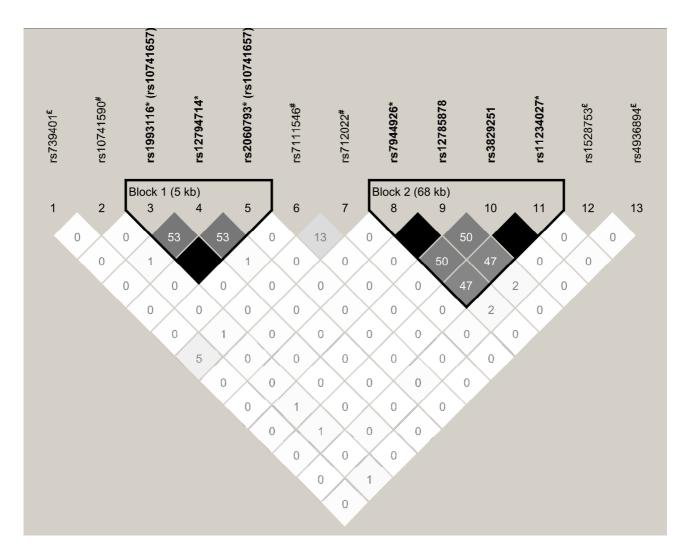


Supplementary figure A. Number of participants and events in the observational and genetic analyses.

Based on results from genome-wide association and candidate gene studies. selection of 16 SNPs: rs2282679, rs4588, rs7041, rs1155563, rs3829251, rs11234027, rs7944926, rs12785878, rs12794714, rs10500804, rs10741657, rs2060793, rs1993116, rs10877012, rs2228570, rs11568820. Excluding: 1) SNPs in the GC gene due to unpredictable biological effects 2) SNPs only reported in one study. Selection of 7 SNPs for a pilot project: genotyped in 9000 participants from the CCHS: rs11234027, rs7944926, rs12794714, rs10741657, rs10877012, rs2228570, rs11568820. Excluding 3 SNPs due to Inferior F-statistics and Effects sizes: 1) 2 in the *VDR* 2) 1 in the *CYP27B1* gene 4 SNPs genotyped in the CCHS, CGPS, and CIHDS, a total of 95766 particpants: rs11234027, rs7944926, rs12794714,

Supplementary figure B. Flowchart showing the selection process for determining which genetic instruments to use for Mendelian randomization. CCHS = Copenhagen City Heart Study. CGPS = Copenhagen General Population Study. CIHDS = Copenhagen Ischemic Heart Disease Study.

rs10741657,

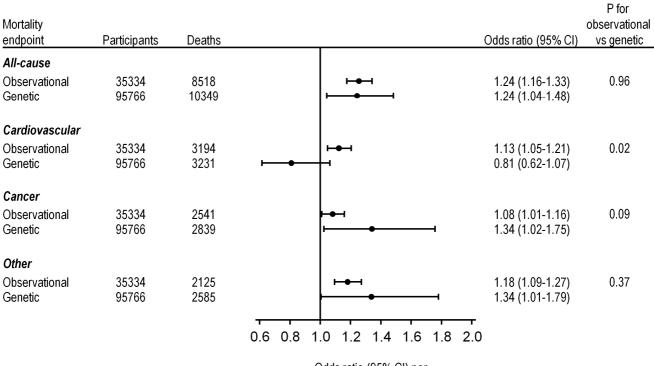


Supplementary figure C. Linkage disequilibrium plot of genetic variants on chromosome 11 found in genome-wide association studies to be associated with mortality, longevity, or 25-hydroxyvitamin D levels. The numbers in the quadrates are R²-values in percent. The marked haplotype blocks are genetic variants associated with 25-hydroxyvitamin D in CYP2R1 (left) and DHCR7 (right). Based on the HapMap population. *Genotyped in the present study or tagging polymorphisms of these genotypes (R²>0.9). "Variants possibly associated with mortality in patients with kidney or heart disease^{1;2}. EVariants associated with mortality/longevity³⁻⁵.

Mortality endpoint	Participants	Deaths		Hazard ratio (95% CI)
All-cause				
CCHS	9902	7132	нн	1.16 (1.12-1.20)
CGPS	25432	1386	⊢	1.17 (1.07-1.29)
Pooled	35334	8518	₩	1.17 (1.13-1.21)
Cardiovasc	ular			
CCHS	9902	2877	I →-I	1.16 (1.09-1.24)
CGPS	25432	317	——	1.23 (1.01-1.49)
Pooled	35334	3194	⊢ •-1	1.17 (1.10-1.24)
Cancer				
CCHS	9902	2161	⊢	1.13 (1.06-1.21)
CGPS	25432	380	⊢	1.04 (0.87-1.23)
Pooled	35334	2541	⊢	1.11 (1.04-1.18)
Other				
CCHS	9902	1815	├	1.22 (1.13-1.32)
CGPS	25432	310	├	1.31 (1.07-1.60)
Pooled	35334	2125	⊢	1.25 (1.16-1.34)
			0.8 1.0 1.2 1.4 1.6 1.	8 2.0
			Hazard ratio (95% CI) pe	r

Supplementary figure D. The association of deseasonalised plasma 25-hydroxyvitamin D with cause-specific mortality in the general population. The analyses were by Cox regression adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure time physical activity, systolic blood pressure, body mass index, income, diabetes, plasma cholesterol, and study. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.

20 percentile lower 25(OH)D levels



Odds ratio (95% CI) per 20 percentile lower 25(OH)D levels

Supplementary figure E. Instrumental variable analysis using deseasonalised plasma 25-

hydroxyvitamin D. Observational and genetic risk estimates for all-cause and cause-specific mortality for 20 percentile lower 25-hydroxyvitamin D levels. Observational estimates were by logistic regression and genetic estimates by instrumental variable analyses. Observational analyses were adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure time physical activity, systolic blood pressure, body mass index, income, diabetes, plasma cholesterol, and study. Genetic analyses were adjusted for age, year of birth, sex, and study. Observational estimates were based on participants from the Copenhagen City Heart Study and Copenhagen General Population Study combined, while genetic estimates were based on participants from the Copenhagen City Heart Study, Copenhagen General Population Study, and Copenhagen Ischemic Heart Disease Study combined. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.

Regression model	Participants	Deaths							Estimate	s (95% CI)
Cardiovascular mortality	,									
Cox	35334	3194				•	—		Hazard ratio	1.18 (1.09-1.28)
Competing risk	35334	3194		-	•				Subhazard ratio	1.14 (1.05-1.23)
Cancer mortality										
Cox	35334	2541			-				Hazard ratio	1.12 (1.03-1.22)
Competing risk	35334	2541		┢	•	-			Subhazard ratio	1.08 (1.00-1.17)
Other mortality										
Cox	35334	2125			-		•	 -	Hazard ratio	1.27 (1.15-1.40)
Competing risk	35334	2125			-	•			Subhazard ratio	1.21 (1.11-1.33)
			0.9 1	.0	1.1	1.2	1.3	1.4		
			Н			d ratio (95% 25(OH)D le	, ,			

Supplementary figure F. The association of plasma 25-hydroxyvitamin D with cause-specific mortality in the general population using Cox and competing risks regression. The analyses were carried out using Cox regression or Fine and Gray's competing risk proportional subhazard models adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure time physical activity, systolic blood pressure, body mass index, income, diabetes, plasma cholesterol, season (month and year of blood sample), and study. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.

Mortality endpoint	Participants	Deaths		Hazard ratio (95% CI)
All-cause				
CCHS	9902	7132	1 ← 1	1.16 (1.12-1.20)
CGPS	25432	1386	⊢	1.17 (1.07-1.29)
Pooled	35334	8518	H + 1	1.17 (1.13-1.21)
Cardiovascu	ular			
CCHS	9902	3475	⊢	1.19 (1.10-1.28)
CGPS	25432	451	——	1.35 (1.06-1.74)
Pooled	35334	3926	⊢• ⊣	1.21 (1.12-1.30)
Cancer				
CCHS	9902	2221	⊢	1.14 (1.04-1.25)
CGPS	25432	421	├	0.96 (0.77-1.20)
Pooled	35334	2642	⊢	1.11 (1.02-1.21)
Other				
CCHS	9902	2413	⊢ •−−1	1.26 (1.15-1.37)
CGPS	25432	332	├	1.38 (1.04-1.84)
Pooled	35334	2745	⊢	1.27 (1.17-1.39)
			0.8 1.0 1.2 1.4 1.6 1.8 2.0)
			Hazard ratio (95% CI) per	

Supplementary figure G. The association of plasma 25-hydroxyvitamin D with cause-specific mortality in the general population using an alternative classification of cause-specific mortality. The regression model was identical to the main analyses; however, endpoints were classified in an overlapping manor, e.g., if there was both a cardiovascular and a cancer diagnosis on a death certificate that person would be included in analyses of both endpoints. Furthermore, all diagnoses were used and not only the three ranked diagnoses per person. There were up to 32 years of follow-up in the Copenhagen City Heart Study whereas it was up to 9.4 years in the Copenhagen General Population Study. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval. CCHS = Copenhagen City Heart Study. CGPS = Copenhagen General Population Study.

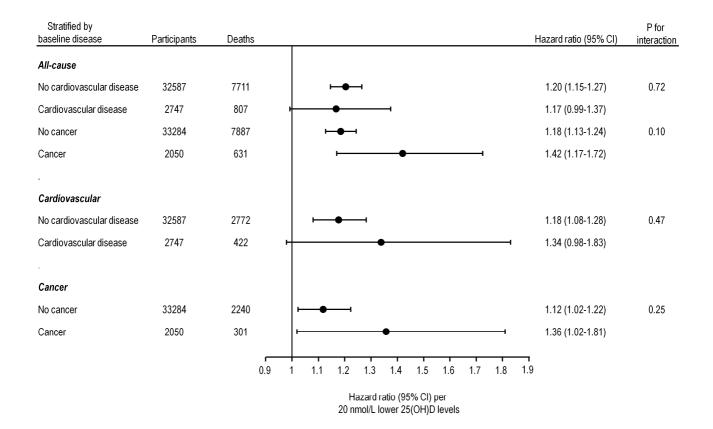
20 nmol/L lower 25(OH)D levels

25(OH)D, nmol/L	Participants	Deaths		Hazard ratio (95% CI)	P _{trend}
All-cause					
>75	5854	767	•	1.00	2·10 ⁻¹⁵
50.1-75	11119	2118	H 1	1.04 (0.96-1.14)	
25.1-50	13095	3398	⊢	1.11 (1.02-1.21)	
≤25	5266	2235	⊢	1.36 (1.24-1.49)	
Cardiovascu	ılar				
>75	5854	269	•	1.00	9.10-6
50.1-75	11119	723		0.99 (0.86-1.15)	
25.1-50	13095	1321	 • • • • • • • • • • • • • • • • • • •	1.08 (0.94-1.24)	
≤25	5266	881	├	1.30 (1.12-1.50)	
Cancer					
>75	5854	239	•	1.00	0.002
50.1-75	11119	650	 • • • • • • • • • •	1.08 (0.93-1.25)	
25.1-50	13095	1024	 • • •	1.12 (0.97-1.30)	
≤25	5266	628	├	1.26 (1.08-1.48)	
Other					
>75	5854	187	•	1.00	4·10 ⁻⁷
50.1-75	11119	530	 	1.15 (0.96-1.37)	
25.1-50	13095	808	 	1.15 (0.96-1.37)	
≤25	5266	600		1.58 (1.31-1.90)	
		г 0.8	3 1.0 1.2 1.4 1.6 1.8 1	T 2.0	
			Hazard ratios (95% CI)		

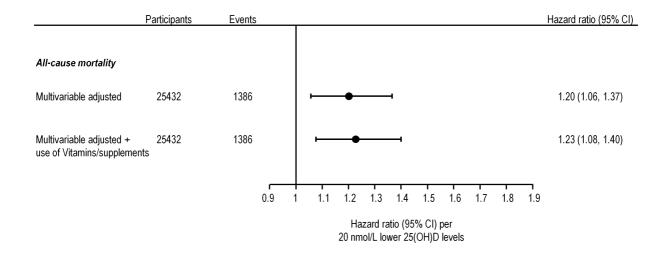
Supplementary figure H. The association of plasma 25-hydroxyvitamin D with cause-specific mortality in the general population using plasma 25-hydroxyvitamin D in clinical categories. The analyses were by Cox regression adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure time physical activity, systolic blood pressure, body mass index, income, diabetes, plasma cholesterol, season (month and year of blood sample), and study. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.

Mortality endpoint	Participants	Deaths	Haz	zard ratios (95% CI)
Cardiovascul	lar			
Coronary	35334	1424	1	.21 (1.07-1.38)
Stroke	35334	789	1	.16 (0.98-1.38)
Other types	35334	1097	1	.19 (1.04-1.35)
Cancer				
Lung	35334	624	1	.28 (1.06-1.54)
Colorectal	35334	330 ⊢	1	.05 (0.84-1.34)
Other types	35334	1592	1	.07 (0.96-1.20)
Other				
Respiratory	35334	838	⊢ 1	.51 (1.28-1.77)
Others	35334	1287	1	.13 (0.99-1.28)
		0.8	1.0 1.2 1.4 1.6 1.8	
			Hazard ratios (95% CI) per 20 nmol/L lower 25(OH)D levels	

Supplementary figure I. The association of plasma 25-hydroxyvitamin D with cause-specific mortality using further subdivision of mortality endpoints. The analyses were by Cox regression adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure time physical activity, systolic blood pressure, body mass index, income, diabetes, plasma cholesterol, season (month and year of blood sample), and study. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval. Cardiovascular (ICD-8: 390-458, ICD-10:100-199). Coronary (ICD-8: 410-414, ICD-10: I20-I25). Stroke (ICD-8: 430-438, ICD-10: I60-I69). Cancer (ICD-8: 140-209, ICD-10:C00-C97). Lung (ICD-8: 162, ICD-10:C33-C34). Colorectal (ICD-8: 153-154, ICD-10:C18-C21). Other (remaining ICD diagnoses). Respiratory (ICD-8: 460-519, ICD-10: J00-J99).



Supplementary figure J. The association of plasma 25-hydroxyvitamin D with all-cause, cardiovascular, and cancer mortality in analyses stratified according to baseline disease. The analyses were by Cox regression adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure time physical activity, systolic blood pressure, body mass index, income, diabetes, plasma cholesterol, season (month and year of blood sample), and study. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.



Supplementary figure K. The association of plasma 25-hydroxyvitamin D with all-cause mortality in analyses with and without adjustment for vitamin or nutritional supplement intake in CGPS. The analyses were by Cox regression adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure time physical activity, systolic blood pressure, body mass index, income, diabetes, plasma cholesterol, season (month and year of blood sample), and study. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.

Mortality endpoint	Participants	Deaths		Hazard ratio (95% CI) W	eight, %
All-cause					
CCHS CGPS CIHDS Meta-analysis	9763 79640 6363 95766	4298 3949 2102 10349	→ →	0.99 (0.97-1.01) 1.04 (1.01-1.06) 1.03 (0.99-1.06) 1.02 (1.00-1.03)	41 39 20
$I^2 = 72\%$, p = 0.03					
Cardiovascular CCHS CGPS CIHDS Meta-analysis $ ^2 = 0\%, p = 0.50$	9763 79640 6363 95766	1506 786 939 3231	*	0.97 (0.93-1.01) 1.01 (0.96-1.07) 0.98 (0.94-1.04) 0.98 (0.96-1.01)	47 25 28
Cancer					
CCHS CGPS CIHDS Meta-analysis	9763 79640 6363 95766	1282 1161 396 2839		1.00 (0.96-1.05) 1.04 (1.00-1.09) 1.08 (1.00-1.17) 1.03 (1.00-1.06)	45 41 14
$I^2 = 37\%$, p = 0.20					
Other CCHS CGPS CIHDS Meta-analysis I ² = 13%, p = 0.32	9763 79640 6363 95766	1193 913 479 2585		1.01 (0.96-1.05) 1.05 (0.99-1.10) 1.06 (0.99-1.14) 1.03 (1.00-1.06)	45 37 18
			0.9 1 1.1	1.2	

Hazard ratio (95% CI) per one increase in DHCR7/CYP2R1 allele score

Supplementary figure L. All-cause and cause-specific mortality according to the DHCR7/CYP2R1 allele score using meta-analysis with fixed effect estimates instead of pooling of the studies. The analyses were carried out using Cox regression adjusted for age, year of birth, and sex. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval. CCHS = Copenhagen City Heart Study. CGPS = Copenhagen General Population Study. CIHDS = Copenhagen Ischemic Heart Disease Study.

Mortality endpoint	Participants	Deaths		Hazard ratio (95% CI)
All-cause				
CCHS	9763	1801	⊢	1.02 (0.98-1.05)
CGPS	79640	3949	├	1.04 (1.01-1.06)
CIHDS	6363	1728	⊢	1.03 (0.99-1.07)
Pooled	95766	7478	H -	1.03 (1.01-1.05)
Cardiovascu	ılar			
CCHS	9763	770	⊢	1.01 (0.95-1.06)
CGPS	79640	786	├	1.01 (0.96-1.07)
CIHDS	6363	800	├	0.99 (0.94-1.05)
Pooled	95766	2356	└	1.00 (0.97-1.03)
Cancer				
CCHS	9763	665		1.04 (0.98-1.10)
CGPS	79640	1161	,	1.04 (1.00-1.09)
CIHDS	6363	339	1	1.10 (1.01-1.20)
Pooled	95766	2165		1.05 (1.02-1.09)
				,
Other				
CCHS	9763	366		1.00 (0.92-1.09)
CGPS	79640	913	 	1.05 (0.99-1.10)
CIHDS	6363	408	⊢	1.06 (0.98-1.15)
Pooled	95766	1687	├ ─ 	1.04 (1.00-1.08)
			1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
			0.9 1.0 1.1	1.2

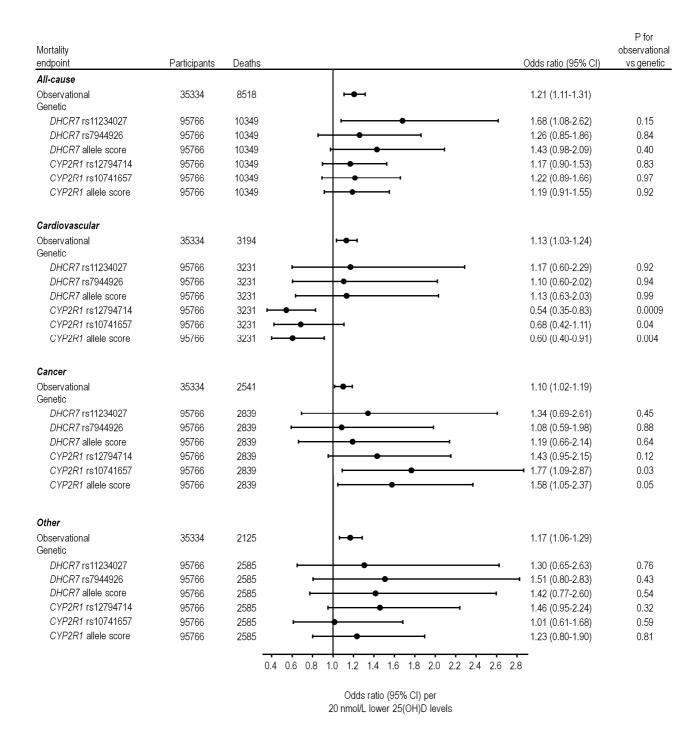
Hazard ratio (95% CI) per one increase in DHCR7/CYP2R1 allele score

Supplementary figure M. All-cause and cause-specific mortality according to the DHCR7/CYP2R1 allele score using Cox regression restricted to 9.4 years of follow-up. The analyses were carried out using Cox regression adjusted for age, year of birth, sex, and study; the latter only in the pooled analyses. Restriction in follow-up corresponded to the longest follow-up in the Copenhagen General Population Study, which started recruiting last. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval. CCHS = Copenhagen City Heart Study. CGPS = Copenhagen General Population Study. CIHDS = Copenhagen Ischemic Heart Disease Study.

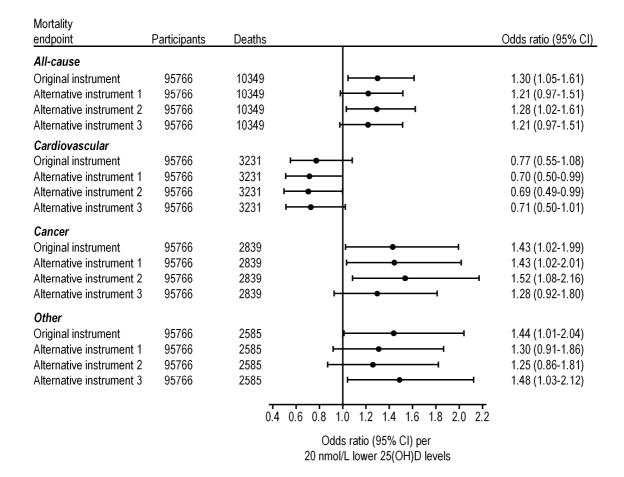
Regression model	Participants	Deaths					Estimate	s (95% CI)
Cardiovascular mor	tality							
Logistic	95766	3231			\dashv		Odds ratio	0.98 (0.94-1.01)
Competing risk	95766	3231					Subhazard ratio	0.98 (0.95-1.00)
Cancer mortality								
Logistic	95766	2839					Odds ratio	1.04 (1.00-1.07)
Competing risk	95766	2839				•——	Subhazard ratio	1.03 (1.00-1.06)
Other								
Logistic	95766	2585				-	Odds ratio	1.04 (1.00-1.07)
Competing risk	95766	2585				•	Subhazard ratio	1.03 (1.00-1.06)
				1		ı		
		1	0.90	0.95	1.00	1.05	1.10	

Odds or subhazard ratio (95% CI) per one increase in DHCR7/CYP2R1 allele score

Supplementary figure N. All-cause and cause-specific mortality according to the DHCR7/CYP2R1 allele score using logistic or competing risks regression. The analyses were carried out using logistic regression or Fine and Gray's competing risk proportional subhazard models adjusted for age, year of birth, sex, and study; the latter only in the pooled analyses. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.



Supplementary figure O. All-cause and cause-specific mortality when using each genotype as an instrument separately. Genetic estimates were by instrumental variable analyses for 20 nmol/L lower 25-hydroxyvitamin D levels. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.

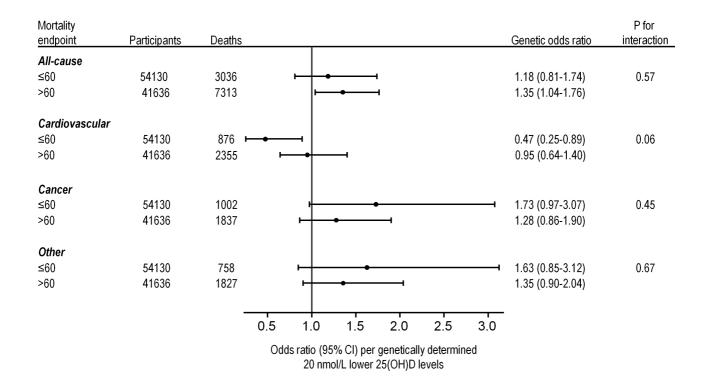


Supplementary figure P. All-cause and cause-specific mortality when using alternative definitions of the instrument. Genetic estimates were by instrumental variable analyses for 20 nmol/L lower 25-hydroxyvitamin D levels. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.

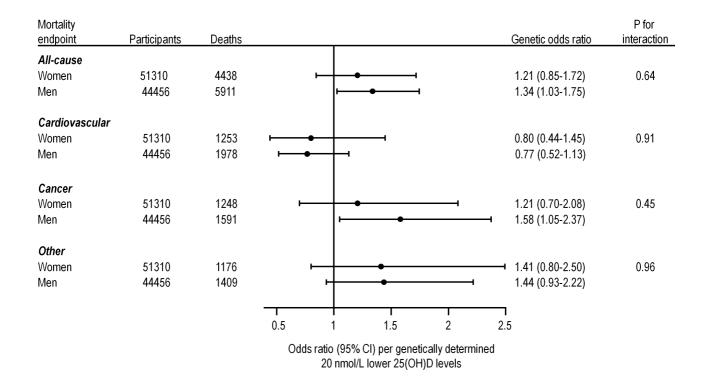
Alternative instrument 1 = allele score based on *DHCR7* rs7944926 + *CYP2R1* rs10741657 + *CYP2R1* rs12794714

Alternative instrument 2 = allele score based on *DHCR7* rs11234027 + *CYP2R1* rs10741657 + *CYP2R1* rs12794714

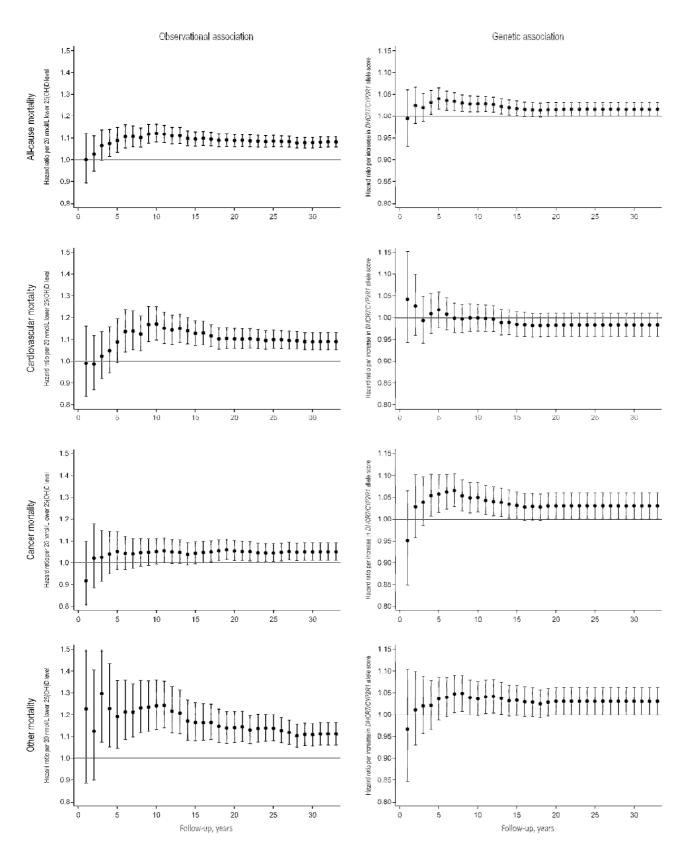
Alternative instrument 3 = allele score based on DHCR7 rs7944926 + CYP2R1 rs12794714



Supplementary figure Q. Genetic risk estimates for all-cause and cause-specific mortality according to age stratified analyses. Genetic estimates were by instrumental variable analyses for a 20 nmol/L lower 25-hydroxyvitamin D levels. Genetic estimates were based on participants from the Copenhagen City Heart Study, Copenhagen General Population Study, and Copenhagen Ischemic Heart Disease Study combined. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.



Supplementary figure R. Genetic risk estimates for all-cause and cause-specific mortality according to sex stratified analyses. Genetic estimates were by instrumental variable analyses for a 20 nmol/L lower 25-hydroxyvitamin D levels. Genetic estimates were based on participants from the Copenhagen City Heart Study, Copenhagen General Population Study, and Copenhagen Ischemic Heart Disease Study combined. 25(OH)D = 25-hydroxyvitamin D. CI = confidence interval.



Supplementary figure S. Observational and genetic analyses according to restriction of follow-up from 1 to 32 years to evaluate the dependence of risk estimates on follow-up time. In observational analyses, Cox regression models were adjusted for age, sex, smoking status, cumulative tobacco consumption, alcohol consumption, leisure time physical activity, systolic blood pressure, body mass index, income,

diabetes, plasma cholesterol, season, and study. Observational estimates were based on participants from the Copenhagen City Heart Study and Copenhagen General Population Study combined (n = 35334). The genetic risk factor was one increase in DHCR7/CYP2R1 allele score. In genetic analyses, models were adjusted for age, year of birth, sex, and study. Genetic estimates were based on participants from the Copenhagen City Heart Study, Copenhagen General Population Study, and Copenhagen Ischemic Heart Disease Study combined (n = 95766). Filled dots represent the point estimates and the whiskers represent the 95% confidence intervals. 25(OH)D = 25-hydroxyvitamin D.

Tables Supplementary table A. Baseline characteristics in the general population and their association with age, sex, season, and study adjusted 25hydroxyvitamin D (25(OH)D) quintiles.

		Adjus	sted 25(OH)D qui	intiles		P values ^a
	1 st (Lowest) N = 7068	2 nd N = 7066	3 rd N = 7068	4 th N = 7066	5 th (Highest) N = 7066	•
Age, years	58 (49-66)	57 (48-66)	58 (49-67)	59 (49-67)	58 (49-67)	0.62
Men, %	`43	`46	`47	`45	43	0.75
Current smoker, %	40	33	29	27	26	2·10 ⁻¹⁰⁰
Cumulative tobacco consumption, pack years ^c	24 (12-38)	20 (10-34)	19 (8-34)	18 (8-32)	18 (8-32)	9.10-42
Alcohol consumption, units/weekd	6 (2-14)	7 (2-14)	7 (3-14)	7 (3-14)	7 (3-14)	0.12
Leisure-time physical activity <2 hours/week, %	16	10	9	7	6	3.10-85
Systolic blood pressure, mmHg	139 (125-153)	136 (122-150)	136 (123-150)	135 (121-150)	133 (120-148)	8.10-32
Body mass index, kg/m ²	26 (23-30)	26 (23-29)	25 (23-28)	25 (23-28)	24 (22-27)	1.10-223
Low income, %e	46	39	38	37	36	$4 \cdot 10^{-30}$
Diabetes, %	6	4	4	3	3	4·10-13
Cholesterol, mmol/L	5.8 (5.1-6.6)	5.8 (5.0-6.4)	5.7 (5.0-6.4)	5.6 (4.9-6.4)	5.4 (4.7-6.2)	1.10-119
Vitamin D, nmol/L	23 (16-32)	38 (28-46)	49 (39-57)	62 (52-70)	84 (73-98)	<1.10-300

Continuous variables are summarised as median and interquartile range.

aP-values were calculated using linear regression or logistic regression as appropriate.

cln current and former smokers only

d1 unit ~ 12 g alcohol

elncome was classified differently in the 2 cohorts: 3 groups in CCHS and 4 groups in CGPS.

Supplementary table B. Baseline characteristics in the general population and their association with the DHCR7/CYP2R1 allele score.

		DHCR7/CYP2R1 allele score						
	0-1 N = 15560 ^b	2 N = 21842	3 N = 16172	4-5 N = 27986	6-8 N = 7843	•		
Age, years	57 (47-66)	57 (47-66)	57 (47-66)	57 (47-66)	57 (47-66)	0.06		
Men, %	`45	`45	`45	`45	`45	0.61		
Current smoker, %	23	23	23	23	23	0.11		
Cumulative tobacco consumption, pack years ^c	24 (12-38)	20 (10-34)	19 (8-34)	18 (8-32)	18 (8-32)	0.37		
Alcohol consumption, units/weekd	8 (3-15)	8 (3-15)	8 (3-15) [°]	7 (3-15) [°]	8 (3-15)	0.49		
Leisure-time physical activity <2 hours/week, %	`7 ′	`7 ′	`7 ′	`7 ′	`7 ′	0.80		
Systolic blood pressure, mmHg	136 (123-150)	135 (122-150)	136 (122-150)	136 (122-150)	136 (122-150)	0.03 ^{NS}		
Body mass index, kg/m ²	26 (23-28)	25 (23-28)	26 (23-28)	26 (23-28)	25 (23-28)	0.96		
Low income, %e	`36	`37	`36	`37	37	0.25		
Diabetes, %	4	4	4	4	4	0.99		
Cholesterol, mmol/L	5.6 (4.9-6.3)	5.6 (4.9-6.3)	5.6 (4.9-6.3)	5.6 (4.9-6.3)	5.6 (4.9-6.3)	0.65		
Vitamin D, nmol/Lf	55 (16-32)	53 (28-46)	51 (39-57)	49 (52-70)	47 (73-98)	4.10-72		

Continuous variables are summarised as median and interquartile range.

^aP-values were calculated using linear regression or logistic regression as appropriate.

b5460 participants attended both the 1981–1983 examination with 25(OH)D measurements and the 1991–1994 and/or 2001–2003 examinations with DNA available.

cln current and former smokers only

d1 unit ~ 12 g alcohol

elncome was classified differently in the 2 cohorts: 3 groups in CCHS and 4 groups in CGPS.

NSNot significant after correcting for 11 parallel tests (required p = 0.05/11 = 0.0045)

f30792 participants only

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