Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials

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Cite this as: *BMJ* 2014;348:g3174
doi: 10.1136/bmj.g3174

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g3174

bmj.com

- Clinical review: The diagnosis and management of gastric cancer (*BMJ* 2013;347:f6367)
- Letter: Should *H pylori* always be eradicated? (*BMJ* 2012;344:e2145)
- Clinical review: Treatment of *Helicobacter pylori* infection (*BMJ* 2008;337:a1454)
- Editorial: Who benefits from *Helicobacter pylori* eradication? (*BMJ* 2006;332:187)

STUDY QUESTION

Does searching for *Helicobacter pylori* and treating with eradication therapy among healthy asymptomatic infected individuals reduce the subsequent incidence of gastric cancer?

SUMMARY ANSWER

Yes, only 51 (1.6%) gastric cancers occurred among 3294 individuals who received eradication therapy compared with 76 (2.4%) in 3203 control subjects (relative risk 0.66, 95% confidence interval 0.46 to 0.95).

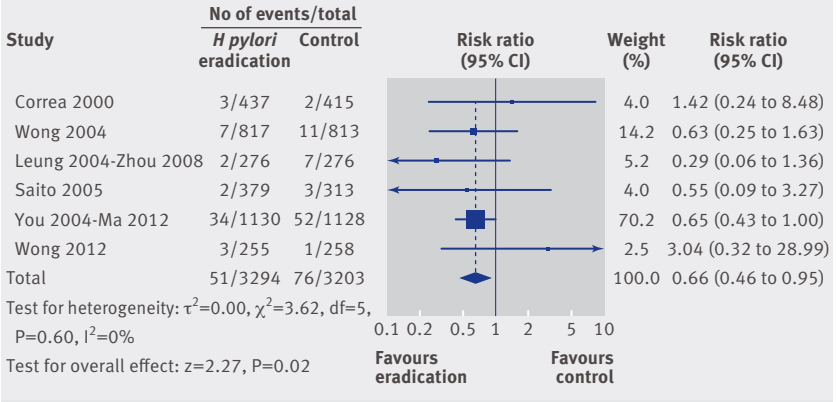
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Searching for and eradicating *H pylori* could, theoretically, reduce the incidence of gastric cancer, but evidence is conflicting. In this meta-analysis of randomised controlled trials gastric cancer incidence was significantly lower in healthy asymptomatic infected individuals who received eradication therapy compared with those who received placebo or no treatment, with a number needed to treat of 124 overall. If the benefit of eradication therapy was assumed to persist lifelong the number needed to treat was as low as 15 for Chinese men, and as high as 245 for US women.

Selection criteria for studies

We searched Medline, Embase, and the Cochrane central register of controlled trials through to December 2013, conference proceedings between 2001 and 2013, and bibliographies of relevant studies. Eligible studies were randomised controlled trials examining the effect of at least seven days of eradication therapy on subsequent occurrence of gastric cancer in adults infected with *Helicobacter pylori* who were otherwise healthy and asymptomatic. The control arm had to receive placebo or no treatment. Subjects had to be followed for at least two years, and studies had to report at least two cases of gastric cancer to be included.

Effect of *H pylori* eradication therapy on subsequent occurrence of gastric cancer



Primary outcome(s)

The primary outcome, defined a priori, was the effect of eradication therapy on the subsequent occurrence of gastric cancer, expressed as a relative risk of gastric cancer with 95% confidence intervals.

Main results and role of chance

The search strategy identified 1560 citations, of which six individual randomised controlled trials were eligible. Fifty one (1.6%) gastric cancers occurred among the 3294 individuals who received eradication therapy, compared with 76 (2.4%) in the 3203 control subjects (relative risk 0.66, 95% confidence interval 0.46 to 0.95), with no heterogeneity between studies (I^2=0%, P=0.60) (figure). If the benefit of eradication therapy was assumed to persist lifelong the number needed to treat was as low as 15 for Chinese men (who have a high lifetime risk of gastric cancer) and as high as 245 for US women (who have a low lifetime risk).

Overall, there were 24 deaths (1.1%) from gastric cancer among 2242 individuals randomised to eradication therapy, compared with 36 (1.6%) deaths in 2233 participants allocated to placebo (relative risk of death from gastric cancer 0.67, 0.40 to 1.11), with no heterogeneity (I^2=0%, P=0.90). In total, 192 (7.3%) of 2639 subjects who received eradication therapy were dead from any cause at the last point of follow-up, compared with 175 (6.7%) of 2614 individuals who received placebo or no treatment (relative risk of death from any cause 1.09, 0.86 to 1.38), with no heterogeneity (I^2=6%, P=0.36).

Bias, confounding, and other reasons for caution

Only three of the six randomised controlled trials we identified were at low risk of bias. All but one study was conducted in East Asia, so it is not possible to assess the effect of searching for and eradicating *H pylori* in Western populations. Individual adverse events data were not reported by many of the trials we identified, so we were not able to assess the balance of benefits and harms if searching for and eradicating *H pylori* infection were to be adopted in the general population.

Study funding/potential competing interests

This study was unfunded. The authors declare no competing interests.

Effects of nutritional supplementation for HIV patients starting antiretroviral treatment: randomised controlled trial in Ethiopia

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Cite this as: *BMJ* 2014;348:g3187
doi: 10.1136/bmj.g3187

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g3187

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STUDY QUESTION

Can three months' intervention with a lipid based nutrient supplement containing either whey or soy protein improve regain of lean body mass, grip strength, physical activity, and immune recovery in patients with HIV starting antiretroviral treatment in a food insecure setting?

SUMMARY ANSWER

Supplementation resulted in greater gains of lean body mass, grip strength, and immune recovery in Ethiopian patients with HIV, compared with patients initiating antiretroviral treatment without a nutrient supplement. No major differences between the two supplements were observed

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Poor nutritional status at initiation of antiretroviral treatment is associated with impaired treatment outcomes among African patients with HIV. This study shows that provision of a lipid based nutrient supplement during the initial phase of antiretroviral treatment has beneficial effects.

Design

In this randomised controlled trial patients received 200 g/day lipid based nutrient supplement containing whey or soy during the first three months of antiretroviral treatment (ART). A control group received the supplement during the subsequent three months. Allocation to intervention groups was based on block randomisation and administered by a person not involved in recruitment or data collection. Supplement type (whey or soy) was masked with codes and blinded to everyone involved, while allocation to early or delayed supplementation was blinded to data assessors and data analysts only. We carried out three main comparisons. Whey and soy containing supplements were each compared with no supplement in participants with BMI >17, as a delayed supplementation groups served as controls. In addition, we compared whey and soy containing supplements with each other among all participants with BMI >16. Secondly, we compared early and delayed supplementation in participants with BMI >17 to investigate potential effects of timing of supplementation.

Effects (95% CI) of whey and soy containing supplements at three months in HIV patients with BMI >17 (n=282). Estimates are adjusted for sex, age, and education. Reference group was 93 patients who received delayed supplement

	Whey (n=94), P value	Soy (n=95), P value
Lean body mass (kg)	0.85 (0.16 to 1.53), 0.018	0.97 (0.29 to 1.64), 0.005
Grip strength (kg)	0.68 (−0.11 to 1.46), 0.090	0.93 (0.16 to 1.70), 0.019
PAEE (kJ/kg/day)	1.06 (0.87 to 1.29), 0.56	1.10 (0.91 to 1.33), 0.31
CD4 (cells/μL)	25 (−2 to 53), 0.073	15 (−12 to 42), 0.28
CD3 (cells/μL)	150 (24 to 275), 0.020	79 (−44 to 202), 0.21
CD8 (cells/μL)	112 (15 to 209), 0.023	60 (−35 to 154), 0.22

PAEE=physical activity energy expenditure.

Participants and setting

Adults with HIV eligible for ART with body mass index (BMI) >16 in Jimma, south west Ethiopia.

Primary outcomes

Lean body mass, grip strength, and physical activity at three months after initiation of antiretroviral treatment.

Main results and the role of chance

The effects of supplementation were considerable, resulting in a more than threefold weight gain, compared with the effects of ART alone, and with substantially more lean body mass gained. The increase of lean mass was accompanied by an effect on grip strength, though no effect on physical activity was observed. Furthermore, the whey containing supplement was associated with increases in CD3 and CD8 counts, and results also suggested an effect on CD4 counts. No such effects on immune recovery were shown for the soy containing supplement, but when the two supplements were compared, there were no significant differences in their effects. Patients receiving delayed supplementation had a greater weight gain but less gain in grip strength and physical activity than those receiving early supplementation.

Harms

No harms of nutritional supplementation were observed.

Bias, confounding, and other reasons for caution

The risk of selection bias was low as patient recruitment was consecutive, group allocation was concealed, and the study had a high follow-up rate (88% at three months). For many patients, however, we had incomplete data on physical activity, and we might not have been able to detect a potential effect of supplementation on this outcome.

Generalisability to other populations

Our findings are relevant for the treatment of all patients with HIV in food insecure settings. We included only patients with BMI >17 in the comparison with an unsupplemented group during the first three months of antiretroviral treatment, but previous observational studies have shown associations between weight gain and improved treatment outcomes across all BMI strata. We therefore conclude that the beneficial effects of supplementation can be generalised to HIV patients with inadequate access to food regardless of initial BMI status.

Study funding

The study was funded by US Dairy Export Council, International Atomic Energy Agency (IAEA), and Ministry of Foreign Affairs of Denmark (DANIDA). Nutriset developed the supplements and partially covered transportation expenses.

Non-publication and delayed publication of randomized trials on vaccines: survey

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Cite this as: *BMJ* 2014;348:g3058
doi: 10.1136/bmj.g3058

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g3058

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STUDY QUESTION

What is the extent of non-publication or delayed publication of registered randomized trials on vaccines, and what are the potential determinants of delay to publication?

SUMMARY ANSWER

Most trials on vaccines are published eventually or the results are posted in ClinicalTrials.gov, but delays of several years to publication are common.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A growing body of evidence indicates that an important proportion of results from randomized controlled trials remains unpublished, or is published after major delay; however, only two studies focused on vaccines. The amount of randomized evidence on vaccines that remains unpublished may be lower than that for other medical specialties, but actions are still required to ensure timely public dissemination of trial data in published reports that can be easily linked to the codes for trial registration.

Participants and setting

We included randomized trials evaluating the safety or the efficacy or immunogenicity of papillomavirus (HPV), pandemic A/H1N1 2009 influenza, and meningococcal, pneumococcal, and rotavirus vaccines, that were registered in ClinicalTrials.gov, Current Controlled Trials, WHO International Clinical Trials Registry Platform, Clinical Study Register, or Indian, Australian New Zealand, and Chinese trial registries in 2006-12. To identify published manuscripts we searched electronic databases (Scopus, PubMed, Google) up to February 2014. We also reviewed the results available in ClinicalTrials.gov.

Design

Survey.

Primary outcomes

Publication status of trial results and time from completion to publication in peer reviewed journals.

Main results and the role of chance

We analysed 384 trials (85% sponsored by industry). Of 355 trials (404 758 participants) that were completed, 176 (n=151 379) had been published in peer reviewed journals. Another 42 (total sample 62 765) remained unpublished but reported results in ClinicalTrials.gov. The proportion of trials published 12, 24, 36, and 48 months after completion was 12%, 29%, 53%, and 73%, respectively. Including results posted in ClinicalTrials.gov, 48 months after study completion results were available for 82% of the trials and 90% of the participants. Delay to publication between non-industry and industry sponsored trials did not differ, but non-industry sponsored trials were 4.42-fold (P=0.008) more likely to report negative or mixed findings. Negative results were reported by only 2% of the published trials. 132 of the 176 published reports were retrieved by typing the trial registration code in Scopus or PubMed or following a direct link from ClinicalTrials.gov. To find the other 44 publications, a challenging search had to be performed for each of the remaining 223 completed trials.

Bias, confounding and other reasons for caution

Firstly, we may have missed some published reports, but any missed papers are unlikely to be identified during routine or even systematic searches. Secondly, some trials may not have been registered, but such trials are likely to be less influential in the current environment, where registration is widely accepted. Thirdly, registry information is inconsistently updated, and even when data are reported, the registry or published primary outcomes or sample size might differ. However, we found discrepancies between registered and published outcomes or sample size for few trials, and when trials with missing data were excluded the results were comparable. Similarly, the results did not change when we excluded trials registered after the start of the study.

Study funding/potential competing interests

This study was not funded. We have no competing interests.

Publication rates for randomized trials on five vaccines registered in 2006-12

Variables	Results
Median time from completion to publication	26.4 months
No of trials (No in total sample)	384 (607 076)
No of completed trials (No in sample)	355 (404 758)
No of completed trials published in peer reviewed journals (No in sample)	176 (151 379)
No of completed trials remaining unpublished but with results in ClinicalTrials.gov (No in sample)	42 (62 765)
% of trials (% of sample) published:	
12 months after completion*	11.9 (9.3)
24 months after completion*	28.8 (28.2)
36 months after completion*	53.1 (59.1)
48 months after completion*	73.0 (80.6)
Published trial results (No, %):	
Positive	158 (89.8)
Mixed	14 (7.9)
Mostly negative	4 (2.3)

*See the full paper on bmj.com for number of trials included in this analysis.