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**Randomised clinical trial: *Helicobacter pylori* eradication is associated with a significantly increased body mass index in a placebo-controlled trial**

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1  
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6 **Running head**

7 The impact of *H. pylori* eradication on BMI and weight  
8

9 **Keywords**

10 *Helicobacter pylori*, body mass index, weight, randomised controlled trial, obesity,  
11 dyspepsia  
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## ABSTRACT

### Background

Body mass index (BMI) increased following *Helicobacter pylori* eradication in several Japanese cohorts which requires further investigation.

### Aim

To determine the impact of *H. pylori* eradication on BMI in a European population.

### Methods

10,537 unselected people aged 20-59 years were screened for *H. pylori*. 1558 of the 1634 infected participants were randomised to intervention (eradication therapy: ranitidine bismuth citrate 400 mg and clarithromycin 500 mg twice daily) or placebo for two weeks with follow-up at six months (92%) for weight and dyspepsia symptoms (epigastric pain).

### Results

The mean weight of participants in the intervention group increased from 77.7 kg at baseline to 78.4 kg at six months (unadjusted increase 0.7 kg) and [REMOVE: the participants mean weight changed] from 76.8 kg to 77.2 kg (0.5 kg) in the placebo group. The adjusted difference between [REMOVE: the] randomised groups [REMOVE: at six months] was **statistically significant** at 0.6 kg (95% confidence interval (CI) 0.31, 0.88). **Significantly** more participants gained [REMOVE at least]  $\geq 3$  kg in the intervention group (138/720, 19.2%) compared to the placebo group (92/706, 13.0%) (odds ratio (OR) 1.57 (95% CI 1.17, 2.12)). The mean BMI increased from 27.5 kg/m<sup>2</sup> to 27.8 kg/m<sup>2</sup> at six months in the intervention group compared with 27.0 kg/m<sup>2</sup> to 27.2 kg/m<sup>2</sup> in the placebo group (adjusted difference between groups **was statistically significant** at 0.2 kg/m<sup>2</sup> (95% CI 0.11, 0.31)). Dyspepsia was less frequently reported by intervention group participants (168/736, 22.8%, placebo group 209/711, 29.4%), OR 0.71 (95% CI 0.55, 0.93).

### Conclusions

BMI increased **significantly** following randomisation to *H. pylori* eradication therapy, possibly due to dyspepsia resolution.

## INTRODUCTION

A meta-analysis of observational studies investigating the role of *H. pylori* infection and cardiovascular risk factors concluded that infected individuals had a slightly but significantly higher body mass index (BMI)(1). Some recent studies with representative populations have also observed an association of *H. pylori* infection with BMI (2-4), whereas others, such as the NHANES III study, have not(5). These conflicting results highlight the difficulties in identifying an association with cross-sectional study designs where individuals differ by factors other than *H. pylori* infection status, for example age and gender, so potentially confounding the association.

The impact of *H. pylori* eradication on BMI and weight has been investigated previously in Japan in four cohort studies and one randomised controlled trial. BMI increased by 0.8 kg/m<sup>2</sup> over three years in a trial with 90 non-ulcer dyspepsia patients(6). However, the analysis only included those participants in whom *H. pylori* eradication had been successful. The four observational studies comprised one cohort of industrial workers and three of patients with peptic ulcer disease or gastritis. BMI and weight were increased after *H. pylori* eradication in these cohort studies when compared to either individuals where eradication had failed,(7-9) or to controls matched for age and sex(10).

We have investigated the impact of *H. pylori* eradication on BMI, weight and dyspepsia in a large population-based randomised controlled trial. This trial utilises a robust placebo-controlled design and also explores the role of a potential causal mechanism, namely dyspepsia.

## MATERIALS AND METHODS

### Study population

This study is nested in a large randomised controlled trial of the effects of *H. pylori* eradication on the symptoms, treatment and costs of dyspepsia (described fully elsewhere)(11;12). In brief, 26,203 individuals unselected for dyspepsia symptoms, aged 20-59 years and registered at seven general practices in South West England were invited by letter to participate between 1996 and 1999. 10,537 attenders were screened for *H. pylori* infection using the <sup>13</sup>C-labeled urea breath test (UBT) and infected participants were randomised to an intervention of *H. pylori* eradication therapy or placebo. The local research ethics committee approved the study and written informed consent was obtained from participants (trial registration ISCTRN44816925).

### Study design

This is a randomised placebo controlled trial (Figure 1). Participants who tested positive for *H. pylori* with the UBT (using a standard test meal of citric acid and orange juice with a cutoff of  $C\delta^{13} 3.5$  per  $cm^3$ ) (13) were randomised either to *H. pylori* eradication therapy (ranitidine bismuth citrate 400 mg and clarithromycin 500 mg twice daily for two weeks) or to placebo. Randomisation was stratified by gender and age (20-29, 30-39 40-49 and 50-59 years). Staff independent of the study prepared the randomisation sequence, which was generated by computer with a block size of 10. Medication packs were prepared by pharmacists who had no contact with participants and were dispensed by research nurses who were blind to the allocation. *H. pylori* status was assessed in both groups by a UBT six months after randomisation. All participants and research staff were blinded to the allocation and the UBT results until trial completion at two years. Two year follow-up in randomised participants was by postal questionnaire to collect symptoms and medical note review for the primary outcome (without no repeat of anthropometric measures). The primary outcome of the overall trial was consultations in primary care at two years. There was

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3 no further follow-up of *H. pylori* negative participants after the initial screening  
4 phase.  
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### 8 9 **Data collection and outcome measures**

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12 Height and weight (without coats or shoes) were measured at enrolment by research  
13 nurses using a stadiometer and a beam balance. Weight was measured at six months  
14 only in randomised participants. Participant socio-demographics and lifestyle  
15 characteristics (e.g. smoking status) were collected at baseline. Dyspepsia frequency  
16 (defined as epigastric pain) over the previous three month period was measured with  
17 five-point Likert scales rated from 1 (none) to 5 (daily) in validated participant-  
18 completed questionnaires(14;15). Regular or frequent symptoms were defined by the  
19 questionnaire developers as occurring on two or more occasions over each of the  
20 previous three months. Dyspepsia symptoms were measured at enrolment and six  
21 months in all randomised participants. Participants who did not attend follow-up  
22 appointments or had moved from the area were posted questionnaires.  
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### 34 **Statistical analyses**

#### 35 *Baseline data*

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38 Analyses included all *H. pylori* positive participants (1634) and a computer-generated  
39 random sample of the uninfected participants (3268/8901, 36.7%). The sampling  
40 strategy was devised to generate a 2:1 ratio of *H. pylori* negative to positive  
41 participants as a higher ratio may not have increased the precision of estimates and  
42 would have substantially increased study costs. BMI was calculated as the weight (kg)  
43 divided by the square of the height (metres) whilst obesity was defined as a minimum  
44 BMI of 30 kg/m<sup>2</sup>. Mean weight and BMI were compared in turn between infected and  
45 uninfected individuals using regression models, the crude differences in means being  
46 presented with 95% confidence intervals (95% CI). Adjusted differences of means  
47 were obtained by controlling for confounders of BMI and weight by adding the  
48 following measures as covariates in the regression models, namely age (bands 20-39,  
49 40-49, 50-59 years with the lowest two groups combined as few participants were in  
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3 the youngest age group (12)), gender, adult social class (categorised as social class I  
4 and II = professional, III = skilled, IV and V = partly or unskilled), childhood social  
5 class (owner-occupied accommodation or rented/other), smoking status (never, past  
6 and current) and alcohol consumption (low = less than 14 units/week for women or 21  
7 units for men and high = greater than 13 units for women or 20 units for men).  
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9 Ethnicity was excluded from the analyses as the study population was predominantly  
10 white (97%). Similar logistic regression models estimated the associations of  
11 dyspepsia and obesity with *H. pylori* infection as odds ratios (OR). Adjustment was  
12 also made for potential clustering by residential location by including general practice  
13 in the models (Stata version 10; College Station, Texas, USA).  
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### 23 *Randomised trial data*

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27 The primary outcome of the nested study was the impact of randomisation to *H. pylori*  
28 eradication on BMI and weight at six months. The overall trial sample size calculation  
29 of 1550 participants was based on rates of consultation for dyspepsia in primary care  
30 at two years(12). There were five planned secondary analyses in this trial(11). No  
31 power calculation or analysis plan existed for this nested study due to the exploratory  
32 nature of the hypothesis and the absence of prior high quality evidence. Differences in  
33 means were the effect measure estimates calculated by the ANCOVA(16) technique  
34 that incorporates baseline covariates in the analytic model to account for chance  
35 baseline differences between randomised groups. Analyses were also adjusted for the  
36 randomisation strata of age and gender. We also explored whether a paired data  
37 method comparing the mean individual weight differences between the two  
38 randomised groups altered the effect estimates. Data are presented with 95% CI.  
39 Analyses (unless specified otherwise) were conducted on an intention-to-treat basis  
40 (ITT) with all randomised individuals included in the analysis regardless of  
41 subsequent *H pylori* status. Analyses utilised an approach based on levels of evidence  
42 rather than p value thresholds(17). Dyspepsia symptoms and the numbers of obese  
43 participants at six months were each compared on an ITT basis between the two  
44 groups as randomised with the intervention effect estimate presented as ORs. An  
45 exploratory sub-group analyses in the intervention group investigated the weight of  
46 individuals with dyspepsia at six months compared with those without symptoms  
47 (including participants whose symptoms had resolved from baseline measurement).  
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3 The lowest two age strata (20-29 and 30-39 years) were combined for all the analyses  
4 as there were fewer participants due to the inverse relationship of *H. pylori* prevalence  
5 and age(12).  
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## RESULTS

### Study population

The 10,537 participants had a mean age of 45.8 years (SD 8.95) and 46 % were male. Participants infected with *H. pylori* were heavier than uninfected individuals although this was no longer apparent with confounding controlled (0.4 kg, 95% CI -0.47, 1.22)(Table 1). BMI also did not differ by *H. pylori* status (0.3 kg/m<sup>2</sup> following adjustment, 95% CI 0.0, 0.57). Obesity was more prevalent in *H. pylori* infected participants compared with uninfected participants with an adjusted odds ratio of 1.19 (95% CI 1.02, 1.38) (Table 1). Dyspepsia symptoms did not differ by *H. pylori* status (805/3156, 25.5% negative: 402/1564, 25.7% positive, OR 0.988, 95% CI 0.86, 1.83).

### *H. pylori* prevalence and eradication

1636 participants were positive for *H. pylori* (15.5%). 1558 participants agreed to be randomised (95%) with 787 randomised to the intervention and 771 to placebo (Figure 1). Random allocation resulted in two groups that were comparable for the measured baseline variables (Table 2). Follow-up of randomised participants at six months was 92% (1427). The rate of *H. pylori* eradication in the intervention group was 90.7% (659/727). At two years participants reported what sort of tablets they thought they had received or whether they were unsure (266 participants guessed that they had received active treatment at two years in the eradication group compared with 241 expected by chance ( $\chi^2 = 1.90$ ,  $p = 0.1683$ ), indicating that blinding had been successful.

### BMI, weight and dyspepsia following *H. pylori* eradication therapy

The differences in the unadjusted weight and BMI over six months in both randomised groups is shown in Figure 2. The overall difference in mean weight between the randomised groups was 0.6 kg (95% CI 0.31, 0.88) at six months (Table 3). The paired data analysis also gave an effect estimate of 0.6 kg, 95CI 0.30, 0.87). The overall difference in mean BMI was 0.2 kg/m<sup>2</sup> (95% CI 0.11, 0.31). In the intervention group more participants gained at least 3 kg over six months following randomisation (138/720, 19.2%) compared to the placebo group (92/706, 13.0%),

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3 giving an OR of 1.58 (1.19, 2.10). There was also a greater proportion of obese  
4 participants in the eradication group (26.2%) compared to the placebo group (22.1%)  
5 but this was not statistically significant (Table 3).  
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10 Dyspepsia symptoms were less frequently reported by the intervention group  
11 participants (168/736, 22.8%) compared with those in the placebo group (209/711,  
12 29.4%). The OR for dyspepsia reduction in the intervention group was 0.71 (95% CI  
13 0.55, 0.93). In a sub-group analysis of participants in the intervention group with and  
14 without dyspepsia at six months the adjusted effect estimate for weight between the  
15 two groups was 0.6 kg (95% CI 0.23, 0.90).  
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## DISCUSSION

Randomisation to *H. pylori* eradication therapy resulted in a mean weight gain of 0.6 kg and an increase in BMI of 0.2 kg/m<sup>2</sup> within six months compared with participants who had received placebo. A higher proportion of individuals gained at least 3kg over the six months in the intervention group. Dyspepsia symptoms were less frequent in the intervention group at six months and may provide a potential casual pathway for the recorded increases in BMI and weight.

There are several strengths to this study, notably the randomised study design which enrolled a large community-based population of both sexes over a wide age range. The UBT detection method minimised *H. pylori* misclassification by identifying only those individuals with current infections (most of the previous cross-sectional studies were based on ELISA tests which also detect past infections). An efficacious *H. pylori* eradication regime reduced contamination of the intervention group through individuals with failed eradication whilst the successful concealment of treatment allocation and blinding of participants and study staff ensured unbiased assessment of outcomes(11). Nevertheless, limitations exist to this study because it was nested within a longer term trial so these results warrant confirmation in other populations and countries. The principal limitation is the duration of follow-up as weight and BMI gains have been observed previously for up to three years after *H. pylori* eradication (6) but the overall trial follow-up at two years was by postal questionnaire and medical note review with no anthropometry. Lifestyle changes which could have influenced BMI e.g. smoking cessation, increased alcohol consumption and levels of exercise were not measured again at six month follow-up, but successful blinding of participants and trial staff with a placebo comparator should have ensured that any such effects were distributed by chance across the two groups. Blood samples were not taken to maximise trial participation but they could have been used to investigate biological intermediates more recently identified on the putative causal pathway. There was also no opportunity to measure the weight and BMI of the *H. pylori* negative participants again as trial follow-up was restricted to randomised individuals due to logistics and funding.

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3 A meta-analysis of 18 observational studies of cardiovascular risk factors and *H.*  
4 *pylori* concluded that BMI was slightly greater in infected individuals(1). This study  
5 found no difference in BMI by *H. pylori* status which concurs with some recent  
6 population-based studies(5;8;18;19) although several other studies showed an  
7 association,(2-4) which may reflect the various geographical origins of the  
8 populations or the degree of adjustment for confounding.  
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16 All previous studies on the impact of *H. pylori* eradication on BMI were conducted in  
17 Japan where the mean population BMI is markedly lower than in western countries  
18 and obesity is classified at 25 kg/m<sup>2</sup> rather than 30 kg/m<sup>2</sup> as in the rest of the  
19 world(20). There are also other differences between Asian and non-Asian countries in  
20 the patterns of *H. pylori* and gastritis, the relative frequency of different *H. pylori*  
21 sub-types and the incidence of gastric cancer(21). The analysis of a randomised trial  
22 of *H. pylori* eradication in non-ulcer dyspeptic patients was not conducted on an ITT  
23 basis so the gain in BMI was only measured in those individuals with successful  
24 eradication so is difficult to interpret more generally(6). In four cohort studies with  
25 industrial workers or patients with peptic ulcer disease, non-ulcer dyspepsia or  
26 gastritis, BMI increased following *H. pylori* eradication compared to individuals  
27 where eradication therapy failed (6-9) or to age and sex matched controls(10).  
28 However, no adjustment was made for confounding in any cohort study.  
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41 The improvement in dyspepsia symptoms observed in this study at six months in the  
42 intervention group and previously reported at two years(11) may have stimulated the  
43 appetite and subsequently caused the gain in weight and BMI through increased food  
44 intake. An exploratory sub-group analyses of intervention group individuals who had  
45 resolution of dyspepsia symptoms did not show a greater weight gain than the overall  
46 comparison but the lack of statistical power for this analysis does not make this a  
47 robust finding. Hyperlipidaemia was also shown to increase following *H. pylori*  
48 eradication in two Japanese studies(8;10). Some of these effects may be mediated  
49 through hormonal systems by ghrelin and leptin, two peptides located in the stomach  
50 wall which regulate food intake and appetite (ghrelin negatively and leptin  
51 positively)(22;23). Studies in healthy volunteers,(5;19;24) however, found no  
52 association of serum leptin with *H. pylori* status nor changes following *H. pylori*  
53 eradication in patients with chronic gastritis or in healthy volunteers(7;25). However,  
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3 gastric leptin values were elevated in *H. pylori* infected individuals and decreased  
4 following eradication(26). Plasma ghrelin levels were lower in *H. pylori* positive  
5 individuals in some studies,(19;27;28) although two small studies differed as to  
6 whether levels altered following eradication.(25;27) Recently, *H. pylori* eradication  
7 increased weight and decreased plasma ghrelin levels (but increased gastric levels) in  
8 men participating in a Japanese gastric cancer surveillance programme(29). Large  
9 studies now are required to clarify the role of these peptides to mediate the influence  
10 of *H. pylori* eradication on BMI.  
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19 Randomisation to *H. pylori* eradication therapy increased BMI in a large population-  
20 based randomised trial after six months. These changes could become clinically  
21 significant if the weight gain continued as indicated by previous cohort studies. *H.*  
22 *pylori* eradication may possibly be contributing in part to the recent dramatic rise in  
23 obesity in Western populations given the concurrent decline in prevalence but this  
24 hypothesis relies on the far less robust ecological evidence and requires further  
25 investigation(30;31). Currently, patients being treated with *H. pylori* eradication  
26 therapy should be advised of the possibility of weight gain following eradication  
27 given that obesity is a risk factor for many other diseases, including GORD(32) and  
28 cardiovascular disease(1).  
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3 This research was presented at the American Gastroenterology Association meeting  
4 in May 2003 and was subsequently published in abstract form (*Gastroenterology*  
5 2003; 124 S4:A622).  
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### 10 **Contributors**

11 JAL ran the project on a daily basis, analysed the results and wrote the paper. RH  
12 conceived and designed the study and helped write the final version of the paper. PN  
13 helped initiate the project. LM, IH and JD helped plan the project and produce the  
14 final version of the paper. JAL wrote the initial draft of the paper and all authors  
15 contributed to the final version. JAL is the guarantor.  
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24 programme (South and West) and GlaxoSmithKline (GSK).  
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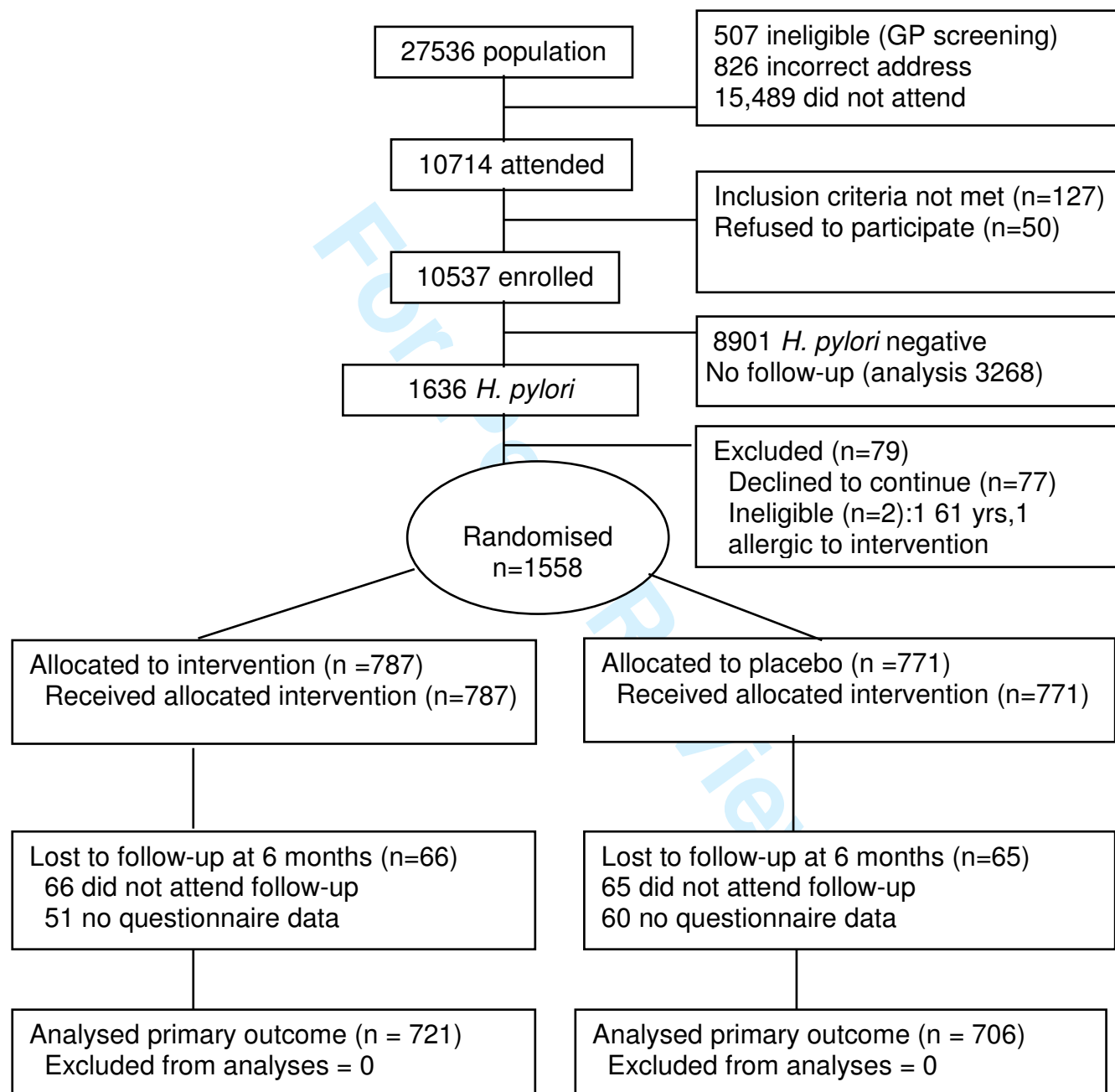
### 29 **Competing interests statement**

30 The randomisation sequence was generated by one of the funders (GSK) but the  
31 sponsors had no further role in the study design, data collection, analyses or writing  
32 up of reports and publications. JAL and RH received financial support from GSK to  
33 attend the American Gastroenterology Association meeting in May 2000.  
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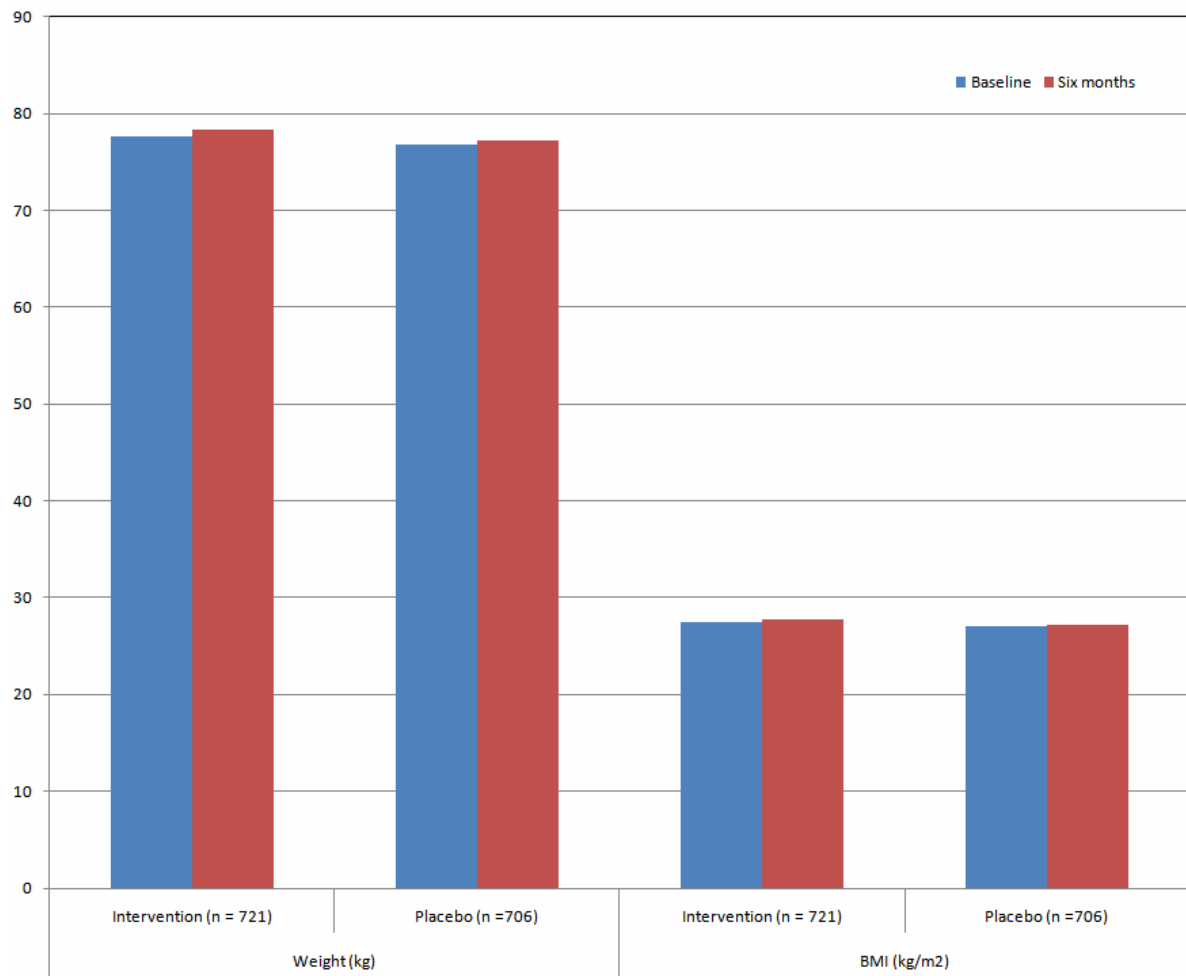
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46 medication respectively and Dr Chris Metcalfe of the School of Social and  
47 Community Medicine for statistical advice.  
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Figure 1 Trial profile



**Figure 2** Mean unadjusted weight and BMI at randomisation and six months later in the intervention and placebo groups



**Table 1** BMI, weight and frequency of obesity in *H. pylori* positive and negative individuals prior to randomisation of infected individuals

	<i>H. pylori</i> positive (n = 1632)	<i>H. pylori</i> negative (n = 3260)	Effect measure estimate	Unadjusted effect (95% CI)	Adjusted effect (95% CI) <sup>a</sup>
Mean BMI kg/m <sup>2</sup> (SD)	27.2 (4.6)	26.7 (4.5)	Difference in means	0.6 (0.28, 0.82)	0.3 (0.00, 0.57)
Mean weight (kg)(SD)	77.2 (15.4)	75.9 (14.9)	Difference in means	1.2 (0.34, 2.13)	0.4 (-0.44, 1.28)
Number of obese (%)	382 (23.4)	638 (19.6)	Odds ratio	1.26 (1.09, 1.45)	1.19 (1.02, 1.39)

<sup>a</sup>Adjusted for age, gender, adult and childhood social class, general practice, smoking status and alcohol consumption.

**Table 2** Characteristics of *H. pylori* infected participants at randomisation

	Intervention group (%) (n = 787)	Placebo group (%) (n = 771)
<b>Sex</b>		
Men	385 (49.0)	378 (49.0)
Women	402 (51.1)	393 (51.0)
Mean age in years (SD)	48.4 (8.0)	48.6 (7.9)
<b>Socioeconomic status*</b>		
I and II	233 (30.0)	233 (30.7)
III	387 (50.0)	363 (47.8)
IV and V	155 (20.0)	164 (21.5)
<b>Ethnic origin</b>		
White <sup>+</sup>	758 (97.1)	748 (97.9)
Non-white	23 (2.9)	16 (2.1)
<b>Smoking status</b>		
Never	405 (52.8)	389 (50.9)
Past smoker	179 (23.3)	190 (24.9)
Current smoker	183 (23.9)	185 (24.2)
<b>Alcohol consumption</b>		
None	145 (19.5)	123 (17.0)
Low alcohol intake	541 (72.8)	534 (74.0)
High alcohol intake <sup>**</sup>	57 (7.7)	65 (9.0)
<b>NSAID usage</b>		
None	558 (76.5)	526 (72.7)
Less than daily	132 (18.1)	154 (21.3)
Daily	39 (6.0)	43 (6.0)
<b>Dyspepsia symptoms<sup>\$\$</sup></b>	185 (24.3)	194 (26.6)
<b>Anthropometry</b>		
Height (cm) (SD)	167.7 (9.2)	168.3 (8.9)
Weight (kg) (SD)	77.7 (15.9)	76.8 (15.1)

\* Social class; I and II = professional, III = skilled occupation, IV and V = partly or unskilled occupations

<sup>+</sup>Non-white participants grouped due to low numbers enrolled

<sup>\*\*</sup> Greater than 20 units per week for men and 13 units for women

<sup>\$\$</sup> Epigastric pain symptoms on two or more occasions in each of the previous three months

**Table 3** BMI, weight and frequency of obesity six months after randomisation to *H. pylori* eradication therapy or placebo

	Placebo group (n = 706)	Intervention group (n = 721)	Effect measure estimates	Unadjusted effect (95% CI)	Adjusted effect (95% CI) <sup>a</sup>
Mean BMI in kg/m <sup>2</sup> (SD)	27.2 (4.5)	27.8 (4.8)	Difference in means	0.6 (0.15, 1.11)	0.2 (0.11, 0.31)
Mean weight in kg (SD)	77.2 (15.2)	78.4 (15.8)	Difference in means	1.2 (-2.8, 0.41)	0.6 (0.31, 0.88)
Number of obese (%)	156 (22.1)	189 (26.2)	Odds ratio	1.25 (0.98, 1.60)	1.30 (0.81, 2.10)

<sup>a</sup>Adjusted for age, gender and baseline values of the outcome.

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**CONSORT checklist: full details reported in the 2006 BMJ paper (332:199-204)**  
**Randomised controlled trial of *Helicobacter pylori* eradication and dyspepsia,**  
**health resource utilisation and quality of life: Bristol Helicobacter project**

J Athene Lane, LJ Murray, S Noble, M Egger, IM Harvey, JL Donovan, P Nair, RF Harvey

	Number	Descriptor	Page number
<b>Title and abstract</b>	1	How participants were allocated to interventions (eg, "random allocation", "randomised", or "randomly assigned").	1-2
<b>Introduction</b>			
Background	2	Scientific background and explanation of rationale.	3
<b>Methods</b>			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected	4
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	4
Objectives	5	Specific objectives and hypotheses.	4-5
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors, &c).	4-5
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	2006
Randomisation			
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).	2006
Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	2006
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	2006
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were aware of group assignment. If not, how the success of masking was assessed.	2006
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	5
<b>Results</b>			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	2006 Fig 1
Recruitment	14	Dates defining the periods of recruitment and follow-up.	4
Baseline data	15	Baseline demographic and clinical characteristics of each group.	2006
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	6 table 2
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g. 95% confidence intervals)	6 table 2
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	na
Adverse events	19	All important adverse events or side-effects in each intervention group	2006

<b>Discussion Interpretation</b>	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	7-9
<b>Generalisability</b>	21	Generalisability (external validity) of the trial findings.	7-9
<b>Overall evidence</b>	22	General interpretation of the results in the context of current evidence.	7-9

For Peer Review