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RESEARCH

Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis

David Moore, Paul Aveyard, Martin Connock, Dechao Wang, Anne Fry-Smith, Pelham Barton

School of Health and Population Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT

Correspondence to: D Moore
d.j.moore@bham.ac.uk

Cite this as: *BMJ* 2009;338:b1024
doi:10.1136/bmj.b1024

ABSTRACT

Objective To determine the effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking.

Design Systematic review of randomised controlled trials.

Data sources Cochrane Library, Medline, Embase, CINAHL, PsychINFO, Science Citation Index, registries of ongoing trials, reference lists, the drug company that sponsored most of the trials, and clinical experts.

Review methods Eligible studies were published or unpublished randomised controlled trials that enrolled smokers who declared no intention to quit smoking in the short term, and compared nicotine replacement therapy (with or without motivational support) with placebo, no treatment, other pharmacological therapy, or motivational support, and reported quit rates. Two reviewers independently applied eligibility criteria. One reviewer assessed study quality and extracted data and these processes were checked by a second reviewer. The primary outcome, six months sustained abstinence from smoking beginning during treatment, was assessed by individual patient data analysis. Other outcomes were cessation and reduction at end of follow-up, and adverse events.

Data synthesis Seven placebo controlled randomised controlled trials were included (four used nicotine replacement therapy gum, two nicotine replacement therapy inhaler, and one free choice of therapy). They were reduction studies that reported smoking cessation as a secondary outcome. The trials enrolled a total of 2767 smokers, gave nicotine replacement therapy for 6-18 months, and lasted 12-26 months. 6.75% of smokers receiving nicotine replacement therapy attained sustained abstinence for six months, twice the rate of those receiving placebo (relative risk (fixed effects) 2.06, 95% confidence interval 1.34 to 3.15; (random effects) 1.99, 1.01 to 3.91; five trials). The number needed to treat was 29. All other cessation and reduction outcomes were significantly more likely in smokers given nicotine replacement therapy than those given placebo. There were no statistically significant differences in adverse events (death, odds ratio 1.00, 95% confidence interval 0.25 to 4.02; serious adverse events, 1.16, 0.79 to 1.50; and discontinuation because of adverse events, 1.25, 0.64 to 2.51) except nausea, which was more common with nicotine replacement therapy (8.7% *v* 5.3%; odds ratio 1.69, 95% confidence interval 1.21 to 2.36).

Conclusions Available trials indicate that nicotine replacement therapy is an effective intervention in achieving sustained smoking abstinence for smokers who have no intention or are unable to attempt an abrupt quit. Most of the evidence, however, comes from trials with regular behavioural support and monitoring and it is unclear whether using nicotine replacement therapy without regular contact would be as effective.

INTRODUCTION

In the UK the licence for some nicotine replacement therapies has been extended to help those who are unwilling or unable to quit abruptly to cut down smoking to facilitate quitting, so called nicotine assisted reduction to stop. We carried out a systematic review of randomised controlled trials to determine the effectiveness of nicotine assisted reduction to stop and whether there are associated harms. We focused on sustained cessation from smoking, widely considered the superior outcome measure for effectiveness.[1 2]

METHODS

Studies were eligible if they were randomised controlled trials of smokers who were unable or unwilling to stop abruptly; used gum or inhaler nicotine replacement therapy alone or as part of combination therapy; used placebo, no treatment, non-nicotine replacement therapy drugs, or psychological interventions as comparators (if the intervention included adjunct therapy the comparator also had to); and used abstinence from smoking as the outcome.

The quality of included studies was assessed[3] and data extracted by one reviewer and checked for accuracy by a second. Disagreements were resolved by discussion, and with a third reviewer if necessary.

Studies were grouped according to outcome and comparison groups. The primary outcome for the review was six months' sustained abstinence starting during treatment. Secondary outcomes were point prevalence abstinence at end of follow-up; sustained abstinence from early in treatment to end of follow-up; sustained reduction from week 6 to end of follow-up;

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2009;338:b1024

point prevalence reduction at end of follow-up; and adverse events throughout follow-up (see bmj.com).

Meta-analysis was carried out using Stata (version 10). For smoking outcomes we summarised data with relative risks. For adverse events we summarised data using Peto odds ratio.[4]

In studies of nicotine assisted reduction to stop, participants can use nicotine replacement therapy for a prolonged period (≤18 months) and make several attempts to quit. Unlike normal studies on cessation, treatment continues regardless of failure to quit. We counted the number that maintained abstinence for at least six months, starting during treatment. By applying the probability that a smoker who abstained for x months would go on to abstain for six months to those smokers who were abstinent for x months at the end of study, we developed a method to determine what proportion of quitters late in treatment would sustain abstinence of six months if follow-up had been long enough. This calculation was based on probabilities derived from analyses using individual person data of all quit attempts in each of the studies for which individual person data were available.

RESULTS

Seven randomised controlled trials[w1-w7] (12 articles) met the inclusion criteria (see bmj.com). Six were sponsored by industry,[w1-w6] two of which were unpublished.[w3 w6] Unpublished trial reports were obtained for all six trials, of which five reports[w1 w3-w6] contained individual patient data allowing calculation of at least six months' sustained abstinence. The seventh trial[w7] was independent, and unpublished data were obtained from the authors.

All the studies recruited smokers who were unwilling or unable to quit abruptly, and none emphasised reduction then stop on recruitment. Consequently the primary outcome was reduction and not cessation.

All the studies were randomised parallel group trials with nicotine replacement therapy and placebo arms. One trial[w3] randomised people to four arms; two of the arms were not included in this review because participants were randomised to reduction over only one month. Another trial[w7] had three arms (no pharmacotherapy, placebo, nicotine replacement therapy). For consistency we analysed differences between nicotine replacement therapy and placebo.

Intervention

Four trials used gum,[w1 w3 w5 w6] two used inhalers,[w2 w4] and one used choice of gum, inhaler, or patch.[w7] Prior to randomisation in two trials,[w5 w6] smokers were stratified by nicotine dependence (Fagerström score); the less dependent were given 2 mg gum and the more dependent 4 mg gum. The other gum trials used 4 mg gum. The trial with three arms[w7] used a 15 mg/16 hour patch, 4 mg gum, or inhaler.

Nicotine replacement therapy was available for six months,[w7] nine months,[w3] 12 months,[w1 w4-w6] and 18 months.[w2]

Behavioural support

The trial with three arms[w7] had no clinic visits and no behavioural support, but participants received a booklet with reasons for reducing cigarette consumption and methods to achieve reduction.

In the other reports behavioural support was described as moderate,[w5] or participants were provided with ways to reduce smoking,[w4] or the intervention was not described.[w1 w2] The unpublished reports,[w1-w6] however, indicated that behavioural support was similar in all these studies. Participants were given written advice on using gum or an inhaler. Staff followed a behavioural support protocol giving information on how much nicotine replacement therapy to use and how to use it to substitute for cigarettes. At each visit the therapist also elicited problems from the participants, helped them find solutions, and related their progress back to their goals. Smokers were encouraged to quit during the study. At six and nine months, participants were instructed to stop smoking, regardless of reduction achieved. At all visits smoking status was monitored, exhaled carbon monoxide recorded, and feedback given on progress towards goals. Behavioural support and clinic visits were repeated on five or more occasions up to at least a year, and in some trials to 18 or 24 months.

Outcomes

The primary outcome in the trials was sustained reduction. In the industry sponsored trials[w1-w6] this was defined as reported cigarette consumption of less than 50% of baseline from week 6 to week 16, although in some trials this was also to later visits. Sustained reduction was measured by self reported cigarettes smoked a day and validated by the carbon monoxide level that was at least 1 ppm less than at baseline each time it was checked. Secondary outcomes were prolonged abstinence from the week 6 visit to end of follow-up and 7 day point prevalence abstinence, and point prevalence of reduction at various follow-up times.

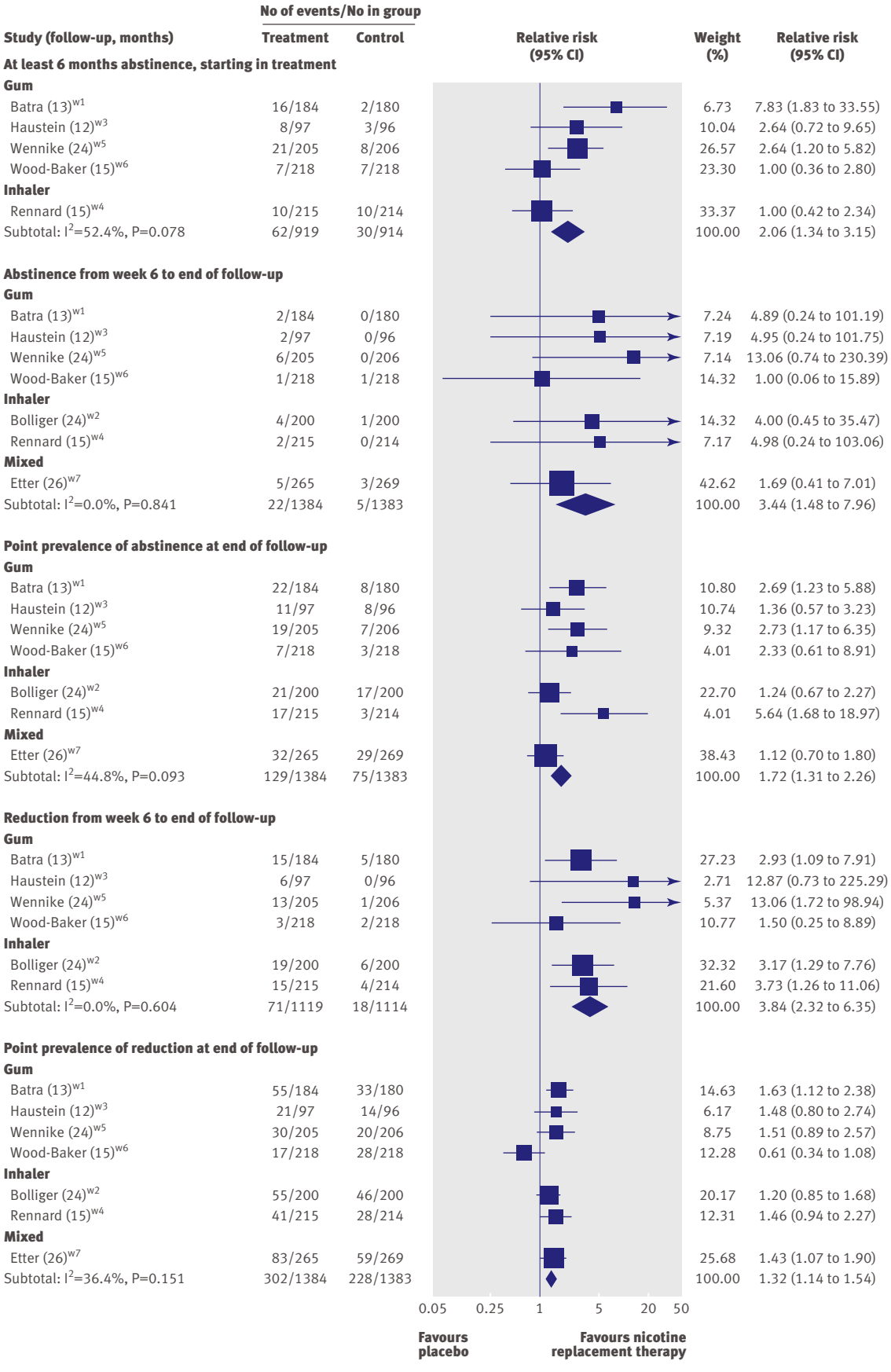
In the trial with three arms,[w7] point prevalence abstinence and point prevalence reduction for the past seven days and four weeks were the main outcomes at six and 26 months.

Quality of included studies

All the trials were of high quality (see bmj.com). Although trials blinded participants to allocation, it is difficult to blind people to psychoactive drugs. At six months, participants in the three arm trial[w7] guessed more accurately than would be expected by chance the group to which they were allocated.

Sustained six months' abstinence

Individual person data were available from one trial using inhaler[w4] and four using gum,[w1 w3 w5 w6] allowing the calculation and meta-analysis of sustained abstinence of at least six months.[w1 w3-w6] The proportion of smokers achieving such abstinence with nicotine replacement therapy was double that with placebo (relative risk 2.06, 95% confidence interval 1.34 to 3.15; figure), but the rates were low (6.75% *v* 3.28%). Moderate



Meta-analysis of smoking outcomes

heterogeneity was suggested (I^2=53%). There was no evidence to indicate that this was due to the type of active treatment used, and the inclusion criteria and protocols of the trials were similar. By a random effects model the relative risk was 1.99 (1.01 to 3.91).

Other smoking outcomes

Sustained abstinence was measured from six weeks (two weeks in one study[w1]) to the end of follow-up. Point prevalence abstinence was also measured at last follow-up, which was one month,[w1] three months,[w3 w4 w7] six months,[w2] 12 months,[w5] and 20 months[w7] after the end of treatment. Sustained reduction and point prevalence reduction was measured at these times during treatment and at follow-up.

Sustained abstinence rates starting from six weeks were low; 1.6% in the nicotine replacement therapy groups and 0.4% in the placebo groups. Point prevalence rates of abstinence at the end of follow-up were 9.3% and 5.4%, respectively.

Successful reduction was more common. In those receiving active treatment, 21.8% had reduced consumption by more than 50% at final follow-up compared with 16.5% receiving placebo. Sustained reduction from early in treatment to final follow-up occurred in 6.3% of those receiving active treatment and 1.6% receiving placebo.

Adverse events

Overall, 1384 smokers received nicotine replacement therapy for six to 18 months and 1383 received placebo. Four deaths occurred in those receiving nicotine replacement therapy and four in those receiving placebo: odds ratio 1.00 (95% confidence interval 0.25 to 4.02; see bmj.com). Serious adverse events occurred in fewer than 8% of participants in both arms: 1.09 (0.79 to 1.50; see bmj.com). In no cases were these judged likely to have been due to treatment. Discontinuation of treatment because of adverse events was rare, with 1.7% in the nicotine replacement therapy group and 1.3% in the placebo group: odds ratio 1.27 (0.64 to 2.51; see bmj.com). Nausea was slightly and significantly more common in the nicotine replacement therapy group: 8.6% *v* 5.3%, 1.69 (1.21 to 2.36; see bmj.com).

DISCUSSION

This review found evidence that nicotine assisted reduction to stop can be effective in achieving sustained abstinence from smoking of six months. Nicotine replacement therapy was well tolerated, with almost no difference in discontinuation because of side effects compared with those receiving placebo. Nausea was significantly more common with nicotine replacement therapy than with placebo, but in only one in 30 users. The results imply that compared with placebo twice the number of smokers sustained six months' abstinence with nicotine replacement therapy. This equates to an additional 3% of all smokers quitting who would otherwise not have done so.

Three reviews, comprising a Health Technology Assessment,[5] a Cochrane review,[6] and a qualitative review[7] examined smoking cessation in smokers recruited to randomised controlled trials of smoking reduction interventions. The present review is an extension and update of the Health Technology Assessment report[5] and differs from the other reviews.[6 7] We report sustained abstinence derived from analysis of individual patient data, whereas the other reviews were restricted to point prevalence of smoking cessation at the end of follow-up, a measure that cannot inform about the duration of cessation, which is the outcome most relevant to health. We included an additional trial[w6] not included in the qualitative review. Our review focused on nicotine replacement therapy whereas both the other reviews encompassed multiple interventions and did not meta-analyse data on safety outcomes. The qualitative review concluded that smoking reduction increased the probability of future cessation, whereas the Cochrane review concluded that people unwilling to quit were helped by nicotine replacement therapy to cut down on cigarette consumption.

The licence for nicotine replacement therapy is for reduction then stopping, whereas the trials in our review recruited smokers motivated only to reduce consumption. We excluded one study in which participants wanted to quit by reduction,[8] which was included in both the Cochrane and the qualitative reviews. The odds ratio for point prevalence of abstinence at the end of follow-up from this study was similar to our pooled effect estimate (2.34, 95% confidence interval 1.16 to 4.74); this suggests that whether smokers are motivated to reduce then quit or simply motivated to reduce may make little difference to the efficacy of nicotine replacement therapy in supporting cessation. Intentions to stop smoking are volatile[9] so a stated intention to stop at a specified future time may have little long term meaning for many smokers. Instruction to stop was delivered in the trials, although the importance of this instruction has not been tested. We believe that encouraging smokers prepared to reduce consumption to use nicotine replacement therapy regardless of their subsequent intention to quit is appropriate because this is the population included in the trials.

Currently, nicotine assisted reduction to stop is licensed in the UK but recent guidance from the National Institute for Health and Clinical Excellence and a recent US Clinical Practice Guideline recommend its use only in the context of further research.[10 11] Survey data show that large numbers are using nicotine replacement therapy to reduce consumption,[12] but whether they are reading the packet inserts and following a nicotine assisted reduction to stop programme is uncertain. Furthermore, most people who are reducing with nicotine replacement therapy are using a patch,[12] which is not licensed for this use. It is therefore unclear whether the outcomes observed in the trials are being achieved through such use.[13]

In summary, these trials have shown that people who have no intention of quitting may be helped to stop over a longer period by using drugs formerly reserved for

WHAT IS ALREADY KNOWN ON THIS TOPIC

Most smokers are not ready to quit and might not respond to interventions of abrupt cessation

Nicotine replacement therapy (NRT) is licensed for smoking reduction in smokers not ready to stop but there is no evidence that it leads to sustained abstinence

No review has assessed the safety of concurrent smoking and use of long term NRT

WHAT THIS STUDY ADDS

This systematic review of randomised clinical trials in smokers not ready to stop found that with NRT support twice as many quitters achieve six months of sustained abstinence

This equates to an additional 3% of sustained quitters compared with placebo

Using NRT while smoking did not lead to serious health problems

abrupt cessation. The contribution of behavioural support is unknown, and the optimum advice for people in reduction programmes is also unknown as these have not been manipulated in comparative trials. Importantly, these trials show that treating a population of smokers not ready to stop means more of them stop.

Contributors: AFS designed and implemented the searches. DW, MC, and PA extracted the data. DW and MC selected studies and did the meta-analyses. DM supervised the project and is the guarantor. All authors wrote the manuscript.
Funding: This work was funded by the UK Health Technology Assessment Programme (National Institute for Health Research).
Competing interests: See bmj.com.
Ethical approval: Not required.

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Accepted: 14 January 2009

Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials

Siddhartha Gogia, Harshpal Singh Sachdev

Department of Paediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, B-16 Qutab Institutional Area, New Delhi 110016, India

Correspondence to: H S Sachdev, E-6/12 Vasant Vihar, New Delhi 110057, India
hpssachdev@gmail.com

Cite this as: *BMJ* 2009;338:b919
doi:10.1136/bmj.b919

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2009;338:b919

ABSTRACT

Objective To evaluate the effect of neonatal vitamin A supplementation on infant mortality, morbidity and early adverse effects.

Design Systematic review, meta-analysis, and meta-regression of randomised controlled trials.

Data sources Electronic databases and hand search of reviews; abstracts and proceedings of conferences.

Review methods Randomised or quasi-randomised or cluster randomised, placebo controlled trials evaluating the effect of prophylactic, neonatal (<1 month) supplementation with synthetic vitamin A on mortality or morbidity within infancy (<1 year), and early adverse effects (≤7 days).

Results The six included trials were from developing countries. There was no convincing evidence of a reduced risk of mortality during infancy (relative risk 0.92, 95% confidence interval 0.75 to 1.12, P=0.393 random effect; I^2=54.1%) or of an increase in early adverse effects including bulging fontanelle (1.16, 0.81 to 1.65, P=0.418; I^2=65.3%). No variable emerged as a significant predictor of mortality, but data for important risk groups (high maternal night blindness prevalence and low birth weights) were restricted. Limited data (from one to four trials) did not indicate a reduced risk of mortality during the neonatal period (0.90, 0.75 to 1.08, P=0.270; I^2=0%), cause specific mortality, common morbidities (diarrhoea and others), and admission to hospital. There was, however, evidence of an increased risk of acute respiratory infection and a reduced risk of clinic visits.

Conclusions There is no convincing evidence of a reduced risk of mortality and possibly morbidity or of increased early adverse effects after neonatal supplementation with vitamin A. There is thus no justification for initiating such supplementation as a public health intervention in developing countries for reducing infant mortality and morbidity.

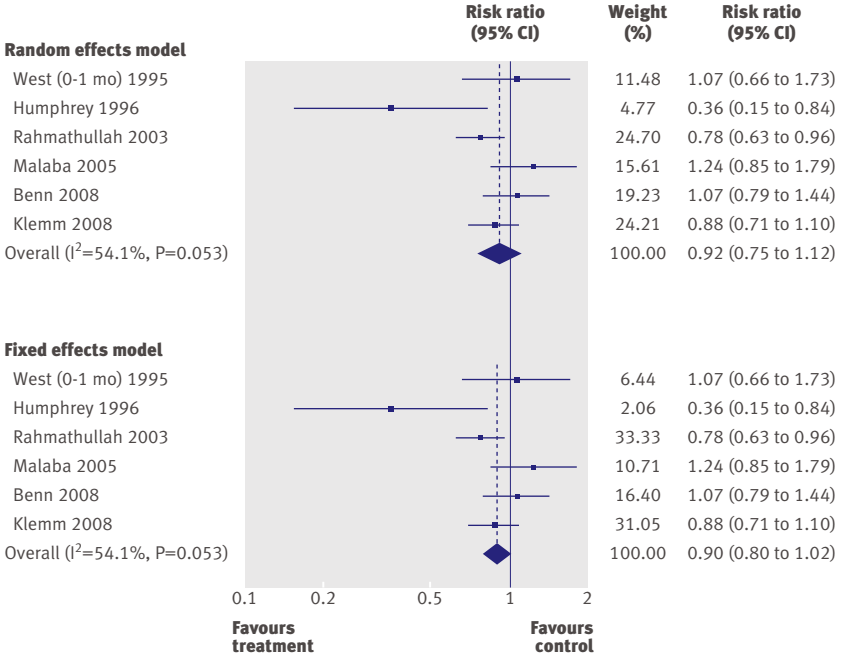
INTRODUCTION

Prophylactic vitamin A supplementation for children aged 1-4 is considered to be an effective intervention for improving child survival in developing countries.[1] Three previous systematic reviews[2-4] have shown associated reductions of 23-30% in childhood mortality. Similar survival benefits have also been reported in some trials that included infants aged 6-11 months.[5-7] There is, however, no evidence of a reduction in mortality at 1-6 months.[8-11w1] A recent review concluded that neonatal vitamin A supplementation is associated with 20% reduction in mortality in babies under 6 months and included it as a core public health intervention for the Asian region.[12] These findings have been contested because relevant but negative data were ignored.[13] We conducted a systematic review of randomised controlled trials to evaluate the effect of prophylactic neonatal supplementation with synthetic vitamin A on mortality and morbidity in infancy and early adverse effects.

METHODS

We evaluated the effect of prophylactic supplementation with synthetic vitamin A in the neonatal period on mortality and morbidity in infancy, and early adverse effects.

We planned to carry out eight prespecified subgroup analyses for the all cause mortality within 1 year: cumulative vitamin A dose received until the age of 1 month; number of vitamin A doses received; maternal postpartum vitamin A supplementation; baseline maternal vitamin A status; birth weight of the offspring; infant mortality rate in the placebo group to examine the possibility of a greater response with higher baseline mortality; follow-up age to examine the possibility of a greater response in the first half of infancy; and development status of the trial area.



Forest plots for relative risk of mortality during infancy

Criteria for inclusion

Types of trial—We included randomised or quasi-randomised or cluster randomised, placebo controlled trials, regardless of publication status and language, that evaluated the effect of prophylactic supplementation with synthetic vitamin A initiated in the neonatal period (<1 month), irrespective of maternal antenatal or postnatal vitamin A supplementation status, on mortality or morbidity in infancy (<1 year), or early adverse effects (within a week after the intervention).

Types of participant—Participants were apparently healthy infants. We excluded trials conducted on selected subgroups of infants, such as those who were very low birth weight (<1500 g), HIV positive, born to HIV positive mothers, or sick or admitted to hospital.

Types of intervention—Synthetic oral vitamin A supplementation compared with placebo administered to the infant and either placebo or no supplementation in the mother.

Types of outcome measure

Primary—All cause mortality in the child at two time points: during infancy, in the period between initiation of intervention and the last follow-up within the age of 1 year; and during the neonatal period between initiation of intervention and the last follow-up within the age of 1 month.

Secondary—In the period between initiation of the intervention and the last follow-up within the age of 1 year we measured cause specific mortality because of diarrhoea, acute respiratory infections, and causes other than these; morbidities because of diarrhoea, acute respiratory infection or respiratory difficulty, cough or running nose, ear infection, fever, and vomiting; and severity of morbidities as assessed by clinic or hospital visits and admissions to hospital. We also measured early adverse effects including bulging fontanelle, vomiting, irritability, diarrhoea, and fever within one week after the intervention.

Searches

We searched databases including Medline, CENTRAL, Embase, IBIDS, CINAHL, and HealthSTAR and the clinical trials website up to 5 July 2008 with no language restrictions. We reviewed reference lists, abstracts and proceedings of international conferences. We contacted donor agencies, "experts," and authors of vitamin A supplementation trials.

Assessment of quality of methods

We assigned scores for randomisation, allocation concealment, attrition, and blinding. Our prespecified sensitivity analyses on the basis of trial quality were allocation concealment, attrition, and blinding.

Statistical analysis

For computing the summary relative risk, we used relative risks and 95% confidence intervals or standard errors from individual studies. We applied, and where possible reconstructed, intention to treat estimates. For cluster randomised trials, we used the stated cluster adjusted relative risk. If there were no events (or all events) in both groups the trial was automatically omitted from the meta-analysis.[14]

We evaluated the presence of bias in the extracted data using funnel plots,[15] carried out formal statistical tests for funnel plot asymmetry,[16 17] and calculated Cochran Q and I^2 to test for heterogeneity. We carried out sensitivity and subgroup analyses for the primary outcome. A separate analysis was done for trials providing information for mortality for low birthweight and non-low birthweight infants.

RESULTS

Included trials

We identified 19 potentially eligible references.[w1-w19] We excluded eight references.[w2-w9] The 11 remaining references provided data on six trials that satisfied the inclusion criteria; six trials provided mortality data, three had relevant data on morbidity, and six provided data on adverse effects.

The baseline characteristics of the included trials are in tables A and B and appendix 1 on bmj.com.

Quantitative data synthesis

Mortality during infancy

The six trials were conducted in developing countries (four in Asia and two in Africa). Two cluster randomised trials were included.[w1 w14] All trials were double blind with adequate allocation concealment, and loss to follow-up was below 10% in four trials. Three trials followed up participants up to 6 months of age. Two trials gave simultaneous maternal postpartum vitamin A supplementation. In all trials the cumulative dose of vitamin A was ≤50 000 IU, given as a single dose in five trials and as two doses in one trial. Information on prevalence of maternal night blindness was available in only three trials; of these one recorded a prevalence <5%. Three trials presented results separately for low birthweight and non-low birthweight infants.

The funnel plot was symmetrical, suggesting the absence of publication bias, which we confirmed using Egger's (weighted regression) method (P=0.931for bias) and Begg's (rank correlation) method (continuity corrected P=1.0). There was no convincing evidence of a reduced risk of mortality during infancy; the pooled relative risk was 0.92 (95% confidence interval 0.75 to 1.12, P=0.393; I^2=54.1%, P=0.053) by random effects model (figure). Prespecified sensitivity, subgroup, and meta-regression analyses did not identify a consistently significant predictor of mortality response (see bmj.com). Stratified analysis of limited data (three trials), however,

Summary of pooled analyses for all outcomes (relative risks)

Outcomes	No of trials	RR (95% CI); P value		Heterogeneity I_2 (%); Q (P value)
		Random effects model	Fixed effects model	
Mortality during infancy	6	0.92 (0.75 to 1.12); 0.393	0.90 (0.80 to 1.02); 0.090	54.1; 10.90 (0.053)
Mortality during neonatal period	3	0.90 (0.75 to 1.08); 0.270	0.90 (0.75 to 1.08); 0.270	0; 0.36 (0.834)
Cause specific mortality:				
Respiratory	4	1.11 (0.82 to 1.51); 0.484	1.11 (0.82 to 1.51); 0.484	0; 0.34 (0.951)
Diarrhoeal	4	0.98 (0.42 to 2.28); 0.955	0.95 (0.61 to 1.48); 0.809	66; 8.83 (0.032)
Others	4	0.76 (0.56 to 1.02); 0.064	0.78 (0.65 to 0.94); 0.009	48.2; 5.79 (0.122)
Morbidities:				
Diarrhoea	3	1.04 (0.99 to 1.09); 0.097	1.04 (0.99 to 1.09); 0.097	0; 0.99 (0.609)
Acute respiratory infection or respiratory difficulty	2	1.11 (1.02 to 1.21); 0.015	1.11 (1.02 to 1.21); 0.015	0; 0.03 (0.867)
Cough or running nose	3	0.98 (0.85 to 1.13); 0.770	1.03 (0.98 to 1.07); 0.240	68.7; 6.4 (0.041)
Ear infection	1	0.33 (0.03 to 3.38); 0.350	0.33 (0.03 to 3.38); 0.350	NA
Fever	2	0.84 (0.48 to 1.47); 0.548	1.02 (0.99 to 1.05); 0.209	61.8; 2.62 (0.106)
Vomiting	1	1.22 (0.57 to 2.61); 0.608	1.22 (0.57 to 2.61); 0.608	NA
Severe morbidity requiring:				
Clinic visits	2	0.81 (0.72 to 0.91); 0.001	0.81 (0.72 to 0.91); 0.001	0; 0.37 (0.542)
Admission to hospital	1	0.75 (0.26 to 2.16); 0.593	0.75 (0.26 to 2.16); 0.593	NA
Early adverse effects:				
Bulging fontanelle	5	1.16 (0.81 to 1.65); 0.418	1.06 (0.91 to 1.25); 0.457	65.3; 11.52 (0.021)
Vomiting	4	0.92 (0.77 to 1.09); 0.308	0.91 (0.80 to 1.02); 0.109	23.7; 3.93 (0.269)
Vomiting*	5	0.91 (0.78 to 1.06); 0.214	0.90 (0.80 to 1.02); 0.092	13.9; 4.65 (0.326)
Irritability	3	0.98 (0.86 to 1.11); 0.713	0.98 (0.86 to 1.11); 0.700	1.0; 2.02 (0.364)
Diarrhoea	3	0.92 (0.64 to 1.33); 0.660	0.93 (0.79 to 1.09); 0.358	70.1; 6.69 (0.035)
Fever	4	0.99 (0.79 to 1.24); 0.916	0.99 (0.79 to 1.24); 0.916	0; 1.86 (0.603)

NA=not applicable.
*If all early adverse effects are presumed to be vomiting in Rahmathullah trial[w17] (see explanation in appendix 1 on bmj.com).

suggested a greater response with ≥5% prevalence of maternal night blindness.

Mortality during neonatal period

We pooled data from three trials, two from Asia[w12 w14] and one from Africa.[w11] Data from the African trial pertained to the first seven days of life only. There was no convincing evidence of a reduced risk of mortality during the neonatal period; pooled relative risk for mortality was 0.90 (0.75 to 1.08, P=0.270; I^2=0%, P=0.834) by random and fixed effects models.

Cause specific mortality

We pooled data ascertained by verbal autopsy from four trials,[w11 w12 w15 w17] two each from Africa and Asia. There was no convincing evidence of a reduced risk of mortality from respiratory, diarrhoeal, or other causes by random effects model (table).

Morbidities and their severity

We pooled data from three trials, two from Asia[w12 w18] and one from Africa.[w16] There was no evidence of a reduced risk of diarrhoea, cough or running nose, ear infection, fever, or vomiting (table). There was an increased risk of acute respiratory infection or respiratory difficulty (1.11, 1.02, 1.21; P=0.015; I^2=0, two trials). There was a reduced risk of clinic visits (0.81, 0.72, 0.91; P=0.001; I^2=0, two trials) and no evidence of a reduced risk of admission to hospital (0.75, 0.26, 2.16; P=0.593; one trial).

Early adverse effects

We pooled data from six trials (four from Asia[w10 w14 w18 w19] and two from Africa[w13 w16]); one trial did not record any episode of bulging fontanelle[w17] and one did not record any irritability[w19] in either group. In two trials physicians recorded bulging of fontanelle.[w10 w16] There was no convincing evidence of an increased risk of bulging fontanelle, vomiting, irritability, diarrhoea, or fever (table).

DISCUSSION

We found no convincing evidence of a reduced risk of all cause mortality during infancy or of an increased risk of early adverse effects after neonatal supplementation with synthetic vitamin A. Limited data did not indicate a reduced risk of mortality during the neonatal period, cause specific mortality, morbidities (diarrhoea and others), and admission to hospital. There was, however, evidence of an increased risk of acute respiratory infection and a reduced risk of clinic visits. No variable emerged as a consistent significant predictor of mortality during infancy but the data for important risk groups were quite restricted.

Strengths and limitations of analyses

Analysis of six trials indicated no formal evidence of publication bias. The main conclusion regarding all cause mortality remained stable over a large spectrum of sensitivity analyses.

Our study has some specific limitations. All the trials we included were conducted in developing countries, which limits the generalisation of findings. We had limited data on high risk groups (maternal night blindness ≥5% and low birthweight infants). Duration of follow-up was variable, which precluded constitution of a uniform measure to explore baseline mortality as a predictor. Finally, we used multiple subgroup and meta-regression analyses, which increased the possibility of false positive results.

There was no convincing evidence of a reduced risk of mortality during infancy with data from HIV positive mothers included (0.96, 0.80, 1.15; P=0.674; I^2=65%).[w9] We restricted age at intervention to the first month of life because of pragmatic considerations.

Our control group comprised neonates who were given placebo and whose mothers had received either placebo or no supplementation. Postpartum vitamin A supplementation to HIV positive mothers whose infants remained polymerase chain reaction-negative at 6 weeks[w9] was associated with increased mortality by age 2 (hazard ratio 1.82, 0.99 to 3.31; P=0.05). Other trials of antenatal and/or postnatal maternal supplementation[18w15] also documented an increased risk mortality for offspring (relative risk 1.05 and 1.26; P>0.05).

No possible at risk groups for evaluating selective supplementation—namely, ≥5% prevalence of maternal night blindness and low birth weight— emerged as significant predictors of mortality but the data were limited for a confident interpretation. Appropriately designed trials are required to evaluate survival benefit in these groups. The contradictory findings of an increased risk of acute respiratory infections and a decreased risk of clinic visits are difficult to explain. As earlier reviews in older children have also documented an increased risk of acute respiratory tract infections after vitamin A supplementation,[19 20] this observation might not represent a chance finding.

Comparison with earlier reviews

Our findings are at variance with a recent review, which showed a 20% reduction in mortality in babies younger than 6 months.[12] The authors excluded relevant but negative data from three sources.[w1 w11 w15] In a subsequent reappraisal after correspondence,[13] the authors included data from two of the earlier excluded sources.[21] This pooled estimate did not document any convincing evidence of a reduction in mortality (relative risk 0.88, 0.73 to 1.06; P=0.19) after supplementation within three days of birth, which agrees with the results of our meta-analysis.

Region specific analyses have suggested evidence of a benefit in south Asia but not in Africa.[21] On meta-regression, region was not a significant predictor of heterogeneity (P=0.133), although the effect sizes seemed disparate (1.13, 0.90 to 1.43, I^2=0%, in Africa and 0.82, 0.66 to 1.02, I^2=45%, in Asia). More trials are required to determine if there are regional differences.

We also found no evidence of a reduction in mortality after vitamin A supplementation between 1 and

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous systematic reviews have documented that vitamin A supplementation in children over 6 months of age results in 23-30% reduction in childhood mortality

There is no evidence of reduction in mortality after supplementation between 1 and 6 months

The public health role of neonatal (<1 month) supplementation in reducing mortality and morbidity in developing countries is controversial

WHAT THIS STUDY ADDS

There is no convincing evidence of a reduced risk of all cause mortality during infancy or of an increased risk of early adverse effects after neonatal vitamin A supplementation

Risk of neonatal mortality, cause specific mortality, common morbidities, and admission to hospital was not reduced with supplementation, though risk of acute respiratory infection was increased and risk of clinic visits reduced (data from one to four trials)

In developing countries there is no justification for initiating neonatal vitamin A supplementation as a public health intervention for reducing infant mortality and morbidity

6 months of age.[w1 8-11] It is difficult to explain the differences from earlier systematic reviews[2-4] documenting 23-30% reduction in childhood mortality after intervention after the age of 6 months. There was no evidence of benefit in child survival in a trial conducted recently on one million children in rural India (0.96, 0.88 to 1.05).[22] In high risk settings, a vitamin A deficient state is much more likely after the age of 6 months, when supplementation is more likely to have a beneficial effect.

We were unable to identify any significant predictor of substantial heterogeneity for mortality. Additional variables, not examined by us, might explain the observed differences.

Implications for policy

Currently, a public health programme of neonatal synthetic vitamin A supplementation to reduce infant mortality and morbidity in developing countries is not justified in these settings because there is no convincing evidence of survival benefit or a reduction in morbidity.

Implications for future research

Future research and trials on neonatal vitamin A supplementation should examine effects on mortality and morbidity in important risk groups; mortality in more settings in Asia and Africa to understand regional differences; morbidities and their severity; and relation of mortality to potential predictors of response.

Conclusions

There is no convincing evidence of a reduced risk of all cause mortality during infancy or of an increased risk of early adverse effects after synthetic neonatal vitamin A supplementation. Limited data do not indicate a reduced risk of mortality during the neonatal period, cause specific mortality, or common morbidities.

We are grateful to Clive Osmond, MRC Epidemiology Resource Centre, University of Southampton, Southampton, for statistical advice.
Contributors: See bmj.com.
Funding: This study was funded by Departments of Child and Adolescent Health and Development, and Nutrition for Health and Development, World Health Organisation, Geneva. The funding source had no involvement in the study or the decision to publish the manuscript.
Competing interests: None declared.
Ethical approval: Not required.

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Accepted: 29 December 2008

Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study

Farhad Islami,[1,2,3] Akram Pourshams,[1] Dariush Nasrollahzadeh,[1,4] Farin Kamangar,[5] Saman Fahimi,[1,6] Ramin Shakeri,[1] Behnoush Abedi-Ardekani,[1] Shahin Merat,[1] Homayoon Vahedi,[1] Shahryar Semnani,[7] Christian C Abnet,[5] Paul Brennan,[2] Henrik Møller,[3] Farrokh Saidi,[1] Sanford M Dawsey,[5] Reza Malekzadeh,[1] Paolo Boffetta[2]

EDITORIAL by Whiteman

[1]Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, 14117 Tehran, Iran
[2]International Agency for Research on Cancer, Lyon, France
[3]King's College London, Thames Cancer Registry, London
[4]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA
[6]Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge
[7]Golestan Research Center of Gastroenterology and Hepatology, Gorgan University of Medical Sciences, Gorgan, Iran
Correspondence to: R Malekzadeh malek@ams.ac.ir or P Boffetta boffetta@iarc.fr

Cite this as: *BMJ* 2009;338:b929
doi:10.1136/bmj.b929

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ABSTRACT

Objective To investigate the association between tea drinking habits in Golestan province, northern Iran, and risk of oesophageal squamous cell carcinoma.

Design Population based case-control study. In addition, patterns of tea drinking and temperature at which tea was drunk were measured among healthy participants in a cohort study.

Setting Golestan province, northern Iran, an area with a high incidence of oesophageal squamous cell carcinoma.

Participants 300 histologically proved cases of oesophageal squamous cell carcinoma and 571 matched neighbourhood controls in the case-control study and 48 582 participants in the cohort study.

Main outcome measure Odds ratio of oesophageal squamous cell carcinoma associated with drinking hot tea.

Results Nearly all (98%) of the cohort participants drank black tea regularly, with a mean volume consumed of over one litre a day. 39.0% of participants drank their tea at temperatures less than 60°C, 38.9% at 60-64°C, and 22.0% at 65°C or higher. A moderate agreement was found between reported tea drinking temperature and actual temperature measurements (weighted κ 0.49). The results of the case-control study showed that compared with drinking lukewarm or warm tea, drinking hot tea (odds ratio 2.07, 95% confidence interval 1.28 to 3.35) or very hot tea (8.16, 3.93 to 16.9) was associated with an increased risk of oesophageal cancer. Likewise, compared with drinking tea four or more minutes after being poured, drinking tea 2-3 minutes after pouring (2.49, 1.62 to 3.83) or less than two minutes after pouring (5.41, 2.63 to 11.1) was associated with a significantly increased risk. A strong agreement was found between responses to the questions on temperature at which tea was drunk and interval from tea being poured to being drunk (weighted κ 0.68).

Conclusion Drinking hot tea, a habit common in Golestan province, was strongly associated with a higher risk of oesophageal cancer.

INTRODUCTION

Golestan province in northern Iran has one of the highest incidence rates for oesophageal squamous cell carcinoma in the world.[1] Smoking and alcohol consumption are not major risk factors for oesophageal cancer in this area[2 3] and women are as likely to develop the cancer as men.[4] Studies in Golestan have suggested that low intake of fresh fruits and vegetables, low socioeconomic status, and opium consumption are associated with a higher risk of oesophageal cancer.[2 3] Studies have also pointed towards the possible role of drinking very hot tea.[5]

We investigated the association between tea drinking habits and risk of oesophageal cancer in Golestan. We also measured the usual temperature at which tea was drunk and collected data on tea drinking habits in a large scale cohort study in Golestan. We report the results of the case-control study, and tea drinking patterns among 48 582 healthy participants within the cohort study.

METHODS

Between December 2003 and March 2007 doctors in the study area referred patients with suspected cancers of the upper gastrointestinal tract to Atrak Clinic, where they underwent video oesophagogastroduodenoscopy. Patients with suspicious oesophageal lesions were invited to participate in the study. Only newly diagnosed patients with histologically confirmed oesophageal cancer were included as case participants. For each case participant we tried to select two population based controls matched on place of residence, age, and sex.

Using a questionnaire trained interviewers collected information on personal characteristics, potential confounders, and tea drinking temperature. Participants were asked whether they drank tea and whether it was drunk warm, lukewarm, hot, or very hot. They were also questioned about the interval (in minutes) between tea being poured and drunk. We asked separately about consumption of black and green tea, using a food frequency questionnaire specifically designed for this population and administered by a nutritionist.[6] We asked about the usual frequency of drinking tea and the volume of cups used.

The Golestan Cohort Study is a prospective study that recruited 50 045 adults, aged 40-75, between January 2004 and June 2008. Overall, 16 599 people were selected randomly from Gonbad City, and all residents of villages in the study area in the specified age range were invited to participate. In urban areas, 10 032 participants were enrolled (70% of women and 50% of men participated). In rural areas, 40 013 participants were enrolled from 326 villages (84% of women and 70% of men participated). The same questions for tea temperature were asked as in the case-control study. In addition we measured the temperature of tea drunk by the participants (see bmj.com).

Statistical analysis

The usual interval between tea being poured and drunk was categorised as four or more minutes, 2-3 minutes, and less than two minutes. Within the case-control study the amount of black tea consumed each day (millilitres) was categorised into fifths. As only a small number of participants drank green tea, we present only frequency of consumption. Data on tea temperature were available for over 99% of cases and of controls, whereas the amount of tea was available for 89% of cases and 67% of controls. We excluded those with missing data on a variable from the corresponding analysis. Conditional logistic regression was used to calculate odds ratios and 95% confidence intervals. We used logistic regression models to adjust for potential confounders, including ethnicity, daily vegetable intake, alcohol consumption, tobacco or opium use, duration of residence in rural areas, education level, and car ownership (indicators of socioeconomic status), and other tea drinking variables. P values for trend were obtained from adjusted conditional logistic regression models by assigning consecutive numbers to categories within each categorical variable. We tested the agreement between tea temperature categories and the interval between tea being poured and drunk by weighted κ statistics and Spearman's rank correlation coefficients.

Less than 3% of the cohort had missing values in tea drinking variables and were excluded from analyses. We calculated means and standard deviations for daily intake of black and green tea among the cohort participants and the percentage of participants who drank these two kinds of tea daily, weekly, or less. In addition, we examined the validity of the questionnaire data on tea temperature within the cohort study. For this we categorised tea temperature measurements as less than 65°C, 65-69°C, and 70°C or more, because their distribution was close to that of the categorical variable used in the questionnaire. We then compared them with the questionnaire data, using weighted κ statistics and Spearman's rank correlation coefficients. We considered two sided P values <0.05 as significant. Statistical analyses were done using Stata version 10.0.

RESULTS

Case-control study

A total of 300 cases and 571 controls were recruited. All cases had at least one matched control (see bmj.com). Only one participant did not drink tea.

Tea temperature was significantly associated with risk of oesophageal cancer (table). Compared with drinking warm or lukewarm tea, drinking hot tea (odds ratio 2.07, 95% confidence interval 1.28 to 3.35) or very hot tea (8.16, 3.93 to 16.91) was associated with an increased risk of oesophageal cancer (P for trend <0.001). The risk associated with drinking hot tea did not vary by education level. The interval between tea being poured and drunk was inversely associated with risk of oesophageal cancer (table). Compared with an interval of four or more minutes, intervals of 2-3 minutes (odds ratio 2.49, 95% confidence interval 1.62 to 3.83) and less than two minutes (5.41, 2.63 to 11.14) were associated with an increased risk of oesophageal cancer (P for trend <0.001). The weighted κ statistic and Spearman's rank correlation coefficient for agreement between these two variables were 0.68 and 0.69 (see

Distribution of usual tea drinking habits and corresponding odds ratios (95% CIs) among 300 cases with oesophageal squamous cell carcinoma and 571 matched controls, in Golestan, northern Iran, 2003-7. Values are numbers (percentages) of participants unless stated otherwise

Variables	Cases (n=300)	Controls (n=571)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	P value for trend†
Tea temperature:					
Warm or lukewarm	127 (42.6)	394 (69.4)	1.00	1.00	<0.001
Hot	108 (36.2)	155 (27.3)	2.14 (1.52 to 3.01)	2.07 (1.28 to 3.35)	
Very hot	63 (21.1)	19 (3.3)	9.33 (5.26 to 16.56)	8.16 (3.93 to 16.91)	
Interval between tea being poured and drunk (minutes):					
≥4	132 (44.3)	394 (69.5)	1.00	1.00	<0.001
2-3	112 (37.6)	138 (24.3)	2.32 (1.68 to 3.23)	2.49 (1.62 to 3.83)	
<2	54 (18.1)	35 (6.2)	4.03 (2.50 to 6.49)	5.41 (2.63 to 11.14)	
Amount of black tea consumed (ml/day):					
0-675	48 (18.0)	81 (21.0)	1.00	1.00	0.03
676-920	40 (15.0)	75 (19.5)	0.85 (0.46 to 1.58)	0.91 (0.43 to 1.91)	
921-1215	37 (13.9)	86 (22.3)	0.68 (0.38 to 1.23)	0.68 (0.34 to 1.37)	
1216-1725	65 (24.3)	70 (18.2)	1.57 (0.89 to 2.75)	1.46 (0.75 to 2.86)	
≥1726	77 (28.8)	73 (19.0)	1.86 (1.07 to 3.23)	1.83 (0.93 to 3.59)	
Frequency of green tea consumption:					
Never, <weekly	249 (93.6)	356 (92.2)	1.00	1.00	0.82
Daily, weekly	17 (6.4)	30 (7.8)	0.65 (0.32 to 1.31)	0.89 (0.38 to 2.09)	

Because of missing data and one participant who did not drink tea, number of cases and controls for some variables may be less than 300 and 571, respectively.
*Adjusted for ethnicity (non-Turkmen or Turkmen), daily vegetable intake (logarithmic scale), alcohol consumption (never or ever), tobacco or opium ever use (none, only tobacco, only opium, or both), duration of residence in rural areas (0, 1-20 years, or >20 years), education level (no school, primary school, or middle school or higher), car ownership (no or yes), and variables listed in table, excluding interval variable; interval variable was not adjusted for tea temperature.
†P values come from adjusted conditional logistic regression models in which consecutive integers were assigned to consecutive categories of each variable.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Heavy alcohol and tobacco use are major risk factors for oesophageal squamous cell carcinoma, a disease more common in men than women

In some areas with a high incidence of oesophageal cancer, alcohol and tobacco use are not prominent risk factors, and women are as likely to develop oesophageal cancer as men

Common risk factors among both sexes may have a role in the carcinogenesis of oesophageal cancer; drinking hot beverages is a suggested risk factor

WHAT THIS STUDY ADDS

The risk of oesophageal cancer was noticeably increased in adults in Golestan Province, northern Iran, who drank tea hot

Drinking hot beverages is common and may account for a substantial number of cases of oesophageal squamous cell carcinoma, especially in areas with a high incidence

bmj.com). Information on amount of tea drunk was available for only 267 cases and 385 controls. No clear pattern of association was found between the amount of black tea consumed and risk of cancer in crude or multivariate analyses, but the trend test was statistically significant (P value for trend 0.03). There was no statistically significant association between frequency of green tea consumption and risk of cancer.

Cohort study

Data on tea drinking variables were available for 48 582 cohort participants. Most (96.8%, 47 043 participants) drank black tea daily; mean 1179 ml (SD 761) a day. Only 2802 participants (5.8%) drank green tea daily; mean 48 ml (SD 228) a day (see bmj.com). Overall, 18 947 (39.0%) participants drank tea at temperatures <60°C, 18 889 (38.9%) at 60-64°C, and 10 688 (22.0%) at ≥65°C (see bmj.com).

DISCUSSION

Almost everyone in Golestan Province drinks tea. They drink large amounts of black tea daily. We found a strong increase in the risk of oesophageal squamous cell carcinoma associated with drinking hot or very hot tea but not with the amount of tea consumed, consistent with the previous literature.[7]

One study on the effect of hot beverages on intraoesophageal temperature in humans showed that after drinking beverages up to 65°C, distal oesophageal temperature increased to as high as 53°C.[8] The volume swallowed in each sip was more important than the temperature of the beverage in determining intraoesophageal temperature.[8] We did not analyse data on sipping or gulping tea because few participants gulped their tea.

The mechanism by which thermal injury can cause oesophageal cancer is not clear. Some authors have proposed that inflammatory processes associated with chronic irritation of the oesophageal mucosa by local hyperthermia might stimulate the formation of reactive nitrogen species and subsequently N-nitroso compounds.[9] Thermal injury can also impair the barrier function of the oesophageal epithelium, which may increase the risk of damage from intraluminal carcinogens[10-12] such as polycyclic aromatic hydrocarbons. The population of Golestan is highly exposed to these chemicals, probably through diet.[13 14]

After adjustment for tea temperature and other factors we did not find a clear association between the amount of tea consumed and the risk of oesophageal cancer. Although the P value for trend for this association was statistically significant, the risk decreased from the first to the third fifths and then increased, so there was no consistent pattern.

The results of the cohort study showed that most inhabitants of Golestan drink more than one litre of tea a day at temperatures higher than 60°C. Several studies have assessed temperature preferences for beverages, with the reported preference in the United Kingdom being 56-60°C among healthy populations.[15-20]

Strength and limitation of study

To our knowledge the Golestan Cohort Study is the largest epidemiological study to measure tea drinking temperature. The strengths of our case-control study include histological verification of oesophageal cancer, administration of a structured questionnaire by trained interviewers, and adjustment for potential confounders. Furthermore, with no or minimal confounding from alcohol or tobacco use, other risk factors for oesophageal cancer can be better studied in Golestan. As in all case-control studies, however, data on the amount and temperature of consumed tea can be subject to information bias. We found good agreement between questions on the temperature that tea was drunk and the interval between tea being poured and drunk (see bmj.com), but responses to both could have been biased. The validation study in the cohort was carried out among healthy people, so the observed acceptable validity may not apply to case participants. We tried to minimise the risk of information bias by not discussing the study hypotheses with interviewers. The questionnaires were fairly extensive, studying multiple hypotheses. Case participants with no formal education might be less aware of the study hypotheses, so they might be less prone to recall bias. In our sensitivity analyses we found no substantial difference in the risk associated with hot tea drinking between participants with and without formal education, or between urban and rural areas. Another problem with a case-control design is selection bias. Since ascertainment of cases and controls in our study was high, selection bias may only explain our findings if the small proportion of non-participating cases were overwhelmingly drinkers of "cold tea" or, conversely, the non-participating controls were overwhelmingly drinkers of "hot tea." The questions on amount of tea drunk came from a nutritional questionnaire administered by a nutritionist. On some days no nutritionist was available, therefore this variable has some missing data. Since we used

conditional logistic regression models, in which each case is compared with their matched controls, the missing values are not expected to differentially distort our findings even if there are some differences in the characteristics of participants with or without missing values. Overall, we believe that the strong association between drinking hot tea and risk of oesophageal cancer is unlikely to be completely due to bias, considering its agreement with the previous literature and our efforts to collect accurate and valid data.

We thank the staff of the Atrak Clinic, including Karim Aghcheli, Noushin Taghavi, Haji-Amin Marjani, Rabaeh Rajabzadeh, Monireh Badakhshan, Bita Mohammadi, Halimeh Eskandarnejhad, Safora Kor, Soleiman Kasalkheh, and Ashor Yolmeh; Noorli Radgohar, Abdolazim Khozeini, Rahmat Ghaziani, Mohammad Hasan Brazandeh, Abdolhakim Ebadati, Naser Keramat, and Ahmad Nosrati for their valuable help; the local health networks and health workers (Behvarzes) in the study area for their assistance in recruitment of controls; the Iranian Social Security Organization for their local support; and the Golestan Cohort Study Center staff for their dedicated work.

Contributors: See bmj.com.

Funding: This study was supported by the Digestive Disease Research Center of Tehran University of Medical Sciences (grant No 82-603), by an intramural programme of the National Cancer Institute, National Institutes of Health, and by the International Agency for Research on Cancer. The funding sources had no role in the design, conduct, statistical analysis and interpretation of results, or writing of the manuscript.

Competing interests: None declared.

Ethical approval: The case-control study was reviewed and approved by the institutional review boards of the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences and the US National Cancer Institute. Both cases and controls gave written informed consent for the interview. The conduct of Golestan Cohort Study was reviewed and approved by the institutional review boards of DDRC, the International Agency for Research on Cancer, and the US National Cancer Institute.

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Accepted: 18 December 2008

A memorable ward round

Some 25 years ago, I was a young consultant physician about to start an early morning ward round with my usual team of registrar, senior house officer, and preregistration house physician. All started according to plan except that the SHO was absent. I knew her to be diligent, so I assumed she had probably been distracted by some other pressing call of duty. By the time we had progressed to our third patient, however, I was starting to feel uneasy about her continued absence. Suddenly it came to me: a colleague had mentioned that she was using a novel device to infuse insulin continuously—she was diabetic. We broke off the round and conferred in the ward sister's office. We knew that our SHO lived with her husband out of town and that he was also a junior doctor, but at another large hospital about 50 miles away.

We telephoned this hospital and tracked him down. He provided us with their address and the name of her general practitioner. A quick telephone call, and the GP was round at her house in a jiffy. There was no answer to the door bell, but he noticed that a bedroom window was open. With the athleticism of a cat burglar he gained entry, an action that provoked an observant neighbour to attempt a citizen's arrest. He found our SHO on the bedroom floor in a hypoglycaemic coma, but she recovered promptly when given intravenous glucose and disconnected from the wayward insulin infusion pump. I was surprised to find her back at work on the ward that afternoon, feeling rather embarrassed about the whole episode.

I shudder to think of the consequences if the ward round had continued uninterrupted, and I am grateful that my cerebral cortex kicked in when it did and that we were all able to act quickly enough to prevent serious harm.

Douglas Seaton retired consultant physician, Ipswich
seatons@clara.co.uk

Patient consent obtained.
Cite this as: *BMJ* 2009;338:b447

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Effect of food intake during labour on obstetric outcome: randomised controlled trial

Geraldine O'Sullivan,[1] Bing Liu,[2] Darren Hart,[3] Paul Seed,[2] Andrew Shennan[2]

EDITORIAL by Downe

[1]Department of Anaesthesia, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London SE1 7EH
[2]Maternal and Fetal Research Unit, King's College London, London SE1 7EH
[3]Guy's and St Thomas' NHS Foundation Trust
Correspondence to: A Shennan
andrew.shennan@kcl.ac.uk

Cite this as: *BMJ* 2009;338:b784
doi: 10.1136/bmj.b784

STUDY QUESTION To determine whether food intake in labour affects women's ability to deliver normally, the length of labour, or other obstetric and neonatal end points.

SUMMARY ANSWER Consumption of a light diet during labour did not influence obstetric or neonatal outcomes in participants, nor did it increase the incidence of vomiting. Women who were allowed to eat in labour had similar lengths of labour and operative delivery rates to those allowed water only.

Design
Women were randomised into an "eating" or "water only" group. Entry of a woman's initials, hospital number, and date of birth onto a dedicated computer on the labour ward automatically generated the allocation group together with a study number, which was then recorded on the outcome sheet. Women in the eating group were advised to have a low fat, low residue diet at will.

Participants and setting
2426 nulliparous, non-diabetic women at term, with a singleton cephalic presenting fetus and in labour with a cervical dilatation of at least 5 cm were randomised in a birth centre in a London teaching hospital.

Primary outcome(s)
Normal vaginal delivery rate.

Main results and the role of chance
By intention to treat, we found no significant difference in the rate of normal vaginal delivery between the two groups. The rates were 533/1219 (44%) in the eating group and 534/1207 (44%) in the water only group (risk ratio 0.99, 95% confidence interval 0.90 to 1.08). We found no significant difference in the duration of labour between the two groups: the geometric mean duration was 597 minutes for the eating group and 612 minutes for the water group (ratio of geometric means 0.975, 0.927 to 1.025). We found no significant difference between the groups with respect to the rate of instrumental vaginal delivery or caesarean delivery, the incidence of maternal vomiting, or the use of epidural analgesia or of oxytocin for augmentation of labour (table).

We also found no differences between the two groups with respect to infants' Apgar scores or admission to neonatal intensive care or special care units.

Harms
No cases of aspiration occurred during the study period. One maternal death occurred in the water only group, related to a cerebral event.

SECONDARY OUTCOMES FOR WOMEN WHO ATE OR TOOK ONLY WATER DURING LABOUR

Outcome	No (%) of women		Risk ratio (95% CI)
	Eating group	Water only group	
Instrumental delivery	324 (27)	310 (26)	1.04 (0.91 to 1.19)
Caesarean section	362 (30)	363 (30)	0.99 (0.87 to 1.12)
Vomited	430 (35)	406 (34)	1.05 (0.94 to 1.17)
Oxytocin for augmentation	647 (53)	673 (56)	0.95 (0.88 to 1.02)
Intravenous fluid >500 ml	820 (67)	838 (69)	0.97 (0.92 to 1.02)

Bias, confounding, and other reasons for caution
When we compared women who ate with those who did not the results were similar (normal vaginal delivery 44% *v* 44%; risk ratio 0.99, 0.91 to 1.08).

Generalisability to other populations
We did not recruit multiparous women, given their potentially quicker labours and low operative delivery rates—that is, less exposure to the intervention and high prevalence of the primary outcome measure. As no effect was found in a primiparous population, this is likely to be so in multiparous women. We excluded women who had a known obstetric or medical complication that could have increased the likelihood of an operative delivery, were in severe pain, or intended to use parenteral opioids for analgesia during labour.

Study funding/potential competing interests
This study was supported by a grant from the Obstetric Anaesthetists' Association and the Special Trustees of the St Thomas' Hospital. AS is supported by Tommy's—The Baby Charity.

Trial registration number
Current Controlled Trials ISRCTN33298015

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This is a sumary of a paper that was published on bmj.com as: *BMJ* 2009;338:b784