Genetically low vitamin D concentrations and increased mortality: mendelian randomisation analysis in three large cohorts

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EDITORIAL by Welsh and Sattar

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STUDY QUESTION

Are genetically low 25-hydroxyvitamin D concentrations associated with increased mortality when a mendelian randomisation approach is used?

SUMMARY ANSWER

Genetically low 25-hydroxyvitamin D concentrations were associated with increased all cause mortality, cancer mortality, and other mortality but not with cardiovascular mortality.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Observational studies have suggested that lower levels of vitamin D are associated with increased mortality, but such associations can be difficult to interpret owing to bias and confounding. Our findings are compatible with the notion that genetically low 25-hydroxyvitamin D concentrations may be causally associated with cancer and other mortality, but the observational association with cardiovascular mortality could be the result of confounding.

Participants and setting

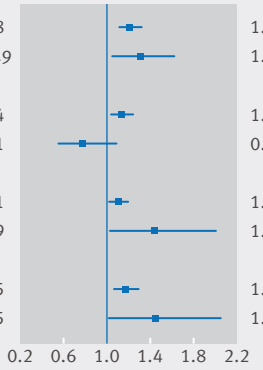
We included 95 766 white participants of Danish descent from three cohorts: two from the general population and one from patients referred for coronary angiography.

Design, size, and duration

We genotyped all 95 766 participants for genetic variants in *DHCR7* and *CYP2R1* affecting plasma 25-hydroxyvitamin D concentrations; 35 334 also had plasma 25-hydroxyvitamin D measurements. The participants were followed from study entry through 2013, during which time 10 349 died, with median follow-up times of 19.1, 5.8, and 7.9 years in the three cohorts.

Observational and genetic risk estimates for all cause and cause specific mortality for 20 nmol/L lower 25-hydroxyvitamin D concentration

Mortality endpoint	Participants	Deaths	Odds ratio (95% CI)	P for observational *v* genetic
All cause				
Observational	35 334	8518	1.21 (1.11 to 1.31)	0.54
Genetic	95 766	10 349	1.30 (1.05 to 1.61)	
Cardiovascular				
Observational	35 334	3194	1.13 (1.03 to 1.24)	0.03
Genetic	95 766	3231	0.77 (0.55 to 1.08)	
Cancer				
Observational	35 334	2541	1.10 (1.02 to 1.19)	0.06
Genetic	95 766	2839	1.43 (1.02 to 1.99)	
Other				
Observational	35 334	2125	1.17 (1.06 to 1.29)	0.26
Genetic	95 766	2585	1.44 (1.01 to 2.04)	



Main results and the role of chance

The multivariable adjusted hazard ratios for a 20 nmol/L lower plasma 25-hydroxyvitamin D concentration were 1.19 (95% confidence interval 1.14 to 1.25) for all cause mortality, 1.18 (1.09 to 1.28) for cardiovascular mortality, 1.12 (1.03 to 1.22) for cancer mortality, and 1.27 (1.15 to 1.40) for other mortality. Each increase in *DHCR7*/*CYP2R1* allele score was associated with a 1.9 nmol/L lower plasma 25-hydroxyvitamin D concentration and with increased all cause, cancer, and other mortality, but not with cardiovascular mortality. The odds ratio for a genetically determined 20 nmol/L lower plasma 25-hydroxyvitamin D concentration was 1.30 (1.05 to 1.61) for all cause mortality, with a corresponding observational multivariable adjusted odds ratio of 1.21 (1.11 to 1.31). Corresponding genetic and observational odds ratios were 0.77 (0.55 to 1.08) and 1.13 (1.03 to 1.24) for cardiovascular mortality, 1.43 (1.02 to 1.99) and 1.10 (1.02 to 1.19) for cancer mortality, and 1.44 (1.01 to 2.04) and 1.17 (1.06 to 1.29) for other mortality. The results were robust in sensitivity analyses.

Bias, confounding, and other reasons for caution:

We tried to test for assumptions underlying the mendelian randomisation approach and found no violations. However, not all assumptions are testable, so unknown confounding or bias may have affected our results. Furthermore, we assumed a simple linear effect of plasma 25-hydroxyvitamin D concentration on mortality, which probably led to conservative estimates. Lastly, our analysis used genetic variants affecting synthesis but not metabolism of 25-hydroxyvitamin D, so strictly speaking our results pertain to the synthesis pathway and not the metabolic pathway.

Generalisability to other populations

25-hydroxyvitamin D concentrations are known to vary with sun exposure and skin colour, and we studied only white Danes, thus potentially limiting the generalisability of the results to other geographical regions.

Study funding/potential competing interests

The Copenhagen General Population Study and Copenhagen City Heart Study are supported by the Danish Heart Foundation, Danish Medical Research Council, Copenhagen County Foundation, and Herlev Hospital, Copenhagen University Hospital.

Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis

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STUDY QUESTION

What is the difference between cobalt-chromium everolimus eluting stents and bare metal stents in terms of cardiac mortality and non-fatal safety endpoints, including non-fatal myocardial infarction and stent thrombosis?

SUMMARY ANSWER

Cobalt-chromium everolimus eluting stents are associated with improved cardiovascular outcomes including cardiac survival, myocardial infarction, and overall stent thrombosis compared with bare metal stents.

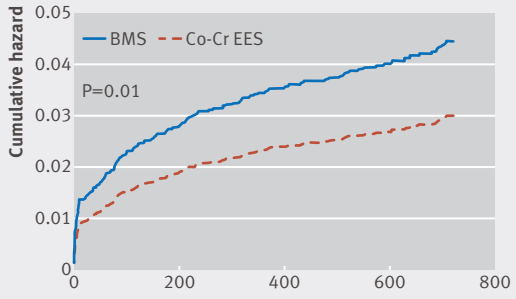
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Network meta-analyses have suggested that cobalt-chromium everolimus eluting stents are associated with a reduction in stent thrombosis compared with bare metal stents but the clinical implications of this finding remain unclear. This individual patient data meta-analysis of randomised trials shows a consistent reduction of several fatal and non-fatal ischaemic endpoints in favour of the drug eluting stents, including cardiac mortality, stent thrombosis, and myocardial infarction throughout the two year follow-up.

Selection criteria for studies

Medline, Embase, and the Cochrane Central Register of Controlled Trials databases were searched for randomised controlled trials that compared cobalt-chromium everolimus eluting stents and bare metal stents. Studies were included if they had randomised treatment allocation, compared cobalt-chromium everolimus eluting stents with bare metal stents, and had a follow-up of at least two years. Exclusion criteria were equivocal or non-random treatment allocation, lack of outcome data up to one year, and duplicate reports. The principal investigators whose trials met the inclusion criteria provided data for individual patients.

Cumulative hazard curves for key efficacy endpoint of cardiac death in bare metal stent (BMS) and everolimus eluting stent (EES) group



No of patients					
BMS	2444	2349	1939	1927	0
EES	2452	2376	1975	1958	0

Primary outcome

The primary outcome was cardiac mortality.

Main results and role of chance

Of the 346 citations screened, five randomised controlled trials were included, providing data on 4896 patients. As a result of the inclusion of two all comer percutaneous coronary intervention studies and one all comer ST segment elevation myocardial infarction trial, 44% of patients (n=2130) received stenting as a primary percutaneous coronary intervention and more than 87% (n=4279) of patients underwent coronary treatment for an unstable presentation, including 22% (n=1083) of patients with non-ST elevation myocardial infarction. Compared with patients receiving bare metal stents, those who received cobalt-chromium everolimus eluting stents had a significant reduction in cardiac mortality (hazard ratio 0.67, 95% confidence interval 0.49 to 0.91; P=0.01), myocardial infarction (0.71, 0.55 to 0.92; P=0.01), definite stent thrombosis (0.41, 0.22 to 0.76; P=0.005), definite or probable stent thrombosis (0.48, 0.31 to 0.73; P<0.001), and target vessel revascularisation (0.29, 0.20 to 0.41; P<0.001) at a median follow-up of 720 days. There were no significant differences in all cause death between groups (0.83, 0.65 to 1.06; P=0.14). Findings remained unchanged at multivariable regression after adjustment for the acuity of clinical syndrome (for instance, acute coronary syndrome *v* stable coronary artery disease), diabetes mellitus, female sex, use of glycoprotein IIb/IIIa inhibitors and up to one year versus longer duration of dual antiplatelet therapy.

Bias, confounding, and other reasons for caution

Heterogeneity was null or minimal for the endpoints assessed. Actual dual antiplatelet therapy status at follow-up was not recorded or was recorded suboptimally in two of the five included studies. Hence, the role of concomitant antiplatelet therapy should be further explored, bearing in mind that no single study has so far reported a cardiac mortality benefit of clopidogrel therapy beyond one month.

Study funding/potential competing interests

MV has received honorariums for lectures/advisory board from Abbott Vascular. MS, AC, and SG have received honorariums for lectures/advisory board and research grants from Abbott Vascular.

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Law enforcement duties and sudden cardiac death among police officers in United States: case distribution study

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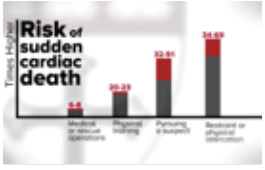

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STUDY QUESTION

Are stressful law enforcement duties in police offers associated with an increased risk of sudden cardiac death compared with routine/non-emergency duties?

SUMMARY ANSWER

Among law enforcement officers in the United States, risk of sudden cardiac death was 34-69 times higher during restraints/altercations; 32-51 times higher during pursuits; 20-23 times higher during physical training; and 6-9 times higher during medical/rescue operations, compared with routine/non-emergency activities.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Studies in fire fighters suggest that the risk of acute death from cardiac disease is increased during stressful duties compared with non-emergency duties. The current study provides data for the impact of stressful duties on the risk of sudden cardiac death among police officers when they are on duty.

Participants and setting

We identified sudden cardiac deaths and associated duties among US police officers in databases provided by the National Law Enforcement Officers Memorial Fund and the Officer Down Memorial Page. We also reviewed data from deaths related to cardiovascular disease that had been submitted for inclusion but were ultimately rejected by the memorial fund. We combined the case series of sudden cardiac deaths with estimates of the proportion of time police officers spend across various duties from surveys of front line officers and police chiefs.

Design, size, and duration

Case distribution study of 441 sudden cardiac deaths identified among more than 4500 US police officer deaths that occurred between 1984 and 2010.

Primary outcome, risks, exposures

Relative risks comparing rates of sudden cardiac death during specific strenuous duties versus routine/non-emergency activities. We explored the impact of varying exposure assessments, covariates, and missing deaths, in sensitivity and stability analyses.

Main results and the role of chance

We were able to identify the duty associated with the sudden cardiac death for 431 of the cases (98%). Events were associated with restraints/altercations (25%); physical training (20%); suspect pursuits (12%); medical/rescue operations (8%); routine duties (23%); and other activities (11%). The risk of sudden cardiac death was increased during stressful duties compared with routine/non-emergency duties. These results were robust to sensitivity and stability analyses.

Bias, confounding, and other reasons for caution

There have been no large scale studies of how US law enforcement officers in different locations spend their time so we had to rely on survey data that might not fully reflect the experience of the officers who died. No single database catalogues all on duty law enforcement fatalities related to cardiovascular disease, and databases selectively include events occurring during stressful situations. We obtained data on deaths related to cardiovascular disease that were not included by the National Law Enforcement Officers Memorial Fund, and there are good reasons to believe that most cases of sudden cardiac death in police officers are submitted for consideration. We relied on information abstracted from brief summaries to identify sudden cases of cardiac death and associated duties. We could not assess the contribution of risk factors for cardiovascular disease (other than age) to risk of sudden cardiac death.

Generalisability to other populations

Our findings are likely to be applicable in non-US settings because law enforcement duties show substantial variation across jurisdictions in the US. Furthermore, triggering of sudden cardiac death by acute exposure of susceptible individuals to physical or psychological stress is a mechanism shared by other occupations characterised by short bursts of stressful and physically demanding tasks.

Risk of sudden cardiac death among law enforcement officers engaged in emergency and strenuous duties compared with routine/non-emergency duties (1984-2010). Estimates based on frontline police officers survey

Duty	Observed events (%)	% time per duty*	Expected events	Relative risk* (95% CI)
Routine/non-emergency	101 (23.4)	77.4	333.6	Reference
Disturbance	20 (4.6)	9.6	41.4	1.60 (0.99 to 2.58)
Testifying in court	3 (0.7)	1.4	6.0	1.64 (0.52 to 5.18)
Serving warrant	6 (1.4)	1.6	6.9	2.87 (1.26 to 6.55)
Transporting or supervising prisoners	18 (4.2)	2.2	9.5	6.27 (3.80 to 10.4)
Medical and rescue operations	34 (7.9)	2.9	12.5	8.98 (6.09 to 13.3)
Physical training	88 (20.4)	2.9	12.5	23.3 (17.5 to 30.9)
Pursuit	53 (12.3)	0.8	3.5	50.8 (36.4 to 70.8)
Restraint, physical altercation	108 (25.1)	1.2	5.2	69.0 (52.6 to 90.5)

*Ordered by magnitude.

Study funding/potential competing interests

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