(such as age and social class) are found to be associated, even after adjustment, it seems sensible to treat such associations with caution until evidence of causality can be obtained—in this case from a prospective randomised controlled trial of the eradication of *H pylori* infection. We therefore believe that eradication of *H pylori* infection on the grounds of the risk of cardiovascular disease alone, like that of gastric cancer alone,⁴ is not supported by the current evidence.

BRENDAN C DELANEY
Lecturer in general practice
F D RICHARD HOBBS
Professor of general practice
ROGER HOLDER
Lecturer in statistics

Department of General Practice,
University of Birmingham,
Birmingham B15 2TT

- 1 Patel P, Mendall MA, Carrington D, Strachan DP, Leatham E, Molineaux N, *et al*. Association of *Helicobacter pylori* and *Chlamydia pneumoniae* infections with coronary heart disease and cardiovascular risk factors. *BMJ* 1995;311:711-4. (16 September.)
- 2 Delaney BC, Kenkre JE, Hobbs FDR. A whole blood NPT for antibodies to *H pylori*: effect on the management of dyspepsia in primary care [abstract]. *Fam Pract* 1995;12:263-4.
- 3 Webb PM, Knight T, Greaves S, Wilson A, Newell DG, Elder J, *et al*. Relation between infection with *Helicobacter pylori* and living conditions in childhood: evidence for person to person transmission in early life. *BMJ* 1994;308:750-3.
- 4 EUROGAST Study Group. An international association between *Helicobacter pylori* infection and gastric cancer. *Lancet* 1993;341:1359-62.

Authors' reply

EDITOR,—Brendan C Delaney and colleagues point out that the association between seropositivity for antibodies to *Helicobacter pylori* and coronary heart disease (based on history alone) in our study failed to reach significance. It is more important, however, to look at the odds ratio and confidence interval. We suggest that an odds ratio of 1.87 (95% confidence interval 0.87 to 4.02) is important in a common disease like coronary heart disease.

The reason for Delaney and colleagues' failure to find an association between *H pylori* infection and a history of ischaemic heart disease (as ascertained from general practice records) is unclear, but selection bias may have been a problem as the subjects were all attending their general practice. In any event, the confidence interval for the odds ratio that they observed (0.63 (0.32 to 1.26)) overlaps ours. An association of a similar magnitude to that observed in our study has been reported recently in a large population based study of 2000 subjects aged 25-65 that used the Rose angina questionnaire to define coronary heart disease. The odds ratio for *H pylori* infection in patients with coronary heart disease as defined by the questionnaire was 1.68 (0.89 to 3.10) in men after adjustment for age, smoking, and social class.¹ Furthermore, the association between *H pylori* infection and coronary heart disease was shown in patients with disease evident on angiography in our original study² and in patients with myocardial infarction in another study.³

With regard to the predictive value of electrocardiographic findings of coronary heart disease, we would refer Delaney and colleagues to the Whitehall study, in which the abnormalities we chose were validated in relation to subsequent death from coronary heart disease.⁴ Most electrocardiographic abnormalities involved Q waves (22 patients had *H pylori* infection out of 26 with Q wave abnormalities). Rates of infection in those with ST depression (5/6), T wave inversion (7/11), and left bundle branch block (2/4) were slightly lower, possibly reflecting the reduced specificity of these abnormalities for coronary heart disease.

The relation between *H pylori* and *Chlamydia pneumoniae* infection and coronary heart disease was assessed by logistic regression models with the outcome variables being, in turn, history of angina or myocardial infarction; electrocardiographic

evidence of ischaemia or infarction; and prevalent coronary heart disease (defined as either a history of the disease or electrocardiographic evidence of it). In the model *H pylori* and *C pneumoniae* infections were individually treated as dichotomous variables (0,1) and no separate term for both infections was included as they correlated with each other weakly (as shown in table I in our paper). Furthermore, there was no evidence of statistical interaction between *H pylori* and *C pneumoniae* infection as suggested by the unadjusted data, nor was there an a priori biological reason to suspect this.

Delaney and colleagues are incorrect in saying that generalised linear interactive modelling gives inaccurate results for logistic regression when there are few results in a particular group. The validity of unconditional estimates of regression variables depends on whether the number of variables fitted approaches the total number of independent observations (study subjects). In our study this ratio was less than 10%.

We appreciate the comment on confounding by age and social class, but residual confounding was unlikely or small because there was little difference in the odds ratio after adjustment. Finally, we agree (as we stated clearly in our paper) that further studies including interventional and prospective trials need to be carried out to address this issue further.

P PATEL (registrar in gastroenterology), M A MENDALL (consultant gastroenterologist), D CARRINGTON (senior lecturer in virology), D P STRACHAN (senior lecturer in epidemiology), E LEATHAM (senior registrar in cardiology), N MOLINEAUX (research nurse), J LEVY (research assistant), C BLAKESTON (research assistant), C A SEYMOUR (professor in biochemistry and chemical pathology), A J CAMM (professor in cardiology), T C NORTHFIELD (professor in gastroenterology)

St George's Hospital Medical School,
London SW17 0RE

- 1 Murray LJ, Bamford KB, O'Reilly DPJ, McCrum EE, Evans AE. *Helicobacter pylori* infection: relation with cardiovascular risk factors, ischaemic heart disease, and social factors. *Br Heart J* 1995;74:497-501.
- 2 Mendall M, Goggin P, Levy J, Molineaux N, Strachan D, Camm A, *et al*. Relation of *Helicobacter pylori* infection and coronary heart disease. *Br Heart J* 1994;71:437-9.
- 3 Martin-de-Arriba C, Boixeda D, Canton R, Gisbert JP, Fuentes A. High seroprevalence of *Helicobacter pylori* infection in coronary heart disease. *Lancet* 1995;346:310.
- 4 Rose G, Baxter PJ, Reid DD, McCartney P. Prevalence and prognosis of electrocardiographic findings in middle-aged men. *Br Heart J* 1978;40:636-43.

Increasing prescription of drugs for secondary prevention of myocardial infarction

Authors' recommendations are too restrictive

EDITOR,—Janet Smith and Kevin S Channer state that "there are few published data on the efficacy of multiple combinations for secondary prophylaxis" after acute myocardial infarction.¹ Consequently, they recommended to colleagues the long term use of aspirin and one other drug. We assume that the second drug was most commonly either a β blocker or an angiotensin converting enzyme inhibitor. We believe that this commonly adopted approach is much too restrictive.

The Norwegian timolol trial² and the β blocker heart attack trial of propranolol³ reported a major survival benefit in patients with clinical evidence of heart failure. Indeed, the criteria used to define this subgroup in the β blocker heart attack trial formed the basis of the inclusion criteria in the acute infarction ramipril efficacy study.⁴ Furthermore, in the latter study, as with the other trials of angiotensin converting enzyme inhibitors, at least a quarter of patients selected for treatment were receiving a β blocker at the time of randomisation.⁵ This subgroup also showed a sizeable reduction in all cause mortality as a result of treatment with an

angiotensin converting enzyme inhibitor. Taken with similar findings in the survival and ventricular enlargement trial and thetrandolapril cardiac evaluation study,⁶ these data strongly support the use of both agents in some patients.

ROBERT J SAPSFORD
Cardiology research registrar
MIKE B ROBINSON
Senior lecturer in public health
ALISTAIR S HALL
Lecturer in cardiology

University of Leeds,
Leeds LS2 9JT

- 1 Smith J, Channer KS. Increasing prescription of drugs for secondary prevention after myocardial infarction. *BMJ* 1995; 311: 917-8. (7 October.)
- 2 Norwegian Multicentre Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;304:801-7.
- 3 Beta-blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247:1707-14.
- 4 Hall AS, Winter C, Bogle SM, Mackintosh AF, Murray GD, Ball SG. The acute infarction ramipril efficacy (AIRE) study: rationale, design, organization, and outcome definitions. *J Cardiovasc Pharmacol* 1991;18(suppl 2):S105-9.
- 5 Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821-8.
- 6 Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliassen P, Lyngborg K, *et al* for the Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670-6.

Lipid lowering drugs should be considered too

EDITOR,—Janet Smith and Kevin S Channer describe the lack of translation into clinical practice of evidence from trials of secondary prevention of myocardial infarction.¹ It is notable that lipid lowering interventions were not included in the list of treatments used for secondary prevention. While further definitive evidence of the effect on total mortality of lowering cholesterol concentrations in this context was published recently,² a considerable number of studies—for example, the St Thomas's atherosclerosis regression study³—have shown regression of coronary atherosclerosis, and meta-analysis has shown a reduction in mortality from coronary heart disease.⁴ The problem of objectivity in discussions of drug interventions in cardiovascular disease has been described before.⁵

A TAYLOR
Consultant clinical biochemist
J PRECKLESS
Consultant physician

Royal United Hospital,
Bath BA1 3NG

- 1 Smith J, Channer KS. Increasing prescription of drugs for secondary prevention after myocardial infarction. *BMJ* 1995; 311:917-8. (7 October.)
- 2 Scandinavian Simvastatin Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994;344:1383-9.
- 3 Watts GF, Lewis B, Brunt JNH, Lewis ES, Coltart DJ, Smith LDR, *et al*. Effects on coronary heart disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' atherosclerosis regression study (STARS). *Lancet* 1992;339:563-9.
- 4 Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308: 367-72.
- 5 Durrington PN, Bhatnagar D. Wrong lesson from Finnish trial of cardiovascular disease prevention. *Lancet* 1992;339:488.

Managing cleft lip and palate

EDITOR,—The letters¹ commenting on Tony Markus and Peter Ward Booth's editorial on the management of cleft lip and palate² raise the spectre of two surgical specialties at public loggerheads. Unfortunately, the dispute has had important consequences for those who should be able to

get treatment of the highest surgical and ethical standard: the interests of parents and patients may, we fear, be suffering as a result.

In the past two months both the Cleft Lip and Palate Association and the charity Changing Faces have received calls from anxious and confused parents and patients who have been told categorically that one course of surgery is preferable or, worse, that their surgery to date has been poor and needs revision. In our view, this is an unacceptable and unprofessional way for patients to be treated.

Our response to such distressing calls is to emphasise the importance of a multidisciplinary approach to the management of cleft lip and palate so that specialists, including psychologists, speech therapists, and paediatricians, together agree the priorities and objectives for surgery and therefore the most appropriate procedures in consultation with fully informed parents and patients. This is almost impossible at present because plastic surgeons and oral surgeons do not seem to be collaborating in clinical practice; rather, they seem to be in open competition.

As lay people we are unable to judge the strength of the arguments on both sides, and more research over 10-20 years may well be called for. Meanwhile, patients should not be pawns in a professional (unprofessional) feud. The Royal College of Surgeons or some other powerful agency urgently needs to organise discussion in camera before more distress is caused.

GARETH DAVIES
Chief executive

Cleft Lip and Palate Association,
134 Buckingham Palace Road,
London SW1

JAMES PARTRIDGE
Director

Changing Faces,
London W2 1PN

1 Managing cleft lip and palate [letters]. *BMJ* 1995;311:1431-3. (25 November.)

2 Markus T, Ward Booth P. Managing cleft lip and palate. *BMJ* 1995;311:765-6. (23 September.)

Risk of breast cancer is also increased among Danish female airline cabin attendants

EDITOR,—Eero Pukkala and colleagues report the incidence of cancer among a cohort of Finnish airline cabin attendants.¹ Women made up the overwhelming majority of the cohort, and they were found to have an excess risk of cancer of the breast (number of cases observed, 20; standardised incidence ratio 1.87 (95% confidence interval 1.15 to 2.23)). Excess risks were also found for cancer of the bone and leukaemia, on the basis of only two cases of each of these diseases.

In Denmark the incidence of cancer has been monitored for 17 years for the cohort of participants in the 1970 census.² The standardised incidence ratio was calculated for each occupational group on the basis of the incidence for all economically active people. In 1970, 915 women were registered as airline cabin attendants in Denmark, while 362 men were registered as cabin attendants and 620 men as pilots. Table I shows the Danish data for the three types of cancer found in excess among

the Finnish workers. The standardised incidence ratio for breast cancer in the Danish female cabin attendants is 1.61 (0.9 to 2.7), while that in all women in social class I is 1.40. The Danish data thus support the Finnish observation that the risk of breast cancer in female airline cabin attendants is higher than that for their social class.

ELSEBETH LYNGE
Head of department

Danish Cancer Society,
Copenhagen,
Denmark

1 Pukkala E, Auvinen A, Wahlberg G. Incidence of cancer among Finnish airline cabin attendants, 1967-92. *BMJ* 1995;311:649-52. (9 September.)

2 Lynge E, Thygesen L. Occupational cancer in Denmark. Cancer incidence in the 1970 census population. *Scand J Work Environ Health* 1990;16(suppl 2):1-35.

Effect of intensive treatment in insulin dependent diabetes mellitus with microalbuminuria

Sample size was too small

EDITOR,—The Microalbuminuria Collaborative Study Group concludes that intensive glycaemic control has no effect on the progression of albuminuria in people with insulin dependent diabetes mellitus who already have microalbuminuria.¹ These conclusions have important implications for the care of diabetic patients and should not go unchallenged.

The main problem with this study, as the authors admit, is the sample size. If we assume that 21% of patients with microalbuminuria will progress to overt albuminuria, as shown in this and other studies, and we wish to show a reduction in progression by 50% in the intensively treated group (that is, a rate of progression of 10.5%) with 80% power and a significance level of 5%, we would need 412 participants (206 in each group). A more modest reduction in risk would require a larger sample. Thus the inclusion of just 70 patients is not enough, even if the risk of progression in the intensively treated group was close to zero.

The authors quote earlier studies showing significant reductions in risk associated with intensive treatment, which had similar sample sizes to theirs. But these results could partly have been due to a type I error. The authors also quote findings from the diabetes control and complications trial in support of their conclusions. In this trial the difference in the rate of change in albumin excretion rate in the group given intensive treatment compared with the group given conventional treatment was similar in patients with normal albumin excretion to that in patients with microalbuminuria at baseline.² But this difference was significant only in those with normal albumin excretion rates as the number of participants with microalbuminuria was too small to provide adequate power.

The authors' study had two main outcome measures—progression to clinical albuminuria and rate of change in the albumin excretion rate. Only detailed results for the former are presented, and we are not shown how the rate of change in the

albumin excretion rate differed between the two groups. Simply stating that these differences were not significant is inadequate: rates of change for each group, with confidence intervals, should be presented.

Little mention is made of retinopathy in this paper, but the EURODIAB insulin dependent diabetes mellitus complications study has shown that about half the patients with microalbuminuria have some degree of retinopathy,³ the progression of which is slowed by improved glycaemic control.⁴

We believe that this study has important methodological limitations and that the target of improving glycaemic control in patients with insulin dependent diabetes mellitus with microalbuminuria should not be abandoned.

NISH CHATURVEDI
Research fellow

JOHN H FULLER
Reader in epidemiology

EURODIAB,
Department of Epidemiology and Public Health,
University College,
London WC1E 6BT

1 Microalbuminuria Collaborative Study Group, United Kingdom. Intensive therapy and progression to clinical albuminuria in patients with insulin dependent diabetes mellitus and microalbuminuria. *BMJ* 1995;311:973-7. (14 October.)

2 Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the diabetes control and complications trial. *Kidney Int* 1995;47:1703-20.

3 Stephenson JM, Fuller JH, Viberti GC, Sjolie AK, Navalesi R, EURODIAB IDDM Complications Study Group. Blood pressure, retinopathy and urinary albumin excretion in IDDM: the EURODIAB IDDM complications study. *Diabetologia* 1995;38:599-603.

4 Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.

Work in non-insulin diabetes corroborates study's findings

EDITOR,—The Microalbuminuria Collaborative Study Group suggests that arterial blood pressure rather than glycated haemoglobin concentration is the main predictor of progression from microalbuminuria to clinical albuminuria.¹ Our work in non-insulin dependent diabetes corroborates these findings.

We undertook a prospective five year study of 42 patients (median (range) age 62 (32-71)) with non-insulin dependent diabetes and microalbuminuria (albumin excretion rate > 20 µg/min). They were divided into two groups on the basis of diastolic pressure. Those with a diastolic pressure > 85 mm Hg on two occasions (group 1) were treated with an angiotensin converting enzyme inhibitor and the rest (group 2) were not. There was no significant difference in initial albumin excretion rate or haemoglobin A_{1c} concentration between the two groups. In group 1, 17 of the 29 patients were taking antihypertensive treatment before the addition of the angiotensin converting enzyme inhibitor and 11 had complications (all macro-

Table 1—Blood pressure and albumin excretion rate (AER) at start and end of five year study in patients with non-insulin dependent diabetes and microalbuminuria treated with angiotensin converting enzyme inhibitor (group 1) and serving as controls (group 2). Figures are medians (ranges)

	Start of study	End of study	P value
Group 1			
Blood pressure (mm Hg):			
Systolic	170 (120-252)	146 (120-200)	<0.01
Diastolic	100 (80-105)	80 (70-100)	<0.001
AER (µg/min)	48 (20-282)	30 (7-200)	NS
Group 2			
Blood pressure (mm Hg):			
Systolic	162 (150-180)	158 (120-175)	NS
Diastolic	82 (70-84)	78 (65-84)	NS
AER (µg/min)	53 (20-115)	85 (7-227)	<0.03

Table 1—Observed and expected numbers of cases of breast and bone cancer and leukaemia among Danish female and male airline crews

	Breast		Bone		Leukaemia	
	Observed	Expected	Observed	Expected	Observed	Expected
Women:						
Cabin attendants	14	8.67	0	0.04	0	0.56
Men:						
Cabin attendants	0	0.02	0	0.04	1	0.38
Pilots	0	0.04	0	0.07	0	0.69