Acute coronary syndrome and chronic infection in the Cork coronary care case–control study

J Sheehan, P M Kearney, S O Sullivan, C Mongan, E Kelly, I J Perry

Objective: To examine the association between chronic infection and cumulative burden of infection and acute coronary syndrome.

Design: The 5C (Cork coronary care case–control) study was a community based case–control study. Patients and controls underwent a standard physical examination and had blood samples taken for serological analysis for *Helicobacter pylori* (IgG), *Chlamydia pneumoniae* (IgA, IgM, and IgG), cytomegalovirus (IgG), and herpes simplex virus types 1 and 2 (IgG).

Setting: Patients were recruited from four hospitals in Cork City and Mallow Town. Controls, individually matched on age and sex, were selected by incident density sampling from the same general practices as the referent case.

Main outcome measures: Age and sex adjusted and fully adjusted odds ratios for acute coronary syndrome by seropositivity and by increasing number of infections.

Results: Cases and controls did not differ significantly in seropositivity to *C pneumoniae*, cytomegalovirus, herpes simplex viruses, and *H pylori*. In unconditional logistic regression analysis adjusted for age, sex, waist to hip ratio, smoking, physical activity, alcohol consumption, and social class there was no evidence of an increasing risk for acute coronary syndrome with increasing burden of infection.

Conclusions: The findings do not support an association between specific infectious agents and acute coronary syndrome and do not provide evidence of a burden of infection effect.

Chronic infection has been proposed as a possible causative agent in the development of acute coronary syndrome. Many pathogens have been implicated in the development of acute coronary syndrome including *Chlamydia pneumoniae*, cytomegalovirus, *Helicobacter pylori*, and herpes simplex virus (HSV) types 1 and 2.

A recent meta-analysis of observational studies did not support the hypothesis linking specific microorganisms to acute coronary syndrome. Similarly, promising preliminary findings from randomised controlled trials of antimicrobial agents have not been reproduced in more recent work. More recently attention has broadened to include the burden of infection per se but the cumulative burden of infection that increases a person’s risk of acute coronary syndrome.

Diseases of the circulatory system, of which coronary heart disease is the largest component, accounted for 41% of deaths in Ireland, and Ireland has one of the highest rates of mortality for cardiovascular disease in the European Union. Acute coronary syndrome, defined as acute myocardial infarction or unstable angina, is one of the most common reasons for emergency admission to hospital in Ireland. The aim of this study was to examine the association between chronic infection, specifically seropositivity for *C pneumoniae*, cytomegalovirus, HSV types 1 and 2, and *H pylori*, and acute coronary syndrome and to assess the odds of acute coronary syndrome with increasing burden of infection.

METHODS

Design, participants, and methods of data collection

The 5C (Cork coronary care case–control) study was a community based case–control study. The study was carried out in four Cork area hospitals and 86 general practices in Cork and Kerry. The case group (n = 227) was recruited from consecutive patients aged between 35–74 years (inclusive) admitted with a first acute myocardial infarction or first event unstable angina, defined on the basis of standard World Health Organization criteria, to four Cork area hospitals over a 26 month period. Controls were matched by age (within five years) and sex and were selected by incident density sampling from the age–sex registers or practice lists of the general practices from which the cases were referred (86 practices). In the original study protocol, the study had a power of 90% to detect an odds ratio of 2 for the association between *C pneumoniae* and acute coronary syndrome (assuming a *C pneumoniae* seropositivity of 50% in controls and a sample size of 300 cases and 600 controls). The power of the study was recalculated based on the achieved sample size and the power was 80% to detect an odds ratio of 1.7 for the association between *C pneumoniae* and acute coronary syndrome.

Exclusion criteria

The following characteristics were exclusion criteria for the study: (1) age < 35 years or > 74 years; (2) documented history of previous myocardial infarction, angina, other heart disease or stroke; (3) previous (old) 12 lead ECG showing pathological Q waves, ST segment deviation, T wave inversion, bundle branch or atrioventricular block, or tachyarrhythmia other than isolated extrasystoles; (4) documented coagulation disorder or myeloproliferative

Abbreviations: 5C, Cork coronary care case–control; ACADEMIC, azithromycin in coronary artery disease: elimination of myocardial infection with chlamydia; BRHS, British regional heart study; CI, confidence interval; EIU, enzyme immune units; ELISA, enzyme linked immunosorbent assay; HSV, herpes simplex virus; ISAR-3, intracoronary stenting and antithrombotic regimen; ROXIS, randomised trial of roxithromycin in non-Q-wave coronary syndromes; STAMINA, South Thames trial of antibiotics in myocardial infarction and unstable angina; WIZARD, weekly intervention with Zithromax for atherosclerosis and its related disorders
were measured by the same standardised methods used in measurements for height, weight, and waist to hip ratio. These methods were used in a sensitivity of 100% and a specificity of 92.7%. 19 The Diamedix enzyme immunoassay has a sensitivity of 91% and a specificity of 80% and 88% for IgG and IgA, respectively.

**Measurement of chronic infections**

*Helicobacter pylori* antibody status was tested in the microbiology laboratory in the Mercy Hospital, Cork, with the Biomaster Assay Junior. The assay used was the Premier *H pylori* assay kit (Meridian Bioscience Inc, Cincinnati, Ohio, USA). This assay has a sensitivity of 88% and a specificity of 96%. 15 Serum was tested for *cytomegalovirus* infection with the Biotest anti-human cytomegalovirus recombinant IgG enzyme linked immunosorbent assay (ELISA) in the National Virus Reference Laboratory, University College Dublin. The Biotest IgG ELISA has a sensitivity of 100% and a specificity of 99%.

*C pneumoniae* antibody status was measured in the Virus Reference Laboratory in University College Dublin with an ELISA. Antibody status to *C pneumoniae*, IgM, and IgG antibodies. The antibodies were measured in enzyme immune units (EIU). For IgA antibodies a value of > 12 EIU was treated as positive, a value of 8–12 EIU was equivocal, and a value of < 8 EIU was negative. For IgG antibodies > 45 EIU was positive, 30–45 EIU was equivocal, and < 30 EIU was negative. For IgM > 1.1 EIU was positive, 0.5–1.1 EIU was equivocal, and < 0.5 was negative. For the purposes of the analysis equivocal results were regarded as negative. The Labsystems enzyme immunoassay has a sensitivity of 91% and 85% and specificity of 80% and 88% for IgG and IgA, respectively.

**Statistical analysis**

The data were entered on to an OmniForm database (ScanSoft, Peabody, Massachusetts, USA) and analysed with Minitab for Windows (version 13; Minitab, State College, Pennsylvania, USA) and SAS version 10 (SAS Institute, Cary, North Carolina, USA). Adjusted means were compared by the analysis of variance-general linear model function on Minitab. Proportions were compared by $\chi^2$ tests. Matched and unmatched analyses were conducted by, respectively, unconditional and conditional logistic regression. Odds ratios were calculated as the estimate of association. The results of the analyses were similar; therefore, only the unmatched analyses are reported here.

**Ethics**

The study complies with the Declaration of Helsinki. Patients gave informed consent for the study, which has been approved by the local ethics committee.

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**Table 1** Baseline physical characteristics of patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 227)</th>
<th>Controls (n = 277)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.4 (58.2 to 60.7)</td>
<td>59.0 (57.9 to 60.1)</td>
<td>0.63</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.2 (167.1 to 169.4)</td>
<td>170.0 (169.1 to 171.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.6 (77.7 to 81.6)</td>
<td>79.0 (77.5 to 80.5)</td>
<td>0.60</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>28.1 (27.5 to 28.6)</td>
<td>27.3 (26.8 to 27.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>97.5 (92.9 to 99.2)</td>
<td>94.4 (93.0 to 95.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>102.3 (100.9 to 103.6)</td>
<td>104.6 (103.7 to 105.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.95 (0.95 to 0.99)</td>
<td>0.90 (0.89 to 0.91)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Man</td>
<td>162 (71.4%)</td>
<td>160 (71.3%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Current smokers</td>
<td>81 (36.2%)</td>
<td>85 (36.1%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Heavy drinkers</td>
<td>39 (18.1%)</td>
<td>39 (17.8%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Social class 1–2</td>
<td>24 (10.6%)</td>
<td>26 (9.7%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Self reported hypertension</td>
<td>59 (26.0%)</td>
<td>52 (19.2%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Self reported diabetes mellitus</td>
<td>7 (3.1%)</td>
<td>5 (1.8%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>123 (57.5%)</td>
<td>113 (42.0%)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Data are mean (95% confidence interval (CI)) or number (%). BMI, body mass index; CVD, cardiovascular disease.
In this community based case–control study we found no evidence of an association between acute coronary syndrome and *C pneumoniae*, *H pylori*, cytomegalovirus, and HSV types 1 and 2 infections. The findings with regard to the individual organisms are consistent with previous studies. A meta-analysis performed by Danesh and colleagues in 2000 identified 15 prospective studies of *C pneumoniae* IgG titres and coronary heart disease. The partially adjusted odds ratio for coronary heart disease for all 15 studies combined was 1.19 (95% CI 0.99 to 1.41). Adjustment for adult and childhood socioeconomic status did not significantly alter the results. In a meta-analysis examining the association between cytomegalovirus infection and coronary heart disease, Danesh and colleagues found no association between seropositivity to cytomegalovirus infection and coronary heart disease (odds ratio 0.91, 95% CI 0.69 to 1.19). The evidence to date on the association between *H pylori* infection and coronary heart disease has been inconclusive due to contradictory results from different studies. 

Several randomised controlled trials have investigated the effects of antimicrobial agents on the risk of recurrent coronary heart disease, including ROXIS (randomised trial of roxithromycin in non-Q-wave coronary syndromes), ACADEMIC (azithromycin in coronary artery disease: elimination of myocardial infection with chlamydia), ISAR-3 (intracoronary stenting and anti thrombotic regimen 3), STAMINA (South Thames trial of antibiotics in myocardial infarction and unstable angina), and WIZARD (weekly intervention with Zithromax for atherosclerosis and its related disorders). 

Overall in the trials antibiotics have not had a beneficial effect in the treatment of coronary heart disease.

Some studies have reported an association between number of infections and risk of coronary heart disease. Espinola-Klein and colleagues assessed the impact of infectious burden on extent and long term prognosis of atherosclerosis and reported a positive association between increasing level of seropositivity to infection and risk of atherosclerosis. Zhu and colleagues and Rupprecht and colleagues considered and approved by the Cork Teaching Hospitals research ethics committee.
associates reported similar findings, though the numbers were small.

Conclusion

In this community based case–control study we found no association between *C pneumoniae*, *H pylori*, cytomegalovirus, and HSV types 1 and 2 infections and acute coronary syndrome. We also found no evidence of a burden of infection effect.

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Authors’ affiliations

J Sheehan, P Kearney, S O Sullivan, I J Perry, Department of Epidemiology and Public Health, University College Cork, Cork, Ireland C Mongan, E Kelly, National Virus Reference Laboratory, University College Dublin, Dublin, Ireland

Conflicts of interest: None

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Intracerebral haematoma masquerading as ventricular standstill

A K J Mandal, S Baltszezk, C G Missouris

An 82 year old man was referred to the emergency room by his general practitioner for a right frontoparietal headache. The preceding day he had tripped and fallen, hitting the back of his head on the floor. Computed tomography showed a cortical contue coup haematoma. In view of ventricular standstill noted on ECG, a temporary pacing wire was inserted and a dual chamber permanent pacemaker was subsequently implanted. Intracerebral bleeding was treated conservatively and the patient made a good recovery. All patients admitted with head injury and sinus bradycardia or sinus arrest should be nursed at 15° to 30° with instructions to avoid the head up and supine positions. Furthermore, brain CT should be promptly recorded to assess for intracerebral haematoma and raised intracranial pressure and, if they are confirmed, these patients with cardiovascular compromise should benefit from close collaboration between neurosurgeon and cardiologist. Urgent pacing should be considered for all patients with head injury who experience symptomatic bradycardia or ventricular standstill. (Heart 2005;91:e1) www.heartjnl.com/cgi/content/full/91/1/e1
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