**Helicobacter pylori** infection and iron deficiency in teenage females in New Zealand

Alan G Fraser, Robert Scragg, David Schaaf, Patricia Metcalf, Cameron C Grant

### Abstract

**Background** Iron deficiency is an important problem in New Zealand children and young adults. Iron deficiency and *Helicobacter pylori* (*H. pylori*) infection are each more common in Māori and Pacific Island ethnic groups.

**Aims** This study seeks to determine if *H. pylori* infection is associated with iron deficiency.

**Methods** 792 female students from 7 Auckland high schools (median age 16 years) had *H. pylori* serology and tests for iron deficiency assessed by a combination of serum ferritin, iron saturation and mean cell volume.

**Results** The prevalence of positive *H. pylori* serology was highest for Pacific Island students (49.0%; CI 38.0–60.0), intermediate for Māori (26.7%; CI 16.9–36.4) and Asian (24.7%; CI 12.6–36.7) and lowest for European (13.7%; CI 6.0–21.4) p<0.0001. Students with positive *H. pylori* serology had lower mean levels of iron saturation (p=0.013), but not of ferritin (p=0.068), haemoglobin (p=0.08) or mean cell volume (p=0.16), compared to those with negative serology. Positive *H. pylori* serology was associated with increased risk of iron deficiency (RR 1.20; CI 1.08–1.34), but not anaemia (RR 1.01; CI 0.87–1.18), after adjusting for age, ethnicity and school SES decile.

**Conclusions** This study indicates that *H. pylori* infection is associated with iron deficiency in adolescent females. There are significant differences in *H. pylori* serology amongst different ethnic groups in New Zealand.

Iron deficiency is an important problem in New Zealand children and young adults. A survey of girls from 8 Auckland high schools found that 18.3% of girls had iron deficiency and 11.5% had anaemia.1 Iron deficiency was more common in Māori and Pacific Island ethnic groups. A longitudinal study of Dunedin children (predominantly European) found lower but still significant rates of anaemia and iron deficiency by the age of 21 years (5.8% and 6.7% respectively).2 The reasons for these ethnic differences remain unclear.

*Helicobacter pylori* (*H. pylori*) infection is found more frequently in Māori and Pacific Island ethnic groups and this is a potential explanation for the difference in prevalence of iron deficiency.3,4 There are a number of possible mechanisms by which *H. pylori* may affect iron metabolism. There may be occult bleeding because of gastritis or ulceration, impaired absorption of non-haem iron because of decreased acid secretion or the bacteria itself may be a scavenger for iron thereby competing with the host for dietary iron or ferritin.5,6
Results from cross-sectional studies suggest that the impact of *H. pylori* infection may vary between different countries and also vary according to socioeconomic status within a country.7–12 One previous New Zealand study has shown a significantly lower serum iron in *H. pylori*-infected adults selected from the electoral roll but no difference in serum ferritin or the prevalence of anaemia.8

This study sought to determine if *H. pylori* was an explanation for the high prevalence of iron deficiency in female teenage children in Auckland schools that had a high proportion of Māori and Pacific Island students.

Methods

The participants in this report come from a cross-sectional survey, carried out during May 1997 to September 1998, of 2549 Year 11-13 students attending schools in South, Central and West Auckland. The main aim of the survey was to compare cardiovascular risk factors in Pacific Island students with those of other ethnicities. We randomly selected 10 (out of 32) schools with a proportion (>15%) of Pacific Island students and invited all Year 11–13 students at each school to take part. Information on iron and anaemia status was collected from students at 8 of these schools. The results and methods have been reported previously.1 The current report on *H. pylori* and iron status is limited to female students (at 7 schools) because of their increased prevalence of iron deficiency and anaemia compared with males.

After an overnight fast, students were interviewed in the mornings in groups of up to 10. At the time of this interview a fasting venous blood sample was collected from each student to measure glucose, lipids, iron indices and haemoglobin. Each student then completed a 15-minute self-administered questionnaire which documented age, gender, ethnicity (self-defined), past medical history, and general lifestyle patterns. The Ministry of Education classification of schools by socioeconomic decile, from 1 (low) to 10 (high), was used to code socioeconomic status (SES).13 The number of surveyed students at each school, in this report, ranged from 34 to 373.

All blood samples were separated within 2 hours of collection at a community laboratory, and tested for cardiovascular risk factors and iron status. The following methods were used to determine iron status: serum ferritin was measured by microparticle enzyme immunoassay (Abbott Laboratories); iron (transferrin) saturation was derived from serum iron and unsaturated iron binding capacity by a colourimetric method (Roche); C-reactive protein (CRP) was measured by nephelometry (Behring Diagnostics); haemoglobin (using a cyanmethaemoglobin method) and mean cell volume (MCV) were measured on a Technicon H*3. Any remaining serum was stored at -80°C.

**Definition of anaemia and low ferritin**—Cut-points from the United States NHANES III survey are used in the current report.7 Anaemia was defined as haemoglobin <120 g/L for females. Iron deficiency was defined as any two (or more) of the following three: serum ferritin <12 ug/L; iron (transferrin) saturation <14%; MCV <81 fl which was the 5th percentile for the reference group of students in the sample who met all the following criteria: CRP <4 mg/L, haemoglobin g/L >118 (10th percentile), iron saturation >8%, and ferritin ≥10 ug/L. This definition of iron deficiency is based on that used in the NHANES surveys.7

The only difference is that we have used MCV as a third test of iron deficiency in place of measuring erythrocyte protoporphyrin, since the latter test was not readily available in Auckland at the time of the survey.14 *H. pylori* antibody was determined by enzyme immunoassay using commercially available kits which were validated by comparison with urea breath test.15

Data analyses in this report are restricted to 792 (out of 922 surveyed) female students with measured *H. pylori* antibodies, after excluding 61 students with missing information on *H. pylori* status, 44 students with CRP >5 mg/L (to exclude any students with possible acute phase reaction (which affects serum ferritin, iron saturation and haemoglobin concentration)) and 25 students with missing CRP values. Statistical analyses were made using SAS SURVEYFREQ and SURVEYMEANs procedures (Release 9.2, Research Triangle Park, NC, 2005) which corrects standard errors and confidence intervals for any design effect from clustering of students by school. The Rao-Scott modified Chi-Squared test was used. The STATA command binreg was used to calculate unadjusted and adjusted risk ratios. The natural logarithm of ferritin was used in analyses to normalise its distribution.
Results

278 students tested positive for *H. pylori* antibodies, giving a prevalence of 35.1% (95%CI 23.5–46.7). Table 1 shows the prevalence of *H. pylori* for demographic variables. The prevalence of positive serology was highest for Pacific Island students (49.0%), intermediate for Māori (26.7%) and Asian (24.7%) and lowest for European (13.7%) (p<0.0001). The prevalence of positive *H. pylori* serology varied across schools from 24.6% up to 60.9%. The prevalence varied with school SES decile, being nearly twice as high for students in SES decile 1 schools (53.1%) compared with decile 2 and 3 schools (28.6%) (p=0.036), but did not vary with age (p=0.19).

Table 1. Prevalence of positive *H. pylori* serology by level of demographic variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>H. pylori positive % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤15</td>
<td>200</td>
<td>35.5 (21.7–46.6)</td>
<td>0.19</td>
</tr>
<tr>
<td>16</td>
<td>283</td>
<td>31.5 (16.8–46.1)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>200</td>
<td>36.0 (23.0–49.0)</td>
<td></td>
</tr>
<tr>
<td>≥18</td>
<td>109</td>
<td>42.2 (33.1–51.4)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>386</td>
<td>49.0 (38.0–60.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Māori</td>
<td>120</td>
<td>26.7 (16.9–36.4)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>162</td>
<td>24.7 (12.6–36.7)</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>124</td>
<td>13.7 (6.0–21.4)</td>
<td></td>
</tr>
<tr>
<td>School SES decile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (low)</td>
<td>211</td>
<td>53.1 (44.9–61.2)</td>
<td>0.036</td>
</tr>
<tr>
<td>2 and 3</td>
<td>581</td>
<td>28.0 (27.0–30.2)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>792</td>
<td>35.1 (23.5–46.7)</td>
<td></td>
</tr>
</tbody>
</table>

Comparisons of adjusted mean values for serum iron measures and haemoglobin, between students with positive and negative *H. pylori* serology are shown in Table 2. Students with positive serology had significantly lower mean iron saturation (p=0.013), compared with students with negative serology. Mean ferritin (p=0.068), haemoglobin (p=0.08) and MCV (p=0.16) did not vary with *H. pylori* serology.

Table 2. Mean (95% confidence interval) of blood iron measures and haemoglobin, by category of *H. pylori* serology, adjusted for age, ethnicity and school SES decile

<table>
<thead>
<tr>
<th>Blood variable</th>
<th>H. pylori serology</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Ferritin (ug/L)</td>
<td>21.7 (18.5–25.4)</td>
<td>23.8 (21.4–26.6)</td>
</tr>
<tr>
<td>Iron saturation (%)</td>
<td>20.1 (18.7–21.4)</td>
<td>22.0 (20.7–23.3)</td>
</tr>
<tr>
<td>Mean cell volume (fl)</td>
<td>85.9 (85.4–86.3)</td>
<td>86.7 (86.0–87.4)</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>130.3 (129.4–131.2)</td>
<td>131.5 (130.9–132.0)</td>
</tr>
<tr>
<td>N</td>
<td>278</td>
<td>514</td>
</tr>
</tbody>
</table>
Table 3 shows risk ratios for iron deficiency and anaemia associated with positive *H. pylori* serology, adjusting for age, ethnicity and school SES decile. There was a significantly higher risk of iron deficiency in students with positive *H. pylori* serology (p=0.001), but not anaemia (p=0.88).

The prevalence of iron deficiency ranged from 24.2% (se=5.9) in Māori students, 18.9% (3.1) in Pacific, 12.3% (2.1) in Asian to 7.2% (1.9) in European students (p=0.0049). Mean ferritin levels were not significantly different for Māori, Pacific and Asian students, when compared with European, adjusting for age and school SES (p>0.05).

In contrast, after adjusting for age and school SES, mean iron saturation was significantly lower in Māori (by 6.0%), and in Pacific (by 6.5%) students (p<0.05), but not in Asian students, when compared with European; while mean MCV also was significantly lower in all three non-European groups compared with European students (Māori by 4.4 fl, Pacific by 3.2 fl, Asian by 3.1 fl).

### Table 3. Risk ratios for iron deficiency and anaemia, associated with positive *H. pylori* serology († row percents)

<table>
<thead>
<tr>
<th>H. pylori serology</th>
<th>Iron deficiency</th>
<th>Relative risk (95% CI)</th>
<th>Adjusted for age, ethnicity and school SES decile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Positive</td>
<td>56 (20.1%)†</td>
<td>222</td>
<td>1.28 (1.19–1.39)</td>
</tr>
<tr>
<td>Negative</td>
<td>74 (14.4%)</td>
<td>440</td>
<td>1.00</td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>33 (11.9%)</td>
<td>245</td>
<td>1.06 (0.90–1.26)</td>
</tr>
<tr>
<td>Negative</td>
<td>56 (10.9%)</td>
<td>458</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### Discussion

This study has shown a significant association between *H. pylori* and iron deficiency, including iron saturation. The magnitude of this effect is small but may be of some clinical importance. There was no association between *H. pylori* and anaemia.

Data from some other population studies has suggested an association of *H. pylori* with iron deficiency but the magnitude of the effect may be small and may depend on the definition of iron deficiency.

A US study using the National Health and Nutrition Examination survey 1999–2000 found a significantly lower serum ferritin in *H. pylori* infected adults (56 compared with 65 ug/L); there was a significant adjusted odds ratio for iron deficiency anaemia but not for iron deficiency (similar definition to this study). A further report from the 2003 NHANES survey has shown similar results.

Several studies have shown a lower serum ferritin with *H. pylori* infection without showing any effect on iron deficiency anaemia. In a large population study from Germany of subjects aged 18–89 years serum ferritin in *H. pylori*-infected individuals was 54.5 ug/dL compared with 63.8 ug/dL in the uninfected subjects. The association did not vary by age, gender or iron intake.
In another population study of 2794 adults in Denmark serum ferritin was lower in men (114 vs 120ug/L, p=0.01) and in post-menopausal women (63 vs 77 ug/L, p=0.02) who were *H. pylori* positive.\(^\text{10}\) An small Australian study found significantly lower ferritin levels among women with *H. pylori* infection compared with non-infected controls (59 vs 88 ug/L)\(^\text{17}\) In a study of 2080 native Alaskans (78% positive for *H. pylori*) there was a significant association between low serum ferritin and positive *H. pylori* serology, particularly in subjects less than 20 years of age.\(^\text{11}\)

Most of these reports have included mainly adult subjects. There is limited data on the possible association in children.\(^\text{12,18,19}\) In a study of 688 Alaskan children 38% were found to have iron deficiency and 7.8% iron deficiency anaemia. There was an association with *H. pylori* infection but it is perhaps difficult to make strong conclusions as 86% of children had *H. pylori* infection.\(^\text{19}\)

The other form of evidence for a relationship between *H. pylori* and iron deficiency comes from *H. pylori* eradication studies. Most studies have involved small numbers of subjects and have been non-randomised.\(^\text{20–22}\) In a small randomised study from Korea, 22 *H. pylori*-positive subjects (mean age 15 years) were randomised to *H. pylori* eradication, ferrous sulphate alone or both *H. pylori* eradication and iron supplementation. Eradication treatment, with or without iron resulted in a significant increase in haemoglobin.\(^\text{23}\)

A randomised study of children in rural Alaska showed no difference between treatment with iron supplementation alone and iron treatment combined with *H. pylori* eradication treatment at 14 months follow-up although there was a difference in iron-deficiency anaemia at 40 months follow-up despite a 50% re-infection rate with *H. pylori*.\(^\text{24,25}\)

A randomised study of 200 Bangladeshi children aged form 2–5 years showed no additional benefit of *H. pylori* eradication on iron deficiency compared to iron treatment alone at 90 days. The strength of this study was a randomization to iron treatment alone, *H. pylori* eradication alone or the combination. In addition, *H. pylori* status was assessed again at 90 days by urea breath testing and the analysis of children with successful eradication versus persisting infection showed no difference in iron deficiency.\(^\text{26}\)

The reasons for these variable results are unclear. It is likely that *H. pylori* has a small effect on iron balance by decreasing absorption or increasing iron loss leading to iron deficiency but that this effect is not large enough to lead to iron deficiency anaemia in most populations. There may be regional differences or unknown factors that determine whether there is a pangastritis (causing a decrease in acid secretion) or perhaps a hemorrhagic gastritis (as has been commonly observed in Alaskans).

An older population may have more advanced *H. pylori*-related changes in the gastric mucosa (although limited negative data in elderly subjects does not support this concept).\(^\text{28}\) Several studies have shown that acid secretion does improve after *H. pylori* eradication particularly if there is corpus-predominant gastritis or pangastritis.\(^\text{28,29}\) However the impact of optimal gastric acid secretion on iron absorption may have been overstated.
A study of iron absorption in children aged 2–5 years in Bangladesh showed that gastric acid secretion improved after *H. pylori* eradication but iron absorption did not improve after eradication treatment.\(^3^0\)

*H. pylori* infection is claimed to be associated with a number of extra-gastric manifestations. Most of these associations have not been confirmed by larger well conducted studies that control for confounding issues such as socioeconomic status. One major example is the debate over the possible association of *H. pylori* with coronary heart disease.\(^3^1\)

This study shows that *H. pylori* is associated with iron deficiency but this weak effect is unlikely to explain the major ethnic differences in iron deficiency anaemia. Dietary intake of iron appears to be similar in different ethnic groups in New Zealand.\(^3^2\)

The prevalence rates of *H. pylori* infection in European, Māori and Pacific island children in this study (collected 1997–98) are similar to data reported from samples taken from 11 year old South Auckland school children in 1988.\(^3\)

This study confirms the significant public health issue of *H. pylori* infection particularly for Pacific Islanders who will carry a burden of upper gastrointestinal disease into coming decades, causing both peptic ulceration and gastric cancer, because of high rates of *H. pylori* infection.\(^4\)

Further studies on the reasons for high rates of acquisition of *H. pylori* infection in some ethnic groups are required. Targeted testing and eradication depending on ethnicity may be sensible to prevent later consequences of *H. pylori* infection.\(^4\)

**Competing interests:** None known.

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**References:**