

# Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies

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Research: Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis (*BMJ* 2010;341:c4229)

Research: Effect of intervention aimed at increasing physical activity, reducing sedentary behaviour, and increasing fruit and vegetable consumption in children (*BMJ* 2014;348:g3256)

Research: Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies (*BMJ* 2013;347:f5001)

## STUDY QUESTION

What is the association between consumption of fruit and vegetables and risk of all cause, cardiovascular, and cancer mortality?

## SUMMARY ANSWER

Evidence from prospective cohort studies shows that higher consumption of fruit and vegetables is associated with a reduced risk of mortality from all causes, particularly cardiovascular disease. Higher consumption is not, however, appreciably associated with cancer mortality.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Fruit and vegetable consumption might be associated with risk of mortality, but the dose dependency of these associations has not been determined in a meta-analysis. This meta-analysis of prospective cohort studies shows an inverse association between fruit and vegetable consumption and risk of all cause mortality, with 5% reduction in risk of all cause mortality for each additional serving a day of fruit and vegetables (6% for fruit and 5% for vegetables).

## Selection criteria for studies

We searched Medline, Embase, and the Cochrane library up to 30 August 2013 without language restrictions. We also screened reference lists of retrieved articles. We included prospective cohort studies that reported risk estimates for all cause, cardiovascular, and cancer mortality by levels of fruit and vegetable consumption.

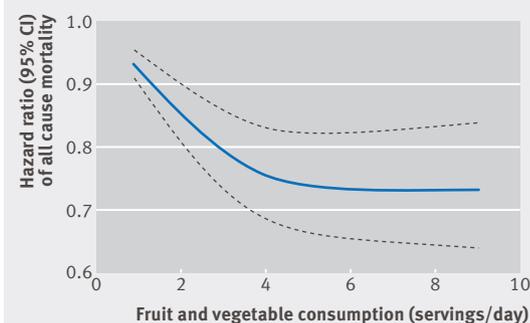
## Primary outcomes

The main outcomes were total and cause specific mortality.

## Main results and role of chance

Sixteen prospective cohort studies were eligible in this meta-analysis, including a total of 56 423 deaths (11 512 from cardiovascular disease and 16 817 from cancer) among 833 234 participants during follow-up periods ranging from 4.6 to 26 years. Higher consumption of fruits and vegetables was significantly associated with a lower risk of all cause mortality. Pooled hazard ratio of all cause mortality was 0.95 (95% confidence interval 0.92 to 0.98) for an increment of one serving a day of fruits and vegetables ( $P=0.001$ ), 0.94 (0.90 to 0.98) for fruit ( $P=0.002$ ), and 0.95 (0.92 to 0.99) for vegetables ( $P=0.006$ ). We observed a threshold around five servings of fruits and vegetables a day, after which the risk of all cause mortality did not

## Dose-response relation between fruit and vegetable consumption and risk of all cause mortality



reduce further. There was a significant inverse association for cardiovascular mortality (hazard ratio for each additional serving a day of fruits and vegetables 0.96, 95% confidence interval 0.92 to 0.99), while higher consumption of fruits and vegetables was not appreciably associated with risk of cancer mortality.

## Bias, confounding, and other reasons for caution

Heterogeneity observed in this meta-analysis was mainly attributed to one study with a large sample size. Sensitivity analyses with that study excluded did not appreciably alter the pooled hazard ratios. There was suggestive evidence for funnel plot asymmetry in the Egger's test; however, no missing studies were imputed in the contour enhanced funnel plots in the trim and fill analysis, minimising the concern of publication bias. Most of included studies adjusted for known risk factors of mortality, including age, body mass index, physical activity, smoking, and alcohol consumption, but confounding by residual or unmeasured factors could partially explain our findings. In particular, some studies did not adjust for other dietary factors in addition to total energy intake. The inverse association between fruit and vegetable consumption and mortality could be related to a generally more healthy diet and lifestyle.

## Study funding/potential competing interests

This work was funded by National Natural Science Foundation (NSFC 81071081) of China. WB was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health.

# Operative versus non-operative treatment for closed, displaced, intra-articular fractures of the calcaneus: randomised controlled trial

Damian Griffin, Nick Parsons, Ewart Shaw, Yuri Kulikov, Charles Hutchinson, Margaret Thorogood, Sarah E Lamb for the UK Heel Fracture Trial (UK HeFT) investigators

## EDITORIAL by Scammell

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## Trial registration number

Current Controlled Trials  
ISRCTN 37188541.

## STUDY QUESTION

In patients with typical displaced intra-articular calcaneal fractures, does operative treatment lead to better outcomes than non-operative treatment over a two year period after injury?

## SUMMARY ANSWER

Outcomes were not improved by surgery and operative care was associated with a higher rate of complications.

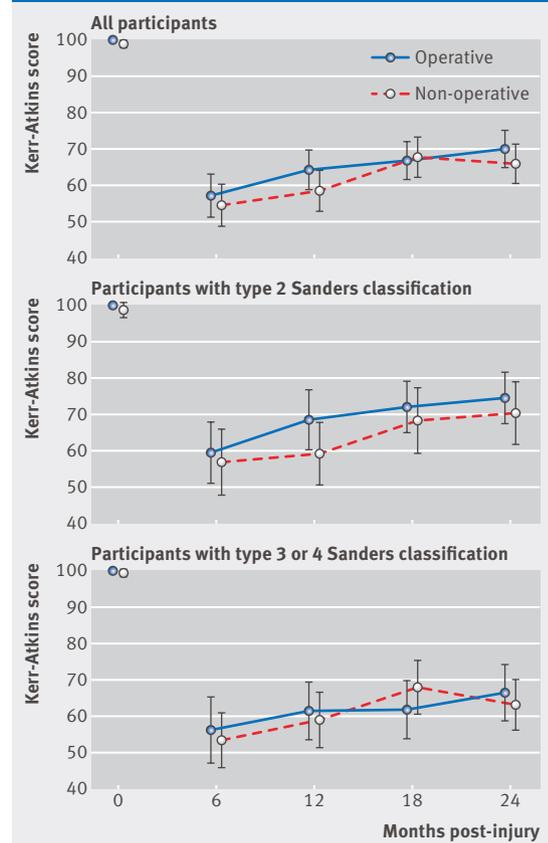
## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Surgical treatment for calcaneal fractures has been used for at least 50 years, but there has been controversy over whether the benefits outweigh the risks. This study shows that in most patients with displaced fractures, surgery by open reduction and internal fixation provides no benefit over non-operative care.

## Design

A pragmatic, multicentre, parallel group, assessor blinded, randomised controlled trial. Participants were allocated to open reduction and internal fixation with a plate and screws or to non-operative care.

## Kerr-Atkins scores (95% confidence intervals) at baseline (pre-injury) and 6, 12, 18, and 24 months post-injury



## Participants and setting

We recruited 151 participants in 22 UK hospitals. All had closed, displaced, intra-articular fractures of the calcaneus. We excluded patients who had open or grossly displaced fractures, and patients who were not fit for surgery, had other serious injuries to the same leg, or were unable to adhere to the trial procedures.

## Primary outcome

The Kerr-Atkins score for calcaneal fracture, a patient reported pain and function score, obtained at two years after injury. A score of 100 indicates normal function, 80-100 indicates slight pain or minor restrictions to walking ability, and 60-80 indicates moderate pain, restricted walking.

## Main results and the role of chance

We randomly allocated 73 participants to surgery and 78 to non-operative care; 95% follow-up data were available for analysis. Intention to treat analysis showed no difference in outcome in the first two years after injury: The Kerr-Atkins scores were similar between the operative (69.8) and non-operative (65.7) groups, with an unadjusted effect size of 4.1 points (95% confidence interval -3.4 to 11.5,  $P=0.28$ ). No treatment effect was observed after adjustment for potential confounders. There was no evidence for treatment effects for general health (SF-36 physical or mental component scores), or quality of life (EQ5-D).

## Harms

Significantly more patients experienced complications and reoperations in the operative group than in the non-operative group (23% v 4%,  $P<0.01$ ). The most common complication was surgical site infection (19%); a third of these required remedial surgery. Three more patients had reoperations to remove painful, prominent screws and plates.

## Bias, confounding, and other reasons for caution

We reported the outcome for only the first two years after injury. The rate of late reconstruction surgery (such as subtalar fusion) may be different between groups after this time, and the success of such surgery may be affected by initial treatment allocation.

## Generalisability to other populations

This study was performed in 22 NHS hospitals in the United Kingdom by surgeons who provide regional specialist services for these patients. This and the pragmatic approach to the details of surgery give us confidence that the results are generalisable, both nationally and internationally.

## Study funding/potential competing interests

This study was funded by Arthritis Research UK (grant No 15964). We have no competing interests.

# Population red blood cell folate concentrations for prevention of neural tube defects: bayesian model

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## STUDY QUESTION

Is population red blood cell (RBC) folate concentration a generalizable biomarker for risk of neural tube defects?

## SUMMARY ANSWER

RBC folate concentrations are a generalizable biomarker for risk of neural tube defects and could be used in the establishment and monitoring of prevention programs.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Increased intake of folate/folic acid increases RBC folate concentrations, and folic acid intake reduces the risk of a neural tube defect affected pregnancy. RBC folate concentration distributions can be used to consistently predict neural tube defect risk across populations; concentrations above about 1000 nmol/L are associated with what could be considered optimal prevention of folate sensitive neural tube defects.

## Participants and setting

We used data from two population based studies: the Community Intervention Project (CIP), a prospective cohort study in China (1993-95) to prevent neural tube defects in pregnant women with 400 µg/day folic acid supplementation (n=247 831), and the Folic Acid Dosing Trial (FADT), a randomized trial (2003-05) to evaluate the effect of folic acid supplementation on blood folate concentration among Chinese women of reproductive age (n=1194).

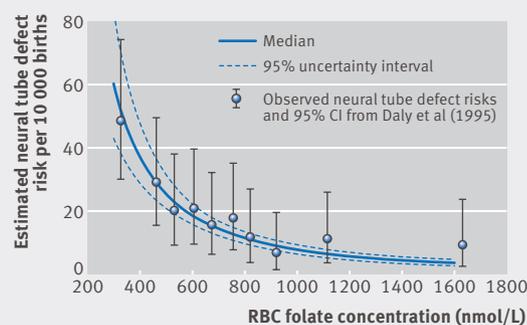
## Design, size, and duration

Women in the CIP were encouraged to consume a 400 µg/day folic acid supplement from the time of enrollment to the end of their first trimester. Women in FADT consumed 400 µg/day of folic acid for six months. We used bayesian statistical methods to estimate the association between estimated RBC folate concentration at the time of neural tube closure (day 28 of gestation) and risk of neural tube defects among the CIP participants by using imputed RBC folate concentrations from the FADT.

## Main results and the role of chance

In the CIP, risk of neural tube defects was high at the lower estimated RBC folate concentrations (for example, 25.4 (95% uncertainty interval 20.8 to 31.2) per 10 000 births at 500 nmol/L) and decreased as estimated RBC folate concentration increased. Risk of neural tube defects was substantially attenuated at estimated RBC folate concentrations above about 1000 nmol/L (for example, 6 per 10 000 births at 1180 (1050 to 1340) nmol/L). The modeled dose-response relation in this Chinese population was consistent with that in an Irish population. Estimates of

Estimated risk of neural tube defect per 10 000 births by RBC folate concentration at time of neural tube closure among participants in CIP and observed risk values at measured RBC folate concentrations reported by Daly et al (1995)



CIP=Community Intervention Project; RBC=red blood cell

predicted risk of neural tube defects developed by applying the model and US population level RBC folate concentrations were consistent with the prevalence of neural tube defects in the US population before and after fortification of food with folic acid.

## Bias, confounding, and other reasons for caution

A limitation of our analysis is the lack of measured RBC folate concentrations and *MTHFR* genotyping (important for determining response to folic acid supplementation) among CIP study participants. However, we were able to use an estimate of the association between time and duration of folic acid intake and subsequent RBC folate concentrations observed in an independent Chinese cohort, and the bayesian modeling approach gave us a mechanism to incorporate uncertainty associated with these assumptions into the final estimates.

## Generalizability to other populations

The modeled association between RBC folate concentrations in early pregnancy and risk of neural tube defects seems to be generalizable between the Irish and Chinese populations. Additionally, using published population based RBC folate concentrations from the overall US population, we were able to predict risk of neural tube defects and show the effect of folic acid fortification on prevalence of neural tube defects as a result of changes in distribution of RBC folate concentrations. Additional research is needed to determine whether these apply to other populations.

## Study funding/potential competing interests

Funding for salaries of employees was provided by the Centers for Disease Control and Prevention. No specific funding was provided for this project.