

Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP)

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BMJ 2007;334:885-8

doi: 10.1136/bmj.39147.604896.55

ABSTRACT

Objective To examine the effects of reduction in dietary sodium intake on cardiovascular events using data from two completed randomised trials, TOHP I and TOHP II.

Design Long term follow-up assessed 10-15 years after the original trial.

Setting 10 clinic sites in 1987-90 (TOHP I) and nine sites in 1990-5 (TOHP II). Central follow-up conducted by post and phone.

Participants Adults aged 30-54 years with prehypertension.

Intervention Dietary sodium reduction, including comprehensive education and counselling on reducing intake, for 18 months (TOHP I) or 36-48 months (TOHP II).

Main outcome measure Cardiovascular disease (myocardial infarction, stroke, coronary revascularisation, or cardiovascular death).

Results 744 participants in TOHP I and 2382 in TOHP II were randomised to a sodium reduction intervention or control. Net sodium reductions in the intervention groups were 44 mmol/24 h and 33 mmol/24 h, respectively. Vital status was obtained for all participants and follow-up information on morbidity was obtained from 2415 (77%), with 200 reporting a cardiovascular event. Risk of a cardiovascular event was 25% lower among those in the intervention group (relative risk 0.75, 95% confidence interval 0.57 to 0.99, $P=0.04$), adjusted for trial, clinic, age, race, and sex, and 30% lower after further adjustment for baseline sodium excretion and weight (0.70, 0.53 to 0.94), with similar results in each trial. In secondary analyses, 67 participants died (0.80, 0.51 to 1.26, $P=0.34$).

Conclusion Sodium reduction, previously shown to lower blood pressure, may also reduce long term risk of cardiovascular events.

INTRODUCTION

Evidence from observational and randomised trials shows that reduced sodium intake lowers blood pressure and can prevent hypertension. In contrast, data on the effect of dietary sodium intake on subsequent morbidity and mortality are limited and inconclusive. Several ecological studies support a direct association between higher sodium intake or urinary sodium

excretion and mortality from stroke.^{1,2} Results from prospective studies are mixed but generally support a positive association.³⁻¹⁰

We followed up participants in two randomised lifestyle intervention trials—the trials of hypertension prevention phase I (TOHP I)¹¹ and phase II (TOHP II).¹² Both found small but significant direct effects of sodium reduction on reducing blood pressure in diverse samples of normal weight and overweight adults with high normal blood pressure. We determined the long term effects, over a period of 10-15 years, of sodium reduction on cardiovascular disease and mortality.

METHODS

TOHP I

The first TOHP trial tested the feasibility and efficacy of seven non-pharmacological interventions in reducing blood pressure in people with high normal blood pressure. Interventions included weight loss, sodium reduction, stress management, and nutritional supplements. Participants aged 30-54 were eligible if their mean diastolic blood pressure was 80-89 mm Hg without antihypertensive medication. Of the 2182 total participants, 327 were randomised to a sodium reduction intervention and 417 to a usual care control group.

The active intervention, involved dietary and behavioural counselling on how to identify sodium in the diet, self monitor intake, and select or prepare lower sodium foods and condiments suited to personal preferences. Participants in the control group followed their usual diets and were given general guidelines for healthy eating. Follow-up was 18 months. In the intervention group, the net decrease in sodium excretion from baseline to 18 months was 44 mmol/24 h, and net changes in systolic/diastolic blood pressure were $-1.7/-0.8$ ($P<0.01$ and <0.05 , respectively).¹¹

TOHP II

The second TOHP trial tested the effects of weight loss and sodium reduction on incident hypertension and blood pressure over three to four years. Intervention groups were weight loss alone, sodium reduction

This article is an abridged version of a paper that was posted on bmj.com on 20 April 2007. Cite this version as: *BMJ* 2007;334:885-8. doi: 10.1136/bmj.39147.604896.55 (abridged text, in print: *BMJ* 2007;334:885-8).

alone, a combination of weight loss and sodium reduction, and a usual care group. Participants were aged 30-54 years, weighed 110-165% of desirable weight, and had average blood pressure of 83-89 mm Hg for diastolic and <140 mm Hg for systolic without anti-hypertensive medication. A total of 2382 participants were randomised. The active sodium reduction intervention was similar to that in TOHP I.

At 36 months, the pooled active sodium groups experienced a net decrease in sodium excretion of 33 mmol/24 h, with no significant blood pressure reduction.¹² The sodium reduction alone group experienced a net 40 mmol/24 h reduction in sodium excretion with corresponding blood pressure reductions of 1.2/0.7 mm Hg compared with usual care, which was significant ($P=0.02$) for systolic blood pressure only.¹² The sodium reduction only intervention resulted in lower incidence of hypertension, with a relative risk of 0.82 ($P=0.05$) compared with usual care.

Follow-up study

The observational follow-up for cardiovascular disease began in January 2000, about 10 years after the end of TOHP I and five years after the end of TOHP II, and ended in 2004-5. We collected data on all events occurring since the end of the trials using postal questionnaires followed by phone calls as needed. We sent additional questionnaires to responders at two year intervals through early 2005.

Our prespecified primary outcome was cardiovascular disease, a composite of myocardial infarction, stroke, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), or death with a cardiovascular cause. We repeated analyses excluding CABG and PTCA and, to examine

consistency of results and eliminate any potential diagnostic bias, we repeated the analysis for total mortality. On notification of a potential non-fatal outcome, a study physician, blinded to randomisation assignment, reviewed the records. We also searched the national death index to identify deaths to December 2003 among those not responding to the questionnaires.

There were 297 non-fatal outcomes reported, including multiple reports per person. We obtained records for 196 and confirmed occurrence of cardiovascular disease in 178 reports (91% of those reviewed), including multiples reports per person. We included in these analyses all reported outcomes except those that did not meet our criteria on record review. We collected information on self reported sodium intake on the final follow-up questionnaire. See bmj.com.

Statistical methods

We compared trial characteristics at baseline and examined response to the follow-up questionnaire with logistic regression. The primary analysis was a time to event analysis of first cardiovascular event after randomisation with Cox's proportional hazards regression model among responders to the follow-up. We pooled the two trial periods using stratification in the model. We plotted cumulative incidence curves, adjusted for clinic, age, and sex, for each trial separately. Because mortality follow-up was virtually complete, we included all randomised participants in analyses of mortality alone in a full intention to treat analysis. We conducted additional analyses within subsets. We analysed questions on current sodium preferences after the trial. See bmj.com.

RESULTS

A total of 744 participants were randomised to a sodium intervention or control in TOHP I and 2382 in TOHP II. Baseline characteristics were evenly distributed, except for age, which was higher in the sodium reduction intervention group in each trial. Change in weight was similar, and change in sodium excretion was greater among those randomised to sodium reduction interventions. See bmj.com

We obtained follow-up information on cardiovascular outcomes or death for 2415 participants (77%). Follow-up rates were similar in the sodium intervention and control groups, with higher response among those in TOHP II (table). We had information on mortality for all participants, including non-responders. Two hundred participants (8% of the responders) experienced study outcomes.

After adjustment for baseline characteristics, particularly the imbalance in age, there were significant differences between groups. Figure 1 shows adjusted cumulative incidence rates of cardiovascular disease by trial and intervention. After we controlled for clinic site, demographic information, and randomisation to a weight loss intervention (in TOHP II), the estimated reduction in relative risk of cardiovascular disease among those in the sodium reduction versus control

Response to follow-up and cardiovascular disease and total mortality according to allocation to sodium intervention or control group

	Intervention (%)	Control (%)	P value (pCMH*)	Odds ratio or hazard ratio (95% CI)
Follow-up response				
Overall	1169/1518 (77.0)	1246/1608 (77.5)	0.75 (0.62)	0.93† (0.78 to 1.11, $P=0.42$); 0.93‡ (0.78 to 1.11, $P=0.42$)
TOHP I	231/327 (70.6)	311/417 (74.6)	0.23	—
TOHP II	938/1191 (78.8)	935/1191 (78.5)	0.88	—
Cardiovascular disease§ (among responders in TOHP follow-up)				
Overall	88/1169 (7.5)	112/1246 (9.0)	0.19 (0.21)	0.75¶ (0.57 to 0.99, $P=0.044$); 0.70** (0.53 to 0.94, $P=0.018$)
TOHP I	17/231 (7.4)	32/311 (10.3)	0.24	0.48** (0.25 to 0.92, $P=0.027$)
TOHP II	71/938 (7.6)	80/935 (8.6)	0.43	0.79** (0.57 to 1.09, $P=0.16$)
Total mortality (among all randomised)				
Overall	35/1518 (2.3)	42/1608 (2.6)	0.58 (0.64)	0.81¶ (0.52 to 1.27, $P=0.35$); 0.80** (0.51 to 1.26, $P=0.34$)
TOHP I	10/327 (3.1)	14/417 (3.4)	0.82	0.76** (0.33 to 1.74, $P=0.52$)
TOHP II	25/1191 (2.1)	28/1191 (2.4)	0.68	0.83** (0.48 to 1.41, $P=0.49$)

*From Cochran-Mantel-Haenszel test stratifying by trial.

†Odds ratio from logistic regression adjusted for trial, clinic, age, race, sex, and weight loss intervention.

‡Odds ratio additionally adjusted for baseline weight and sodium excretion.

§Myocardial infarction, stroke, revascularisation, or death due to cardiovascular cause.

¶Hazard ratio from Cox regression analysis stratified by trial and adjusted for clinic, age, race, sex, and weight loss intervention.

**Hazard ratio additionally adjusted for baseline weight and sodium excretion.

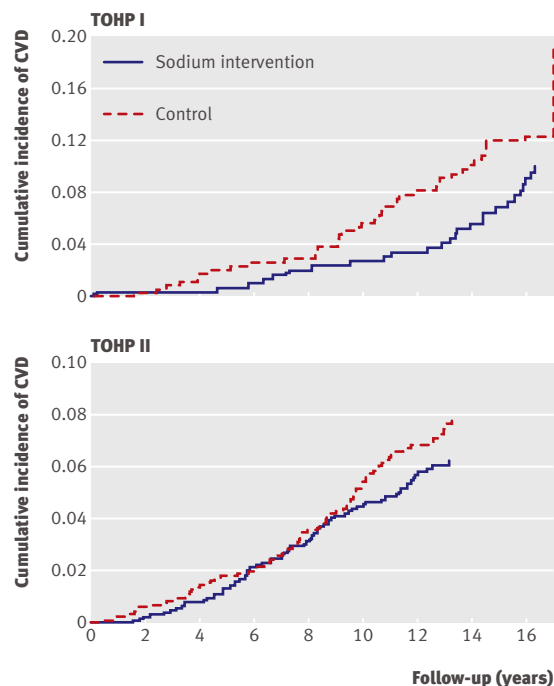


Fig 1 Cumulative incidence of cardiovascular disease (CVD) by sodium intervention group in TOHP I and II, adjusted for age, sex, and clinic

interventions was 25% (table). Additional adjustment for baseline weight and sodium excretion strengthened the association. Effect estimates were similar, although less significant, after further adjustment for change in weight during the trials (0.74, 0.55 to 1.01, $P=0.06$). Analyses for interactions indicated that effects of the sodium reduction intervention were similar across categories defined by sex ($P=0.98$), race (white *v* black $P=0.79$, white *v* other $P=0.63$), age (30-44 *v* 45-54 years, $P=0.43$), body mass index (<25 *v* ≥ 25 , $P=0.34$), and active weight loss intervention overall ($P=0.55$) or within TOHP II only ($P=0.17$). When we excluded revascularisation procedures from the composite outcome, 124 participants experienced cardiovascular disease (76 myocardial infarctions, 19 strokes, six both, and 23 cardiovascular deaths with no previous reported myocardial infarction or stroke). The fully adjusted point estimates were similar to those for the primary outcome, but were not significant (0.72, 0.50 to 1.03, $P=0.07$).

Sixty seven of the 3126 participants died; 35 in the intervention groups and 42 in the comparison groups. The magnitude of risk reduction in this full intention to treat analysis was consistent with results for the primary outcome (table and fig 2). After adjustment for baseline characteristics, including weight and sodium excretion, there was a 20% lower mortality among those in the sodium reduction intervention. Twenty five deaths were due to cardiovascular disease; 10 in the intervention groups and 15 in the comparison groups (0.62, 0.28 to 1.40, $P=0.25$).

The final follow-up questionnaire in 2004-5 about sodium use after the trial was received from 1400 (65%) of the 2164 event-free participants, with a higher response among those in the sodium reduction intervention in TOHP I (77% *v* 66% in intervention *v* control, respectively, $P=0.01$). In the two groups, 48% versus 32% ($P<0.001$) reported that they disliked salty foods, and 71% versus 64% ($P=0.003$) reported that they liked low sodium or unsalted foods. Additionally, 47% versus 29% reported that they usually or always used low sodium products ($P<0.001$); 66% versus 44% read food labels for sodium ($P<0.001$); and 28% versus 20% at least sometimes kept track of their daily intake of sodium ($P<0.001$) in the two groups, respectively.

DISCUSSION

In this long term follow-up of two completed lifestyle intervention trials, people with prehypertension assigned to a sodium reduction intervention experienced a 25-30% lower risk of cardiovascular outcomes in the 10 to 15 years after the trial. This magnitude of risk reduction was evident in each trial, in most subgroup analyses, and in various sensitivity analyses.

Strengths and weaknesses

Our follow-up study was of sufficient size and duration to assess the effects of sodium reduction on cardiovascular outcomes based on randomised trial data. Problems with measuring sodium intake may explain the inconsistent and sometimes paradoxical findings from other studies.^{4,59} Observational studies

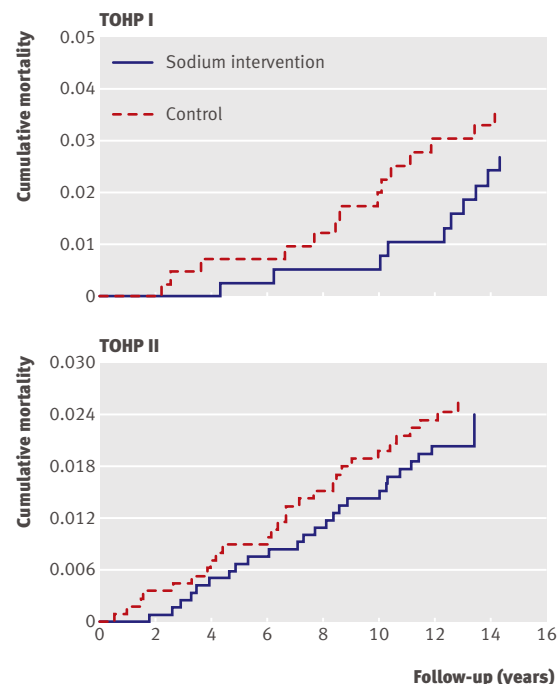


Fig 2 Total mortality by sodium intervention group in TOHP I and II, adjusted for age, sex, and clinic

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised trials in people with and without hypertension show reduction in blood pressure with lower sodium intake

Few observational studies and virtually no trial data exist on the effect of sodium intake on subsequent cardiovascular disease

WHAT THIS STUDY ADDS

Reduction in dietary sodium intake also seems to prevent cardiovascular disease

measuring sodium excretion have found a more consistent positive association.^{7,8}

Our study has several additional strengths. Firstly, participants were demographically heterogeneous, and all had prehypertension.^{13,14} Secondly, measurements of dietary sodium intake during the trial phase were based on repeat 24 hour urinary excretions. One limitation of the study is the less than complete rate of follow-up. The response rate was similar by intervention group and thus unlikely to bias the results. In addition, analysis of total mortality showed a lesser but consistent reduction in risk.

A further limitation is the lack of direct measurement of blood pressure, weight, and sodium intake during follow-up, though questionnaire data support the presence of long term effects of the intervention. If we assume the attenuation of effect that is often seen in studies of dietary change, these results might underestimate the potential public health benefits.

Other research

Long term clinical trials evaluating the efficacy of sodium reduction on clinical events have not been conducted. There is, however, some evidence that sodium reduction has long term beneficial effects on blood pressure, even in the absence of continued intervention.^{15,16} An expanding body of evidence suggests that a high sodium intake has detrimental cardiovascular effects independent of blood pressure. High sodium intake increases extracellular sodium concentrations and may adversely affect vascular reactivity and growth and stimulate myocardial fibrosis.¹⁷⁻¹⁹ Additionally, several cross sectional studies²⁰⁻²³ and one small clinical study²⁴ have documented a direct relation between sodium intake and left ventricular mass. Results of our follow-up study reinforce recommendations to lower dietary sodium intake as a means of preventing cardiovascular disease in the general population.²⁵

We thank David Gordon, Jean MacFadyen, and their staff at the TOHP coordinating centre for their efforts in conducting the follow-up study.

Contributors: See bmj.com.

Funding: TOHP I and II were supported by cooperative agreements HL37849, HL37852, HL37853, HL37854, HL37872, HL37884, HL37899, HL37904, HL37906, HL37907, and HL37924, and the TOHP follow-up study was supported by grant HL057915, all from the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD.

Competing interests: None declared.

Ethical approval: Institutional review boards of each participating centre approved the study.

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Accepted: 7 February 2007