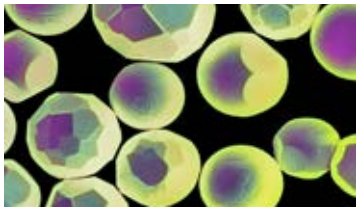
research

Mendelian randomisation analyses of vitamin D levels and calcium intake from dairy sources show no evidence of an effect on fracture p 227



Greater exposure to arsenic, lead, cadmium, and copper is associated with an increased risk of cardiovascular disease p 228

Prescribed, diverted, and illicit opioids all contributed to opioid related deaths in a Canadian population in 2016 p 230

ORIGINAL RESEARCH Genome wide association and mendelian randomisation study

Assessment of the genetic and clinical determinants of fracture risk

Trajanoska K, Morris JA, Oei L, Zheng H-F, et al;

on behalf of the GEFOS/GENOMOS consortium and the 23andMe research team

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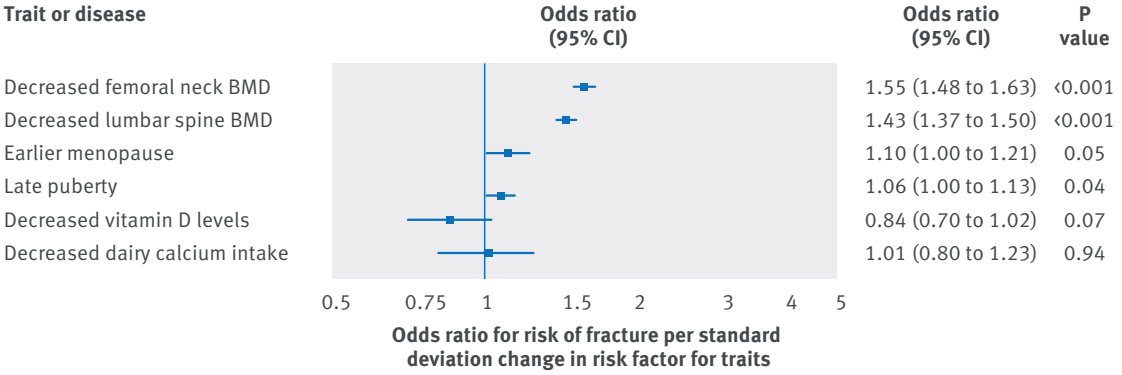
Study question In community dwelling individuals, what are the genetic determinants of fracture risk, and which clinical factors are causally related to fracture risk?

Methods This large meta-analysis of genome-wide association studies evaluated the influence of genetic variation on fracture risk, including a discovery set of 37 857 fracture cases and 227 116 controls; with replication in up to 147 200 fracture cases and 150 085 controls. Fracture cases were defined as individuals (>18 years old) who had fractures at any skeletal site confirmed by medical, radiological, or questionnaire reports. Instrumental variable analyses were then performed to estimate effects of 15 selected clinical risk factors for fracture in a two sample mendelian randomisation framework, using the largest previously published meta-analysis of genome-wide association studies of each risk factor.

Study answer and limitations In a genome-wide association study, 15 genome-wide significant loci were associated with fracture risk across cohorts from Europe, the US, east Asia, and Australia. All identified loci had been previously associated with bone mineral density and mapped to genes clustering in pathways known to be critical to bone biology (eg, *SOST*, *WNT16*, and *ESR1*) or novel bone pathways (*FAM210A*, *GRB10*, and *ETS2*). Furthermore, the mendelian randomisation analyses indicated that a standard deviation decrease in genetically determined bone mineral density of the femoral neck was associated with a 55% increase in fracture risk (odds ratio 1.55 (95% confidence interval 1.48 to 1.63; $P=1.5\times10^{-68}$)). The remaining clinical risk factors evaluated through mendelian randomisation analyses (including vitamin D levels and calcium intake from dairy sources) showed no evidence for an effect on fracture. However, neither non-linear threshold relations nor dose-response relations could be accounted for within the study design.

What this study adds Genetic predisposition to lower vitamin D levels and estimated calcium intake from dairy sources were not associated with fracture risk.

Funding, competing interests, data sharing Full details on funding and competing interests can be found on bmj.com. All data are available for unrestricted use through the GEFOS consortium and can be downloaded at http://www.gefos.org/.



Forest plot showing effect of a selection of genetically determined risk factors on fracture risk. BMD=bone mineral density

Environmental metals and cardiovascular disease

ORIGINAL RESEARCH Systematic review and meta-analysis

Environmental toxic metal contaminants and risk of cardiovascular disease

Chowdhury R, Ramond A, O'Keeffe LM, et al

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Study question Are arsenic, lead, cadmium, mercury, and copper associated with cardiovascular disease?

Methods Studies published before December 2017 were identified through electronic searches using PubMed, Embase, and Web of Science. Eligible studies included prospective cohort, case-control, or nested case-control studies reporting risk estimates for total cardiovascular disease, coronary heart disease, and stroke by levels of arsenic, lead, cadmium, mercury, or copper in drinking water, urine, toenail, blood, or hair samples. Information on study characteristics and outcomes was extracted by two investigators independently in accordance with PRISMA and MOOSE guidelines. Relative risks were standardised to a common scale and pooled across studies for each marker using random effects meta-analyses.

Study answer and limitations Results of this meta-analysis indicate that higher levels of exposure to arsenic, lead, cadmium, and copper are associated with an increased risk of cardiovascular disease and coronary heart disease compared with lower levels. Comparing the top versus bottom thirds of baseline levels, pooled relative risks for arsenic and lead were 1.30 (95% confidence interval 1.04 to 1.63) and 1.43 (1.16 to 1.76) for cardiovascular disease, 1.23 (1.04 to 1.45) and 1.85 (1.27 to 2.69) for coronary heart disease, and 1.15 (0.92 to 1.43) and 1.63 (1.14 to 2.34) for stroke. Relative risks for cadmium and copper were 1.33 (1.09 to 1.64) and 1.81 (1.05 to 3.11) for cardiovascular disease, 1.29 (0.98 to 1.71) and 2.22 (1.31 to 3.74) for coronary heart disease, and 1.72 (1.29 to 2.28) and 1.29 (0.77 to 2.17) for stroke. Mercury had no distinctive association with cardiovascular outcomes. However, this review presents only observational associations, therefore, causality cannot be assumed.

What this study adds The findings of this study reinforce the likely importance of environmental toxic metals in the risk of cardiovascular outcomes, beyond the roles of conventional behavioural risk factors (such as smoking, poor diet, and physical inactivity). In addition, the study highlights the potential need for additional worldwide efforts and strategies to reduce exposures in humans even in settings where there is a relatively lower average level of exposure (such as in many Western countries). However, further detailed work is required to better characterise these associations and to assess causality.

Funding, competing interest, data sharing This study was not externally funded. The authors have no competing interests. The dataset is available from the corresponding author.

COMMENTARY Metals are an important but neglected source of cardiovascular risk

Evidence on the role of environmental metals in cardiovascular disease has rapidly increased over the past two decades. Chowdhury and colleagues report analyses of data from about 350 000 people from 37 countries showing that exposures to arsenic, lead, cadmium, and copper are associated with an increased risk of cardiovascular disease incidence and mortality. This is an important call for attention to an emerging group of risk factors with a high prevalence in populations around the world.

Safe threshold?

Chowdhury and colleagues paid special attention to the dose-response effect. Most associations were linear, with no clear lower threshold for toxicity. However, the number of studies in populations with low levels of exposure remains insufficient to reach firm conclusions on the shape of the dose-response curve at low levels. This is critical information for public health authorities and should be a priority for future research.

The study reported no association between mercury exposure and cardiovascular disease. Methylmercury contamination of fish is the primary source of mercury in most populations and these null results must be interpreted carefully, given the complexity of fish intake and the large number of potential confounders of this association.

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Metals are associated with cardiovascular disease even at relatively low levels of exposure

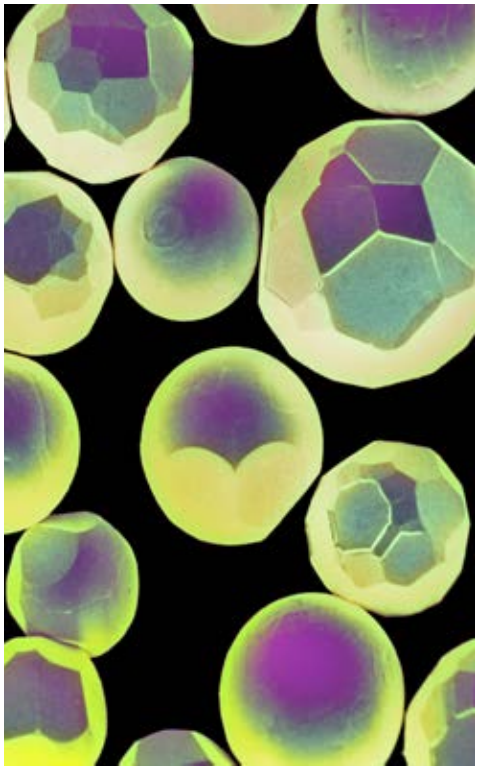
Experimental studies evaluating the role of metals as disruptors of redox, epigenetic, and endocrine pathways support the causal role of metals in atherosclerosis.[2-4] Other lines of evidence include a double blind randomised trial suggesting that chelation therapy, which increases urinary excretion of heavy metals, may provide some benefit in secondary prevention of cardiovascular disease.[5]

The US conducts nationally representative biomonitoring of arsenic, lead, cadmium, and mercury through regular National Health and Nutrition Examination Surveys (NHANES). These surveys document a marked reduction in population exposure to lead and cadmium (the metals monitored for longest), largely reflecting large scale public health policies on the control of tobacco, reduction of air pollution, remediation of hazardous waste, renovation of drinking water infrastructures, and banning of lead in petrol.[7 8]

Concomitant with these reductions, cardiovascular mortality rates in the US decreased by 43% from 1988-94 to 1999-2004.[9] An analysis that accounted for traditional cardiovascular disease risk factors showed that 32% of this reduction in cardiovascular mortality could be explained by the decline in lead and cadmium exposures.[9] The health impact of recent reductions in arsenic exposure,[10] however, has not been evaluated.

Widespread contamination

Exposure to environmental metals remains substantial because of widespread soil contamination; persistence of past uses (house paint and plumbing for lead); continuing industrial uses (plastics and batteries); and presence in tobacco and tobacco smoke, drinking water and ambient air, and dust near industrial sources and waste sites.[7 8] Cadmium content in fertilisers provides an additional exposure pathway through diet and tobacco since vegetables and grains bioconcentrate cadmium. Emerging tobacco products such as electronic cigarettes also increase metal exposure.[11] The main



Metals	No of studies	No of participants	No of events	Relative risk (95% CI)	Relative risk (95% CI)
Arsenic					
Cardiovascular disease	7	135 943	3208		1.30 (1.04 to 1.63)
Coronary heart disease	8	190 816	4640		1.23 (1.04 to 1.45)
Stroke	4	134 526	961		1.15 (0.92 to 1.43)
Lead					
Cardiovascular disease	10	110 382	4970		1.43 (1.16 to 1.76)
Coronary heart disease	8	91 779	2228		1.85 (1.27 to 2.69)
Stroke	6	89 494	518		1.63 (1.14 to 2.34)
Cadmium					
Cardiovascular disease	6	50 674	3756		1.33 (1.09 to 1.64)
Coronary heart disease	5	32 070	1654		1.29 (0.98 to 1.71)
Stroke	3	9123	601		1.72 (1.29 to 2.28)
Mercury					
Cardiovascular disease	4	11 410	4866		0.94 (0.66 to 1.36)
Coronary heart disease	5	9169	3838		0.99 (0.65 to 1.49)
Copper					
Cardiovascular disease	4	5385	538		1.81 (1.05 to 3.11)
Coronary heart disease	4	7299	492		2.22 (1.31 to 3.74)
Stroke	2	728	100		1.29 (0.77 to 2.17)

Summary of the association of environmental contaminants with cardiovascular outcomes. Pooled risk estimates were calculated using random effects meta-analyses. The relative risk compares the risk for each outcome in individuals in the top third with those in the bottom third of baseline levels of the environmental contaminants (ie, extreme thirds). Risk estimates from separate studies were typically adjusted for basic demographics (eg, age, sex, systolic blood pressure, smoking, history of diabetes, etc)

source of metals in electronic cigarettes seems to be the heating coil, from where metals leach into the inhaled aerosol. [11] In low and middle income countries, including many countries in Africa and Asia, exposure to high levels of arsenic and lead is still a serious threat to public health that requires urgent action.[12-14]

Despite widespread distribution of toxic metal contaminants, technical reports from environmental and public health agencies often disregard the mounting evidence of associated cardiovascular risk.[15 16] Similarly, metal exposures are neglected by the organisations that produce cardiovascular prevention guidelines.

In communities affected by disproportionate environmental and occupational exposure, surveillance systems should monitor metal biomarkers and cardiovascular disease events and implement cardiovascular disease prevention programmes. Since metals are associated with cardiovascular disease even at relatively low levels of exposure, population-wide strategies to minimise exposure can further contribute to overall cardiovascular prevention efforts.

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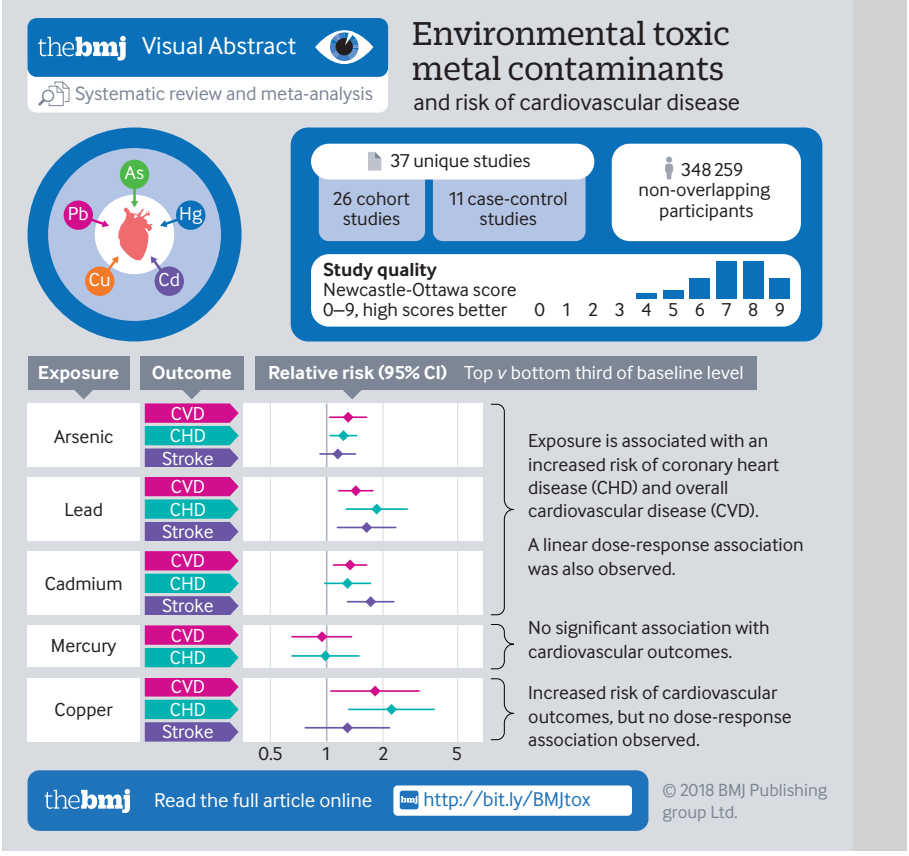

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Contributions of prescribed and non-prescribed opioids to opioid related deaths

Gomes T, Khuu W, Martins D, et al

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Study question What are the contributions of prescribed and non-prescribed opioids to opioid related deaths in Ontario, Canada?

Methods This was a population based cohort study among all Ontarians who died between January 2013 and December 2016. Active opioid prescriptions were defined as those with a duration overlapping the date of death, and postmortem toxicology results were used to characterise deaths on the basis of presence of prescribed and non-prescribed (that is, diverted or illicit) opioids, overall and stratified by year and age.

Study answer and limitations Among the 2833 opioid related deaths identified, the prevalence of an active opioid prescription on the date of death declined slightly throughout the study period (38.2% in 2013 and 32.5% in 2016; P for trend=0.03). Among people with active opioid prescriptions at time of death, 37.8% (375/993) also had evidence of a non-prescribed opioid on postmortem toxicology. A limitation of this analysis is that the possibility that some deaths seeming to involve diverted opioids might instead represent old prescriptions to the same person cannot be excluded. Differentiation between prescribed and illicit fentanyl was also not possible.

What this study adds This study found that prescribed, diverted, and illicit opioids all played an important role in opioid related deaths in 2016. One third of opioid related deaths were among people actively treated with a prescription opioid. A concerning trend of increased involvement of non-prescribed fentanyl was seen in 2016, which aligns with the recent introduction of illicit fentanyl to the market.

Funding, competing interests, data sharing This study was funded by grants from the Ontario Ministry of Health and Long-Term Care and the Canadian Institutes for Health Research. MMM has received personal fees from Celgene, NovoNordisk, and Allergan outside the submitted work. Data access may be granted to those who meet prespecified criteria for confidential access, described at www.ices.on.ca/DAS.

Prevalence of opioid prescriptions among patients who died from opioid related causes in Ontario, 2013 to 2016. Values are numbers (percentages) unless stated otherwise

Measures	2013 (n=631)	2014 (n=635)	2015 (n=712)	2016 (n=855)	P value (trend test)
Active opioid prescription on date of death	241 (38.2)	224 (35.3)	254 (35.7)	278 (32.5)	0.03
Opioid prescription within previous:					
30 days	301 (47.7)	283 (44.6)	338 (47.5)	367 (42.9)	0.15
180 days	390 (61.8)	368 (58.0)	432 (60.7)	508 (59.4)	0.61
1 year	–*	414 (65.2)	473 (66.4)	555 (64.9)	0.87
2 years	–*	–*	520 (73.0)	616 (72.0)	0.66†
3 years	–*	–*	–*	653 (76.4)	–
Active benzodiazepine prescription on date of death	207 (32.8)	207 (32.6)	237 (33.3)	236 (27.6)	0.04
Active opioid and benzodiazepine prescription on date of death	127 (20.1)	118 (18.6)	147 (20.6)	138 (16.1)	0.10
Sensitivity analysis: active opioid prescription among non-fentanyl opioid related deaths	182/494 (37)	161/464 (35)	196/500 (39)	200/503 (40)	0.18

*Data omitted owing to incomplete data capture in lookback period.
†P value derived from χ^2 test; all other P values reflect two tailed, exact Cochran-Armitage trend tests.

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