

# Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis

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Clinical review: Omega 3 fatty acids and cardiovascular disease—fishing for a natural treatment (*BMJ* 2004;328:30)

**STUDY QUESTION** Does increasing dietary omega 6 linoleic acid in the place of saturated fat reduce the risk of death from coronary heart disease?

**SUMMARY ANSWER** In the Sydney Diet Heart Study, a randomized controlled trial conducted in 1966-73, dietary substitution of omega 6 linoleic acid for saturated fat lowered serum cholesterol but increased deaths from all causes, coronary heart disease, and cardiovascular disease.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Substitution of vegetable oils rich in polyunsaturated fatty acids for animal fats rich in saturated fatty acids has been a key component of dietary guidelines for more than 50 years. Evaluation of recovered data from the Sydney Diet Heart Study showed that substituting omega 6 linoleic acid for saturated fat lowered serum cholesterol but increased the risk of death from coronary heart disease and cardiovascular disease; a mechanistic model accounting for these paradoxical findings is presented.

## Design

The Sydney Diet Heart Study was a single blinded, parallel group, randomized controlled dietary trial investigating secondary prevention of coronary heart disease. The intervention group replaced saturated fat (from animal fats, common margarines, and shortenings) with omega 6 linoleic acid (from safflower oil and safflower oil polyunsaturated margarine). Controls received no specific dietary instruction or study foods. We used an intention to treat, survival analysis approach to compare deaths by group and examined whether longitudinal changes in dietary linoleic acid were associated with mortality outcomes.

## Participants and setting

Men (n=458) aged 30-59 years with a recent coronary event.

## Outcomes

Mortality from all causes, cardiovascular disease, or coronary heart disease, with median follow-up of 39 months.

## Main results and the role of chance

The intervention group (n=221) had higher rates of death than controls (n=237; all cause 17.6% v 11.8%, hazard ratio 1.62 (95% confidence interval 1.00 to 2.64), P=0.05; cardiovascular disease 17.2% v 11.0%, 1.70 (1.03 to 2.80), P=0.04; coronary heart disease 16.3% v 10.1%, 1.74 (1.04 to 2.92), P=0.04). Increases in consumption of linoleic acid were significantly associated with higher rates of all cause and cardiovascular disease mortality in crude and adjusted models. Inclusion of these recovered data in an updated meta-analysis of linoleic acid intervention trials showed non-significant trends toward increased risks of death from coronary heart disease and cardiovascular disease.

## Bias, confounding, and other reasons for caution

Some control participants began substituting polyunsaturated margarine for butter, leading to substantial but comparatively modest dietary changes similar to those of the intervention group. These changes could have attenuated the observed differences in mortality between groups, leading to an underestimation of the adverse effects of the intervention. The fatty acid content of blood or adipose tissue was not measured and could not be used to validate the longitudinal seven day food records. However, the significant reduction in serum cholesterol observed in the intervention group broadly accords with the diet assessments. The meta-analytic results should be interpreted with some caution owing to the relatively few randomized controlled dietary trials and the differences in design and population characteristics of each trial.

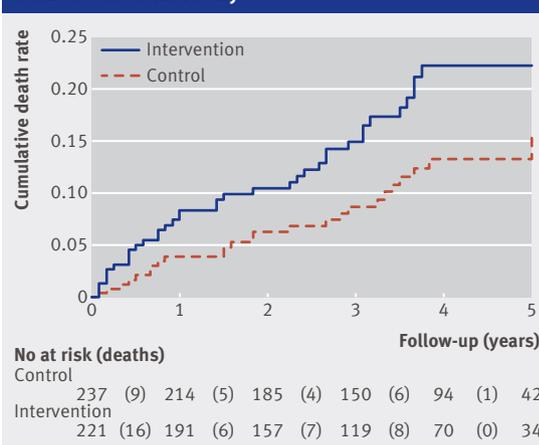
## Generalizability to other populations

Results are not necessarily generalizable to women, men younger than 30 years or older than 59 years, populations without established coronary heart disease, or populations consuming lower amounts of linoleic acid.

## Study funding/potential competing interests

No competing interests declared. The Life Insurance Medical Research Fund of Australia and New Zealand provided a grant in support of the Sydney Diet Heart Study. The Intramural Program of the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, supported data recovery and evaluation.

Kaplan-Meier estimates of cumulative rates of cardiovascular mortality



# Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis

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- Feature: Containing the opioid overdose epidemic (*BMJ* 2012;345:e8340)
- Editor's choice: Slowing the opioid analgesic overdose epidemic (*BMJ* 2013;346:f730)
- Analysis: Facing up to the prescription opioid crisis (*BMJ* 2011;343:d5142)

## STUDY QUESTION

What is the impact of state supported overdose education and nasal naloxone distribution (OEND) programs on rates of opioid related death from overdose and acute care utilization in Massachusetts?

## SUMMARY ANSWER

Death rates from opioid overdose but not acute care utilization rates were reduced in communities where OEND was implemented.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

OEND is an innovative, community based program deployed in many settings that has not been examined in controlled studies. This study provides observational evidence that OEND is an effective public health intervention to address increasing mortality from opioid overdose by training potential bystanders to prevent, recognize, and respond to opioid overdoses. OEND implementation seemed to have a dose related impact where the higher the cumulative rate of OEND implementation, the greater the reduction in death rates.

## Population and setting

19 Massachusetts communities (geographically distinct cities and towns) with at least five fatal opioid overdoses in each of the years 2004-06.

## Design, size, and duration

We conducted an interrupted time series analysis of rates of opioid related deaths from overdose and acute care utilization from 2002 to 2009 that compared community-year strata with high and low rates of OEND implementation to those with no OEND implementation. Poisson regression models were adjusted for community level demographics and substance use related factors.

## Main results and the role of chance

Between 2006 and 2009, Massachusetts OEND programs in 19 communities trained 2912 potential bystanders who reported 327 rescues. Community-year strata with 1-100 enrollments per 100 000 population (adjusted rate ratio 0.73, 95% confidence interval 0.57 to 0.91) and community-year strata with greater than 100 enrollments per 100 000 population (0.54, 0.39 to 0.76) had significantly reduced adjusted rate ratios compared with communities with no implementation. Opioid overdose related visits to emergency departments and hospital admission rates did not differ significantly in communities with low versus high OEND implementation.

## Bias, confounding, and other reasons for caution

This study was observational and cannot demonstrate causality. These analyses were adjusted for several important community level factors, including demographics, use of addiction treatment, and doctor shopping for prescription opioids (those with schedule II opioid prescriptions from  $\geq 4$  prescribers and filled prescriptions at  $\geq 4$  pharmacies over 12 months). Misclassification of outcomes was possible, though unlikely to be directional, and was mitigated because Massachusetts has one centralized medical examiner office.

## Generalisability to other populations

The study was conducted in a region where health department supported OEND at community level was implemented and the findings may not apply to regions where overdose prevention efforts are different.

## Study funding/potential competing interests

All researchers are independent of the funder, the Centers for Disease Control and Prevention. We have no financial relations with any organisations that might have an interest in the submitted work.

Models of OEND implementation and rates of unintentional deaths from opioid related overdose in 19 communities in Massachusetts, 2002-09

Cumulative enrollments per 100 000 population	Rate ratio	Adjusted rate ratio* (95% CI)	P value
No implementation	Reference	Reference	
Low implementation: 1-100 enrollments	0.93	0.73 (0.57 to 0.91)	<0.01
High implementation: >100 enrollments	0.82	0.54 (0.39 to 0.76)	<0.01

\*Adjusted for city/town population rates of age <18, male, race or ethnicity (Hispanic, white, black, other), below poverty level, medically supervised inpatient withdrawal treatment, methadone treatment, funded buprenorphine treatment, prescriptions to doctor shoppers, and year.

# Exposure to bisphosphonates and risk of gastrointestinal cancers: series of nested case-control studies with QResearch and CPRD data

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Research: Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum (*BMJ* 2010;341:c4444)

## STUDY QUESTION

Are bisphosphonates used for the treatment of osteoporosis associated with increased risks of oesophageal, gastric, or colorectal cancers?

## SUMMARY ANSWER

Use of bisphosphonates is in general not associated with increased risks for any common gastrointestinal cancer.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Epidemiological evidence concerning the associations between bisphosphonates and risk of gastrointestinal cancers has been inconsistent. Our study, based on data derived from two general population primary care databases, provides reassurance to physicians prescribing bisphosphonates.

## Participants and settings

Our series of case-control studies was based on patient information from 1303 general practices in the United Kingdom contributing to two primary care research databases. Incident cases of cancer diagnosed between 1997 and 2011 were matched to up to five controls by age, sex, general practice, and calendar year.

## Design, size, and duration

Patients were included if they were aged  $\geq 50$  and had at least two years of medical records. Patients with Paget's disease and patients with bisphosphonate prescriptions licensed for any malignancies were excluded. All bisphosphonate prescriptions, except for the six months before the index date, were used for the analysis. Cumulative exposure was assessed by summing duration of all bisphosphonate prescriptions. To allow for multiple comparisons, significance was set at  $P < 0.01$ .

## Main results and the role of chance

Overall bisphosphonate use (at least one prescription) was not associated with risk of colorectal, oesophageal, or gastric cancers in either database. Adjusted odds ratios (95% confidence intervals) for QResearch and CPRD were, respectively: 0.97 (0.79 to 1.18) and 1.18 (0.97 to 1.42) for oesophageal cancer; 1.12 (0.87 to 1.44) and 0.79 (0.62 to 1.01) for gastric cancer; 1.03 (0.94 to 1.14); and 1.10 (1.00 to 1.22) for colorectal cancer. There was no association with duration of use.

Additional analyses showed no difference between types of bisphosphonate for oesophageal and colorectal cancers. For gastric cancer, alendronate use was associated with an increased risk in QResearch data (1.47, 1.11 to 1.95;  $P=0.008$ ), but not in CPRD data (0.93, 0.71 to 1.22;  $P=0.6$ ). The association seen in QResearch, however, showed association with duration and lacked definitive confirmation from sensitivity analysis.

## Bias, confounding, and other reasons for caution

Odds ratios for bisphosphonate use were adjusted by smoking status, alcohol consumption, osteoporosis and drugs associated with it, upper gastrointestinal disorders diagnosed before bisphosphonate use, and family history of a relevant cancer, but there could still be residual confounding. Limitations of the study include possible uncertainty in site of cancer diagnosis as the selection of cases was based on the first record of cancer and the exact origin site might be confirmed only later. Another limitation is that bisphosphonate use was assessed from prescription information not actual use.

## Generalisability to other populations

This study is based on large representative primary care samples and so is generalisable to the UK population.

**Bisphosphonate use in people with cancer and controls according to length of use and odds ratios (95% confidence intervals) compared with non-use by cancer site and database**

Length of use	QResearch			CPRD		
	Cases	Controls	Adjusted odds ratio (95% CI)	Cases	Controls	Adjusted odds ratio (95% CI)
<b>Oesophageal cancer</b>						
No of people	5364	25 101	—	5132	24 053	—
$\leq 1$ year	94	367	1.03 (0.80 to 1.34)	89	361	1.05 (0.81 to 1.37)
$> 1$ year	158	704	0.92 (0.73 to 1.16)	173	582	1.28 (1.02 to 1.60)*
<b>Gastric cancer</b>						
No of people	3155	14 715	—	3157	14 686	—
$\leq 1$ year	62	195	1.37 (0.98 to 1.90)	60	279	0.84 (0.61 to 1.15)
$> 1$ year	79	385	0.96 (0.71 to 1.31)	79	415	0.75 (0.56 to 1.01)
<b>Colorectal cancer</b>						
No of people	20 106	93 954	—	19 035	89 111	—
$\leq 1$ year	345	1599	1.02 (0.90 to 1.17)	358	1558	1.17 (1.03 to 1.33)†
$> 1$ year	584	2746	1.04 (0.92 to 1.17)	544	2673	1.06 (0.94 to 1.19)

\* $P=0.03$ ; † $P=0.02$ .

## QT interval and antidepressant use: a cross sectional study of electronic health records

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**STUDY QUESTION** What effects do antidepressants such as citalopram have on QT interval, a marker of risk for ventricular arrhythmia?

**SUMMARY ANSWER** In a large clinical cohort escalating doses of citalopram, escitalopram, and amitriptyline were significantly associated with prolonged QT interval, while bupropion was associated with shortened QT interval.

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS** The US Food and Drug Administration issued warnings about the QT prolonging effects of citalopram based on postmarketing surveillance and a small crossover study in healthy individuals. This study confirms a modest prolongation of QT interval with citalopram and identifies other antidepressants with similar observed risk in an older, more medically ill population.

### Participants and setting

The study included 38 397 adult patients in a large New England healthcare system who underwent electrocardiography after prescription of an antidepressant or methadone between February 1990 and August 2011.

### Design

This cross sectional study used electrocardiographic, prescribing, and clinical data drawn from electronic health records to explore the relation between antidepressant dose and corrected QT (QTc) interval. The present analysis included the selective serotonin reuptake inhibitor antidepressants citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; other antidepressants such as amitriptyline, nortriptyline, bupropion, duloxetine, mirtazapine, and venlafaxine; and the opioid methadone, known to prolong QT interval and included to demonstrate assay sensitivity.

### Primary outcome(s)

Relation between antidepressant dose and QTc interval was analysed by linear regression, with adjustment for potential clinical and demographic confounding variables.

### Main results and the role of chance

Dose-response association with QTc prolongation was identified for citalopram (adjusted beta 0.10 (SE 0.04),  $P < 0.01$ ), escitalopram (adjusted beta 0.58 (0.15),  $P < 0.001$ ), and amitriptyline (adjusted beta 0.11 (0.03),  $P < 0.001$ ), while an association with QTc shortening was identified for bupropion (adjusted beta 0.02 (0.01),  $P < 0.05$ ). The seven other antidepressants showed no significant effects. As expected, increasing methadone dose was also associated with increased QTc (adjusted beta 0.30 (0.06),  $P < 0.001$ ).

### Bias, confounding, and other reasons for caution

Antidepressant type and dose were not randomly assigned, and electrocardiography was performed only when clinically indicated, which may introduce bias. However, as the data preceded the US Food and Drug Administration (FDA) warning about the QT-prolonging effects of citalopram, the risk for confounding by indication is low.

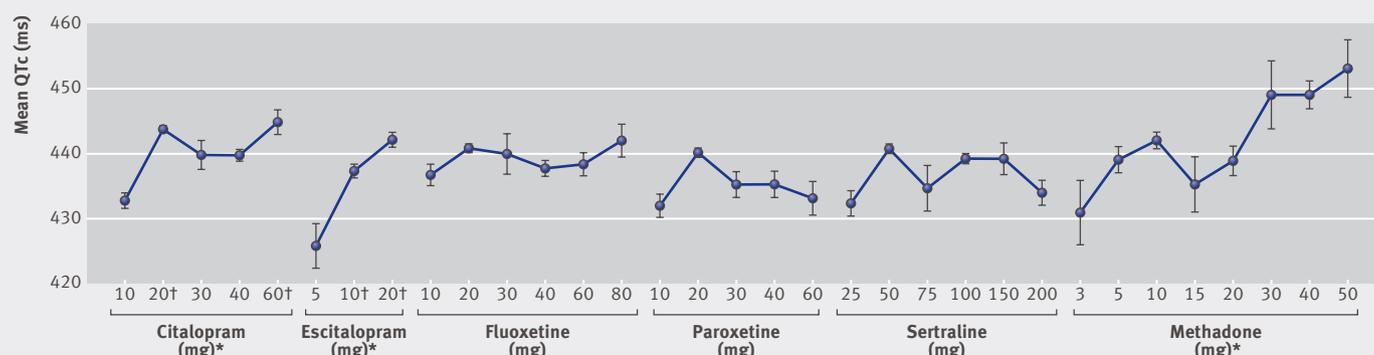
### Generalisability to other populations

The concordance of our results with those of an FDA crossover study suggests their generalisability, though our results may be more relevant to an older, more medically ill population than that studied in the FDA trial.

### Study funding/potential competing interests

The study was funded by the US National Institute of Mental Health.

**Mean (SD) corrected QT (QTc) interval recorded on electrocardiogram 14–90 days after prescription of selective serotonin reuptake inhibitor antidepressant or methadone, by drug dose**



\* Dose a significant predictor of QTc in fully adjusted linear models at  $\alpha=0.05$

† QTc at specified dose is significantly different from that at prior dose in fully adjusted linear models at  $\alpha=0.05$