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Risk factors for coronary heart disease and infection with *Helicobacter pylori*: meta-analysis of 18 studies

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Abstract

Objective: To find out if chronic infection with *Helicobacter pylori* is correlated with risk factors for coronary heart disease.

Design: Meta-analysis of 18 epidemiological studies, involving a total of 10 000 patients, that measured serum antibody titres to *H pylori* and risk factors for coronary heart disease. Any study published in any language before 1998 was eligible for inclusion.

Results: Only small absolute differences in body mass index, blood pressure, or haematological risk factors were found between subjects who were seropositive and those who were seronegative. In those who were seropositive body mass index was slightly higher (0.37, SE 0.09) and concentrations of high density lipoprotein cholesterol were slightly lower (0.032 mmol/l, 0.008). None of the other differences were highly significant.

Conclusion: Previous claims of substantial correlations between *H pylori* seropositivity and certain vascular risk factors were largely or wholly due to chance or the preferential publication of positive results, or both.

Introduction

Epidemiological studies have shown that a weakly positive correlation exists between chronic gastric infection with *Helicobacter pylori* and coronary heart disease.[1] If this association is causal then infection with *H pylori* may increase the incidence of coronary heart disease by affecting other vascular risk factors. If there is a non-causal association between *H pylori* infection and coronary heart disease, then this association must be due to confounding factors. It would be useful to know if infection with *H pylori* is correlated with body mass index, blood pressure, or haematological factors such as blood lipids, particularly if these variables might also be correlated with coronary heart disease.

When examined individually, the findings of published reports of the possible correlates of *H pylori* infection seem to have been prone to the effects of chance, or the preferential publication of positive results (publication bias), or both; most studies have had small sample sizes, reported on several different factors, and omitted to perform systematic reviews of the findings of other studies. Systematic reviews of published evidence can increase the amount of data available for analysis; they can also reduce biases that may be introduced through the use of data from small studies that have not been supported by the results of other studies. Such reviews should be less liable to random error and bias than selective emphasis on particular publications would be. We reviewed published studies of the correlations between *H pylori* seropositivity and variables that might be risk factors for coronary heart disease.

Methods

Epidemiological and clinical studies in any language published before 1998 that reported on correlations between serum antibody concentrations of *H pylori* and specific vascular risk factors were identified by searching Medline, relevant reference lists, and gastroenterology and cardiology journals and by discussing studies with the authors of relevant reports. Risk factors examined were systolic blood pressure, diastolic blood pressure, body mass index, plasma viscosity,

white cell count, and concentrations of total cholesterol, high density lipoprotein cholesterol, triglycerides, fibrinogen, blood glucose, and C reactive protein. Combinations of key words used in the computer search included *Helicobacter pylori*, *Campylobacter pylori*, coronary heart disease, vascular disease, and the vascular risk factors described above. The difference between the mean values of the vascular risk factors in seropositive and seronegative subjects and an estimate of the standard error was obtained from the study or from one of the investigators. Two reports of white cell counts[2 3] and one of blood pressure[4] were excluded because they did not report measurements of *H pylori* serum antibody titres. Eighteen eligible studies were identified.[5–22] The following information was abstracted from each study: the number of people who were seropositive and the number who were seronegative, the difference in the value of the relevant risk factor between subjects who were seropositive and those who were seronegative, and the degree to which adjustments had been made for confounding variables. Studies were classed as having adjusted for age and sex only; for age, sex, and some of the risk factors; or for age, sex, some of the risk factors, and markers of social class. Most of the studies adjusted for more than just age and sex.

In general, studies reported on several vascular risk factors; results are presented for those characteristics that were, in the aggregate, studied in more than 500 subjects. The results from different studies were combined by calculating inverse variance weighted averages of the differences within each study. The variance of a comparison between individuals who were seropositive (n_1) and those who were seronegative (n_2) was calculated by multiplying $1/n_1 + 1/n_2$ by the square of the standard deviation of the relevant variable in the largest study that assessed that variable; for many of the variables this was the study of 2000 people by Murray et al.[10] χ^2 was used to test for heterogeneity.

Results

The numbers available for analysis varied from 600 (for C reactive protein) to 10 000 (for total cholesterol). Overall there were only small absolute differences between subjects who were seropositive and those who were not (table). Most of these differences were not significant. There were differences in plasma viscosity, blood glucose concentrations, body mass index, and concentrations of high density lipoprotein cholesterol. In those who were seropositive the body mass index kg/m^2 was slightly higher (0.37, SE 0.09) and concentrations of high density lipoproteins were slightly lower (0.032 mmol/l, 0.008); these were the only differences that were highly significant ($P<0.0001$).

There was some evidence of heterogeneity between the six studies that measured white cell counts[5 12 13 18 19 21] ($\chi^2=18.3$, df=5, $P<0.01$), between the 13 studies in 10 reports that included measurements of diastolic blood pressure[6 7 9 10 12–16 20] ($\chi^2=25.3$, df=12, $P=0.01$), and between the 11 studies in 10 reports measuring fibrinogen concentrations [5 7 10 13–19] ($\chi^2=19.6$, df=10, $P=0.04$). There were no strong correlations overall between these three factors and *H pylori* seropositivity. Most of the heterogeneity was between studies that had first proposed the associations and larger subsequent studies that had failed to confirm the associations.

Correlation between seropositivity for *Helicobacter pylori* infection and various vascular risk factors in published studies of at least 500 people

Characteristic	No seropositive	No seronegative	Average (SE) difference between groups†	Z ratio‡
Total cholesterol (mmol/l)[5-16]	5106	5274	0.04 (0.02)	1.5
Systolic blood pressure (mm Hg)[6 7 9 10 12-16 20]	4502	4795	0.9 (0.4)	2.1*
Diastolic blood pressure (mm Hg)[6 7 9 10 12-16 20]	4502	4795	0.3 (0.3)	1.2
Body mass index (kg/m^2)[6-8 10 12-16 20]	4459	4739	0.37 (0.09)	4.2****
High density lipoprotein cholesterol (mmol/l)[5 6 8-12 15]	4109	4316	–0.032 (0.008)	4.3****
Triglyceride (mmol/l)[5-7 9 11-13 15 16]	3431	3851	0.02 (0.04)	0.6
Fibrinogen (g/l)[5 7 10 13-19]	2986	2228	–0.02 (0.03)	1.0
Plasma viscosity (mPa.s)[10 18]	1270	942	0.01 (0.004)	2.2*
White cell count (10^9/l)[5 12 13 18 19 21]	664	512	0.16 (0.11)	1.4
Blood glucose (mmol/l)[5 9 12]	570	492	0.14 (0.06)	2.4*
C reactive protein (mg/l)[19 22]	311	292	–0.2 (0.5)	0.4

†Inverse variance weighted average of differences within study (mean in seropositive group minus mean in seronegative group).
‡Ratio of average of differences to SE.
*P<0.05; ****P<0.0001.

Discussion

There have been several claims of strong and significant correlations between chronic *H pylori* infection and various possible vascular risk factors, such as fibrinogen concentration,[5 17] white cell count,[5] blood pressure,[23] body mass index,[23] blood lipid concentrations,[11] low alcohol consumption,[24] or concentrations of C reactive protein[22] (which, like the white cell count, may just be a non-specific marker of systemic inflammation). Our review of the published evidence provides results that are more reliable than any individual report. We found no significant correlations between infection with *H pylori* and blood pressure, white cell count, or concentrations of total cholesterol, fibrinogen, triglycerides, or C reactive protein. The differences in body mass index and high density lipoprotein cholesterol are both highly significant but, since the absolute differences between subjects who were seropositive and those who were seronegative are small and may have been exaggerated by publication bias, these variables are unlikely to be of much relevance to any association between infection with *H pylori* and coronary heart disease. The increases in plasma viscosity and blood glucose are only marginally significant; they may be largely or wholly due to chance or publication bias. More importantly, even if they are real, the absolute differences are too small to have a substantial effect on any epidemiological association between chronic infection and coronary heart disease.

Systematic reviews limit spurious associations that may arise from small sample sizes, multiple statistical comparisons, and a selective emphasis on extreme findings in particular studies. Despite our inclusion of studies reported as letters and as abstracts, and of data previously unavailable from published reports, some publication bias may remain; this reinforces our conclusion that correlations found in other studies

Key messages

- Epidemiological studies suggest that there is a weakly positive association between coronary heart disease and chronic infection with *Helicobacter pylori*
- A number of reports have also claimed that there are strong correlations between infection with *H pylori* and an increase in vascular risk factors, such as plasma fibrinogen concentrations
- Meta-analysis of 18 studies that involved 10 000 people found no strong correlations between *H pylori* seropositivity and vascular risk factors; previous findings of the existence of such correlations in small studies were largely or wholly due to chance or to the preferential publication of positive results

between *H pylori* seropositivity and these vascular risk factors are largely due to chance, or selective publication, or both. The clinical implication is that if there is any relation between chronic *H pylori* infection and coronary heart disease,[1] then it is not likely to be dependent on the risk factors described here.

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Contributors: JD initiated and performed the study, drafted the manuscript, and is guarantor for the study. RP helped interpret the data and draft the manuscript.

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Growth hormone as a risk for premature mortality in healthy subjects: data from the Paris prospective study

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The influence of growth hormone on mortality in adults is well known in conditions such as growth hormone deficiency and acromegaly.[1 2] In both diseases the excess mortality is principally from cardiovascular disorders, but the occurrence of malignant disorders has also been reported in acromegaly.[2] To our knowledge the long term effect of physiological growth hormone on mortality in healthy adults has not been reported.

Subjects, methods and results

We studied 864 policemen aged 48 to 52 years who did not have cardiovascular disease, diabetes, or glucose intolerance and who had complete data in the Paris prospective study.[3] They were examined between 1967 and 1973 then followed for mortality until January 1989. The body mass index (weight(kg)/(height(m)^2)), ratio of iliac to thigh circumference (a marker of central fat distribution), heart rate, and both diastolic and systolic blood pressures were measured and smoking habits determined. Blood samples were taken at fasting to measure cholesterol and triglyceride concentrations and mean corpuscular volume, and both at fasting and 2 hours after a 75 g oral glucose tolerance test for concentrations of non-esterified fatty acids, glucose, insulin, and growth hormone with a technique described previously.[4]