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Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis

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ABSTRACT

Objective To compare the effectiveness and safety of three types of stents (sirolimus eluting, paclitaxel eluting, and bare metal) in people with and without diabetes mellitus.

Design Collaborative network meta-analysis.

Data sources Electronic databases (Medline, Embase, the Cochrane Central Register of Controlled Trials), relevant websites, reference lists, conference abstracts, reviews, book chapters, and proceedings of advisory panels for the US Food and Drug Administration. Manufacturers and trialists provided additional data.

Review methods Network meta-analysis with a mixed treatment comparison method to combine direct within trial comparisons between stents with indirect evidence from other trials while maintaining randomisation. Overall mortality was the primary safety end point, target lesion revascularisation the effectiveness end point.

Results 35 trials in 3852 people with diabetes and 10 947 people without diabetes contributed to the analyses. Inconsistency of the network was substantial for overall mortality in people with diabetes and seemed to be related to the duration of dual antiplatelet therapy (P value for interaction 0.02). Restricting the analysis to trials with a duration of dual antiplatelet therapy of six months or more, inconsistency was reduced considerably and hazard ratios for overall mortality were near one for all comparisons in people with diabetes: sirolimus eluting stents compared with bare metal stents 0.88 (95% credibility interval 0.55 to 1.30), paclitaxel eluting stents compared with bare metal stents 0.91 (0.60 to 1.38), and sirolimus eluting stents compared with paclitaxel eluting stents 0.95 (0.63 to 1.43). In people without diabetes, hazard ratios were unaffected by the restriction. Both drug eluting stents were associated with a decrease in revascularisation rates compared with bare metal stents in people both with and without diabetes.

Conclusion In trials that specified a duration of dual antiplatelet therapy of six months or more after stent implantation, drug eluting stents seemed safe and effective in people both with and without diabetes.

INTRODUCTION

People with diabetes are at an increased risk for coronary heart disease and have more restenoses after the implantation of coronary stents. Sirolimus eluting and paclitaxel eluting stents are associated with a noticeable reduction in target lesion revascularisation compared with bare metal stents, whereas the rates of overall mortality and cardiac mortality are similar.[1]

Randomised trials have reported a reduced revascularisation rate with sirolimus eluting and paclitaxel eluting stents than with bare metal stents in people with diabetes,[2-4w1-w3] but a subsequent meta-analysis of four early trials in 428 people with diabetes that compared sirolimus eluting stents with bare metal stents for up to four years suggested a strongly increased risk of mortality (hazard ratio 2.90, 95% confidence interval 1.38 to 6.10),[5] which translated into a number needed to harm to cause one death over four years as low as 4 (95% confidence interval 2 to 22). In a previous network meta-analysis[1] we determined the average benefits and harms of all three stents and provided preliminary results for overall mortality and the composite of death or myocardial infarction stratified according to diabetes status. Here we extend that analysis.[6,7] We prespecified overall mortality as the primary safety outcome and explored the consistency of mortality data in people with diabetes.

METHODS

We included randomised controlled trials in people with symptoms or signs of myocardial ischaemia that compared two first generation drug eluting stents (containing paclitaxel or sirolimus) with each other or with a bare metal stent. Trials had to have a clinical follow-up of at least six months.

We specified overall mortality as the primary safety outcome and target lesion revascularisation as the

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primary effectiveness outcome. Secondary safety outcomes were cardiac death, a composite of death or myocardial infarction, and stent thrombosis, in accordance with criteria of the Academic Research Consortium. We also recorded stent thrombosis according to the definitions used in individual trials (per protocol definition). The numbers of patients experiencing an event and the overall number of patients at risk were recorded separately for years 1 to 4.

To tackle potential sources of inconsistency we determined the month of completed patient recruitment as a measure of the time period when a trial was done, the duration of follow-up (years), and the duration (months) of dual antiplatelet therapy and assessed concealment of allocation, blinding of staff adjudicating clinical outcomes, and adherence to the intention to treat principle, with trials considered to be of high quality that satisfied all three criteria.

Statistical analysis

We used a hierarchical random effects model[8] for mixed treatment comparisons[9] based on piecewise constant hazards, with random effects at the levels of trials, adjacent time periods, and comparisons. We simultaneously estimated log hazard ratios and the difference in log ratios for people with and without diabetes. From the posterior distribution of the difference we estimated the P values for interaction between treatment effect and diabetes status. Hazard ratios were estimated from the median, and the accompanying 95% credibility intervals from the 2.5th and 97.5th centiles of the posterior distribution. As event rates were low we derived relative risks of stent thromboses using a random effects Poisson regression model.[10] We did separate analyses according to time of occurrence of stent thrombosis and an analysis of per protocol definitions of stent thrombosis.

We evaluated the inconsistency expressed as the percentage difference in hazard ratios between direct comparisons within trials and indirect comparisons between trials. Values of 0% indicate no inconsistency of comparisons in the network, 100% indicate high inconsistency (see bmj.com)..We evaluated heterogeneity between trials, defined as variability of results across trials within comparisons over and above chance, and the model's goodness of fit to the data.

To investigate potential sources of variation in the network, we included the characteristics of the trials as covariates in the network meta-analysis of the primary safety outcome. We used prespecified cut-off points of two years for follow-up, January 2004 for completed patient recruitment, and six months for dual antiplatelet therapy. We used a random effects Poisson regression model for analyses where the number of trials and events was too low to allow the estimation of random effects at the level of time periods.[10] P values for interaction between trial characteristics and treatment effect were derived from the posterior distribution of covariates. Duration of dual antiplatelet therapy was the only variable with an interaction with $P<0.05$. Therefore we restricted the dataset to trials with a duration of dual antiplatelet therapy of six months or longer and repeated all analyses.

RESULTS

Thirty five trials[w1-w14 w16-w33 w35 w38 w40] were included (3852 with diabetes and 10 947 without diabetes). Additional data were provided for 32 trials.[w1 w4-w14 w16-w19 w21-w33 w35 w38 w40] Recruitment was completed between January 2001[w16] and November 2005.[w5] Data stratified according to diabetes status were available for all trials on all outcomes, except stent thrombosis. Twenty nine trials reported appropriate allocation concealment,[w1 w2 w7 w8 w11-w14 w16-w33 w35 w38 w40] and 28 trials reported blind adjudication for clinical outcomes.[w1 w4 w7 w9-w14 w16-w26 w28-w30 w32 w33 w35 w38 w40] For 30 trials patients could be included according to the intention to treat principle.[w1 w3-w7 w9 w11 w13 w14 w16-w23 w25-w33 w35 w38 w40] Twenty four trials were of high quality.[w1 w7 w11 w13 w14 w16-w23 w25 w26 w28-w30 w32 w33 w35 w38 w40]

Duration of dual antiplatelet therapy

Study protocols specified the duration of dual antiplatelet therapy as two months in five,[w16 w18-w20 w26] three months in three,[w3 w7 w17] six months in 18,[w2 w5 w9-w14 w21 w22 w24 w28 w29 w32 w33 w35 w38 w40] nine months in one,[w4] and 12 months in eight trials.[w1 w6 w8 w23 w25 w27 w30 w31] All eight trials with dual antiplatelet therapy lasting less than six months compared sirolimus eluting stents with bare metal stents. Auxiliary information indicated that the percentage of patients actually receiving therapy of six months or more was likely to be below 10% in five trials,[w7 w16-w19] and for the other three trials between 10% and 20%,[w20] 40% and 50%[w26] and 50% and 60%.[w3] One head to head comparison had specified a minimal duration of therapy for two months with sirolimus stents and six months with paclitaxel stents, but the actual duration was only one month shorter for patients receiving siroliumus stents than for those receiving paclitaxel stents, and about 50% of patients allocated to either stent were still receiving therapy after eight months.[w32]

Network of all trials: overall mortality

In people with diabetes the estimated hazard ratio was 1.14 for sirolimus compared with bare metal stents (95% credibility interval 0.74 to 1.60), 1.09 for paclitaxel versus bare metal stents (0.71 to 1.66), and 1.02 for sirolimus versus paclitaxel stents (0.70 to 1.57), compatible with both substantial harm and moderate benefit of either drug eluting stent compared with bare metal stents (see bmj.com). The

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corresponding values for people without diabetes were 1.02 (0.77 to 1.29), 0.90 (0.67 to 1.16), and 1.13 (0.83 to 1.54; see bmj.com). A moderate to high inconsistency of 61% was found among people with diabetes, but none among people without diabetes.

Exploration of sources of variation

Estimates of relative risk comparing sirolimus stents with paclitaxel stents depended to some extent on the quality of the trials, length of follow-up, and time of completed recruitment (see bmj.com), but 95% credibility intervals were wide and tests for interaction negative (P≥0.16). The estimated relative risk of death when sirolimus stents were compared with bare metal stents was greater when dual antiplatelet therapy lasted less than six months (2.37, 95% credibility interval 1.18 to 5.12) compared with six months or longer (0.89, 0.58 to 1.40, P for interaction 0.02), however. When three trials originally classified to have a short duration of dual antiplatelet therapy[w3 w20 w26] were reclassified to have a duration of six months or longer, reflecting the auxiliary information indicating that more than 10% of patients in these trials were still receiving therapy at six months, differences were maintained.

Restricted network: overall mortality

When the network was restricted to trials with dual antiplatelet therapy of six months or longer (see bmj.com), the hazard ratios of death overall among people with diabetes were below 1: sirolimus stents compared with bare metal stents 0.88 (95% credibility interval 0.55 to 1.30), paclitaxel stents compared with bare metal stents 0.91 (0.60 to 1.38), and sirolimus compared with paclitaxel stents 0.95 (0.63 to 1.43). Compared with the network of all trials the inconsistency decreased to 20% and credibility intervals of hazard ratios became more narrow in the restricted network. Among people without diabetes results were much the same in the overall and the restricted network (see bmj.com). The hazard ratio was 1.05 for sirolimus stents compared with bare metal stents (0.69 to 1.73), 0.89 for paclitaxel stents compared with bare metal stents (0.66 to 1.18), and 1.23 for sirolimus compared with paclitaxel stents (0.82 to 1.69). See figures on bmj.com for cumulative incidences of death for the three stent types estimated from the restricted network meta-analysis for people with and without diabetes. The incidence of death was about twice as high in people with diabetes compared with people without diabetes. Tests for interaction between treatment effect and diabetes status were negative for all comparisons (P≥0.28).

Restricted network: secondary safety outcomes

Among people with diabetes, hazard ratios for drug eluting stents compared with bare metal stents became more beneficial for drug eluting stents for the outcomes of cardiac death, the composite of death or myocardial infarction, and stent thromboses in the restricted network compared with the network of all trials (see bmj.com). The inconsistency decreased mainly for cardiac death and per protocol definitions of stent thromboses. No differences between overall and restricted network meta-analysis were observed for myocardial infarction. Among people without diabetes, results from overall and restricted network meta-analysis were similar. Corresponding cumulative incidences for the three stent types are on bmj.com. Again, incidences were higher in people with diabetes than without, with most pronounced differences observed for cardiac death. Tests for interaction between treatment effect and diabetes status were negative for all comparisons on cardiac death, myocardial infarction, and their composite (P≥0.47).

Among people with diabetes little evidence was found for an increased risk of definite or per protocol stent thrombosis associated with sirolimus stents compared with either of the two other stents; all point estimates were below 1 and differences in favour of sirolimus stents became more pronounced with the use of per protocol definitions (see bmj.com). For the comparison of paclitaxel stents with bare metal stents all estimates were imprecise for both the Academic Research Consortium definition of definite stent thrombosis and the per protocol definitions. Among people without diabetes relative risks were generally higher for both definitions, but tests for interaction between treatment effect and diabetes status were positive only for sirolimus compared with bare metal stents on per protocol definitions of stent thrombosis between day 0 and 4 years and between day 30 and 4 years (P for interaction=0.01).

Restricted network: target lesion revascularisation

Both drug eluting stents were robustly associated with a decrease in revascularisation rates compared with bare metal stents, network inconsistency was low, and results were unaffected by the restriction of the analysis to trials with dual antiplatelet therapy of six months or more in people with and without diabetes (see bmj.com). Differences between sirolimus and paclitaxel stents tended to be less pronounced among people with diabetes, and credibility intervals overlapped 1. Tests of interaction between treatment effect and diabetes status were negative (P≥0.44).

Between trial heterogeneity, model fit, and comparison with conventional meta-analyses

After restricting the network to trials with dual antiplatelet therapy of six months or more, heterogeneity between trials was low for all outcomes except stent thrombosis. For people without diabetes heterogeneity between trials was low for death, myocardial infarction, and their composite, and moderate for

WHAT IS ALREADY KNOWN ON THIS TOPIC

People with diabetes are at an increased risk for coronary heart disease and have more restenoses after the implantation of coronary stents

A meta-analysis suggested a strongly increased risk of death associated with sirolimus eluting stents compared with bare metal stents in people with diabetes

WHAT THIS STUDY ADDS

Reported increases in the risk of death associated with drug eluting stents compared with bare metal stents in people with diabetes were probably due to dual antiplatelet therapy lasting less than six months in early trials

In trials with dual antiplatelet therapy for six months or longer drug eluting stents were safe and effective in people both with and without diabetes

In clinical practice it seems prudent to adhere to a minimal duration of dual antiplatelet therapy of six months in all patients undergoing implantation of a drug eluting coronary stent

most comparisons on the other outcomes. The model fit was adequate for all outcomes.

DISCUSSION

Our collaborative network meta-analysis suggests that previously reported increases in the risk of death associated with sirolimus eluting stents compared with bare metal stents in people with diabetes[5] probably resulted from the restricted duration of dual antiplatelet therapy of less than six months in early trials. In trials with therapy of less than six months, the risk of death associated with sirolimus stents was more than twice that associated with bare metal stents—that is, a number needed to harm as low as 7 to cause one death over four years. Conversely, trials with therapy of six months or more showed no increase in risk from using sirolimus stents compared with bare metal stents. Restricting the network to trials with therapy of six months or longer resulted in a clear reduction of the inconsistency and hazard ratios near 1, which were robust to all sensitivity analyses. We found similar patterns for analyses of cardiac death and stent thromboses.

Compared with bare metal stents, target lesion revascularisation rates are strongly decreased by the use of sirolimus and paclitaxel eluting stents in people with and without diabetes. Numbers needed to treat to reduce one event over four years are 6 in people with diabetes and 8 in people without diabetes. Numbers needed to treat assuming revascularisation rates as observed in routine clinical practice without active angiographic follow-up [11] were estimated 13 for people with diabetes and 18 for people without diabetes.

Our study comprises a large body of evidence from randomised controlled trials in people with and without diabetes treated with one of two drug eluting stents or bare metal stents. Additional data were provided according to uniform outcome definitions, including stent thrombosis according to the Academic Research Consortium consensus.[7] This increases comparability between trials and limits bias.

Our model was based on relative treatment effects (log hazards ratio). Variations in characteristics of patients or lesions between trials are fully accounted for by maintaining randomised comparisons within each trial.[1] Network meta-analysis makes similar assumptions to standard meta-analysis of direct comparisons within trials, but requires that these assumptions hold over the entire set of trials in the network.[12] The smaller the heterogeneity between trials and the smaller the inconsistency of the data, the more likely relative treatment effects originate from the same distribution and the less likely small trials get undue weight in the analysis.

Our exploration of inconsistency is observational in nature and has the same limitations as other observational studies.[13] Most importantly, earlier trials had specified shorter durations of dual antiplatelet therapy than later trials. The duration of therapy was therefore bound to be negatively correlated with the duration of follow-up, and confounding could exist between these variables. Other potential confounders include changes over time in patient selection and procedural characteristics or methodological quality. We addressed this by repeating tests of interaction between treatment effect and components of methodological quality or length of follow-up after the exclusion of trials with dual antiplatelet therapy lasting less than six months and found no evidence for an interaction in any of these analyses (data available on request).

Our results could have been corroborated by an analysis of the actual duration of dual antiplatelet therapy in individual patients, but precise durations were unavailable in most trials and we lacked the resources to retrospectively ascertain and validate usage data. Eight trials had specified a duration of therapy of less than six months. For five trials we are confident that the actual duration corresponded to the specified duration in at least 90% of patients[w7 w16-w19]; in three trials between 10% and 50% of the patients had dual antiplatelet therapy at six months.[w3 w20 w26] Results were unaffected by the reclassification of these three trials as having a duration of dual antiplatelet therapy of six months or longer, and the P value for interaction between relative risk of death and duration of therapy became even smaller. Additionally, strut thickness or type of bare metal stent used in comparison groups might affect clinical outcomes.[w21] Despite our results being robust to the adjustment for these characteristics,[1] we cannot fully exclude the possibility that differences in bare metal stents as comparators contributed to the observed variation in mortality between trials with short and long durations

of therapy. Finally, we were unable to record information on specific antidiabetic treatment or on glycaemic control in people with diabetes mellitus and to perform separate analyses for people with diabetes who did or did not use insulin. Although these aspects are related to cardiovascular outcomes,[14] they were per definition randomly distributed across comparison groups within each trial and it seems unlikely that they influenced results.

We found that the duration of dual antiplatelet therapy modified the safety profile of drug eluting stents mainly in people with diabetes. The beneficial effect of prolonged therapy in people with diabetes may be mainly related to differences in lesion characteristics—people with diabetes tend to have smaller vessels and longer lesions than people without diabetes. Previous studies have identified these variables as predictors of stent thrombosis,[15] which may explain the predisposition of people with diabetes to stent thrombosis in the absence of adequate antiplatelet therapy. Delays in arterial healing and re-endothelialisation may be more pronounced in people with diabetes, particularly in the absence of dual antiplatelet therapy.[16 17] Finally, people with diabetes may be more likely to experience aspirin resistance than people without diabetes[18] and may have a particular benefit from a complementary antiplatelet therapy with clopidogrel or ticlopidine.

Conclusion

In trials with a duration of dual antiplatelet therapy of six months or longer drug eluting stents were safe and effective in people with and without diabetes. It seems prudent to adhere to a minimal duration of therapy for six months in patients having drug eluting coronary stents.

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Adherence to Mediterranean diet and health status: meta-analysis

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ABSTRACT

Objective To systematically review all the prospective cohort studies that have analysed the relation between adherence to a Mediterranean diet, mortality, and incidence of chronic diseases in a primary prevention setting.

Design Meta-analysis of prospective cohort studies.

Data sources English and non-English publications in PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials from 1966 to 30 June 2008.

Studies reviewed Studies that analysed prospectively the association between adherence to a Mediterranean diet, mortality, and incidence of diseases; 12 studies, with a total of 1 574 299 subjects followed for a time ranging from three to 18 years were included.

Results The cumulative analysis among eight cohorts (514 816 subjects and 33 576 deaths) evaluating overall mortality in relation to adherence to a Mediterranean diet showed that a two point increase in the adherence score was significantly associated with a reduced risk of mortality (pooled relative risk 0.91, 95% confidence interval 0.89 to 0.94). Likewise, the analyses showed a beneficial role for greater adherence to a Mediterranean diet on cardiovascular mortality (pooled relative risk 0.91, 0.87 to 0.95), incidence of or mortality from cancer (0.94, 0.92 to 0.96), and incidence of Parkinson's disease and Alzheimer's disease (0.87, 0.80 to 0.96).

Conclusions Greater adherence to a Mediterranean diet is associated with a significant improvement in health status, as seen by a significant reduction in overall mortality (9%), mortality from cardiovascular diseases (9%), incidence of or mortality from cancer (6%), and incidence of Parkinson's disease and Alzheimer's disease (13%). These results seem to be clinically relevant for public health, in particular for encouraging a Mediterranean-like dietary pattern for primary prevention of major chronic diseases.

INTRODUCTION

The Mediterranean diet has been widely reported to be a model of healthy eating for its contribution to a favourable health status and a better quality of life.[1 2] Since the first data from the seven countries study,[3] several studies in different populations have established a beneficial role for the main components of the Mediterranean diet on the occurrence of cardiovascular diseases and chronic degenerative diseases.[2 4] However, research interest in this field over the past years has been focused on estimating adherence to the whole Mediterranean diet rather than analysing the individual components of the dietary pattern in relation to the health status of the population.[5] The aim of this study was to systematically review all the available prospective cohort studies in order to establish the role of adherence to a Mediterranean diet in primary prevention.

METHODS

Study selection—We identified studies that prospectively evaluated the association of an a priori score used for assessing adherence to a Mediterranean diet and adverse clinical outcomes (see bmj.com for a description of the search strategy). Our initial search yielded 62 reports, of which 12 articles fulfilled our inclusion criteria.[w1-w12]

Data extraction—We extracted the baseline characteristics from the original reports by using a standardised data extraction form and included them in the meta-analysis. Two investigators (FS and FC) collected the data, and disagreements were solved by consensus and by the opinion of a third author (AC), if necessary.

Definition of adherence to Mediterranean diet—Adherence to a Mediterranean diet was defined through scores that estimated the conformity of the dietary pattern of the studied population with the traditional Mediterranean dietary pattern. Values of zero or one were assigned to each dietary component by using as cut offs the overall sex specific medians among the study participants. Differences among the studies existed, especially in relation to the food category of vegetables (grouped with potatoes in one study[w5]), meat and meat products (grouped with poultry in some studies[w4 w6]), and nuts and seeds (grouped with fruits in some studies,[w4 w6 w7 w12] grouped with legumes in one study,[w5] and considered a group by themselves in some others[w8 w10 w11]), as well as milk and dairy products (not present in some studies[w8 w10 w11]) and fish (present only in more recent studies[w4-w12]). Thus, the total adherence scores (estimated as the sum of the above indicated scores of zero and one) varied from a minimum of 0 points indicating low adherence to a maximum of 7-9 points reflecting high adherence to a Mediterranean diet.

Statistical analysis—We used RevMan, version 4.2 for Windows by the Cochrane Collaboration to analyse data. We used the results of the original studies from multivariable models with the most complete adjustment for potential confounders. We used a random effects model that accounts for interstudy variation and provides a more conservative effect than a fixed model. We calculated random summary relative risks with 95% confidence intervals by using an inverse variance method. For details see bmj.com.

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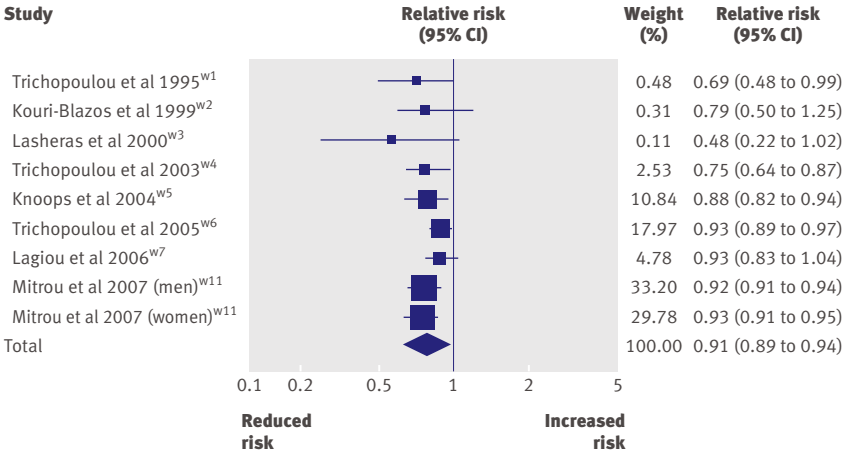

Fig 1 | Risk of all cause mortality associated with two point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% confidence intervals; diamond represents total effect size

RESULTS

Characteristics of study cohorts

Sample sizes varied between 161 and 214 284, with a follow-up time ranging from 3.7 to 18 years. Only six out of 12 studies were done in Mediterranean populations.[w1 w3-w6 w12] The remaining cohorts comprised US populations,[w8-w11] northern Europeans,[w5-w7] and a cohort of Europeans living in Australia.[w3]

Main outcomes

Overall mortality was evaluated in eight cohorts (nine studies) for a total of 514 816 subjects and 33 576 deaths, cardiovascular mortality in three cohorts (four studies) including a total of 404 491 subjects and 3876 fatal events, cancer incidence/mortality in five cohorts (six studies) comprising 521 366 subjects and 10 929 events, and incidence of Parkinson's disease and Alzheimer's disease in two cohorts (three studies) for a total of 133 626 subjects and 783 cases.

Figure 1 shows the cumulative analysis for studies that analysed overall mortality as the primary clinical outcome. A two point increase in score for adherence to a Mediterranean diet was significantly associated with a reduced risk of mortality from any cause (relative risk 0.91, 95% confidence interval 0.89 to 0.94; P<0.0001). Significant heterogeneity was present among the studies (I_2=48.8%; P=0.05). However, after exclusion of the paper by Trichopoulou et al 2003 that analysed the same cohort as Trichopoulou et al 2005,[w4 w6] the significant association with overall mortality remained (relative risk 0.92, 0.91 to 0.94; P<0.0001), showing no significant heterogeneity (I_2=18.3%; P=0.3).

Similarly figure 2 shows that a greater adherence to a Mediterranean diet significantly reduced the risk of mortality from cardiovascular diseases (relative risk 0.91, 0.87 to 0.95; P<0.0001) with non-significant heterogeneity (I_2=32.6%; P=0.2). Furthermore, greater adherence to a Mediterranean diet significantly reduced the occurrence of and mortality from neoplasm (relative risk 0.94, 0.92 to 0.96; P<0.0001) (I_2=0%; P=0.5) (fig 3). Finally, the overall analysis showed a significant reduction in incidence of Parkinson's disease and Alzheimer's disease associated with a higher score of adherence to a Mediterranean diet (relative risk 0.87, 0.80 to 0.96; P=0.004), with no heterogeneity among the studies (I_2=0%; P=0.5) (fig 4).

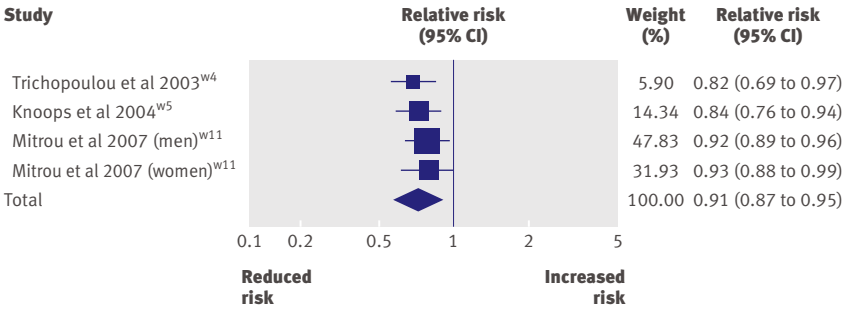

Fig 2 | Risk of mortality from cardiovascular diseases associated with two point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% confidence intervals; diamond represents total effect size

Sensitivity analyses and publication bias

Because heterogeneity of studies is likely to produce heterogeneity of effect sizes across studies, we did some sensitivity analyses. These analyses showed no significant influence of any variable (country of origin of the study, sex, follow-up time, quality of the studies) on the overall results of the meta-analysis. We found no evidence of publication bias (see bmj.com).

DISCUSSION

This meta-analysis, comprising more than 1.5 million healthy subjects and 40 000 fatal and non-fatal events, shows that greater adherence to a Mediterranean diet is significantly associated with a reduced risk of overall mortality, cardiovascular mortality, cancer incidence and mortality, and incidence of Parkinson's disease and Alzheimer's disease. The cumulative analysis of 12 cohort studies shows that a two point increase in the score for adherence to a Mediterranean diet determines a 9% reduction in overall mortality, a 9% reduction in mortality from cardiovascular diseases, a 6% reduction in incidence of or mortality from neoplasm, and a 13% reduction in incidence of Parkinson's disease and Alzheimer's disease. To the best of our knowledge, this is the first report that has systematically assessed, through meta-analysis, the possible association between adherence to a Mediterranean diet, mortality, and the occurrence of chronic diseases in the general population.

Practical implications

We report a significant reduction in risk of all the main clinical outcomes with an increasing score for adherence to a Mediterranean diet. This observation seems to show that a score based on a theoretically defined Mediterranean diet is an effective preventive tool for measuring the risk of mortality and morbidity in the general population.

A Mediterranean diet has been shown to have a beneficial effect on the occurrence of diseases in industrialised and non-industrialised countries.[6-8] Unfortunately, despite this worldwide promotion of the

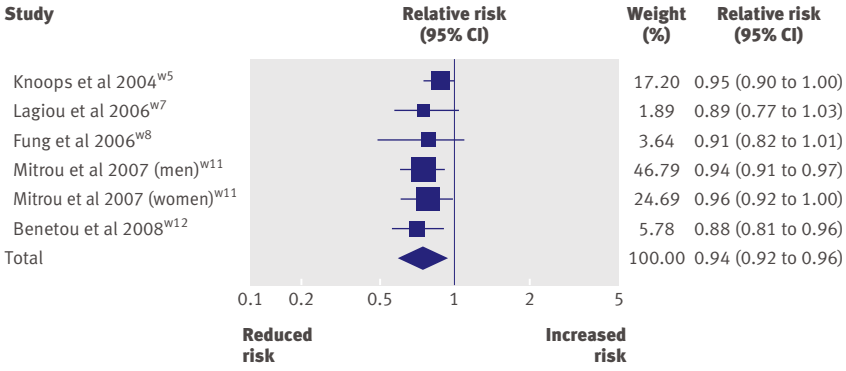

Fig 3 | Risk of occurrence of or mortality from cancer associated with two point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% confidence intervals; diamond represents total effect size

Mediterranean diet, a progressive shift to a non-Mediterranean dietary pattern, even in countries bordering the Mediterranean sea, has progressively developed.[9] It thus seems urgent to identify an effective preventive strategy to decrease the risk burden related to dietary habits in the general population.

Limitations

Some limitations of this study can be identified. The Mediterranean diet is not a homogeneous pattern of eating, and heterogeneity on the score items exists. How to group some food categories such as legumes, nuts, and milk and dairy products; the real importance of different types of meat; and the establishment of the moderate amount of alcohol intake are still matters of dispute among researchers and can differ among the selected studies. None the less, the key characteristics of a Mediterranean diet were present in all the studies, and the overall analysis seemed not to be significantly influenced by these differences. In addition, the use of a score for estimating a dietary pattern is limited by subjectivity, conditioned by the available data and the main objectives of the study, and so possibly determining a great variability in the interpretation of the results.

Finally, a further limitation exists in the different adjustment for potential confounders seen among the included studies. This difference could have determined a residual confounding within the studies, especially for the non-Mediterranean cohorts. However, the sensitivity analysis according to the quality of the studies, which also included the presence or not of adjustment factors, showed no significant influence of residual confounding on the overall findings of our meta-analysis.

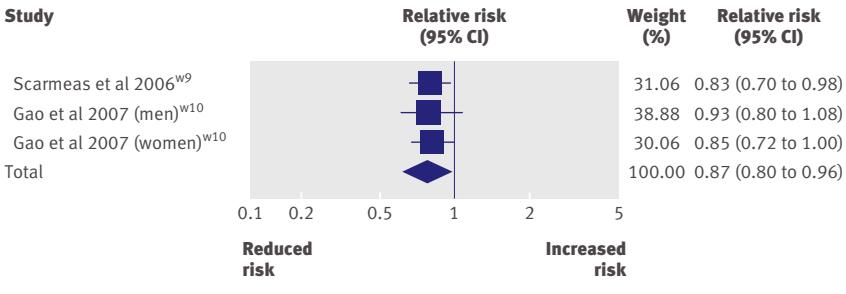

Fig 4 | Risk of Parkinson's disease and Alzheimer's disease associated with two point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% confidence intervals; diamond represents total effect size

WHAT IS ALREADY KNOWN ON THIS TOPIC

The Mediterranean diet is a well known model of diet for primary and secondary prevention of major chronic diseases

An adherence score can be used to assess the adherence of a specific population to the rules of a traditional Mediterranean diet

WHAT THIS STUDY ADDS

Greater adherence to a Mediterranean diet confers a significant protection for overall mortality, as well as cardiovascular disease mortality and incidence of cancer and degenerative diseases

The adherence score based on a theoretically defined Mediterranean diet could be an effective preventive tool for reducing the risk of mortality and morbidity in the general population

Conclusions

This meta-analysis shows that adherence to a Mediterranean diet can significantly decrease the risk of overall mortality, mortality from cardiovascular diseases, incidence of or mortality from cancer, and incidence of Parkinson's disease and Alzheimer's disease. These results are strictly concordant with current guidelines and recommendations from all the major scientific associations that strongly encourage a Mediterranean-like dietary pattern for primary and secondary prevention of major chronic diseases.

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Quality of clinical aspects of call handling at Dutch out of hours centres: cross sectional national study

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ABSTRACT

Objective To assess the quality of telephone triage by following the consecutive phases of its care process and the quality of the clinical questions asked about the patient's clinical condition, of the triage outcome, of the content of the home management advice, and of the safety net advice given at out of hours centres.

Design Cross sectional national study using telephone incognito standardised patients.

Setting The Netherlands.

Participants 17 out of hours centres.

Main outcome measures Percentages of clinical obligatory questions asked and items within home management and safety net advice, both in relation to pre-agreed standards, and of care advice given in relation to the required care advice.

Results The telephone incognito standardised patients presented seven clinical cases three times each over a period of 12 months, making a total of 357 calls. The mean percentage of obligatory questions asked compared with the standard was 21%. Answers to questions about the clinical condition were not always correctly evaluated from a clinical viewpoint, either by triagists or by general practitioners. The quality of information on home management and safety net advice varied, but it was consistently poor for all cases and for all out of hours centres. Triagists achieved the appropriate triage outcome in 58% of calls.

Conclusion In determining the outcome of the care process, triagists often reached a conclusion after asking a minimal number of questions. By analysing the quality of different phases within the process of telephone triage, evaluation of whether an appropriate triage outcome has been arrived at by means of good clinical reasoning or by an educated guess is possible. In terms of enhancing the overall clinical safety of telephone triage, apart from obtaining an appropriate clinical history, adequate home management and safety net advice must also be given.

INTRODUCTION

Most studies on the quality of telephone triage have focused on analysing the outcomes of triage. However, to assess the safety with more accuracy, the quality of the care process itself needs to be analysed. This includes assessment of the clinical quality of questions asked, as well as evaluation of the answers and the care advice given. The objective of this study was to make a global assessment of quality, specifically the quality of the clinical questions asked, the evaluation of the answers, the triage outcomes, and the content of the home management and safety net advice, in telephone consultations carried out by triagists at out of hours centres in the Netherlands.

METHODS

To assess the quality of clinical case handling at out of hours centres, telephone incognito standardised patients presented seven different clinical cases three times each to 17 different out of hours centres over a period of 12 months, totalling 357 calls.

Cases, protocols, and scenarios

The cases were to be based on symptoms that are known to present frequently on the telephone to out of hours centres,[1 2] and the care advice given as an outcome of the telephone consultation needed to be straightforward. In the Netherlands the triagist can select different triage outcomes depending on the degree of urgency. For this study we decided for practical reasons that no case would need an outcome of immediate care or a home visit. The cases were designed to show the importance of accurate history taking. Therefore, six of the seven cases to be presented consisted of three pairs of almost identical cases. For each of these parallel pairs of cases only one answer to an obligatory question differed (the discriminating answer). The box shows the obligatory questions for case 1; see bmj.com for the remaining cases. The table describes the discriminating answers for each parallel pair of cases.

Protocols for telephone triage include questions about possible causes and the consequences of the symptom presented, questions to compensate for the lack of visual information, and advice about home management care to be given if the triage outcome does not include a face to face consultation—for example, type and dose of analgesic drug. Finally, they include advice about the circumstances in which the patient should call back ("safety net advice").[3-5]

Discriminating answer for each parallel pair of cases

Case	Age	Clinical problem	Discriminating answer
1	5 years	Fever	Not applicable
2	Adult	Nosebleed	None
3	Adult	Nosebleed	Noticed several bruises in past few hours
4	Adult	Fever	None
5	Adult	Fever	Irregular usage of antimalarial drugs in past two weeks
6	5 years	Vomiting	None
7	5 years	Vomiting	Had head injury a few hours ago

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Obligatory questions to be asked for case 1, a 5 year old child with fever

- Can you describe the child's behaviour now?
- How high is the temperature of the child?
- Has the child had a fit?
- Does the child have pain anywhere?
- Has the child got, or has he or she had, a headache?
- Can the child touch forehead on knees (or kiss knees)?
- Does the child seem breathless or is there indrawing of the chest/tummy?
- How much fluid has been taken in the past 12 hours?
- When did the child last pass urine?
- Does the child have a rash?
- Did the child recently travel abroad?

We presented these protocols to a panel of general practitioners with experience in telephone triage at out of hours centres. They agreed on the obligatory questions that should be asked about the different clinical symptoms and what should be discussed with the patient in relation to home management and safety net advice.

Telephone incognito standardised patients

Lay people have been used as "unannounced" or "incognito" standardised patients to assess the performance of students and healthcare professionals during face to face and telephone consultations. Evidence shows that this method is a reliable and valid instrument to assess clinical performance.[6-9]

Trained telephone incognito standardised patients presented the cases. They received a validated scenario, with information on their personal data, the clinical problem, their personal situation (such as feeling anxious), and the answers to be given to the obligatory questions if they were asked. If they were invited to come for a consultation at the out of hours centre, they were instructed to ask for the reason for this request.

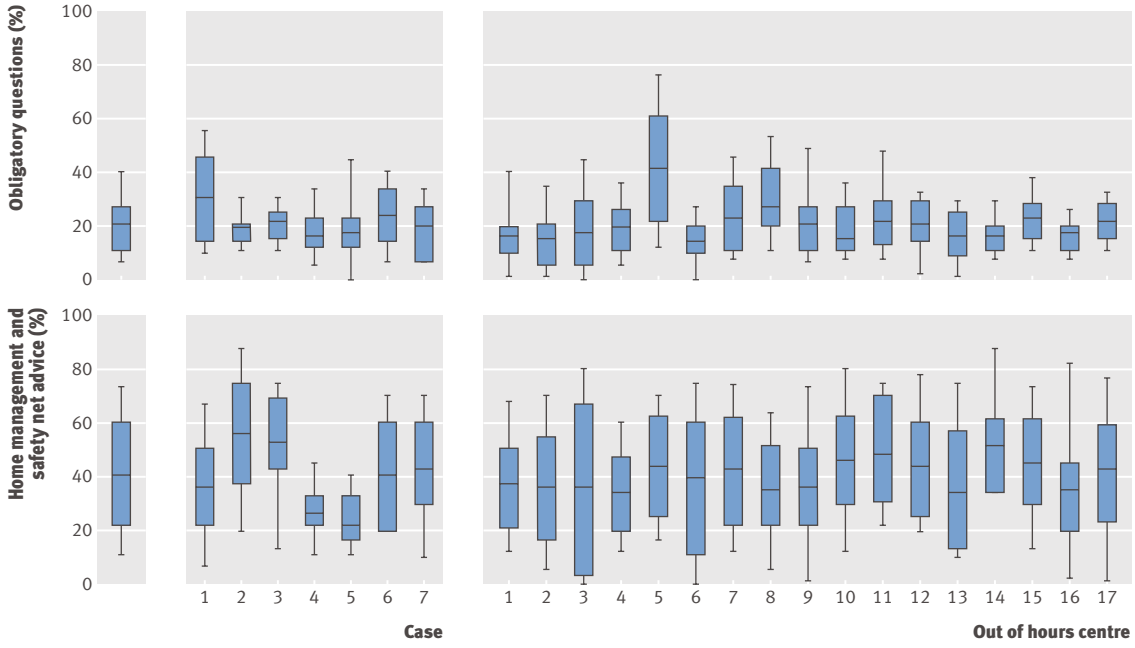
Out of hours centres

We asked all 105 out of hours centres in the Netherlands for permission to be selected for the research study. Of the 98 centres that gave permission, we randomly selected 17 (but did not inform them) on the basis of the size of the 12 provinces of the Netherlands. After the study we asked the 17 out of hours centres by letter whether they had detected a telephone incognito standardised patient during the previous 12 months.

Assessment and analysis

The required frequency of presentation of the cases developed was based on generalisability theory (see bmj.com). In a first batch, the seven cases were presented five times to five of the 17 selected out of hours centres. The remaining 12 out of hours centres were called three times for the same seven cases.

We made a transcript of every recorded call and assigned each call to two medical students as raters. They scored calls independently by using the standard protocol as a checklist. They rated each item by marking "Yes" (=1: question is asked/advice is given) or "No" (=0: question is not asked/advice is not given).



Box plots (distributions) of percentage obligatory questions asked versus standard and percentage home management and safety advice provided versus standard. Left panel shows distribution for all calls (n=357), middle panel shows distributions per case (51 calls per box plot), and right panel shows distributions per out of hours centre (21 calls per box plot). Each box plot shows mean value (solid line), 25th and 75th centiles (lower and higher boundaries of grey box) indicating central part, and 10th and the 90th centiles (grey "whiskers" outside box) indicating outer parts of distribution

WHAT IS ALREADY KNOWN ON THIS TOPIC

Research on the quality of telephone triage is often focused on the quality of the outcomes

Little is known about the quality of the different phases of the care process of telephone triage by triagists

WHAT THIS STUDY ADDS

Care advice was given after asking (too) few obligatory questions

Answers to those questions, if asked, were not always interpreted correctly by the triagist or general practitioner

The quality of home management and safety net advice was low

For each call, we recorded the following variables as indicators of quality: percentage of obligatory questions asked in relation to the agreed standard set of questions; percentage of items within home management and safety net advice in relation to the agreed standard set of items; percentage of obligatory questions asked in relation to all questions asked; percentage of appropriate care advice given in relation to the required care advice. For each of these variables we used the average percentage of the two raters for further analysis of each case for all out of hours centres and for each out of hours centre for all cases.

RESULTS

For 58% of all calls the required urgency level advised was as set by the scenario panel. Urgency was underestimated in 41% of calls and overestimated in 1% of calls. The overall mean percentage of obligatory questions asked was equal to 21% of the standard (figure). The mean percentage varied between 15% at out of hours centre number 6 and 42% at number 5. We found a similar pattern between cases: some variation between cases existed, but for all cases the mean percentage was far below the standard. The overall mean for the content of home management and safety net advice was 40% (figure). The variation between cases was from 26% for the case of an adult with fever to 56% for the case of an adult with a nosebleed. On average, 54% of all questions asked were obligatory questions. This percentage varied from 32% to 73% between cases and from 46% to 65% between out of hours centres.

The figure shows the difference in performance between individual triagists at the same out of hours centre. Some managed a score of almost 90% for relevant home management and safety net advice, and others gave none at all.

The same triagist handled the same case twice in 3% of the calls; all other calls were handled by different triagists. The triagists referred 2% of the telephone incognito standardised patients to the out of hours centre in the region of their permanent residence without any triage. None of the 17 out of hours centres indicated that they had detected any call made by a telephone incognito standardised patient.

For 153 calls the required care advice resulting from the telephone triage was to come to the out of hours centre. This care advice was given on 17 occasions, on seven of which no clinical reason for coming could be identified.

DISCUSSION

The results of this study identify shortcomings and educational needs in telephone triage, indicated by assessing the quality of phase one (asking appropriate questions and evaluating the answers) and phase two (giving care advice) of the process of telephone triage. The mean score for obligatory questions asked was 21% of the agreed standard. Answers to obligatory questions were not always evaluated clinically correctly. The appropriate triage outcome was reached in only 58% of calls.

Strength and weaknesses

Triagists are known to respond very accurately to cases of high urgency but not to moderate and low urgency cases such as those presented in this study.[10] Our study shows underestimation of urgency in 41% of calls and overestimation of urgency in 1%, which is in line with other results.[11-13] As none of the 17 out of hours centres had detected any of the telephone incognito standardised patients and different triagists handled 97% of all calls, we conclude that this study reflects the day to day performance of call handling at those centres.

Cases, protocols, and scenarios

In our study many obligatory questions remained unasked, and triagists often asked questions that the protocol and scenario panels did not consider necessary to determine an urgency level. Research shows that triagists often ask few questions and do not use or follow protocols. The safety of any care process is likely to be improved by following protocols, but little is known about what extent of improvement might occur.

Conclusion

Triagists seemed to carry out a rapid clinical scan before they came to a conclusion, without considering in sufficient detail different causes for a symptom or its possible consequences. Even when the triagist gave the required self care advice, for nearly all calls this choice could be considered to be the correct choice only by means of an educated guess as so few obligatory questions were asked. This study also shows that triagists should ideally recommend a low urgency level of care only after thorough history taking. The quality of information on home management and safety net advice varied to a large extent and was consistently low for each case and each out of hours centre. The safety of telephone triage might be enhanced by using computer based decision support systems,[14 15] but further research is needed.

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Provenance and peer review: Not commissioned; externally peer reviewed.

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Misperceptions and misuse of Bear Brand coffee creamer as infant food: national cross sectional survey of consumers and paediatricians in Laos

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ABSTRACT

Objective To investigate the use of Bear Brand coffee creamer as a food for infants and the impact on consumers of the logo of a cartoon baby bear held by its mother in the breastfeeding position.

Design Interviews with paediatricians throughout the country and a national survey of potential consumers regarding their perceptions and use of the Bear Brand coffee creamer.

Setting 84 randomised villages in south, central, and northern Laos.

Participants 26 Lao paediatricians and 1098 adults in households in a cluster sampling.

Results Of the 26 paediatricians, 24 said that parents "often" or "sometimes" fed this product to infants as a substitute for breast milk. In the capital city, paediatricians said that mothers used the product when they returned to work. In the countryside, they reported that poor families used it when the mother was ill or had died. Of 1098 adults surveyed, 96% believed that the can contains milk; 46% believed the Bear Brand logo indicates that the product is formulated for feeding to infants or to replace breast milk; 80% had not read the written warning on the can; and over 18% reported giving the product to their infant at a mean age of 4.7 months (95% confidence interval 4.1 to 5.3).

Conclusion The Bear Brand coffee creamer is used as a breast milk substitute in Laos. The cartoon logo influences people's perception of the product that belies the written warning "This product is not to be used as a breast milk substitute." Use of this logo on coffee creamer is misleading to the local population and places the health of infants at risk.

INTRODUCTION

The international code of marketing of breast milk substitutes is intended as a minimum requirement by all governments and aims to protect infant health by preventing inappropriate marketing of breast milk substitutes.[1] Product labels are often the only source of information available to consumers regarding the content and uses of a product, and public interest groups have documented multiple instances of formula companies providing misleading information on infant formula labels.[2]

In Laos a popular coffee creamer is marketed with an illustration of a mother bear holding a baby bear in the breastfeeding position (figure). The manufacturing company uses the same Bear Brand logo on its canned sterilised cows' milk product and on infant formula products for infants from 6 months. A warning on the can states "This product is not to be used as breast milk substitute" in English, Thai, and Lao. There is also an illustration of a feeding bottle with a cross through it.

We have encountered infants and children admitted to hospital with protein calorie malnutrition who were

Label from Bear Brand coffee creamer

fed this product exclusively. We conducted two surveys to determine whether or not the practice of feeding this coffee creamer to infants is widespread in Laos. We also explored the impact of the logo on people's perception of the product's appropriateness for infants.

METHODS

Laos is one of the poorest countries in southeast Asia. It is a multiethnic and multilingual country with more than 45 languages spoken. Literacy rates range from 54% in rural areas to 89% in urban areas.[3] There is a high prevalence of stunting (41%) and wasting (15%) among children (0-5 years).[4 5] In Laos, 95% of the mothers breast feed their newborn children but the rate of exclusive breast feeding is below 28%.[6] Inadequate breast feeding and weaning practices contribute to high rates of malnutrition and infant and child mortality.[7 8]

One author (LMS) interviewed 26 paediatricians in eight of the 17 provinces to collect information on parents' use of the Bear Brand coffee creamer as a substitute for breast milk. In 2007 we conducted a sample survey in Laos in five representative provinces. We randomly selected and enrolled 84 villages and an average of 14 households with one adult aged over 18 from each. A semistructured questionnaire examined knowledge and use of the coffee creamer with the Bear Brand logo. Participants gave their informed consent to participate in the survey.

Table 1 | Responses of 1023 adults when asked "What does this logo mean?" (respondents shown Bear Brand logo, see figure)

Response	No (%)
Product is good for infants	402 (39.3)
Product is good for children	115 (11.2)
Advertising	110 (10.7)
Product is replacement for breast milk	66 (6.5)
Product is for adults	13 (1.3)
Product is made from animals	6 (0.6)
Bears love their children	4 (0.4)
Product is for everyone	3 (0.3)
Not sure	242 (23.7)
Other response	2 (0.2)

We calculated that we needed a sample size of 983 people, based on an estimated use of coffee creamer of 20%, a 4% precision with α=0.05, and 90% power, and we added 10% more people to account for incomplete data, resulting in a sample of 1080.

RESULTS

Of the 26 paediatricians interviewed, 13 reported that parents "often" feed the Bear Brand coffee creamer to infants as a substitute for breast milk. Eleven reported that parents "sometimes" feed the product to infants. Paediatricians in Vientiane reported that mothers use the product when they return to work. In the countryside poor families use the product as a breast milk substitute when the mother is ill or dies. Paediatricians have encountered infants and children admitted to hospital with protein calorie malnutrition who had been fed this product exclusively and often reported similar stories (see bmj.com).

Of 1098 respondents, 570 (51%) lived in remote rural area, 364 (33%) lived in a semirural area, and 164 (15%) lived in an urban area. Of the adults interviewed, 1031/1098 (94%) recognised the can; 994/1031 (96%) believed that it contained milk; and only 21/1031 (2%) identified the contents correctly as coffee creamer. In total, 191 (19%) reported giving the coffee creamer with the Bear Brand logo to infants at a mean age of 4.7 months (95% confidence interval 4.1 to 5.3). The main reasons given were that they thought it complemented breast feeding (40%), was good for infants' growth (19%), was a substitute for breast milk (17%), and was cheap (11%).

Of 1031 people, 824 (80%) said they had not read the text warning on the can. Tables 1 and 2 describe the respondents' understanding of the Bear Brand logo and the feeding bottle with a cross through it.

DISCUSSION

Bear Brand coffee creamer is a recognised and well distributed product in diverse parts of Laos. Nearly half of surveyed adults believe that the cartoon logo on the can means that the product is "good for infants" or "a replacement for breast milk." Nearly a fifth of parents had given the product to their young infants.

Table 2 | Responses of 1018 adults when asked "What does this picture mean" (respondents shown picture of feeding bottle with cross through it, see figure)

Response	No (%)
Never noticed it/don't know	557 (49.7)
Product not for infants	319 (31.3)
Product should not be given by bottle	98 (9.6)
Product is dangerous	16 (1.6)
Product is good for babies	10 (1.0)

Paediatricians confirmed that parents use this product as a substitute for breast feeding.

Nearly half of respondents did not notice the written warning on the label or the picture of a baby's bottle with a cross through it. Some (12%) did not understand the meaning of the cross through the bottle. The cartoon bear and her cub seem to provide the most salient misinformation, and the warnings on the label are inadequate to ensure safe and appropriate use of this product. The data suggest that the image of the Bear Brand misleads parents, who believe the coffee creamer is a suitable food for babies.

Protection of breast feeding by limiting the active promotion of the use of breast milk substitutes by formula companies is the central goal of the international code of marketing of breast milk substitutes.[9-11] The sugar based coffee creamer, according to its label, is "not . . . a breast-milk substitute." The logo on the label of the bear holding a cub in the breastfeeding position, however, conveys quite the opposite message, making this a somewhat different type of code violation.

Strengths and limitations

Our study was limited by quota samples in four diverse Lao provinces. We interviewed more women and participants were from less remote villages with limited ethnic diversity. As our sample was more literate than the national average (90% *v* 70%), we might have underestimated the level of misconceptions and the nationwide use of the coffee creamer as a substitute for breast milk because secondary education was associated with a lower risk of giving the coffee creamer to infants (unpublished data). Our research was limited to Laos, so the relevance to other southeast Asian countries is not known.

Conclusion

The Bear Brand logo's non-verbal message implies that the product contained is intended for infants. The powerful visual message is not mitigated by the addition of warning text or by the confusing symbol of the feeding bottle with a cross through it. The sale of coffee creamer with this logo places the health of infants and children at risk in a developing nation that already has extreme levels of malnutrition.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Exclusive breast feeding protects infant health and is recommended for the first 6 months of life

The international code on marketing of breast milk substitutes aims to protect infant health by preventing inappropriate promotion of breast milk substitutes and is considered the minimum requirement to be adopted by all governments

Violations have been reported and addressed

WHAT THIS STUDY ADDS

A cartoon bear holding a cub in the breastfeeding position pictured on cans of coffee creamer implies that the product is suitable for young infants, despite a written warning to the contrary

This product is widely available in the country of Laos and is commonly given to young infants

Use of this logo on coffee creamer is misleading to the local population and places the health of infants at risk

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