Casting a long shadow: the role of household crowding on \textit{Helicobacter pylori} infection, and excess stomach cancer incidence among Māori and Pacific people

\textit{Dr Andrea McDonald}

\textit{Supervised by}
\textit{Assoc. Prof Diana Sarfati, Prof Michael Baker, Prof Tony Blakely}

\textit{28\textsuperscript{th} June 2013}
# Contents

Abstract ................................................................................................................................. 7
Figures .................................................................................................................................. 9
Tables .................................................................................................................................. 10
Acknowledgments ................................................................................................................ 13
Chapter 1: Introduction ........................................................................................................ 15

\textit{H. pylori} the bacterium ............................................................................................... 16
  Acquisition .......................................................................................................................... 16
  Virulence ............................................................................................................................. 16
  Detecting \textit{H. pylori} infection ......................................................................................... 17
  Treatment ............................................................................................................................. 18
  Are there benefits from \textit{H. pylori} infection? ................................................................. 18
Risk factors for \textit{H. pylori} ................................................................................................. 19
  Socioeconomic conditions ............................................................................................... 19
  Close-contact infectious diseases .................................................................................. 20
  \textit{H. pylori} and age ......................................................................................................... 20
\textit{H. pylori} as a cause of stomach cancer ........................................................................ 22
  Necessary factor proposition ............................................................................................ 23
  Subsite of stomach cancer ............................................................................................... 25
  Histology of stomach cancer .......................................................................................... 26
  Histological mechanism ................................................................................................... 28
Other risk factors for stomach cancer ................................................................................ 28
Māori and Pacific have high rates of all three .................................................................... 30
  Distribution of \textit{H. pylori} by ethnicity ............................................................................ 30
  Distribution of household crowding by ethnicity ............................................................ 31
  Epidemiology of stomach cancer by ethnicity ............................................................... 33
  Trends in stomach cancer over time ............................................................................... 35
  Why are there ethnic differences in stomach cancer incidence? .................................... 36
Summary ................................................................................................................................ 37
Aims and objectives ............................................................................................................... 38
Part A: Systematic review of observational studies investigating the association of
household crowding with \textit{H. pylori} and stomach cancer .................................................. 39
  Overview ............................................................................................................................ 39
Chapter 2: Review methods ................................................................................................ 41
Comparing seroprevalence and stomach cancer differences ................................ 82
Contribution of H. pylori ................................................................................... 82
Contribution of smoking to ethnic variation in stomach cancer incidence....... 82
Summary ............................................................................................................ 85
Sensitivity analysis ......................................................................................... 85
Ethical approval .............................................................................................. 86
Chapter 5: Analysis results ............................................................................. 87
H. pylori seroprevalence .................................................................................. 87
Seroprevalence articles .................................................................................. 87
Pooled seroprevalence .................................................................................... 89
Burden of H. pylori caused by household crowding....................................... 92
Upper and lower estimates for seroprevalence ............................................. 93
Stomach cancer incidence .............................................................................. 96
Comparing seroprevalence and stomach cancer differences ...................... 96
Quantifying the contribution of H. pylori and smoking to stomach cancer.... 98
Sensitivity analysis .......................................................................................... 102
Chapter 6: Discussion ..................................................................................... 105
Summary of key findings ............................................................................... 105
Discussion of key findings ............................................................................ 107
Ethnic trends in H. pylori infection and the role of household crowding....... 107
Ethnic trends in stomach cancer and the role of H. pylori......................... 111
Strengths and limitations ............................................................................. 115
Broadly ............................................................................................................ 115
Strengths and weaknesses: meta-analysis of household crowding as a risk factor for H. pylori infection ................................................................. 115
Strengths and weaknesses: comparing ethnic differences in seroprevalence and stomach cancer................................................................. 116
Implications .................................................................................................. 119
Preventing acquisition of H. pylori infection ............................................... 119
Treatment approach ....................................................................................... 121
Further research ............................................................................................. 124
Chapter 7: Conclusion .................................................................................. 127
References ..................................................................................................... 129
Appendix 1: Search strategies for Systematic Literature review .................... 141
Appendix 2: Newcastle Ottawa Scale Adaption ............................................. 144
Appendix 3: Table illustrating more detailed information about included studies... 146
Appendix 4: Table of the characteristics of other stomach cancer risk factors.............. 149
Appendix 5: Population attributable fraction calculations for all stomach cancer and restricted to non-cardia stomach cancer ........................................................................................................................................ 150
Abstract

INTRODUCTION: *Helicobacter pylori* (*H. pylori*) is predominantly acquired in childhood and persists as a chronic infection in the stomach. *H. pylori* has been linked with household crowding and is an important causal factor which is considered necessary for non-cardia stomach cancer. Māori and Pacific peoples in New Zealand experience greater household crowding, *H. pylori* infection and stomach cancer incidence.

OBJECTIVES:

1) To summarise the association between household crowding and *H. pylori* infection in the literature; and estimate the contribution of household crowding to Māori, Pacific and European *H. pylori* seroprevalence.

2) To estimate the excess Māori and Pacific stomach cancer incidence that is attributable to *H. pylori* exposure and smoking.

METHODS: A systematic literature review and meta-analysis was conducted to summarise the evidence on the association between household crowding density and *H. pylori*, and investigate heterogeneity.

Pooled serology data were regionally weighted and adjusted to estimate the Māori, Pacific and European seroprevalence of *H. pylori* by 1926-40, 1941-55, 1956-70 and 1971-85 birth cohorts. In the latter cohort, the meta-analysis odds ratio and household crowding prevalence from the 1986 census were used to estimate the contribution of crowding to *H. pylori* seroprevalence.

For the 1926-40, 1941-55 and 1956-70 birth cohorts, age-standardised Māori and Pacific incidence rates of stomach cancer were compared to European/Other. Rate ratios (RRs) were adjusted for *H. pylori* by restricting to the proportion of each ethnic group who were seropositive, assuming that *H. pylori* is a necessary causal factor for stomach cancer. RRs were adjusted for smoking by probabilistic bias analysis. Adjusted RRs were compared with observed RRs to calculate an 'excess
rate ratio proportion’ which estimates the contribution of *H. pylori* and smoking to excess Māori and Pacific stomach cancer incidence. In order to better meet the necessary factor proposition, analysis was then restricted to non-cardia stomach cancer cases.

RESULTS: Meta-analysis showed that persons experiencing the greatest vs. the least household crowding had 1.73 (95% CI 1.48-2.03, n=28, I²=87%) times greater odds of *H. pylori* infection. Children exposed to household crowding had significantly greater risk of infection (OR 2.06, CI: 1.53-2.77, n=19, I²=86%). The average pooled *H. pylori* seroprevalence was greatest for Pacific (62%), followed by Māori (35%) and European (18%). Seroprevalence declined in subsequent birth cohorts for all ethnic groups but relative ethnic differences in seroprevalence increased. Household crowding among children born 1971-85 contributed to 44% of Pacific (95% CI: 32-54%), 36% of Māori (95% CI: 25-47%), and 14% of European (95% CI: 9-20%) *H. Pylori* seroprevalence.

For men born in the 1926-40, 1941-55 and 1956-70 birth cohorts, *H. pylori* and smoking (to a lesser degree) contributed to more than half of the excess non-cardia stomach cancer among Māori (53%, 65%, 63% respectively) and approximately eight-tenths of the excess non-cardia stomach cancer among Pacific (74%, 83%, 90% respectively).

CONCLUSION: This analysis is distinctive because it quantifies a two-step process from household crowding to *H. pylori* infection, and *H. pylori* infection to stomach cancer; and then distinguishes how this process differs by ethnicity. Household crowding is a major contributing factor to Māori and Pacific *H. pylori* seroprevalence; and the primary driver of excess non-cardia stomach cancer incidence among Māori and Pacific. Household crowding reduction interventions that focus on children are recommended. *H. pylori* ‘screen and treat’ approaches for asymptomatic Pacific and Māori men in NZ require evaluation. Improved sensitivity in *H. pylori* detection measures and better stomach cancer subsite classification will improve future evaluation of the *H. pylori* contribution.
Figures

Figure 1: Seropositivity for cases (solid line) and controls (broken line) in 14 studies. Adapted from Huang et al., 1998. ................................................................. 21

Figure 2: Regional distribution of household crowding in New Zealand, proportion of private occupied dwellings with one or more bedroom deficit, CNOS 2001-2005, (CPRonline, 2013) ........................................ 31

Figure 3: Proportion of population living in households requiring at least one additional bedroom, by ethnic group, 1986–2006 (Ministry for Social Development, 2010a) ......................................................... 32

Figure 4: Age-standardised rates of stomach cancer in New Zealand by gender 1948-2008, standardised to the World Health Organisation population (Ministry of Health, 2012a) ........................................ 35

Figure 5: Proposed relationship between ethnicity, household crowding and outcomes H. pylori infection and stomach cancer, demonstrating the influence of socioeconomic status and age, and their potential confounding effects .................................................................................................................... 40

Figure 6: Identification and selection of eligible studies investigating the association between household crowding and H. pylori. Flowchart adapted from PRISMA (Moher et al., 2009) ........................................... 52

Figure 7: Identification and selection of eligible studies investigating the association between household crowding and stomach cancer. Flowchart adapted from PRISMA (Moher et al., 2009) ........................................ 53

Figure 8: Meta-analysis forest plot showing the summary effect measures for the association between household crowding and H. pylori infection sub-grouped by children and adult exposures to crowding ....................................................................................................................... 56

Figure 9: H. pylori funnel plot considering age at exposure to crowding ........................................... 66

Figure 10: Geographical regions used for weighting in the pooled seroprevalence analysis ............................. 74

Figure 11: The log-linear relationship between stomach cancer incidence and age in the 25-44yo, 45-64yo and 65-74yo age groups with a flattening of incidence rates in the 75+ year old age groups. European/Other, Māori and Pacific peoples are combined. ........................................................... 79

Figure 12: Evidence of the log-linear relationship between stomach cancer incidence and age in the 25-44yo, 45-64yo and 65-74yo age groups (plotted by the age midpoint) across the five-year census time periods for European/Other, Māori and Pacific peoples combined. For the study this graph was created separately for each ethnic group. ................................................................................................. 79

Figure 13: Crude pooled adult seroprevalence estimates in New Zealand by birth cohort and ethnicity, weighted by region .................................................................................................................................. 90

Figure 14: Pooled estimates of adult seroprevalence by birth cohort and ethnicity in New Zealand from seven studies with adjustment for potential selection and measurement biases in two studies, weighted by region. These estimates are used in the analysis .............................................................................................................................. 90

Figure 15: Relative risk of H. pylori seroprevalence by ethnicity in New Zealand calculated from seven pooled studies. Data has been regionally weighted and crude data from two studies was adjusted for selection and measurement bias .................................................................................................................. 92

Figure 16: Best estimates and assigned upper and lower estimates of H. pylori seroprevalence by ethnicity and year of birth. Figures are regionally weighted and adjusted for selection and measurement bias. ................................................................................. 94

Figure 17: Age-standardised stomach cancer incidence rate ratios (RR) comparing ethnic groups in three birth cohorts. RRs are adjusted for H. pylori by restricting the population at risk to those who are H. pylori seropositive. The RR was further adjusted using probabilistic sensitivity analysis to adjust for mediation by 1981 smoking prevalence. The conventional 95% confidence intervals are illustrated with a dash (except for in the smoking adjusted estimate where these are uncertainty intervals which include systematic error) .......................................................................................................................... 101
Tables

Table 1: Meta-analyses of the relationship between H. pylori seropositivity and gastric cancer, adapted from Kato and Asaka (2010), where OR=odds ratio, CCS=case-control study, *=cagA seropositivity only ................................................................. 23

Table 2: Summary of studies showing the incidence of stomach cancer in New Zealand by various subsite groupings and ethnicity - Incidence rates were calculated from the ^NZ 2007 age-standardised rate, the crude rates per 100,000 population in the hospital catchment area (Biggar et al., 2011) and the *1970-74 age-standardised incidence rate, tumours unable to be classified are included in the summarised rates .................................................. 26

Table 3: Summary of studies in New Zealand showing incidence of stomach cancer by histology by ethnicity, rates are calculated from summarised incidence rates given in the study or taken from New Zealand cancer registrations in ^2005 and *1978-80, NR = not reported ........................................... 28

Table 4: Medline search strategy .................................................................................................................. 42

Table 5: Number of full text records assessed, showing the reasons for exclusion, the total number of studies eligible for narrative synthesis and the subset included (incl.) in meta-analysis (studies with ORs adjusted for socioeconomic status and age) ................................................................. 51

Table 6: Summary of outcomes from eligible studies that investigated the association between household crowding and H. pylori or stomach cancer .................................................................................. 54

Table 7: H. pylori meta-analysis study and study population characteristics, CX = cross sectional, CX – retro = determination of exposure was retrospective .................................................. 59

Table 8: Summary of findings table for the meta-analyses investigating the association between household crowding density and H. pylori infection ........................................................................ 60

Table 9: Medline search strategy and results, February 2013 ................................................................ 70

Table 10: Population weights used for the 1926-1940 birth cohort, calculated from the 2006 census data, to account for the regional distribution of 65-79 years olds in each ethnic group .......... 74

Table 11: Summary of pooled studies assigned to five birth cohorts, *all studies used commercial ELISA tests (e.g. Roche) except for Morris (1986) which used pooled whole organism antigen from 14 C pyloridis isolates, the Marshall strain and C pyloridis type organism for its ELISA – which may underestimate H. pylori ................................................................. 88

Table 12: H. pylori seroprevalence from seven New Zealand studies pooled by birth cohort and ethnicity; weighted by distribution of each ethnic population by region in the 1996 census, crude data from two studies was adjusted for selection and measurement bias (n = total participants tested in pooled studies, the summary seroprevalence is an average of the four earliest cohorts) .......... 91

Table 13: Risk differences (RD) (absolute differences) and risk ratios (RR) (relative differences) of Māori and Pacific H. pylori seroprevalence compared to NZ European, by birth cohort. The average is across all four birth cohorts with each given equal weighting. Data has been regionally weighted and crude data from two studies was adjusted for selection and measurement bias .......... 91

Table 14: Contribution of household crowding (taken from the 1986 census) to the pooled seroprevalence in the 1971-85 birth cohort, PAF = population attributable fraction, PAR = population attributable risk, assuming household crowding is causal, applying a 2.52 increased odds of seropositivity taken from meta-analysis for children exposed to greater household crowding. Confidence intervals presented do not account for uncertainty in the seroprevalence figures .......... 93

Table 15: Impact of upper and lower assigned seroprevalence estimates on the relative risk of H. pylori seropositivity between ethnic groups in each birth cohort, the ‘best est.’ is calculated from pooled New Zealand data with weighting for region and adjustment for some biases .......... 95

Table 16: Comparison of cohort specific pooled seroprevalence risk ratios (*weighted by region and adjusted for selection and measurement bias) and stomach cancer age-standardised incidence rate
RATIOS BY ETHNICITY FOR THE NEW ZEALAND POPULATION DURING STUDY PERIOD 1981-2004 (*BASED ON NON-CARDIA STOMACH CANCER PROPORTIONS BY ETHNICITY (BIGGAR ET AL., 2011)) ................................................................. 97

**Table 17:** Differences in stomach cancer incidence by ethnicity in three birth cohorts, before (column C) and after column D) restricting the at risk population to those who are *H. pylori* seropositive (*assuming *H. pylori* is a necessary factor for stomach cancer cases) and using probabilistic sensitivity analysis to adjust for mediation by current smoking prevalence by cohort in 1981, in column F the uncertainty interval (U.I.) includes statistical uncertainty and systematic error from probabilistic bias analysis.......................................................................................................................................................... 98

**Table 18:** Sensitivity analysis showing how excess stomach cancer incidence rates in Māori or Pacific (each compared to European/Other) change by variation in input parameters or methodology, during study period 1981-2004. Absolute changes of more than 5% in the contribution of *H. pylori* are highlighted in bold; where ‘H’ is higher than the principal estimate and ‘L’ is lower than the principle estimate. Where the rate ratio (RR) adjusted for *H. pylori* was less than one, the contribution was assigned the value of 100%. If the RR adjusted for *H. pylori* was greater than the unadjusted RR, then *H. pylori* did not contribute anything to the differences in stomach cancer and the value was assigned to be 0%. .................................................................................................................................................................................. 104
Acknowledgments

Thank you to everyone who has supported me to produce this research. I particularly want to thank and acknowledge my supervisors for your valuable input at every stage; Associate Professor Diana Sarfati, Professor Michael Baker and Professor Tony Blakely. Thank you for all your insightful ideas, helpful feedback and consistent support.

There are many other contributions I wish to acknowledge. Thank you to the New Zealand Cancer Society for their financial contribution to cover costs for accessing data. Thank you to James Stanley for your feedback on my graphs and presentation. I also wish to thank my Wellington colleagues doing the Public Health Masters and Public Health Medicine Training for your encouragement and support, and thank you to all our lecturers for your teaching and inspiration.

For the systematic review; thank you to the Wellington School of Medicine Library staff for your patient assistance with developing the search strategy. Thank you Jasmine Xu for obtaining many of the full text articles. I am also particularly grateful for all the email replies from study authors with additional information on their results. Thank you to Dr Vanessa Jordan for your statistical know-how and advice on the meta-analysis.

For assistance with the analysis; thank you to Dr Rachael McLean for your information on salt intake. Thank you to Dr Alasdair Patrick and Dr John Hsiang from Middlemore hospital for your data on your cohort of patients undergoing gastroscopy and your advice. Thank you to Virginia Signal for access to your preliminary data on subsite of stomach cancer by ethnicity. Thank you to Dr Bruce Chapman for providing detailed information on *H. pylori* seroprevalence in the Christchurch study and other authors who sought to help with my request. I also want to thank Jacqui Kennan for your advice on the microbiology aspects including your input on the tests used to identify *H. pylori* infection.
Chapter 1: Introduction

*H. pylori* is a bacterium that colonises the stomach, causing gastritis, peptic ulcer disease and stomach cancer. It is predominantly acquired in childhood and generally remains as a chronic infection in the stomach into adulthood. The bacterium appears to spread from person to person through faecal-oral or oral-oral transmission pathways.

Acquisition of *H. pylori* infection has been closely linked with greater household crowding and socioeconomic deprivation, particularly in early childhood. Many observational studies have reported an association between household crowding and *H. pylori* infection but no systematic review is available.

*H. pylori* is strongly associated with stomach cancer. The World Health Organization (WHO) has established *H. pylori* as a class 1 carcinogen, which means there is substantial evidence that *H. pylori* causes stomach cancer. Evidence of *H. pylori* infection is present in the majority of people (>80%) who get stomach cancer.

In New Zealand (NZ), Māori and Pacific ethnic groups have the highest rates of household crowding, *H. pylori* and stomach cancer. Studies show that Māori and Pacific are two to three times more likely to be seropositive for *H. pylori* infection than participants of European ethnicity (Fraser et al., 2010). Household crowding (and lower socioeconomic status) is experienced disproportionately by Māori and Pacific peoples in NZ (Baker et al., 2012b, Statistics New Zealand, 2012a). Household crowding is five times more common in Māori and approximately ten times more common in Pacific (Baker et al., 2012b) than in European/Other people. Māori and Pacific people also experience two to three times the rate of stomach cancer compared to the European/Other ethnic group (Blakely et al., 2010).

This study investigates whether disproportionate exposure to household crowding among Māori and Pacific people is associated with increased *H. pylori* infection, and whether greater *H. pylori* infection in Māori and Pacific is a significant contributor to
increased rates of stomach cancer compared to European/Other. The aim was to summarise the international literature for the association between household crowding and *H. pylori* infection, and to estimate the contribution of *H. pylori* to ethnic differences in stomach cancer in NZ by taking a birth cohort approach.

**H. pylori the bacterium**

*H. pylori* is a spiral shaped gram-negative bacterium first discovered in 1982 by Barry Marshall and Robin Warren in the stomach mucosa of patients with gastritis (Warren and Marshall, 1983). Since this time *H. pylori* has been studied extensively. Although most people with *H. pylori* infection remain asymptomatic, an important proportion of people are affected by serious morbidity and mortality, particularly from peptic ulcers and stomach cancer.

**Acquisition**

The mechanisms of transmission of *H. pylori* infection are not entirely clear but appear to be consistent with person-to-person spread (Goodman and Correa, 1995, Goh et al., 2011). Faecal-oral and oral-oral routes of transmission have been described (Goodman and Correa, 1995, Goh et al., 2011). *H. pylori* has been isolated from water sources which supports faecal-oral spread (Goh et al., 2011). The bacterium has also been isolated from the oral cavity which supports transmission through saliva (Goh et al., 2011).

Acquisition of *H. pylori* occurs predominantly in childhood (Lindkvist et al., 1996, Webb et al., 1994, Mitchell et al., 1992). Once infected, the majority of children remain chronically infected into adulthood.

**Virulence**

There is considerable genetic variation between different strains of *H. pylori* infection and some strains are more carcinogenic. Cytotoxin-associated gene A (CagA) encodes for a protein which is a virulence factor and may or may not be present in a strain of *H. pylori*. In populations with *H. pylori* infection a systematic
literature review demonstrates that CagA seropositivity was associated with 1.64 times (CI: 1.21-2.24, n=16) greater risk of stomach cancer (at any site) (Huang et al., 2003). Within an asymptomatic seropositive population in NZ, Māori (27%) and Pacific (24%) had the lowest rates of CagA seropositivity and European (40%) had similar CagA positivity to Caucasian populations elsewhere (Pérez-Pérez et al., 1997).

**Detecting *H. pylori* infection**

There are several tests for assessing *H. pylori* infection. Tests can be distinguished based on whether they test for active infection or for the presence of antibodies, which may persist after resolution of infection (Vakil and Fendrick, 2005).

Tests for active infection include the stool antigen test, urea breath test and gastroscopy with a rapid urease test, microbial culture and biopsy with histological examination (Graham and Qureshi, 2001). These tests do not detect past infection which has resolved.

To test for antibodies, the most commonly used measure is a serological blood test. A positive serology test typically indicates current or previous infection (Graham and Qureshi, 2001) and remains positive for years (van Zanten et al., 1994, Cullen et al., 1993). Even after infection is cured, decrease in titre is slow and unpredictable. However, over time (sometimes decades) most individuals will serorevert (Graham and Qureshi, 2001).

It is widely accepted that serology tests have poor sensitivity in detecting past *H. pylori* infection (de Martel et al., 2013) (Crabtree et al., 1993). For example, three recent prospective studies compare the detection of previous *H. pylori* infection using both ELISA and the Western blot (immunoblot) (de Martel et al., 2013) and show that the use of the immunoblot increased the odds ratio in all studies with up to a three-fold difference (González et al., 2012). The immunoblot test itself is known to have only a 92% sensitivity in detecting past *H. pylori* infection (González et al., 2012).
The sensitivity of serology tests in measuring active infection was demonstrated to average 85% with a specificity of 79% among 21 studies using commercially available ELISA serology kits (Stevens et al., 1997). Other studies have found similar results (Vaira and Vakil, 2001) (Vakil and Fendrick, 2005).

**Treatment**

*H. pylori* is easily tested and treated. The preferred treatment regimen in NZ is a seven day course of the combination of omeprazole, amoxicillin and clarithromycin (OAC). Dispensing the treatment together as a pack has enhanced compliance and has been easy to prescribe (Fraser, 2013). There is no local data on the success rate of this strategy but it is assumed to be >85% (Fraser, 2013). The preferred strategy for second line treatment has been quadruple treatment with colloidal bismuth subcitrate, tetracycline, omeprazole and metronidazole – usually for 7 days (Fraser, 2013).

**Are there benefits from *H. pylori* infection?**

It is postulated that *H. pylori* may be part of the natural ecology of the gut and protect against some diseases such as oesophageal adenocarcinoma, gastro-oesophageal reflux disease (GORD) and Crohns disease (Luther et al., 2010). However there is no evidence that *H. pylori* eradication treatment increases GORD on meta-analysis (Yaghoobi et al., 2010). *H. pylori* is postulated to be protective against Crohns disease (Luther et al., 2010), which occurs less commonly among Māori and Pacific in NZ (Keenan et al., 2011), however more evidence is required.

*H. pylori* infection is negatively associated with oesophageal adenocarcinoma in meta-analysis (Islami and Kamangar, 2008) and *H. pylori* declines in colonisation may partially explain increases in oesophageal adenocarcinoma. However, there is no evidence of an increase in oesophageal cancer incidence in NZ (data includes squamous cell carcinoma which is expected to increase with increasing obesity). Age-standardised incidence rates of oesophageal cancer have remained stable.
through the last 2-3 decades and are roughly half the incidence rate as stomach cancer (Ministry of Health, 2012a), suggesting that if *H. pylori* is truly beneficial, the impact of declining seropositivity on oesophageal cancer rates in NZ is small.

**Risk factors for *H. pylori***

**Socioeconomic conditions**

*H. pylori* infection is consistently associated with household crowding and socioeconomic variables (Goodman and Correa, 1995, Patel et al., 1994, Moayyedi et al., 2002). Many studies have shown that children exposed to household crowding are more likely to have *H. pylori* infection (Brown, 2000) even after adjusting for socioeconomic status (Office of the Deputy Prime Minister London, 2004). Although a considerable amount of research investigates risk factors for *H. pylori* infection, no systematic review or meta-analysis is available investigating the association between household crowding and *H. pylori* infection.

The relative importance of several overlapping elements of socioeconomic status as risk factors for *H. pylori* is disputed. Elements include bed or bedroom sharing, large families, single parent households, ethnicity, absence of fixed hot water supply, rented homes, crowding experienced outside the home such as at childcare (Office of the Deputy Prime Minister London, 2004) and inadequate nutritional status (Brown, 2000). Frequent consumption of fruits and vegetables and of vitamin C, appears to protect against infection with *H. pylori* (Brown, 2000). To establish household crowding as an independent risk factor for *H. pylori* requires careful adjustment for confounding from other socioeconomic risk factors.

Genetic variation as a contribution to *H. pylori* acquisition has been debated internationally and largely refuted. Variation in *H. pylori* risk among ethnic groups appears to be primarily related to differential exposure as a result of cultural background, social, dietary and environmental factors (Malaty, 2007) and much less from genetic variation.
Close-contact infectious diseases

The pattern of ethnic and socioeconomic differences seen with *H. pylori* is similar to that of other close contact infectious diseases (infections transmitted between people). An analysis of infectious disease in 2004-2008 indicated that hospitalisation rates were more than twice as high for Māori and Pacific relative to European/Others and that differences were most marked for close contact infectious diseases (Baker et al., 2012c, Baker et al., 2010).

Household crowding is a plausible contributing factor to the increased incidence of infection in low income groups, because these groups more commonly experience household crowding. Household crowding predisposes individuals to more frequent contacts with more people. Other close-contact diseases with a deprivation and ethnicity gradient include tuberculosis (Das et al., 2006), acute rheumatic fever (Jaine et al., 2008), meningococcal disease (O'Hallahan et al., 2009), childhood pneumonia (Byrnes and Trenholme, 2010) and skin infections (O'Sullivan et al., 2010). A systematic review examining a whole range of close contact infectious diseases demonstrates a consistent statistically significant association between nine infectious diseases and household crowding, particularly household crowding in childhood (Baker et al., 2013).

*H. pylori* and age

Increasing age appears to be particularly strongly associated with greater prevalence of *H. pylori* infection (Figure 1). This trend may be the result of either acquisition of infection with increasing age (van Zanten et al., 1994) or increased acquisition of the infection in childhood among older people (birth cohort effect). There is evidence to suggest that year of birth is the more important influence (Collett et al., 1999). Several cohort studies have followed groups of adults over time and found low rates of antibody acquisition and indeed a decline in *H. pylori* prevalence with age.
(Banatvala et al., 1993) (Cullen et al., 1993, Collett et al., 1999, Banatvala et al., 1993). The increase in seroprevalence among older age groups is largely attributable to greater acquisition in childhood among older persons with a decline in acquisition among subsequent birth cohorts as living standards have improved.

![Graph showing seropositivity for cases and controls](image)

**Figure 1**: Seropositivity for cases (solid line) and controls (broken line) in 14 studies. Adapted from Huang et al., 1998.

Despite this consensus, several studies have shown acquisition of *H. pylori* in adulthood and there are several potential explanations for this. A review of acquisition studies by Weck and Brenner (2011) shows that adult acquisition was mainly observed in studies characterised by changes in circumstances such as joining the military. Surprisingly there was no correlation between the length of follow-up and increasing *H. pylori* acquisition. When acquisition in adulthood does occur it appears to be less associated with age per se but more with changes in circumstances.

Furthermore, the majority (17/32) of eligible studies in the Weck and Brenner (2011) review, recorded adult incidence at less than 1.0% per year. The cumulative incidence in most studies could be explained by the sensitivity and specificity of the diagnostic tests i.e. study results could plausibly have occurred in the absence of any truly new infections because of imprecise diagnostic measures (Weck and Brenner, 2011). Study findings suggesting acquisition of new infection among adults should
be interpreted cautiously in consideration of the potential influence of measurement error on results (Weck and Brenner, 2011).

Measures of seroprevalence in the Dunedin longitudinal study (Fawcett et al., 2005) show that the seroprevalence of \textit{H. pylori} infection was similar in childhood (11 years old) to adulthood (26 years old). Between the ages of 11 and 21 years the seroreversion rate was 0.35% and the seroconversion rate was lower at 0.11% per person-year. These findings are consistent with the majority of acquisition occurring before 11 years old and that in most cases chronic infection persists into adulthood.

\textbf{\textit{H. pylori} as a cause of stomach cancer}

Perhaps even more extensively studied are not the risk factors for \textit{H. pylori} but the impact of the infection on subsequent disease. \textit{H. pylori} has been implicated in the pathogenesis of gastritis, peptic ulcer disease and stomach cancer. It is estimated that approximately 10-20\% of the seropositive population will develop peptic ulcer disease (Kuipers et al., 1995) and 1-2\% will develop stomach cancer (lifetime risk) (Kuipers, 2001, Kuipers, 1999). \textit{H. pylori} infection has also been associated with other diseases outside the stomach (Kato and Asaka, 2010) such as iron-deficiency anaemia (Fraser et al., 2010) although evidence for this is conflicting (Goh et al., 2011).

The World Health Organisation classifies \textit{H. pylori} as a class I carcinogen that is directly involved in causing stomach cancer (IARC Working Group, 1994). Multiple systematic reviews have established the association between \textit{H. pylori} and stomach cancer (Table 1). Meta-analysis odds ratios (ORs) range between 1.92 and 2.56. Many of these studies are case-control designs which are believed to underestimate the true risk because \textit{H. pylori} infection is lost as the mucosa undergoes malignant transformation (Herrera and Parsonnet, 2009). Furthermore, misclassification of previous \textit{H. pylori} infection exposure by the ELISA test may substantially bias odds ratios towards the null. The next section discusses this further.
Several sources propose that *H. pylori* is in fact a necessary causal factor for stomach cancer (Kato and Asaka, 2010) especially for non-cardia (distal) stomach cancer (Kato and Asaka, 2010, Brenner et al., 2004, World Cancer Research Fund and American Institute for Cancer Research, 2007, Fock et al., 2008). Figure 1 is consistent with this proposition because it confirms that seroprevalence in stomach cancer cases is fairly consistent across all age groups at around 80%. The proportion of stomach cancers that tested seropositive for *H. pylori* in another meta-analysis was estimated to average 81.2% (Webb et al., 2001) and as high as 86.0% for non-cardia cancers.

There are several reasons why some stomach cancers might test negative for *H. pylori* infection whilst the necessary factor proposition remains true.

Firstly, those with stomach cancer who test negative for *H. pylori* may have experienced a loss of infection associated with atrophic gastritis with a consequential decline in antibody titre (World Cancer Research Fund and American Institute for Cancer Research, 2007). There may be seroreversion between the time of critical *H. pylori* exposure (e.g. childhood) and diagnosis of cancer (Kikuchi et al., 2000) and because seroreversion may take decades, this is more likely to occur in older age groups.

### Table 1: Meta-analyses of the relationship between *H. pylori* seropositivity and gastric cancer, adapted from Kato and Asaka (2010), where OR=odds ratio, ccs=case-control study, *=cagA seropositivity only

<table>
<thead>
<tr>
<th>Author</th>
<th>Selected papers</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. (1998)</td>
<td>19 cohort, ccs</td>
<td>1.92</td>
<td>1.32–2.78</td>
</tr>
<tr>
<td>Danesh (1999)</td>
<td>10 nested ccs</td>
<td>2.5</td>
<td>1.9–3.4</td>
</tr>
<tr>
<td>Eslick et al. (1999)</td>
<td>42 cohort, ccs</td>
<td>2.04</td>
<td>1.69–2.45</td>
</tr>
<tr>
<td>Webb et al. (2001)</td>
<td>12 nested ccs</td>
<td>2.36</td>
<td>1.98–2.81</td>
</tr>
<tr>
<td>Xue et al. (2001)</td>
<td>11 ccs</td>
<td>2.56</td>
<td>1.85–3.55</td>
</tr>
<tr>
<td>Huang et al. (2003)*</td>
<td>16 ccs</td>
<td>2.28</td>
<td>1.71–3.05</td>
</tr>
</tbody>
</table>
Secondly, measurement error associated with the serology test may contribute to seronegative cancer cases. Studies suggest that ELISA serology tests underestimate the prevalence of active (Vaira and Vakil, 2001) and past *H. pylori* infection (Crabtree et al., 1993). We are interested in the sensitivity of detecting past infection. In an analysis of a large longitudinal European study, it was shown that most non-cardia stomach cancer cases classified as negative by ELISA serology tests were actually false negatives when they were analysed by Western blot, supporting the hypothesis that *H. pylori* may be a necessary condition for non-cardia stomach cancer (González et al., 2012). The study used a commercial immunoblot test that has been shown to have a sensitivity of 92% for previous infection. The study observed that 93% of non-cardia stomach cancer were immunoblot-positive which was consistent with the tests sensitivity and the necessary factor proposition (González et al., 2012).

Finally, *H. pylori* is a more important risk factor for non-cardia than cardia stomach cancer (Huang et al., 1998). Inclusion of cardia cancers in a study appears to result in reduced seropositivity among the cases. *H. pylori* infection is much more strongly associated with non-cardia stomach cancer and may not be associated at all with cardia stomach cancer (de Martel et al., 2013). The necessary factor proposition is more appropriate for the proportion of stomach cancer that is situated in the non-cardia region of the stomach.

Analysis in this dissertation was focussed on data for both non-cardia and cardia stomach cancer because subsite data was limited. However, because the *H. pylori* necessary factor proposition is considered applicable to non-cardia stomach cancer, a sensitivity analysis was carried out which restricted the analysis to non-cardia stomach cancer cases. Overall results are likely to overestimate the contribution of *H. pylori* to excess Māori and Pacific stomach cancer, but will be more accurate for the non-cardia stomach cancer sensitivity analysis approximations.
Subsite of stomach cancer

Risk factors for stomach cancer vary by the location of the cancer in the stomach (subsite). *H. pylori* is a significantly stronger risk factor for non-cardia cancer than for cardia cancer (OR 3.08 vs. 1.23; p=0.003) (Huang et al., 1998). Cardia cancer occurs in the proximal part of the stomach immediately adjacent to the oesophagus, and non-cardia cancer occurs in the other parts of the stomach.

Relatively few studies have stratified stomach cancer results on the basis of subsite (World Cancer Research Fund and American Institute for Cancer Research, 2007). Classification of stomach cancer subsite may vary by time and place, and there may be difficulties distinguishing non-cardia and cardia cancer from other cancers such as oesophageal cancer (de Martel et al., 2013).

Although total rates of stomach cancer have been declining, some developed countries have reported increasing rates of cardia stomach cancer (Cavaleiro-Pinto et al., 2011). There does not appear to be any evidence of this in the available NZ registration data between 2005 and 2009. During this snapshot in time, if anything, registration rates of both cardia and non-cardia cancer have slightly declined.

Ethnic differences in the incidence of non-cardia cancer may be increasing over time. In 1970-74, Stewart et al. (1982) found no statistical difference in stomach cancer subsite distribution between Māori and European participants (n=1193). However recent data shows that non-cardia cancer makes up a larger proportion of the stomach cancer among Māori (87%) and Pacific (88%) patients than among European (51%) (Biggar et al., 2011).

Despite ethnic differences in proportions, the incidence of stomach cancer in the cardia is similar across ethnic groups in NZ (Table 2). The greatest difference between ethnic groups was in the incidence of non-cardia tumours, where Māori and Pacific experienced almost four times the European incidence. The higher rates of non-cardia stomach cancer in Māori and Pacific probably reflects the higher *H. pylori* infection rates in these groups.
*Pylori* seroprevalence, which is a stronger risk factor for non-cardia than for cardia stomach cancer (Huang et al., 1998).

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Site</th>
<th>European Rate</th>
<th>Māori Rate</th>
<th>Pacific Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-2008 North Island (Signal, 2013)</td>
<td>Adenocarcinoma of the stomach n=335</td>
<td>cardia, fundus, body antrum, pylorus</td>
<td>63 2.4</td>
<td>47 5.3</td>
<td>163 6.3*</td>
</tr>
<tr>
<td></td>
<td>SUM</td>
<td></td>
<td>34 1.3</td>
<td>67 7.5</td>
<td>172 19.3*</td>
</tr>
<tr>
<td>2003-2009 South Auckland (Biggar et al., 2011)</td>
<td>Adenocarcinoma of the stomach n=133</td>
<td>proximal body/distal</td>
<td>18 1.4</td>
<td>4 0.8</td>
<td>5 0.8</td>
</tr>
<tr>
<td></td>
<td>SUM</td>
<td></td>
<td>19 1.5</td>
<td>27 5.7</td>
<td>35 5.8</td>
</tr>
<tr>
<td>1970-74 New Zealand (Stewart et al., 1982)</td>
<td>Stomach cancer in males only n=1193</td>
<td>proximal third middle&amp; lower third</td>
<td>20% 3.4</td>
<td>20% 10.9</td>
<td>69% 37.7</td>
</tr>
<tr>
<td></td>
<td>SUM</td>
<td></td>
<td>69% 11.7</td>
<td>69% 37.7</td>
<td>17.0* 54.7*</td>
</tr>
</tbody>
</table>

**Table 2: Summary of studies showing the incidence of stomach cancer in New Zealand by various subsite groupings and ethnicity - Incidence rates were calculated from the ^NZ 2007 age-standardised rate, the crude rates per 100,000 population in the hospital catchment area (Biggar et al., 2011) and the *1970-74 age-standardised incidence rate, tumours unable to be classified are included in the summarised rates.**

**Histology of stomach cancer**

Adenocarcinoma is the most common histological form of stomach cancer (approximately 90%), followed by gastric mucosa-associated lymphoid tissue (MALT) lymphoma and then other types. Adenocarcinoma histology is classically defined as either diffuse- or intestinal-type. Chronic inflammation is characteristic of the pathway to intestinal-type stomach cancer however it is not required for the development of diffuse-type cancers (Polk and Peek, 2010).

Both diffuse and intestinal types appear to be similarly associated with *H. pylori* infection (Kato and Asaka, 2010). A meta-analysis found a small difference in the odds ratio for this association (Huang et al., 1998) but it was not statistically significant. *H. pylori* infection was associated with 2.23 (CI: 1.74-2.87, n=10) greater odds of intestinal-type stomach cancer and 2.85 (CI: 2.14-3.79, n=10) greater odds of diffuse-type stomach cancer (p=0.3).
In recent studies of stomach cancer, there is a predominance of diffuse-type stomach cancer incidence among Māori and Pacific (Biggar et al., 2011) (Blair et al., 2003), whereas intestinal-types were more predominant among European (Table 3). Given that *H. pylori* appears to be similarly associated with intestinal- and diffuse-types, it is surprising that the excess incidence of intestinal-type stomach cancer is not greater among Māori and Pacific. However, it may be that *H. pylori* is truly more important for diffuse than intestinal-type stomach cancer.

Furthermore, diffuse-type morphology is uncommon in cardia cancer and more likely in non-cardia stomach cancer (Kamangar et al., 2006). The Māori and Pacific predominance of diffuse-type stomach cancer is at least partially explainable by the excess incidence of non-cardia stomach cancer among Māori and Pacific. *H. pylori* infection, as a necessary factor for non-cardia stomach cancer, appears to be contributing to the predominance of diffuse stomach cancer among Māori and Pacific.

Lower than expected incidence of intestinal stomach cancer among Māori and Pacific could also be explained by ethnic differences in *H. pylori* seroprevalence, if there are differences in the risk factor (co-factor) profiles for intestinal- and diffuse-type cancer. It is not yet elucidated whether the two types reflect two separate aetiologies with separate risk factors, however we do know that patients with diffuse-type are more likely to be younger and are more frequently female (Wu et al., 1997). CagA (more common in European) appears to enhance the risk of intestinal-type and not diffuse-type stomach cancer (Shibata et al., 2002). Genetic-environment interactions have also been proposed (Biggar et al., 2011).
<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Histology</th>
<th>European Rate</th>
<th>Māori Rate</th>
<th>Pacific Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Biggar et al., 2011) 2003-2009</td>
<td>Adenocarcinoma of Stomach</td>
<td>Intestinal</td>
<td>30</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>South Auckland hospital</td>
<td></td>
<td>Diffuse</td>
<td>7</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SUM</td>
<td>38</td>
<td>34</td>
<td>49</td>
</tr>
<tr>
<td>(Blair et al., 2003) 1998-2001</td>
<td>Adenocarcinoma of Stomach</td>
<td>Intestinal</td>
<td>87</td>
<td>10</td>
<td>nr</td>
</tr>
<tr>
<td>3 hospitals</td>
<td></td>
<td>Diffuse</td>
<td>38</td>
<td>35</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SUM</td>
<td>125</td>
<td>45</td>
<td>29</td>
</tr>
<tr>
<td>(Nevalainen et al., 1988) 1966-1985</td>
<td>Gastric carcinoma</td>
<td>Intestinal</td>
<td>18</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Auckland</td>
<td></td>
<td>Diffuse</td>
<td>28</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SUM</td>
<td>54</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>(Kubo, 1974) -1973</td>
<td>Gastric carcinoma</td>
<td>Intestinal</td>
<td>482</td>
<td>40</td>
<td>13.8</td>
</tr>
<tr>
<td>Lower North Island</td>
<td></td>
<td>Diffuse</td>
<td>172</td>
<td>28</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SUM</td>
<td>656</td>
<td>68</td>
<td>23.4*</td>
</tr>
</tbody>
</table>

Table 3: Summary of studies in New Zealand showing incidence of stomach cancer by histology by ethnicity, rates are calculated from summarised incidence rates given in the study or taken from New Zealand cancer registrations in ^2005 and *1978-80, nr = not reported

Histological mechanism

The mechanism by which *H. pylori* is involved in the carcinogenesis of stomach cancer is not clearly understood (Blaser and Atherton, 2004). However after *H. pylori* acquisition stomach cancer (particularly intestinal-type) generally develops over a multi-step progression from chronic gastritis to atrophic change, intestinal metaplasia to dysplasia, and subsequently to cancer (Fraser, 2004) (Kato and Asaka, 2010). *H. pylori* products can directly or indirectly induce the DNA damage ultimately required for carcinogenesis. Animal models and human studies suggest that the net effect of *H. pylori* colonisation on epithelial cells is pro-proliferative, potentially predisposing to atrophy or increased mutation and malignant transformation (Blaser and Atherton, 2004).

Other risk factors for stomach cancer

Alongside *H. pylori*, additional or alternative contributors to ethnic differences in stomach cancer incidence may be sought by considering the other major risk factors.
(co-factors) for stomach cancer. These are smoking, high salt intake, and inadequate fruit and vegetable intake (Ladeiras-Lopes et al., 2008). For the analysis an assumption is made that *H. pylori* seroprevalence does not differ by these co-factors. For these risk factors to contribute to ethnic differences, it is required that different ethnic groups have different levels of exposure. This question is examined below for each risk factor.

**Salt**

NZ data are limited on salt intake by ethnicity, particularly for the time period for which we are interested. Recent data that does exist does not demonstrate any substantial ethnic differences in salt intake. The 2008/2009 National Nutrition Survey estimated sodium intake (n=3315) in a sub-sample using spot urines to calculate 24-hour urinary sodium excretion (15+yos) (McLean, 2011b) (McLean, 2011a). There was no difference in sodium intake by ethnicity or level of deprivation (although there was greater intake among males) (McLean, 2011a). Of note, almost two-thirds of New Zealanders exceeded the recommended upper limit of intake (74% of males, 53% of females) (McLean, 2011a). There was no available data on salt intake by ethnicity prior to this survey.

**Fruit and vegetables**

Data on vegetable intake is available from National Nutrition Surveys. Differences between ethnic groups are not substantial. For example in 2008/2009 the proportion of Māori and Pacific males who consumed the recommended 3+ servings of vegetables and 2+ servings of fruit per day was very similar to non-Māori and non-Pacific males respectively (RRs between 0.90 and 1.02) (Ministry of Health, 2012c) (Ministry of Health, 2012d). Furthermore, the protective effect of fruit and vegetables against stomach cancer is weak and often inconsistent (World Cancer Research Fund and American Institute for Cancer Research, 2007) (Lunet et al., 2005), limiting the magnitude of its likely impact on ethnic differences and stomach cancer.
Smoking
For smoking however there is good historic data and substantial differences in smoking prevalence by ethnicity (Hill et al., 2003). There is also good evidence of an association between smoking and stomach cancer (Ladeiras-Lopes et al., 2008). In the 1981 census both Māori and Pacific peoples were more likely to be smokers (Hill et al., 2003). A decision was made to include smoking in the analysis in order to quantify its contribution to the remaining ethnic differences in stomach cancer after accounting for \textit{H. pylori}.

Effect modification
If \textit{H. pylori} is a necessary cause we can also assume that these co-factors will only be associated with stomach cancer among persons who are \textit{H. pylori} seropositive. Evidence suggests that \textit{H. pylori} may not be independent of other risk factors and instead it may be a significant effect modifier (e.g. multiplicative) of the other major risk factors (González and López-Carrillo, 2010). Smoking and diet appear to have little association with stomach cancer in the absence of \textit{H. pylori} infection (González and López-Carrillo, 2010). This is what we would expect if \textit{H. pylori} is indeed a necessary risk factor for the majority of cases of stomach cancer.

Māori and Pacific have high rates of all three
In NZ, Māori and Pacific are overrepresented in statistics for household crowding, \textit{H. pylori} infection and stomach cancer incidence.

Distribution of \textit{H. pylori} by ethnicity
Prevalence of \textit{H. pylori} varies considerably by ethnicity in NZ (Fraser et al., 1996, Fraser et al., 2010). Māori and particularly Pacific seroprevalence is consistently greater than European seroprevalence, and many have cited this as a reason for excess stomach cancer incidence among Māori and Pacific (Tukuitonga CF, 1992, Fraser et al., 1996, Blair et al., 2013, Talley and Xia, 1996). However, no studies have quantified the impact of \textit{H. pylori} on ethnic differences in stomach cancer incidence.
Distribution of household crowding by ethnicity

The distribution of household crowding in NZ is unequal with much higher levels for children relative to adults and for Māori and Pacific relative to European/Other (Baker et al., 2012a). There is substantial regional variation (Figure 2) which reflects the distribution of population groups with high levels of household crowding.

In NZ, the Canadian National Occupancy Standard (CNOS) is used to measure household crowding because it is considered to have reasonable face validity, the output it generates is useful for a number of purposes, and it can be calculated with available census data (Baker et al., 2012a) (Goodyear et al., 2011). The CNOS considers a household crowded, if the dwelling requires additional bedrooms to meet set criteria. The criteria focus on the number of persons per bedroom and
limits bedroom sharing to no more than two people. According to the criteria, it is expected that parents or couples will share, children aged <5 years will share, children aged <18 years old of the same sex will share, and adults >18 years old will have a separate bedroom (Goodyear et al., 2011).

In the NZ 2006 census, the proportions exposed to household crowding using the CNOS (1+ bedroom deficit) were 42.6% for Pacific peoples, 22.8% for Māori, and 4.7% for European/Other. Focussing on children <5 years, the exposure to extreme crowding (2+ bedroom deficit) was 10.1% for Māori and 20.6% for Pacific children compared with 1.9% for European/Other. For Māori children this equates to a relative risk of exposure to severe household crowding of 5.4 (95%CI 5.2-5.7) compared with European/Other. For Pacific children, the relative risk of exposure to severe household crowding was 11.1 (95%CI 10.6-11.5) (Baker et al., 2012b).

Although absolute differences in crowding have decreased over time, the relative differences have increased for both Māori and Pacific compared to European (Figure 3).

Figure 3: Proportion of population living in households requiring at least one additional bedroom, by ethnic group, 1986–2006 (Ministry for Social Development, 2010b)

Several factors influence the different rates of household crowding among ethnic groups, including lower incomes, recent migration (for overseas born), larger households, living arrangements and lack of large houses particularly rental houses
(Statistics New Zealand, 2012a). A qualitative study of Tokelau people identified reasons for household crowding which included housing affordability, housing accessibility, and cultural patterns (Howden-Chapman et al., 2000).

Māori and Pacific people disproportionately experience lower socioeconomic status and unaffordable housing. Unaffordable housing is known to be a driver of household crowding (Productivity Commission, 2012). Housing is considered affordable when a household spends no more than 30% of its gross annual income on housing costs, whether for rent or mortgage (Ministry for Social Development, 2010a). In the 1990s, household crowding was strongly associated with reduced housing affordability and the move to market rents (Productivity Commission, 2012). Furthermore, house prices continue to rise and it is predicted that household crowding will rise in response to increased rents (Productivity Commission, 2012).

Accessibility to housing may be experienced differently by different ethnic groups. For example, language and cultural expectations may create a barrier to accessing social housing services such as the accommodation supplements or income related rents. Furthermore, analysis of the NZ Health Survey has shown that Māori are thirteen times more likely than European/Other to experience self-reported racial discrimination when buying or renting housing (Harris et al., 2006).

Cultural factors also appear to contribute to economic decision-making about housing, for example Tokelauan hospitality expectations (Howden-Chapman et al., 2000). However, it is interesting to note that no differences in psychological distress between ethnic groups were evident with similar levels of household crowding (Evans et al., 2000), irrespective of differences in perceptions and tolerance of crowding (Pene et al., 2009).

**Epidemiology of stomach cancer by ethnicity**

There are 370 cases of stomach cancer a year in NZ (2009 figure). Age-standardised rates of stomach cancer for Māori and Pacific are two to three times greater than
for European/Other. From 1981-2004, Māori experienced 2.48 (2.27-2.70) times the rate of stomach cancer compared to European, and Pacific experienced 2.64 (2.23-3.14) times greater incidence (Blakely et al., 2011).

Males are almost twice as likely to be affected by stomach cancer as females (Ministry of Health, 2012b). The age-standardised rates of stomach cancer in 2009 were 7.1 registrations per 100,000 males; and 3.3 registrations per 100,000 females.

Most cases of stomach cancer are fatal. The five-year survival is 22.5% (Ministry of Health, 2010). Stomach cancer is the ninth most common cause of cancer death in NZ and accounts for 2.9% of cancer deaths (Ministry of Health, 2012b). Stomach cancer among Māori men however is the fourth most common cause of cancer death (Robson and Harris, 2007).

Ethnic differences in stomach cancer in NZ appear to be more marked than socioeconomic differences. Between 1981 and 2004, for example, the age-standardised incidence rate of stomach cancer for the third of the population with the lowest income was 1.23 (1.11–1.37) times greater than for the third with the highest income (Blakely et al., 2011). Although there are other ways to measure socioeconomic differences, this is much less than the 2.48 (2.27-2.70) times and 2.64 (2.23-3.14) times increased Māori and Pacific incidence rates respectively.

As discussed above, excess stomach cancer incidence among Māori and Pacific is predominantly non-cardia with diffuse histology. Not only do Māori and Pacific experience more stomach cancer but Māori (59 years) and Pacific (65 years) patients are on average significantly younger at diagnosis than European patients (77 years) (Biggar et al., 2011).

In other countries ethnicity has also been associated with increased rates of stomach cancer. In the United States, Asian / Pacific Island, African-American and Hispanic-American ethnic groups experience the highest rates of stomach cancer incidence (Ward et al., 2004).
Trends in stomach cancer over time

The overall age-standardised rate of stomach cancer in NZ is declining (Figure 4) for both males and females. The ethnicity patterns are less clear. From 1981-2004, for European/Other the rate of stomach cancer fell 33% for males and 42% for females (Blakely et al., 2010) however for Māori and Pacific the picture was mixed (less numbers for accurate estimates) (Soeberg M et al., 2012).

![Age-standardised rates of stomach cancer in New Zealand by gender](image)

Figure 4: Age-standardised rates of stomach cancer in New Zealand by gender 1948-2008, standardised to the World Health Organisation population (Ministry of Health, 2012a).

It is important to understand what is behind the decline in stomach cancer incidence if we are to maximise the benefits for all ethnic and socioeconomic groups. The declining rates of stomach cancer follow a trend seen in many developed countries. Suggested reasons for the decline relate to changes in diet associated with the availability of refrigeration, and reduced exposure to *H. pylori* (World Cancer Research Fund and American Institute for Cancer Research, 2007, Parkin, 2001). Furthermore, discovery of effective antibiotic treatment for *H. pylori* has led to thousands of people being treated since the 1990s and may have contributed to the more recent decade of decline.
Why are there ethnic differences in stomach cancer incidence?

There does not appear to be a clear consensus in NZ on the reasons for ethnic differences in the incidence of stomach cancer (Blair et al., 2013). Before *H. pylori* was extensively studied, an early study hypothesised socioeconomic status, smoking and diet as contributing factors (Dockerty et al., 1991).

Genetic factors have also received attention, particularly for their contribution to the diffuse type of stomach cancer (Biggar et al., 2011). Hereditary Diffuse Gastric Carcinoma (HDGC) among an extended Māori family has been given much attention since the ground-breaking discovery of a E-cadherin mutation contributing to familial stomach cancer (Fraser, 2004). Twenty-five family members died of stomach cancer between 1965 and 1998 at a median age of 33 years (Blair et al., 2006). Although this is the largest known family with this mutation, 25 cases over 33 years is not enough to create ethnic differences in national stomach cancer registrations. Fraser (2004) suggests that the emphasis placed on genetic factors should be replaced with attention to *H. pylori* and its significant contribution to stomach cancer rates in Māori and Pacific men.

The most widely cited reason for differences in stomach cancer by ethnicity in NZ is *H. pylori* infection. The extent of the *H. pylori* contribution has not been quantified. There is no national seroprevalence data available and *H. pylori* trends over time are unknown. Ethnicity specific estimates that take into account year of birth, age and regional variation are not available. However, current study data on *H. pylori* seroprevalence could be pooled to give Māori, Pacific and European estimates by cohort of birth. Seroprevalence estimates could be compared with the stomach cancer registration data to assess the contribution of *H. pylori* to stomach cancer incidence by ethnicity.
Summary

*H. pylori* infection, household crowding and stomach cancer incidence are disproportionately experienced by Māori and Pacific in NZ. This dissertation sought to examine the trends in *H. pylori* infection by ethnicity and quantify the contribution of household crowding; then examine the trends in stomach cancer incidence by ethnicity and examine the contribution of *H. pylori* infection.
Aims and objectives

The aims of this study were to

A. Summarise the international literature on the association of household crowding with *H. pylori* (and stomach cancer), among study participants of any age from any country
   - Estimate the proportion of *H. pylori* seroprevalence among Māori, Pacific and European/Other people that is attributable to childhood household crowding in NZ

B. Estimate the proportion of excess Māori and Pacific stomach cancer incidence in NZ males that is attributable to variable exposure to *H. pylori*
   - Pool NZ data on *H. pylori* prevalence by birth cohort
   - Discuss *H. pylori* trends over time
   - Measure ethnic differences in pooled *H. pylori* prevalence
   - Measure ethnic differences in stomach cancer incidence
   - Determine what proportion of ethnic differences in stomach cancer incidence might be accounted for by *H. pylori* and smoking
Part A: Systematic review of observational studies investigating the association of household crowding with H. pylori and stomach cancer

Overview

Both household crowding and the prevalence of H. pylori infection in NZ are experienced more commonly by Māori and Pacific than by European. Household crowding is proposed as one of the key socioeconomic mechanisms linking ethnicity, H. pylori infection and stomach cancer.

A systematic review of the international literature was conducted to identify studies investigating the association between household crowding density and H. pylori. Eligible studies were combined by meta-analysis to produce a summary OR. This meta-analysis was one segment of a larger systematic review report investigating the association between household crowding and close contact infectious disease (Baker et al., 2013). The study was registered on the PROSPERO Centre for reviews and dissemination, http://www.crd.york.ac.uk/Prospero/.

The conceptual diagram in Figure 5 illustrates the expected pathways linking ethnicity and household crowding with H. pylori infection and stomach cancer. To determine the independent effect of household crowding on the risk of H. pylori infection and stomach cancer, it is important to adjust for the influence of age and socioeconomic status which may increase infection risk through other pathways.
Figure 5: Proposed relationship between ethnicity, household crowding and outcomes \textit{H. pylori} infection and stomach cancer, demonstrating the influence of socioeconomic status and age, and their potential confounding effects.
Chapter 2: Review methods

Systematic search strategy
A comprehensive search strategy was developed, piloted and implemented. The systematic search examined articles published in Medline (1966 to 2012), Embase (1988 to 2012), Scopus, Web of Science, Index New Zealand, Cochrane Library and The Lancet Journal of Infectious Disease. Additional articles were identified by searching references, review articles and expert recommendation. The search was up-to-date on the 6th July 2012 for H. pylori outcomes and the 13th March 2013 for stomach cancer outcomes.

The search aimed to identify all articles measuring the association between household crowding density and H. pylori or stomach cancer. Key word searches were used for all of the databases with the addition of customised subject headings (MeSH terms) for the Medline and Embase databases (see Table 4). Crowding was identified by keyword or by a combination of adjacent keyword terms that referred to concepts of both people and space, to maximise the sensitivity of the search to household crowding. No limits were placed on the year of publication apart from the limits inherent in each database. Searches were limited to articles categorised as human and published in English.
Table 4: Medline search strategy

<table>
<thead>
<tr>
<th>Exposure: household crowding</th>
<th>Outcomes: H. pylori and stomach cancer</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeSH terms</td>
<td>MeSH terms</td>
<td>Human</td>
</tr>
<tr>
<td>Crowding/</td>
<td>exp bacterial infection/</td>
<td>English</td>
</tr>
<tr>
<td>or bed sharing/</td>
<td>helicobacter infection/</td>
<td></td>
</tr>
<tr>
<td>Keywords</td>
<td></td>
<td></td>
</tr>
<tr>
<td>crowd*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or overcrowd*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or per room</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or ((People or person or persons or child* or adult or adults or resident or residents or member*) adj3 (room* or bed* or area or m2 or square meter* or square metre* or ft2 or square feet*))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or ((bed* or room*) adj3 (sharing or share))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or ((hous* or home) adj3 (area or m2 or square meter* or square metre* or ft2 or square feet* or size or density))</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eligibility criteria

Inclusion and exclusion criteria

Eligibility criteria were used to select studies according to their study population, exposures, comparisons, outcomes and study design (PICOS criteria). If a study did not meet one of the following criteria it was excluded.

Study participants who normally lived in a household were eligible. No exclusions were made based on age or country, in order to ensure the broadest range of evidence was examined. Study populations with a high risk of disease were also eligible, such as patients presenting with gastrointestinal symptoms that might be attributable to H. pylori.

Studies were required to evaluate household crowding density as an exposure variable. Eligible crowding measures included crowding indexes that quantified the number of household members per number of rooms, persons per area (such as m\(^2\)), number of persons sharing the same bedroom, and any measure of house area (e.g. number of rooms or m\(^2\)). Measures of area were rarely used but they were
included because of their potential to differentiate crowding density for families of a similar size.

Some household crowding exposures were excluded such as bed sharing, the number of occupants per household and the number of siblings in the household. Bed sharing was excluded because it is more of a behavioural exposure than housing density related. The number of people in a household was excluded because it does not take into account house size and therefore has limited specificity as a density measure.

Mass gathering, prison, military, workplace, day care and institutional measures of crowding were excluded. Studies that had H. pylori infection as an outcome but did not indicate household crowding in the title or abstract were unlikely to be identified, unless there was some indication that crowding may have been measured, such as a multivariate analysis or reference to housing factors.

A comparison was required between greater and lesser levels of household crowding density. Any statistical measure was eligible for narrative synthesis such as an OR, rate ratio (RR), beta coefficient or difference between two means. However, only ORs and RRss were included in the meta-analysis.

Studies were eligible if they measured H. pylori infection or stomach cancer outcomes using laboratory techniques. For H. pylori outcomes, eligible diagnostic measures included measures of active infection (e.g. C labelled urea breath test) and measures of serology indicating active or previous infection (Vakil and Fendrick, 2005).

Any quantitative study design with an individual level of analysis was eligible, including cohort, case-control and cross-sectional studies. Our focus here was on (non-randomised) observational studies. Ecological study designs and neighbourhood measures of crowding were excluded. Systematic reviews and case studies (<20 participants) were also excluded.
Screening

The first screening step was to assess the titles and abstracts of studies from the database search against the (above) eligibility criteria. Endnote was used to manage the references. Full text articles were obtained for the studies potentially consistent with eligibility criteria during the title and abstract screening step.

The second screening step was a more thorough assessment of the full text articles to determine whether they specifically met all of the eligibility criteria (PICOS). The outcome of the assessment was recorded in an Excel spread sheet. The criteria were assessed in the following order: study design, outcome, exposure and then comparison group. Studies which met all criteria were eligible for narrative review.

Eligible studies were included in the meta-analysis if they provided an OR adjusted for confounding from age and socioeconomic status.

Data collection and analysis

Extraction of data

Key information from eligible studies was extracted into a spread sheet. Data included the country, age of participants, exposure measure, outcome measure, study design, number of subjects, crude measure of effect, direction of the effect and statistical significance. The following information was extracted for each study outcome included in the meta-analysis:

1. Identifiers
   a. Disease of interest
   b. Author, year
2. Study design
   a. Study design (e.g. cross-sectional, case-control, cohort)
   b. Outcome measure (most crowded vs. least crowded category)
   c. Exposure measure in crowded vs. not crowded
d. If case-control studies: how were the cases selected and matched?

e. Socioeconomic status variable(s) adjusted for (or considered in brackets)

f. How was age adjusted for?

g. Other crowding variables adjusted for

h. Any other variables adjusted for

3. Study population:

a. Country

b. Years that study was carried out

c. Prevalence of *H. pylori* infection / incidence of stomach cancer

d. Was the study population high risk or population representable?

e. What was the age range of the population studied?

f. How many study participants (if case control: broken down by cases and controls)

4. Unadjusted measure of effect

a. OR: odds ratio / RR: rate ratio

b. LCI: lower 95% confidence interval

c. UCI: upper 95% confidence interval

d. P-value if CI unavailable

5. Adjusted measure of effect (from an eligible model with the most number of variables)

a. OR: odds ratio / RR: rate ratio

b. LCI: lower 95% confidence interval

c. UCI: upper 95% confidence interval

d. P-value if CI unavailable

6. Quality appraisal using an adaption of the Newcastle-Ottawa Scale (NOS)
   (Wells et al., 2000) (Appendix 2)

If adjustments for age and socioeconomic status were described in the study, but the relevant adjusted OR and/or its confidence interval were not reported, study authors were contacted by email and requested to provide the additional data.
Eighteen authors were emailed and three replied with the requested data. Screening and full text extraction was carried out by one reviewer (AM).

**Avoiding duplication**

The contribution of any one study to the meta-analysis was limited to one comparison. If more than one eligible article used the same study data, the most recent article was selected for extraction.

If there were two or more eligible crowding exposures in one study, then one exposure was selected based on the following order of priority: ratio of persons to the number of rooms (prioritising childhood exposure over adult exposures), area per person, persons per bedroom (prioritising siblings closest in age over parents in same bedroom), house area or other. This order is based on the expected validity of each measure in quantifying household crowding density, the potential relevance to transmission of infection and the frequency that each measure is used in the literature.

If a study stratified results by sub-groups and no overall measure of effect was available, one stratum of results was selected for inclusion based on its similarity to the other included studies. For example, one study (Malaty et al., 1996) stratified results by children and adults, and only the results for children were included in the meta-analysis. Another study (Broutet et al., 2001) reported results by whether participants experienced upper gastrointestinal symptoms or not, and only the results for participants without symptoms were included.

**Synthesis of results**

**Narrative synthesis**

The outcomes of eligible studies were considered briefly in a narrative synthesis. The proportion of studies that demonstrated statistically significant associations
between household crowding and H. pylori and stomach cancer were reported along with whether the effect was positive or negative.

Meta-analysis

Meta-analysis was used to summarise the outcomes (and investigate heterogeneity) among studies which provided an OR adjusted for confounding from age and socioeconomic status. Confounding could be adjusted for by stratification, standardisation and/or regression. Socioeconomic status was defined as any measure of income, occupation, education, deprivation, area of residence, or housing quality (such as the presence of a toilet). If there was a choice in a study between different eligible statistical models, the model that adjusted for the greatest number of variables was selected. Adjusted ORs were still considered eligible if age and/or socioeconomic status were excluded from the final model because they lacked predictive or confounding value.

Meta-analysis was only possible for H. pylori outcomes and not for stomach cancer, because there were many eligible studies for H. pylori but only one eligible study for stomach cancer.

Methods were based on the Cochrane Handbook guidance (Higgins and Green, 2011). Data were entered into Revman5 software and combined using the inverse variance function. Adjustment for random effects was carried out to allow for heterogeneity. In order to input data, ORs were converted into natural logarithms [ln(OR)] and the standard error of these logarithms was calculated from the reported 95% confidence intervals by applying the following formula (Higgins and Deeks, 2008):

\[ SE[\ln(OR)] = \frac{\ln(\text{upper limit}) - \ln(\text{lower limit})}{3.92} \]
If confidence intervals were not given, but a p-value was reported, the standard error was calculated from the p-value (Higgins and Deeks, 2008). This assumes a Wald test is used to calculate the reported p-value and uses the following formula:

\[ \text{SE}[\ln(\text{OR})] = \frac{\ln(\text{OR})}{Z_{(p \text{-value})}} \]

Heterogeneity between studies was assessed by visual inspection and the \( I^2 \) statistic (Higgins and Green, 2011). \( I^2 \) describes the percentage of variability in an effect estimate that is due to heterogeneity rather than sampling error (chance). For example if \( I^2 = \)

- 0% to 40%: this might not be important
- 30% to 60%: this may represent moderate heterogeneity
- 50% to 90%: this may represent substantial heterogeneity
- 75% to 100%: this is considerable heterogeneity (Higgins and Green, 2011)

Sub-group meta-analysis was carried out to investigate heterogeneity of results. Sub-groups that were pre-specified included study quality (NOS scale) and country income. Other sub-group analyses considered at the analysis stage included childhood vs. adult exposure to crowding, prevalence of \( H. pylori \) infection in the study population, type of crowding measure, test used to determine \( H. pylori \) infection, year of publication, presence of gastrointestinal symptoms and whether adjustment was made for additional crowding variables.

**Risk of bias in individual studies**

Non-randomised study outcomes such as those included in this review are subject to greater bias than randomised studies. We therefore assessed individual study quality and restricted meta-analysis to studies which controlled for important confounders.
Individual study quality was assessed for each study in the meta-analysis using an adaption of the Newcastle Ottawa Scale (NOS) (Appendix 2). Each study was scored out of ten and this figure was used in a sub-group analysis to see if the summary OR varied significantly by study quality.

The impact of household crowding on *H. pylori* infection is likely to be influenced (confounded) by age and socioeconomic status. *H. pylori* studies are all published in recent decades and so we would expect them to use methodologies that account for potential confounding. We limited the meta-analysis to studies which adjusted for confounding from age and socioeconomic status, in order to estimate the independent impact of household crowding.

**Risk of bias across studies**

Risk of bias across studies was assessed by funnel plot and comparison between meta-analysis and narrative synthesis results. Potential publication bias was evaluated by assessing the symmetry of a funnel plot produced in RevMan5. The narrative synthesis enabled us to explore the consistency of meta-analysis results with results from a broader collection of studies that did not necessarily control for confounding or report a comparable measure of effect.
Chapter 3: Review results

Study selection

The number of studies included in the screening and selection process for *H. pylori* is illustrated by the flowchart in Figure 6 and Figure 7 for stomach cancer. Of the titles and abstracts identified for *H. pylori*, 99 full text articles were obtained for further assessment. Consequently, 38 studies were excluded with reasons (Table 5) and 61 studies were eligible for narrative synthesis. Of the eligible studies, 28 adjusted for age and socioeconomic status and provided an OR, and were therefore included in the meta-analysis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number full text articles screened</th>
<th>Articles excluded with reasons:</th>
<th>Eligible articles included:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study design</td>
<td>Infect. disease outcome</td>
<td>Comparsion group</td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td>99</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>32</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 5: Number of full text records assessed, showing the reasons for exclusion, the total number of studies eligible for narrative synthesis and the subset included (incl.) in meta-analysis (studies with ORs adjusted for socioeconomic status and age).

Of the 242 titles and abstracts identified for stomach cancer, 32 full text articles were obtained for further assessment (Table 5). Only one of these studies met the eligibility criteria (Coggon et al., 1993), but it did not adjust for age and socioeconomic status. No meta-analysis was therefore possible for the stomach cancer outcome.
Studies that adjusted but no OR/RR was available (n= 17)

Studies included in meta-analysis (n=28)

Studies assessed for inclusion in meta-analysis (n=61)

Eligible studies reviewed by narrative synthesis (n= 61)

Full-text studies* assessed for eligibility (n = 99)

Records screened by title and abstract (n = 9,852)

Records after duplicates removed (n = 9,852)

Records excluded (n = 9,006)

Additional records identified through other sources (n = 4)

Records identified through database searching (n = 18,386)

Other close-contact infectious diseases (n = 747)

Figure 6: Identification and selection of eligible studies investigating the association between household crowding and H. pylori. Flowchart adapted from PRISMA (Moher et al., 2009)
Records identified through database searching [Medline 63 Embase 149 Web of Science 111 Cochrane 8 SCOPUS 90] (n = 407)

Additional records identified through other sources – snowball (n = 13)

Records after duplicates removed (n = 242)

Records screened by title and abstract (n = 242)

Records excluded (n = 208)

Full text records unavailable (n = 2)

Full-text studies excluded, with reasons (Table 5) (n = 31)

Full-text studies* assessed for eligibility (n = 32)

Eligible studies reviewed by narrative synthesis (n = 1)

Studies assessed for inclusion in meta-analysis (n = 1)

Studies included in the meta-analysis (n = 0)

Studios with no adjustment for age & SES (n = 1)

Figure 7: Identification and selection of eligible studies investigating the association between household crowding and Stomach cancer. Flowchart adapted from PRISMA (Moher et al., 2009)
Narrative synthesis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Results of studies that were statistically significant (95% level)</th>
<th>Total eligible studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ (%) ns (%) - (%)</td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td>37 (61) 23 (38) 1 (2)</td>
<td>61</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>0 (0) 1 (100) 0 (0)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 6: Summary of outcomes from eligible studies that investigated the association between household crowding and *H. pylori* or stomach cancer

+ = positive association between greater household crowding and the outcomes, which was statistically significant
ns = no statistically significant association
- = negative association, which was statistically significant

After full assessment, 61 *H. pylori* studies were eligible for narrative synthesis. Six-tenths of studies found a positive association between greater household crowding and *H. pylori* infection that was statistically significant (Table 6). Only 1/61 studies showed a negative association that was statistically significant.

Cross-sectional studies were the predominant study design for *H. pylori* studies. This is an efficient design for investigating a common outcome that is chronic and not always symptomatic, such as in the case of *H. pylori*.

The one eligible study identified with a stomach cancer outcome, was a cohort study that investigated the association between household crowding in 1936 and subsequent mortality from stomach cancer from 1951-1989 (Coggon et al., 1993). After adjustment for age, participants who experienced greater crowding (2.5 vs. <1.5 persons per room) had less risk (OR 0.70, CI: 0.40-1.20) of subsequent stomach cancer, however the difference in risk was not statistically significant. The study was limited by small numbers of stomach cancer deaths among children exposed to household crowding at baseline.

The small body of evidence of a relationship between household crowding and stomach cancer is largely based on ecological studies (Barker et al., 1990) and
limited by inadequate control for confounding (Office of the Deputy Prime Minister London, 2004). More evidence is required to determine whether household crowding contributes to increased rates of stomach cancer in later life. However, there is extensive evidence that low socioeconomic status in childhood is linked to stomach cancer in later life (Galobardes et al., 2004, Smith et al., 1998, Power et al., 2005).

**Meta-analysis**

A considerable number of *H. pylori* infection studies were eligible for meta-analysis (n=28). Considering all the studies together, persons experiencing the greatest household crowding had 1.73 (95% CI 1.48-2.03) times the odds of *H. pylori* infection, compared to those experiencing the least crowding (Figure 8). However, there were considerable differences between studies (88% heterogeneity), and the reasons for this were explored in sub-group analysis. The details of each study are shown in Table 7.
Figure 8: Meta-analysis forest plot showing the summary effect measures for the association between household crowding and *H. pylori* infection sub-grouped by children and adult exposures to crowding.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>study design</th>
<th>outcome</th>
<th>exposure</th>
<th>country</th>
<th>prev.</th>
<th>population</th>
<th>age</th>
<th>n</th>
<th>measure of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguemon et al., 2005</td>
<td>cx</td>
<td>serology</td>
<td>more than three persons sharing a room to sleep vs. not sharing room</td>
<td>Benin</td>
<td>62%</td>
<td>healthy individuals in urban and rural households</td>
<td>2-74yo</td>
<td>446</td>
<td>OR 9.82 (4.30 - 23.31)</td>
</tr>
<tr>
<td>Ahmed et al., 2007</td>
<td>cx</td>
<td>gastric biopsy &amp; PCR</td>
<td>more than three vs. zero to one members divided by rooms</td>
<td>Pakistan</td>
<td>80%</td>
<td>upper gastrointestinal symptoms who were not treated for <em>H. pylori</em></td>
<td>30-79yo</td>
<td>200</td>
<td>OR 1.32 (0.61 - 2.83)</td>
</tr>
<tr>
<td>Breuer et al., 1996</td>
<td>cx - retro</td>
<td>serology</td>
<td>persons per room in household at 8yo</td>
<td>Germany</td>
<td>39%</td>
<td>all blood donors</td>
<td>18-61yo</td>
<td>260</td>
<td>OR(linear) 2.14 (1.07 - 4.26)</td>
</tr>
<tr>
<td>Broutet et al., 2001</td>
<td>cx - retro</td>
<td>salivary IgG</td>
<td>more than one person per room growing up</td>
<td>France</td>
<td>25%</td>
<td>patients consulting gastroenterologist with non-upper digestive tract symptoms</td>
<td>18+yo</td>
<td>1450</td>
<td>OR 1.70 (1.20 - 2.20)</td>
</tr>
<tr>
<td>Bures et al., 2006</td>
<td>cx</td>
<td>C-urea breath test</td>
<td>shared room with siblings vs. own room</td>
<td>Czech Republic</td>
<td>42%</td>
<td>GP catchments</td>
<td>5+yo</td>
<td>1350</td>
<td>OR 1.11 (0.77 - 1.60)</td>
</tr>
<tr>
<td>Choe et al., 2002</td>
<td>cx</td>
<td>serology</td>
<td>two or more in house divided by number of rooms vs. less than two</td>
<td>Korea</td>
<td>43%</td>
<td>two schools - one athletics and one not</td>
<td>15-17yo</td>
<td>660</td>
<td>OR 2.49 (1.15 - 5.39)</td>
</tr>
<tr>
<td>Chong et al., 2003</td>
<td>cx</td>
<td>serology</td>
<td>sharing bedroom (may be sharing a bed) vs. single</td>
<td>US</td>
<td>17%</td>
<td>children referred to hospital, GI referral vs. non-GI referral</td>
<td>1-18yo</td>
<td>992</td>
<td>OR 1.63 (0.79 - 3.37)</td>
</tr>
<tr>
<td>Everhart et al., 2000</td>
<td>cx</td>
<td>serology</td>
<td>number of household residents divided by the total number of rooms (excluding bathrooms): 7 levels vs. least crowded members divided by rooms: high vs. low</td>
<td>US</td>
<td>33%</td>
<td>adults in national nutrition survey</td>
<td>20+yo</td>
<td>7465</td>
<td>OR(linear) 1.07 (0.99 - 1.16)</td>
</tr>
<tr>
<td>Ghosh and Bodhankar, 2012</td>
<td>cx</td>
<td>salivary PCR</td>
<td>more than one person by rooms vs. two</td>
<td>India</td>
<td>85%</td>
<td>all asymptomatic</td>
<td>18+yo</td>
<td>1500</td>
<td>OR 1.28 (1.17 - 1.39)</td>
</tr>
<tr>
<td>Goldman et al., 2006</td>
<td>cx</td>
<td>C-urea breath test</td>
<td>risk per each additional room less in a house</td>
<td>Argentina</td>
<td>40%</td>
<td>High risk: children with upper GI symptoms</td>
<td>2-17yo</td>
<td>395</td>
<td>OR-linear 1.0 (0.8 - 1.3)</td>
</tr>
<tr>
<td>Author, year</td>
<td>study design</td>
<td>outcome</td>
<td>exposure</td>
<td>country</td>
<td>prev.</td>
<td>population</td>
<td>age</td>
<td>n</td>
<td>measure of effect</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>---------</td>
<td>----------</td>
<td>---------</td>
<td>-------</td>
<td>------------</td>
<td>-----</td>
<td>----</td>
<td>-------------------</td>
</tr>
<tr>
<td>Goodman et al., 2003</td>
<td>cx</td>
<td>serology</td>
<td>more than one household member per room vs. one or fewer household members per room</td>
<td>US / Mexico</td>
<td>67%</td>
<td>all pregnant women</td>
<td>17-47yo</td>
<td>727</td>
<td>OR 1.40 (0.93 - 2.11)</td>
</tr>
<tr>
<td>Lynn et al., 2007</td>
<td>cx - retro</td>
<td>serology</td>
<td>three or more children sharing a bedroom as a child or sharing a bed</td>
<td>US</td>
<td>24%</td>
<td>non-Native Alaskan educators attending one of three conferences</td>
<td>21-72yo</td>
<td>224</td>
<td>OR 1.6 (0.8 - 3.2)</td>
</tr>
<tr>
<td>Malaty and Graham, 1994</td>
<td>cx - retro</td>
<td>serology</td>
<td>three or more people vs. less than one divided number of rooms (in childhood)</td>
<td>US</td>
<td>54%</td>
<td>Black and Hispanic volunteers who had completed high school, local advertisements children</td>
<td>19-49yo</td>
<td>151</td>
<td>OR 4.50 (3.30 - 5.70)</td>
</tr>
<tr>
<td>Malaty et al., 1996</td>
<td>cx</td>
<td>serology</td>
<td>more than three vs. less than one persons per room</td>
<td>Russia</td>
<td>44%</td>
<td>children from 13 licensed day care centres, primarily enrolling minority children from low-middle socioeconomic classes</td>
<td>1-19yo</td>
<td>307</td>
<td>OR 2.10 (1.20 - 2.50)</td>
</tr>
<tr>
<td>Malaty et al., 2001</td>
<td>cx</td>
<td>serology</td>
<td>one bedroom home vs. three or more bedroom home</td>
<td>US</td>
<td>24%</td>
<td>children from 13 licensed day care centres, primarily enrolling minority children from low-middle socioeconomic classes</td>
<td>2-16yo</td>
<td>356</td>
<td>OR 1.20 (0.60 - 2.20)</td>
</tr>
<tr>
<td>McCallion et al., 1996</td>
<td>cx</td>
<td>serology</td>
<td>more than one person per room vs. less than 0.7 persons per room</td>
<td>UK</td>
<td>32%</td>
<td>children in hospital for routine non-gastrointestinal day surgery</td>
<td>3-15yo</td>
<td>367</td>
<td>OR 3.38 (1.75 - 6.50)</td>
</tr>
<tr>
<td>Mendall et al., 1992</td>
<td>cx - retro</td>
<td>serology</td>
<td>1.30 or more persons per room in childhood vs. 0.70 or less persons per room in childhood</td>
<td>UK</td>
<td>32%</td>
<td>consecutive patients attending a health screening clinic in general practice hospital outpatients</td>
<td>18-82yo</td>
<td>208</td>
<td>OR 6.15 (1.84 - 18.6)</td>
</tr>
<tr>
<td>Miranda et al., 2010</td>
<td>cx</td>
<td>serology</td>
<td>number of rooms (continuous variable)</td>
<td>Brazil</td>
<td>36%</td>
<td>children</td>
<td>326</td>
<td>OR(linear) 0.88 (1.16 - 0.14)</td>
<td></td>
</tr>
<tr>
<td>Nurgalieva et al., 2002</td>
<td>cx</td>
<td>serology</td>
<td>more than three members divided by rooms vs. less than two members per room</td>
<td>Kazakhstan</td>
<td>80%</td>
<td>unrelated healthy individuals</td>
<td>10-60yo</td>
<td>289</td>
<td>OR 1.30 (0.70 - 3.00)</td>
</tr>
<tr>
<td>Author, year</td>
<td>study design</td>
<td>outcome</td>
<td>exposure</td>
<td>country</td>
<td>prev.</td>
<td>population</td>
<td>age</td>
<td>n</td>
<td>measure of effect</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------</td>
<td>---------</td>
<td>----------------------------------------------</td>
<td>-------------</td>
<td>-------</td>
<td>---------------------------</td>
<td>---------</td>
<td>-------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Özen et al., 2006</td>
<td>cohort</td>
<td>C-urea breath test</td>
<td>more than one person per room</td>
<td>Turkey</td>
<td>57%</td>
<td>asymptomatic children</td>
<td>8-17yo</td>
<td>136</td>
<td>OR 2.99 (1.21 - 7.35)</td>
</tr>
<tr>
<td>Patel et al., 1994</td>
<td>cohort</td>
<td>salivary ELISA</td>
<td>more than one person per room</td>
<td>UK</td>
<td>11%</td>
<td>random sample of 30 primary schools in Edinburgh</td>
<td>6-7yo</td>
<td>554</td>
<td>OR 3.10 (1.30 - 7.20)</td>
</tr>
<tr>
<td>Rodrigues et al., 2004</td>
<td>cx</td>
<td>C-urea breath test</td>
<td>more than two persons per room vs. one person per room</td>
<td>Brazil</td>
<td>56%</td>
<td>children random selected from urban neighbourhood</td>
<td>6mo-14yo</td>
<td>353</td>
<td>OR 2.58 (1.40 - 4.60)</td>
</tr>
<tr>
<td>Salomaa-Räsänen et al., 2010</td>
<td>cx</td>
<td>serology</td>
<td>for every increase of one person per room</td>
<td>Finland</td>
<td>12%</td>
<td>all individuals invited from population register</td>
<td>15-40yo</td>
<td>3316</td>
<td>OR(linear) 1.13 (1.01 - 1.26)</td>
</tr>
<tr>
<td>Staat et al., 1996</td>
<td>cx</td>
<td>serology</td>
<td>two or more vs. less than 0.5 persons divided by number rooms</td>
<td>US</td>
<td>25%</td>
<td>national health and nutrition survey</td>
<td>6-19yo</td>
<td>2581</td>
<td>OR 5.60 (2.90 - 10.90)</td>
</tr>
<tr>
<td>Stone et al., 2000</td>
<td>cx - retro</td>
<td>serology</td>
<td>persons per room in childhood</td>
<td>UK</td>
<td>15%</td>
<td>general population sample</td>
<td>21-55yo</td>
<td>1431</td>
<td>OR(linear) 2.08 (1.28 - 3.38)</td>
</tr>
<tr>
<td>Torres et al., 1998</td>
<td>cx</td>
<td>serology</td>
<td>3.6 or more persons per room vs. 1.5 or fewer persons per room</td>
<td>Mexico</td>
<td>66%</td>
<td>national serological survey</td>
<td>1-39yo</td>
<td>11605</td>
<td>OR 1.40 (1.23 - 1.60)</td>
</tr>
<tr>
<td>Webb et al., 1994</td>
<td>cx - retro</td>
<td>serology</td>
<td>greater than one person per room vs. less than one person per room in childhood</td>
<td>UK</td>
<td>37%</td>
<td>male factory workers</td>
<td>18-65yo</td>
<td>471</td>
<td>OR 1.54 (0.87 - 2.75)</td>
</tr>
<tr>
<td>Wizla-Derambure et al., 2001</td>
<td>cx</td>
<td>gastric biopsy</td>
<td>more than one person per room, excluding kitchen and bathroom</td>
<td>France</td>
<td>7%</td>
<td>high risk: children requiring a endoscopy</td>
<td>2-17yo</td>
<td>436</td>
<td>OR 0.60 (0.20 - 2.10)</td>
</tr>
</tbody>
</table>

Table 7: H. pylori meta-analysis study and study population characteristics, cx = cross sectional, cx – retro = determination of exposure was retrospective
## Sub-group analysis

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>Category</th>
<th>n</th>
<th>Summary odds ratio for <em>H. pylori</em> infection [95% CI]*</th>
<th>I²</th>
<th>p-value for sub-group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>-</td>
<td>28</td>
<td>1.73 [1.48, 2.03]</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Children &lt;18yo</td>
<td>19</td>
<td>2.06 [1.53, 2.77]</td>
<td>86%</td>
<td>0.0006</td>
</tr>
<tr>
<td></td>
<td>Adults and children</td>
<td>3</td>
<td>2.11 [1.04, 4.28]</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adults 18+yo</td>
<td>6</td>
<td>1.17 [1.07, 1.28]</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Measure of household crowding</td>
<td>Severe vs. low crowding (&gt;2 persons per room)</td>
<td>9</td>
<td>2.10 [1.50, 2.94]</td>
<td>92%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(exposure)</td>
<td>Moderate vs. low crowding (&gt; 1 person per room)</td>
<td>16</td>
<td>1.75 [1.43, 2.14]</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Small house</td>
<td>3</td>
<td>0.99 [0.84, 1.16]</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Test for <em>H. pylori</em> infection</td>
<td>Measure of active infection (e.g. C-urea breath test, gastric biopsy or PCR)</td>
<td>7</td>
<td>1.29 [1.04, 1.61]</td>
<td>59%</td>
<td>0.009</td>
</tr>
<tr>
<td>(outcome)</td>
<td>Antibody test of current or past infection (e.g. serology)</td>
<td>21</td>
<td>1.93 [1.57, 2.38]</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Low-middle income</td>
<td>11</td>
<td>1.51 [1.23, 1.84]</td>
<td>80%</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>High income</td>
<td>17</td>
<td>1.92 [1.49, 2.48]</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Prevalence of <em>H. pylori</em> in the</td>
<td>&lt;40%</td>
<td>15</td>
<td>1.62 [1.32, 1.99]</td>
<td>80%</td>
<td>0.41</td>
</tr>
<tr>
<td>study population</td>
<td>40+%</td>
<td>12</td>
<td>1.86 [1.44, 2.40]</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>Absent</td>
<td>25</td>
<td>1.84 [1.55, 2.17]</td>
<td>88%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>3</td>
<td>1.03 [0.84, 1.26]</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Quality score (max. 10)</td>
<td>9-10</td>
<td>14</td>
<td>2.08 [1.57, 2.77]</td>
<td>92%</td>
<td>0.03</td>
</tr>
<tr>
<td>(Newcastle-Ottawa Scale adaption)</td>
<td>6-8</td>
<td>14</td>
<td>1.45 [1.22, 1.72]</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Cohort</td>
<td>2</td>
<td>3.05 [1.64, 5.66]</td>
<td>0%</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional - retrospective^</td>
<td>7</td>
<td>2.33 [1.52, 3.58]</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>19</td>
<td>1.45 [1.25, 1.67]</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Year of publication</td>
<td>2001 and later</td>
<td>17</td>
<td>1.38 [1.18, 1.62]</td>
<td>71%</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>2000 and earlier</td>
<td>11</td>
<td>2.40 [1.69, 3.40]</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Additional crowding variables</td>
<td>No over-adjustment</td>
<td>13</td>
<td>1.71 [1.36, 2.14]</td>
<td>92%</td>
<td>0.73</td>
</tr>
<tr>
<td>adjusted for in the final model</td>
<td>1+ additional crowding variable adjusted for</td>
<td>15</td>
<td>1.81 [1.40, 2.34]</td>
<td>76%</td>
<td></td>
</tr>
</tbody>
</table>

Table 8: Summary of findings table for the meta-analyses investigating the association between household crowding density and *H. pylori* infection

Notes: n=number of studies, *random effects meta-analysis was used to take into account heterogeneity, I² is the proportion of heterogeneity, ^cross-sectional study that questioned participants about past household crowding
Several factors in sub-group analysis were associated with statistically different results and explained some of the heterogeneity between studies, indicated by the lower degrees of heterogeneity in some sub-groups than the heterogeneity overall. Differences in the association between household crowding and infection were related to child vs. adult exposure to crowding (p=0.0006), active vs. antibody measure of *H. pylori* infection (p=0.009), and density vs. house size measures of household crowding (p<0.0001) (Table 8).

There was strong evidence (p=0.0002) that exposure to household crowding in childhood was riskier than exposure to crowding in adulthood. The odds of *H. pylori* infection was 2.06 times greater (95% CI 1.53-2.77, 19 studies) with childhood crowding, whereas for adult crowding this figure was much less (OR 1.17, 95% CI 1.07-1.28, 6 studies). These results are consistent with what we would expect given the young age of acquisition for *H. pylori* infection. The evidence for an association between crowding in adulthood and *H. pylori* acquisition is limited and may be accounted for by residual confounding biases.

Serology was the most common measure of *H. pylori* infection and there was good statistical evidence (p=0.009) that seropositivity had a greater association with crowding than measures of active *H. pylori* infection. The ability of serology to detect previous and current infection may make it more sensitive to the overall effect of crowding on infection experienced many years earlier in childhood. For example, *H. pylori* infection may resolve over time due to gastritis and atrophy of the stomach, especially in the elderly. In this situation, antibodies may remain positive for several years, whereas tests of active infection are expected to be negative. Antibodies therefore appear to be more sensitive to whether infection was acquired in childhood.

Results from studies investigating severe household crowding identified slightly greater relative odds of *H. pylori* infection than studies comparing moderate crowding (both vs. low household crowding) but this was not statistically significant (p=0.36). These ORs were both significantly greater than studies using household area as a measure of crowding (p<0.0001) (Table 8). The slight difference in the magnitude of the OR is
understandable given the difference in the degree of crowding that is being measured by these exposure variables.

Sub-group analyses of quality indicators showed mixed results. The half of the studies with the highest quality scores (NOS 9-10 vs. 6-8) were associated with a greater magnitude of crowding-infection association (p=0.03). Combination of the four studies with maximum quality scores (NOS 10) however showed no crowding-infection association. Cohort studies detected a somewhat greater magnitude of association than cross-sectional study designs (p=0.02) and there was no evidence (p=0.73) that controlling for additional crowding variables had an impact on study results.

Studies published after 2000 detected a smaller magnitude of association (OR) than those published in 2000 or earlier (p=0.005). The reason for a change over time is unclear. It may be that later study populations are less heterogeneous in terms of household crowding (ie. living standards have improved over time) and therefore the association with *H. pylori* is weaker or it may be that quality of studies in controlling for confounding has improved.

Context did not appear to significantly modify results. There was no evidence of differences between sub-groups by country income (p=0.14), or prevalence of *H. pylori* in the study population (p=0.41). However, the presence of gastrointestinal symptoms did seem to be important (p<0.0001). The combined results of three diverse studies which investigated symptomatic patients, curiously did not show any statistical evidence of an association between crowding and infection. Only a proportion of people with symptoms are likely to seek specialist care, given that the majority of *H. pylori* infection is asymptomatic. It may be that different care-seeking practices among crowded populations make it difficult to detect an association with crowding in the clinical setting; however reasons for this result remain unclear.

A post hoc analysis can be done to calculate the summary OR among studies which report results for persons exposed to moderate or severe vs. low household crowding (and not household area) in childhood, and studies where the outcome is measured only
using serology. In these studies the overall summary OR was 2.52 (CI: 1.91-3.32, n=13, $I^2$ 70%). If the result was further confined to the best quality studies with a NOS of 9 or 10, then the odds ratio remained similar (OR 2.79, CI 1.86-4.18, n=8, $I^2$ 80%, p=0.28).

**Outliers**

Studies with outlying results can help us understand the variation in study results. Two outlying studies suggested that crowding may decrease the risk of infection although in both cases the results were not statistically significant (Wizla-Derambure et al., 2001) (Miranda et al., 2010).

The former study (Wizla-Derambure et al., 2001) adjusted for an additional crowding variable in the multivariate model. This variable (persons in the home) was a strong predictor of *H. pylori* infection, and may have reduced the independent predictive value of the eligible household density measure, in which we were most interested.

The later study (Miranda et al., 2010) investigated a continuous variable for the number of rooms in the house. This measure of area may not be very sensitive to the aspect of crowding density that is associated with increased transmission of *H. pylori* infection. Furthermore, the authors suspect the results may be influenced by the poor performance of the serology test that identified *H. pylori* infection which has been found to not be very accurate in Brazilian children.

Other outlying studies included Aguemon et al. (2005) and Malaty and Graham (1994) which both measured very high ORs. The former study was not very precise and was carried out in a setting with diverse levels of crowding and high seroprevalence (Benin; 62%). It investigates the difference in risk between two groups with extreme differences in crowding exposure; i.e. participants sharing a room to sleep with more than three others vs. those not sharing at all. The latter study was more precise and was carried out in a study population from the US also with diverse crowding and a high prevalence of *H. pylori* (54%). It also compared two groups with extreme differences in crowding
exposure. It is important to note that the summary effect measures here are not based on absolute measures of crowding but more on relative crowding within a population.

**Study and review level limitations**

Meta-analyses reliant on observational studies are considered lower quality evidence for causality relative to interventional studies (Higgins and Green, 2011), and may be somewhat inflated by reporting bias such as publication bias and incomplete retrieval. The majority were cross-sectional studies reflecting the epidemiology of *H. pylori* infection. The grade of evidence quality is reduced further where there is evidence of poor quality study designs and unexplained heterogeneity. The influence of these factors on meta-analysis results are discussed below.

**Study quality**

Improved study quality (NOS scores of 9 and 10, or cohort study design) was associated with greater ORs for the association between crowding and *H. pylori* infection. It may be that poor quality studies were less equipped to detect the true magnitude of the association.

All studies however were poorly equipped to precisely detect past *H. pylori* infection because available tests have poor sensitivity. Antibody tests do not have perfect sensitivity and specificity for detecting current or previous infection. This means that there will be misclassification of the *H. pylori* outcome using this test. In this way, the meta-analysis odds ratios presented here may be substantial underestimates of the true association between household crowding and seropositivity.

The requirement that study results should be adjusted for age and socioeconomic status is important to control confounding bias and is recommended in meta-analyses of observational studies (Higgins and Green, 2011). Confounding has significant potential to influence meta-analysis results which are based on observational studies, and particularly in the case of crowding which is inherently related to socioeconomic status. Although summary ORs are adjusted for age, socioeconomic status and many other
variables, confounding from unrecorded variables may be affecting our results. Furthermore, residual confounding from age and socioeconomic status may have substantial influence because of the strong association these factors have with household crowding and *H. pylori* infection. It may be difficult to completely adjust for socioeconomic status. The small magnitude of the association between crowding and infection in adults may be in a large part explainable by confounding biases.

**Unexplained heterogeneity**

Finally one must consider heterogeneity which is the differences between study results that are not explainable by chance. There was considerable heterogeneity in the overall summary OR ($I^2$ 88%). Studies used a variety of study designs, several different measures of crowding, and were carried out in a variety of contexts. These factors explained some of the differences in study results however considerable heterogeneity remained in many sub-group analyses (Table 8). Furthermore, the large number of post-hoc sub-group analyses to explain heterogeneity also increases the possibility of chance findings.

**Publication bias**

Publication bias from delayed publication, citation bias and language bias may inflate our results. The inclusion of only English published literature may have introduced bias, however the evidence for this is conflicting (Higgins and Green, 2011). Studies have shown greater and lesser estimates from non-English vs. English published studies. For example, when Moher and colleagues examined the exclusion of trials reported in a language other than English, the exclusion of non-English-language trials did not significantly affect the results (Moher et al., 2003).

Publication bias was investigated by the funnel plot presented in Figure 9. The plot suggests a moderate degree of publication bias because although there is some symmetry around the dotted line (summary OR), studies with larger standard error trended towards greater ORs. Despite this, the summary OR is likely to be stable considering the substantial number of published studies included in the meta-analysis. It
would take a sizable number of studies with quite different results to make a substantial impact on the results presented here.

![Funnel plot](image)

**Figure 9:** *H. pylori* funnel plot considering age at exposure to crowding

**Incomplete retrieval**

Incomplete retrieval may also have affected meta-analysis results. Our review focussed on published papers and limited identification of relevant articles in the grey literature may have restricted the identification of articles with non-significant or negative associations. Furthermore, articles with insignificant crowding results may not refer to crowding in the abstract or key words, and thus remain undetected by our search. However, almost all articles were obtained for full text screening (i.e. no articles were unavailable for *H. pylori*).

It is also noteworthy that stepwise regression within studies often meant that adjusted estimates were more likely to be available when a crowding exposure contributed
significantly to a multivariate model (which was usually in the positive direction) than when crowding did not contribute to the model and it was sometimes discarded. For this reason authors were contacted to provide the missing figures but the proportion responding was low (<20%). Studies without adjusted figures did not contribute to the meta-analysis, however they did contribute to the narrative synthesis; and narrative synthesis results were supportive of meta-analysis findings.

**Summary**

Meta-analysis results demonstrated a statistically significant association between household crowding and *H. pylori* infection, which was significantly greater for children exposed to household crowding. There was moderate evidence of publication bias and some unexplained heterogeneity remained. Results were supported by greater ORs in better quality studies, and a narrative synthesis that was consistent with meta-analysis findings. Misclassification of *H. pylori* infection may have substantially underestimated the magnitude of the association between household crowding and *H. pylori* infection in meta-analysis findings.
Part B: Birth cohort analysis of *H. pylori* seroprevalence and stomach cancer incidence

Overview

Serology data in NZ were pooled, regionally weighted and adjusted to estimate the Māori, Pacific and European seroprevalence of *H. pylori* by fifteen-year birth cohorts (i.e. 1911-25, 1926-40, 1941-55, 1956-70, and 1971-85). In subsequent birth cohorts the seroprevalence trends and the absolute and relative seroprevalence differences by ethnicity were explored. This stage was set before stomach cancer incidence was analysed, so as to generate a ‘prior’ before closely scrutinising the stomach cancer incidence data.

The meta-analysis crowding-infection OR was combined with pooled seroprevalence data and census crowding data from 1986 to calculate population attributable fractions (PAFs). In this way the contribution of household crowding density to seroprevalence among Māori, Pacific and European born 1971-85 in NZ was estimated.

For each birth cohort (1926-40, 1941-55 and 1956-70) during the study period 1981-2004, age-standardised incidence rates for total and non-cardia stomach cancer were calculated for Māori and Pacific men, and compared to European men with age-standardised rate ratios (RRs). RRs were adjusted for *H. pylori* (using pooled prevalence data and assuming that *H. pylori* is a necessary causal factor) and smoking (by probabilistic bias analysis) to estimate the contribution of *H. pylori* and smoking to differences in the incidence of stomach cancer. These steps are discussed in more detail below.
**Chapter 4: Analysis methods**

**Pooled *H. pylori* seroprevalence**

A systematic search of the literature was carried out to identify studies which measure the prevalence of *H. pylori* infection in NZ.

**Search strategy**

Medline, Index New Zealand and Google scholar databases were searched for the keyword terms ‘New Zealand’, ‘Auckland’, ‘Wellington’, ‘Christchurch’ or ‘Dunedin’; in combination with ‘*H. pylori*’ or ‘*Campylobacter pyloridis*’. Keyword search terms were used with the addition of MeSH terms for the Medline search. Contents of the New Zealand Medical Journal were specifically examined. The search was up-to-date as of 31st January 2013. An example search strategy from Medline is shown in Table 9.

<table>
<thead>
<tr>
<th></th>
<th>New Zealand/ or New Zealand.mp. or Auckland.mp. or Christchurch.mp. or Wellington.mp. or Dunedin.mp.</th>
<th>46447</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp <em>H. pylori</em>/ or <em>H. pylori</em>.mp. or campylobacter pyloridis.mp.</td>
<td>31020</td>
</tr>
<tr>
<td>2</td>
<td>1 and 2</td>
<td>40</td>
</tr>
</tbody>
</table>

*Table 9: Medline search strategy and results, February 2013.*

Additional studies were identified by inspecting the references of eligible studies. Researchers in the area were also approached to determine the existence of any other relevant additional published or unpublished studies.

There were 40 hits on Medline, 30 hits searching the New Zealand Medical Journal for ‘*H. pylori*’ and 48 hits searching this journal for the keyword ‘*Campylobacter pylori*’. The most relevant results in Google Scholar were examined on the first set of pages. The titles of these identified articles were screened for potentially relevant articles and full texts were obtained for eligible articles.
Inclusion and exclusion criteria

Studies were included according to whether they met the following criteria addressing study population, available data on age and ethnicity, study outcomes and study design.

Studies were required to measure *H. pylori* seroprevalence among asymptomatic participants who live in NZ. Study populations confined to patients with gastric symptoms were not eligible, because they might be expected to have increased *H. pylori* seroprevalence. Both male and female participants were eligible. Few studies have identified a difference in seroprevalence among males and females and none have done so in NZ. A systematic review reports little difference between genders in *H. pylori* infection with a slight male predominance in adults and no difference among children (OR 1.16 in adults, OR 1.03 in children) (de Martel and Parsonnet, 2006).

Studies were required to provide information on the age and ethnicity of participants. Where more than one age or ethnic group was studied, *H. pylori* seroprevalence for each category of age and ethnicity variables was required.

We were interested in adults and adolescents tested for *H. pylori*, because acquisition and seroconversion almost invariably occurs in childhood.

Measures other than serological testing for *H. pylori* infection were considered, however, serology was the only measure used in identified studies so the analysis was confined to this measure of *H. pylori* prevalence.

There were no limits on study design. However, all seroprevalence studies were observational studies with cross-sectional, case-control or cohort designs. In an included case-control study where the outcome was myocardial infarction, only the seroprevalence rates among controls were pooled. All studies were published after 1985.
Data extraction

*H. pylori* seroprevalence data from eligible studies were entered into a spreadsheet and pooled by birth cohort and ethnic group. European, Māori and Pacific peoples were selected as the ethnic groups of interest according to data availability.

At a minimum, the study (or its authors) had to provide seroprevalence by ethnicity and by age. For two studies (Morris et al., 1986, Scragg et al., 1996) data were not available by age within ethnic groups, and the proportion of seropositive individuals by age and ethnicity was estimated by applying the underlying age structure to each ethnic group: the total participants in each age group was multiplied by the total participants in each ethnicity group, and then divided by the total number of participants in the study (i.e. the generation of expected values assuming independence of the marginal distributions of age and ethnicity). This was done both for the seropositive participants (numerator) and the number of participants tested (denominator).

In order to classify study data by cohort of birth, year of birth was calculated by subtracting age from the year the study was carried out. This enabled seroprevalence data to be assigned to one of five different 15 year birth cohorts; 1911-25, 1926-40, 1941-55, 1956-70, 1971-85. These cohorts were selected to encompass the full range of seroprevalence data and ensure adequate group size. Each study’s age groups were assigned to the cohort that their year(s) of birth fitted best. In one case, participants from an age group had birth dates that straddled two birth cohort categories and the data were therefore assigned to both cohorts.

Only European seroprevalence data were available in the earliest cohort (1911-25) and there were no data for Māori or Pacific for that period. Of the two studies with older participants born in 1911-25, one was in the South Island (Collett et al., 1999) (where the Māori and Pacific population was small) and one was in Auckland restricted to European participants (Fraser et al., 2003). In the 1911-25 cohort it was therefore not possible to compare ethnic differences in seroprevalence and the contribution of *H. pylori* to excess Māori and Pacific stomach cancer.
Conversely, for the youngest most recent cohort born in 1971-85 stomach cancer incidence was the most sparse because the population was generally too young to get stomach cancer during the study period (<35yo). This cohort was examined for seroprevalence only and was unable to contribute to the analysis of stomach cancer incidence.

Analysis of the contribution of *H. pylori* to stomach cancer differences was therefore applied to the three remaining birth cohorts; 1926-40, 1941-55, 1956-70.

**Regional weighting**

In the data at hand, region appeared to have an association with *H. pylori* seroprevalence independent of ethnicity and age. Seroprevalence was 20% greater among European in the North than in the South (standardised by cohort). Regional weighting was therefore applied to better estimate national seroprevalence risk for each ethnic group. Data were regionally weighted to account for differences in seroprevalence between the north and the south, and the disproportionate contribution of Auckland data for Māori and Pacific peoples. Four regions were considered based on the Cancer Network groupings of DHBs; North (includes four northern most DHBs), Mid (three DHBs), Central (eight DHBs) and South (five South Island DHBs) (Figure 10). At the 2006 census, the regional distribution of each ethnic group’s population was used to weight seroprevalence data. An example of the weights used is shown in Table 10. Data used for weighting were based on total ethnicity, both sexes, and the age group corresponding to the birth cohort of interest.
Pacific and Māori seroprevalence data were insufficient outside the North region. To allow for this, firstly we made the assumption that the Pacific seroprevalence in the North was similar to that in the other regions. This is because Pacific peoples are more likely to have migrated recently and experienced greater mobility between regions. The majority of the Pacific population lives in the North (69-71% in each cohort) so the available seroprevalence estimates for this region are relevant for the majority of the Pacific population. The contribution of weighting for Pacific in the south is negligible (i.e. weight of 0.051 in Table 10).
Compared with Pacific, we would expect the Māori population to be more settled and similar to the European population in terms of relative geographical variation in seroprevalence. Therefore, the relative seroprevalence among Māori in the South Island was estimated by applying the European pattern of regional variation to the available data on Māori living in the North region.

A standardised risk ratio (sRR) was estimated to compare the risk of seroprevalence for European in the North vs. European in the South. The sRR takes into account variation in the age structure of European participants from different regions by direct age standardisation. Accordingly, in order to make European data from the North and South comparable by age, the cohort specific seroprevalence rates were weighted according to the number of European participants in each birth cohort (this was the standard population). It was subsequently calculated that the age-standardised seroprevalence was 20% greater among European in the North than in the South (sRR 1.20).

Although calculating a sRR of 1.20 based on data from all cohorts maximises the use of the available data it also assumes that there is no difference in regional variation over time (between birth cohorts). This assumption was tested in sensitivity analysis by applying cohort-specific RRs instead of the sRR of 1.20. The differences in seroprevalence by region appeared to be greater in studies of participants born in the most recent cohorts. This may be a true trend, due to biases or a random variation.

No studies contributed data from the Mid or Central regions. Seroprevalence from these regions had to be estimated for all ethnic groups, and was calculated according to geographical location to be one-third and two-thirds of the difference between the seroprevalence in the North and South regions. This approach was informed by the observed regional variation in another close contact infectious disease; hepatitis B (Blakely et al., 1998).
Adjustment for bias

The best central estimates of seroprevalence were revised to account for potential selection and measurement bias. The influence of studies predicted to be affected by bias was tested by sensitivity analysis.

Two studies (Fraser et al., 1996, Fraser et al., 2010) intentionally selected schools in Auckland with a high proportion of Pacific students in areas of high deprivation (school deciles 1-3) (Fraser et al., 2010). We would expect these studies to measure a higher seroprevalence than that in the overall population, because *H. pylori* is closely related to socioeconomic factors. The seroprevalence estimates were therefore reduced in this birth cohort (1971-1985) to reflect that in these studies the true population seroprevalence is likely to be 20% less than that observed. The figure of 20% was informed by studies specific to NZ that suggest that lower socioeconomic status is associated with small increases in *H. pylori* seroprevalence when considered independently of ethnicity. In the same study, Fraser et al. (1996) demonstrated increased seroprevalence with increased deprivation (statistically significant in European group).

Results from the earliest study (Morris et al., 1986) of Māori and Pacific blood donors were based on an assay specifically developed for use in that study. The detection rate was likely to be less sensitive (microbiologist advice) than the subsequently validated commercial ELISA tests which were used in all the other included studies. Therefore the seroprevalence data from blood donors in the Morris study was increased by 20% to reflect concerns about the lower sensitivity of the assay used.

Uncertainty around seroprevalence

Whilst every effort was made to be as accurate as possible in estimating *H. pylori* seroprevalence, there is still uncertainty around these pooled estimates. Results were therefore presented for different combinations of assigned seroprevalence estimates to see how this might affect the relative differences in seroprevalence by ethnicity (RRs) (Table 15).
In order to assign upper and lower estimates for the pooled seroprevalence data several factors influencing uncertainty were considered, including older age of testing in the earliest cohorts (seroprevalence declines with onset gastritis in older age and may increase with changes in circumstances), a potential ‘healthy worker’ (Scragg et al., 1996) or ‘healthy donor’ effect (Morris et al., 1986) that might increase detected seroprevalence in these studies, smaller sample sizes increasing risk of chance results (for Māori and Pacific), uncertainty around regional weighting (Māori and Pacific), and uncertainty around adjustments for bias.

**Stomach cancer incidence**

Stomach cancer registration data between 1981 and 2004 were used to calculate the age-standardised incidence rates of stomach cancer for each ethnic group in the 1926-40, 1941-55, 1956-70 birth cohorts. The following methods were carried out for each of the three birth cohorts separately.

**CancerTrends**

Data for stomach cancer incidence were calculated from the CancerTrends study. This is a record linkage study of census and cancer registrations from 1981-2004 (Blakely et al., 2010). It includes records for the incidence of stomach cancer by calendar year, age, gender and ethnicity. Pathology reporting is the primary source of cancer registrations.

Incident cases were defined as males diagnosed with stomach cancer in the five years following each of the census nights in 1981, 1986, 1991, 1996 and in the four years following the 2001 census. Males were selected because of the approximately double risk of stomach cancer compared to females, enabling a greater number of cases for analysis in each ethnic group. Numbers of cases were obtained by multiplying the age-specific stomach cancer incidence rates (ASR) by the person years at risk. The ASRs used for this analysis were already weighted for linkage bias (i.e. incomplete linkage to the census) in methods described elsewhere (Blakely et al., 2010).
The denominator for stomach cancer incidence was person-time at risk. This is the five person-years of follow-up time for males resident in NZ on each census night. In the next section it is described how the denominator was restricted to the seropositive population in order to calculate the \( H. pylori \) adjusted rate ratio (RR\(_{HP} \)).

Each age group on each census night was assigned to the corresponding birth cohort. Five-year age groups at each census night were required to match incidence and person-time to birth cohorts. CancerTrends person-time and incidence rates were obtained for the vast majority of five-year age categories.

**Approximating unavailable incidence data**

However, for 10 out of 117 five-year age groups, CancerTrends data were not available due to privacy criteria that mean small numbers of cancer cases (five or fewer) are suppressed. Eight of the age groups not available corresponded to the 1956-70 cohort (8/27 = 30% unavailable data) whereas only one age group was missing from each of the 1926-40 and 1941-55 cohorts (both for Pacific, 1/45 = 2% unavailable data). In all three cohorts, the small proportion of missing five-year age group incidence data were approximated using twenty-year age group CancerTrends data. The following methods describe this process.

Where required, five-year age group incidence rates were approximated by assuming a log-linear association between age and incidence of stomach cancer. Figure 11 and Figure 12 demonstrate the linear trend between 25-74 years when incidence is presented on the log scale (in twenty- and ten-year wide age groups). The rise in incidence rate with age flattens in the 75+ age groups (Figure 11) but there were no missing data for these age groups.
Figure 11: The log-linear relationship between stomach cancer incidence and age in the 25-44yo, 45-64yo and 65-74yo age groups with a flattening of incidence rates in the 75+ year old age groups. European/Other, Māori and Pacific peoples are combined.

Figure 12: Evidence of the log-linear relationship between stomach cancer incidence and age in the 25-44yo, 45-64yo and 65-74yo age groups (plotted by the age midpoint) across the five-year census time periods for European/Other, Māori and Pacific peoples combined. For the study this graph was created separately for each ethnic group.

For each ethnic group, the slope coefficients (shown in Figure 12) were calculated for each time period and averaged. Each ethnicity-specific coefficient ($\beta$) was then exponentiated to give the increase in incidence with every year of age. The relative
increase between each five-year interval and the one that precedes it (within the 25-74yo age range) can be expressed as a rate ratio (RR):

\[ \text{RR}_{\text{Euro}} = \left( e^{\beta_{\text{Euro}}} \right)^5 \]

The following formula was used to calculate the age specific incidence rates \((\text{rate}_i)\) for each five-year age group \((i)\) with missing data; where \(\text{rate}_1\) is the rate in the first five-year age group in the twenty-year age group, and so on. The formula requires the corresponding twenty-year age group age-standardised incidence rate (ASR) and the weights \((w_i)\) used for standardisation recorded in the CancerTrends report (Blakely et al., 2010) (i.e. World Standard).

\[
\text{rate}_1 = \frac{\text{ASR}}{w_1 + \text{RR}.w_2 + \text{RR}^2.w_3 + \text{RR}^3.w_4}
\]

\[
\text{rate}_2 = \text{rate}_1.\text{RR}
\]

\[
\text{rate}_3 = \text{rate}_1.\text{RR}^2
\]

\[
\text{rate}_4 = \text{rate}_1.\text{RR}^3
\]

This formula assumes smooth age effects, and will thus remove some cohort effects – an element of variation in \(H. pylori\) over time. However, only a few rates had to be estimated in this way.

**Age standardisation**

Person-time exposure and stomach cancer incidence were now available for each birth cohort and ethnic group in five-year age groups. These were the best estimates of the number of observed stomach cancer cases in NZ from 1981-2004.
In order to compare stomach cancer incidence by ethnicity, direct age-standardisation was carried out to make the age structure of each ethnic group comparable. The population weights for standardisation were calculated from the total person-time exposed between 1981 and 2004 in each birth cohort, to maximise data precision. It should be noted that the standard population differed between cohorts, but this is not problematic as we were interested in ethnic differences in incidence within a birth cohort rather than between cohorts.

Age-standardised incidence rates were used to calculate rate ratios (RRs) comparing stomach cancer in Māori and Pacific with European/Other (i.e. non-Māori, non-Pacific and non-Asian).

Confidence intervals for incidence rate ratios

Confidence intervals were calculated for the standardised RRs using the formula for standardised measures described by Rothman et al. (2008). Where: Var = variance, \( w_i \) = weight used for each five-year age strata, \( R_i \) = rate in each strata, \( N_i \) = person-time in each strata, \( I_i \) = age-specific incidence rate, \( I_w \) = weighted incidence rate, \( 1 \) = Māori or Pacific, and \( 0 \) = European/Other.

\[
\text{Var}(I_w) = \frac{\sum (w_i^2) \times \text{Var}(I_i)}{(\sum w_i)^2}
\]

\[
\text{Var}(I_i) = \sum \left( \frac{R_i(1 - R_i)}{N_i - 1} \right)
\]

\[
\text{Var}(\ln(sRR)) = \frac{\text{Var}(I_{1w})}{I_{1w}^2} + \frac{\text{Var}(I_{0w})}{I_{0w}^2}
\]

The 95% confidence intervals were calculated from the square root of the variance:

\[
\text{Confidence intervals} = e^{[\log(sRR) \pm 1.96(\text{Var}[\ln(sRR)])^{1/2}]}
\]
Comparing seroprevalence and stomach cancer differences

Contribution of *H. pylori*

Relative ratios of *H. pylori* seroprevalence and stomach cancer incidence by ethnicity were presented for each cohort (1926-40, 1941-55, and 1956-70). If the difference in stomach cancer incidence between ethnic groups was wholly due to *H. pylori*, we would expect the seroprevalence risk ratio to be similar to the incidence rate ratio of stomach cancer.

If we make the assumption that *H. pylori* is necessary for stomach cancer, then a stomach cancer incidence rate ratio adjusted for *H. pylori* (RR_{HP}) can be calculated by restricting the analysis to the seropositive population (i.e. restricting the person-time denominator to the proportion of the population expected to be seropositive for *H. pylori* based on pooled seroprevalence data). In this way new rates of stomach cancer are calculated among the *H. pylori* seropositive population, assuming that all cases occur in this group. The recalculated *H. pylori* adjusted rate ratio by ethnicity (RR_{HP}) can be compared to the unadjusted rate ratio (RR) to calculate the contribution of *H. pylori* (percentage excess rate ratio).

Contribution of smoking to ethnic variation in stomach cancer incidence

The rate ratios of stomach cancer incidence already restricted to the *H. pylori* seropositive population (RR_{HP}) were further adjusted for the potential mediation effect of smoking by quantitative bias analysis. In this way a percentage excess rate ratio could be calculated to determine the contribution of *H. pylori* and smoking to excess Māori and Pacific stomach cancer incidence.

Probabilistic bias analysis based on methods by Lash et al. (2009) was used to assess the effect of smoking (similar mathematically to confounding effect) on the association between ethnicity and stomach cancer. Probability sensitivity analysis was first proposed by Cornfield in 1959 (Cornfield, 1959). The method extends simple sensitivity analysis by applying (Bayesian prior) probability distributions to bias parameters (Greenland and
A bias parameter is randomly selected from the set probability distribution for each iteration of a Monte-Carlo simulation. An uncertainty interval is then calculated which includes 95% of simulated estimates (Greenland and Lash, 2008).

Several bias parameter inputs were required, including the number of stomach cancer cases and person-time exposure by ethnicity (among H. pylori positive individuals only), the prevalence of smoking by ethnicity and an estimate of the association between smoking and stomach cancer in the study population.

Stomach cancer cases and person-time at risk (i.e. the seropositive proportion of each ethnic group) were available by ethnicity and birth cohort based on the analysis above.

Smoking prevalence was taken from the appropriate gender, age and ethnicity groupings in the 1981 census data (Hill et al., 2003); which is the beginning of the study time period (1981-2004). Smoking prevalence was applied to probabilistic bias analysis with a trapezoid distribution. This was chosen to allow for potential biases; i.e. two modes reflected the width of the confidence intervals in the census data, and the maximum and minimum prevalence reflected a ±10% difference in the best estimate from the census. The correlation coefficient for smoking prevalence (and smoking RR) across ethnicity was set to 0.5, reflecting the fact that a high random draw of smoking prevalence in one ethnic group would be expected to mean a higher value in the other ethnic group.

The assumption was made that smoking prevalence was similar in seropositive and seronegative populations and sensitivity analysis was used to evaluate this assumption. Evidence is mixed for this assumption and likely to be context-specific given different social histories. Large studies from Japan, Italy and Denmark have not detected any statistical association (Shinchi et al., 1997) (Russo et al., 1999) (Rosenstock et al., 2000) and one in Japan detected a negative association (Ogihara et al., 2000). UK studies have detected a positive association (Woodward et al., 2000) (Murray et al., 1997).
A relative risk (and its confidence interval) was required for the association of smoking with stomach cancer among *H. pylori* seropositive participants. If there is no association of smoking with seropositivity in each ethnic group, then the RR observed in the total population (which is available for CancerTrends data) will be the same as that among the seropositive only population. In CancerTrends data (Blakely et al., 2013), smoking was associated with 1.42 (1.22–1.66) times greater stomach cancer for current vs. never smokers (Table 3 of Bakely et al). This figure was used as a best estimate for this analysis because it is from the same CancerTrends study population. Other risk ratios were tested in sensitivity analysis including a recent meta-analysis risk ratio (OR 1.74 CI:1.46-2.07, males) by Gandini et al. (2008). A less precise estimate by Siman et al. (2001) from a seropositive only population was also used (OR 2.4, CI:1.1-4.7).

Probabilistic bias analysis was carried out until results were stable (2000+ iterations). The simulated rate ratio output provided the best estimate of the association between ethnicity and stomach cancer after taking into account both *H. pylori* seroprevalence and smoking prevalence. The uncertainty interval from probabilistic sensitivity analysis includes conventional statistical uncertainty and systematic error from the variation allowed for in the input bias parameters (i.e. RR of the smoking-cancer association and smoking prevalence). If *H. pylori* and smoking wholly explain ethnic differences we would expect the simulated rate ratio to approach one (RR=1), where the null hypothesis, that there is no evidence of any remaining differences, is likely to be true.

The proportion of ethnic differences in stomach cancer attributable to *H. pylori* and smoking was estimated by comparing the observed stomach cancer RR with the $\text{RR}_{\text{HP+smok}}$ which is adjusted for *H. pylori* and smoking. The ‘excess rate ratio proportion’ was the primary result of this analysis. The formula for this proportion is summarised here;

$$excess \text{ RR proportion} = \frac{RR - \text{RR}_{\text{HP+smok}}}{RR - 1}$$
Summary

For each cohort, three RRs were calculated to measure the excess Māori and Pacific stomach cancer incidence compared to European/Other. The first was the observed RR adjusted only for age. The second rate ratio (RR_{HP}) was calculated by restricting the denominator to the seropositive population in each ethnic group, which gives an estimate of the excess Māori and Pacific stomach cancer adjusted for *H. pylori*. A third rate ratio (RR_{HP+smok}) was calculated by applying probabilistic bias analysis to further adjust for the mediating effect of smoking prevalence. The observed RR was compared with the *H. pylori* and smoking adjusted RR_{HP+smok} to calculate the ethnic differences in stomach cancer which are attributable to *H. pylori* and smoking; i.e. the excess rate ratio proportion which is the primary result of this analysis.

Sensitivity analysis

Statistical uncertainty was considered by confidence intervals and uncertainty intervals which also include systematic error for probabilistic bias analysis. However, the uncertainty from the pooled seroprevalence data used to calculate RR_{HP} and RR_{HP+smok} is likely to be more important than statistical and systematic uncertainty. Seroprevalence uncertainty was therefore considered extensively by the sensitivity analysis.

Sensitivity analysis was carried out to investigate the stability of the primary results with the substitution of various input parameters. Single parameters in the analysis were adjusted to determine how this affected the final results. Focus was given to the impact of these changes on the excess rate ratio proportion, shown in Table 17.

Sensitivity analysis also illustrated the sensitivity of results to different possible seroprevalence combinations. The analysis was repeated with substitution of the best seroprevalence estimates with high (or low) combinations of pooled seroprevalence estimates (e.g. highest Pacific seroprevalence estimate and the highest European estimate, with a smaller RR). The assigned upper and lower pooled seroprevalence estimates in Table 15 were used for this process.
Sensitivity analysis was used to explore the necessary factor proposition. The evidence for \textit{H. pylori} as a necessary factor is best for stomach cancer in the non-cardia. Our incidence data however included both cardia and non-cardia stomach cancer. Therefore for all stomach cancer the necessary factor proposition is ambitious and will cause our analysis to overestimate the \textit{H. pylori} contribution. The proportion of stomach cancer for which \textit{H. pylori} is a necessary factor (non-cardia cancer) appears to vary by ethnicity. A recent study shows that non-cardia stomach cancer occurs in a greater proportion of the stomach cancer cases among Māori (87\%) and Pacific (88\%) than among European (51\%) (Biggar et al., 2011). In sensitivity analysis this was addressed by using the Biggar et al., 2001 figures to restrict stomach cancer incidence to the proportion of cases expected to be non-cardia stomach cancer.

\textbf{Ethical approval}
Ethical approval was granted for CancerTrends (Ref 04/10/093).
Chapter 5: Analysis results

H. pylori seroprevalence

Seroprevalence articles

Eight articles were identified examining seroprevalence, in seven different asymptomatic study populations between 1983 and 1999 in NZ (Collett et al., 1999, Fawcett et al., 1998, Fraser et al., 1996, Fraser et al., 2010, Morris et al., 1986, Scragg et al., 1996, Fraser et al., 2003). The age of testing for serology ranged from 11 years to more than 85 years old. In total, there were 4463 participants and 1349 were seropositive.

All studies specified the age of participants in five- to fifteen-year age brackets. Three seroprevalence estimates were available for participants in the Dunedin Multidisciplinary Health and Disability longitudinal study measured at ages 11yo, 21yo and 26yo (Fawcett et al., 1998, Fawcett et al., 2005). The 21yo data were selected because they stratified by ethnicity and had the greatest response rate.

In all studies, seroprevalence was available stratified by ethnicity and age. Some studies were limited to one ethnic group. In Auckland, data included only Māori and Pacific peoples (Morris et al., 1986) and one study included only non-Māori-non-Pacific (Fraser et al., 2003). The two studies in the South Island had largely NZ European participants (Collett et al., 1999, Fawcett et al., 1998) reflecting the lower proportion of Māori and Pacific in this region.
<table>
<thead>
<tr>
<th>Year and study id</th>
<th>Study population</th>
<th>Ethnicity (proportion of study population)</th>
<th>Age at test (yrs)</th>
<th>DOB of participating age groups</th>
<th>Assigned cohort</th>
<th>n</th>
<th>H. pylori +ve *</th>
<th>Overall Prev. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUCKLAND</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988-90 (Fraser et al., 1996)</td>
<td>Three South Auckland schools</td>
<td>Pacific (47%) Māori (31%) European (13%)</td>
<td>11-12</td>
<td>1976-79</td>
<td>1971-85</td>
<td>324</td>
<td>109</td>
<td>34</td>
</tr>
<tr>
<td>1997-98 (Fraser et al., 2010)</td>
<td>Seven decile 1-3 Auckland schools</td>
<td>Pacific (49%) Māori (15%) European (16%)</td>
<td>14-18</td>
<td>1979-83</td>
<td>1971-85</td>
<td>792</td>
<td>278</td>
<td>35</td>
</tr>
<tr>
<td>1985 (Morris et al., 1986)</td>
<td>Blood donors in Auckland</td>
<td>Pacific (56%) Māori (40%)</td>
<td>15-20</td>
<td>1965-70</td>
<td>1956-70</td>
<td>175</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21-30</td>
<td>1955-64</td>
<td>1956-70</td>
<td>165</td>
<td>54</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31-40</td>
<td>1945-54</td>
<td>1941-55</td>
<td>93</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>41-50</td>
<td>1935-44</td>
<td>1941-55 &amp; 1926-40</td>
<td>35</td>
<td>19</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51-60</td>
<td>1925-34</td>
<td>1926-40</td>
<td>12</td>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>61-70</td>
<td>1915-24</td>
<td>1911-25</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1988-90 (Scragg et al., 1996)</td>
<td>Randomly selected sample from worksites in Auckland and Tokoroa</td>
<td>Māori, Pacific &amp; European (each 33%)</td>
<td>40-49</td>
<td>1940-49</td>
<td>1941-55</td>
<td>278</td>
<td>133</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50-64</td>
<td>1926-39</td>
<td>1926-40</td>
<td>301</td>
<td>191</td>
<td>63</td>
</tr>
<tr>
<td>1986 – 1988 (Feb) (Fraser et al., 2003)</td>
<td>Controls of myocardial infarction patients taken from the electoral roll</td>
<td>European i.e. non-Māori non-Pacific</td>
<td>35-44</td>
<td>1942-52</td>
<td>1941-55</td>
<td>138</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45-49</td>
<td>1937-42</td>
<td>1926-40</td>
<td>131</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50-54</td>
<td>1932-37</td>
<td>1926-40</td>
<td>162</td>
<td>49</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55-59</td>
<td>1927-32</td>
<td>1926-40</td>
<td>209</td>
<td>99</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60-64</td>
<td>1922-27</td>
<td>1911-25</td>
<td>191</td>
<td>82</td>
<td>43</td>
</tr>
<tr>
<td><strong>SOUTH ISLAND</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993-1994 (Fawcett et al., 1998)</td>
<td>Participants born in Dunedin and recruited to the Dunedin Multidisciplinary Health &amp; Disability Study</td>
<td>European (95%)</td>
<td>21</td>
<td>1972-73</td>
<td>1971-85</td>
<td>785</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>1996 (Collett et al., 1999)</td>
<td>Christchurch electoral roll survey</td>
<td>European (96%) Māori (1.1%) Pacific (0.6%)</td>
<td>11-25</td>
<td>1971-85</td>
<td>1971-85</td>
<td>81</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>26-40</td>
<td>1956-70</td>
<td>1956-70</td>
<td>266</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>41-55</td>
<td>1941-55</td>
<td>1941-55</td>
<td>284</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56-70</td>
<td>1926-40</td>
<td>1926-40</td>
<td>241</td>
<td>84</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71-85</td>
<td>1911-25</td>
<td>1911-25</td>
<td>145</td>
<td>72</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 11: Summary of pooled studies assigned to five birth cohorts, *all studies used commercial ELISA tests (e.g. Roche) except for Morris (1986) which used pooled whole organism antigen from 14 C pyloridis isolates, the Marshall strain and C pyloridis type organism for its ELISA – which may underestimate H. pylori
Pooled seroprevalence

Ethnic differences in seroprevalence in NZ persisted across all four birth cohorts (Figure 13). Averaged across the cohorts and regionally-weighted, Māori had a seroprevalence of 35%, which is 1.93 times greater than the 18% seroprevalence among European study participants (Table 12 and Table 13). Average Pacific seroprevalence was 62% overall and 3.38 times greater than European seroprevalence.

Seroprevalence estimates appeared to decline over time in all ethnic groups so that subsequent birth cohorts were less likely to test positive for *H. pylori* infection (Figure 14). In the crude pooled data the rate of decline flattens out in the youngest birth cohort (Figure 13) however this largely disappears after adjustment for selection and measurement biases (Figure 14).

For both Māori and Pacific, absolute differences (risk differences compared to European peoples) in seroprevalence appear to have decreased in subsequent birth cohorts. Conversely, relative differences (RRs) between Māori or Pacific and European seroprevalence increased in subsequent cohorts (Figure 15). Pacific seroprevalence was 2.38 times greater than European seroprevalence in the 1926-40 cohort, and 5.83 times greater in the 1971-85 cohort.

The greatest sample sizes for seroprevalence data were from the earliest (1926-40) and most recent (1971-85) birth cohorts and there was reasonable data (n>100) for Māori and Pacific in all four cohorts.
Figure 13: Crude pooled adult seroprevalence estimates in New Zealand by birth cohort and ethnicity, weighted by region.

Figure 14: Pooled estimates of adult seroprevalence by birth cohort and ethnicity in New Zealand from seven studies with adjustment for potential selection and measurement biases in two studies, weighted by region. These estimates are used in the analysis.
<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>European n</th>
<th>European seroprevalence</th>
<th>Māori n</th>
<th>Māori seroprevalence</th>
<th>Pacific n</th>
<th>Pacific seroprevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971-85</td>
<td>979</td>
<td>7%</td>
<td>227</td>
<td>18%</td>
<td>542</td>
<td>39%</td>
</tr>
<tr>
<td>1956-70</td>
<td>254</td>
<td>11%</td>
<td>124</td>
<td>24%</td>
<td>167</td>
<td>55%</td>
</tr>
<tr>
<td>1941-55</td>
<td>507</td>
<td>20%</td>
<td>144</td>
<td>42%</td>
<td>155</td>
<td>70%</td>
</tr>
<tr>
<td>1926-40</td>
<td>837</td>
<td>35%</td>
<td>118</td>
<td>57%</td>
<td>128</td>
<td>83%</td>
</tr>
<tr>
<td>1911-25</td>
<td>336</td>
<td>46%</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>SUM</td>
<td>2913</td>
<td>18%</td>
<td>602</td>
<td>35%</td>
<td>976</td>
<td>62%</td>
</tr>
</tbody>
</table>

Table 12: *H. pylori* seroprevalence from seven New Zealand studies pooled by birth cohort and ethnicity; weighted by distribution of each ethnic population by region in the 1996 census, crude data from two studies was adjusted for selection and measurement bias (n = total participants tested in pooled studies, the summary seroprevalence is an average of the four earliest cohorts).

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>RD Māori vs. European</th>
<th>RD Pacific vs. European</th>
<th>RR Māori vs. European</th>
<th>RR Pacific vs. European</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971-85</td>
<td>11%</td>
<td>32%</td>
<td>2.70</td>
<td>5.83</td>
</tr>
<tr>
<td>1956-70</td>
<td>12%</td>
<td>44%</td>
<td>2.09</td>
<td>4.89</td>
</tr>
<tr>
<td>1941-55</td>
<td>22%</td>
<td>50%</td>
<td>2.08</td>
<td>3.45</td>
</tr>
<tr>
<td>1926-40</td>
<td>23%</td>
<td>48%</td>
<td>1.65</td>
<td>2.38</td>
</tr>
<tr>
<td>AVERAGE</td>
<td>17%</td>
<td>44%</td>
<td>1.93</td>
<td>3.38</td>
</tr>
</tbody>
</table>

Table 13: Risk differences (RD) (absolute differences) and risk ratios (RR) (relative differences) of Māori and Pacific *H. pylori* seroprevalence compared to NZ European, by birth cohort. The average is across all four birth cohorts with each given equal weighting. Data has been regionally weighted and crude data from two studies was adjusted for selection and measurement bias.
Burden of *H. pylori* caused by household crowding

The contribution of household crowding density to seroprevalence among Māori, Pacific and European born 1971-85 in NZ was estimated for the 1971-85 cohort for whom data was available. PAFs were calculated using the meta-analysis results for the OR of *H. pylori* seroprevalence among persons who experienced the greatest vs. the least household crowding in childhood (OR 2.52; CI: 1.91-3.32), using pooled *H. pylori* seroprevalence for the 1971-85 cohort and household crowding among <15 year olds in the 1986 census (CNOS 1+ bedroom deficit) (Ministry for Social Development, 2008). The odds ratio for childhood crowding exposure was selected because *H. pylori* is predominantly acquired in childhood and childhood exposure to crowding was available for this birth cohort. The calculation assumes that household crowding is a causal risk factor for *H. pylori* seroprevalence and uses the following formula.

\[
\text{Population attributable fraction (PAF)} = \frac{p (RR - 1)}{p (RR - 1) + 1}
\]

Table 14 demonstrates that 14% (95% CI: 9-20%) of European, 36% (95% CI: 25-47%) of Māori, and 44% (95% CI: 32-54%) of Pacific seroprevalence was attributable to
household crowding among children. This corresponds to a 1 in 6 chance of *H. pylori* seropositivity on account of household crowding for Pacific peoples born in this period. The risk for Māori peoples was less (1 in 15) and for European peoples the risk was lower still (1 in 57).

PAF and PAR figures may be overestimates, because the meta-analysis OR used in the calculation was used to approximate a rate ratio. The OR will only overestimate the RR in the situation where seroprevalence is a relatively common outcome and controls are not selected from a steady state population (Pearce, 2004, Vandenbroucke and Pearce, 2012).

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Seroprevalence %</th>
<th>Household crowding (&lt;15yo) %</th>
<th>Proportion seroprevalence attributable to crowding, PAF % (95% CI)</th>
<th>Absolute seroprevalence attributable to crowding, PAR % (95% CI)</th>
<th>Risk of <em>H. pylori</em> attributable to household crowding in overall population</th>
</tr>
</thead>
<tbody>
<tr>
<td>European/Other</td>
<td>12</td>
<td>11</td>
<td>14 (9-20)</td>
<td>1.8 (1.1-2.5)</td>
<td>1 in 57</td>
</tr>
<tr>
<td>Māori</td>
<td>18</td>
<td>38</td>
<td>36 (25-47)</td>
<td>6.6 (4.6-8.4)</td>
<td>1 in 15</td>
</tr>
<tr>
<td>Pacific</td>
<td>39</td>
<td>51</td>
<td>44 (32-54)</td>
<td>17 (12-21)</td>
<td>1 in 6</td>
</tr>
</tbody>
</table>

Table 14: Contribution of household crowding (taken from the 1986 census) to the pooled seroprevalence in the 1971-85 birth cohort. PAF = population attributable fraction, PAR = population attributable risk, assuming household crowding is causal, applying a 2.52 increased odds of seropositivity taken from meta-analysis for children exposed to greater household crowding. Confidence intervals presented do not account for uncertainty in the seroprevalence figures.

**Upper and lower estimates for seroprevalence**

Upper and lower estimates were assigned to correspond to uncertainties in seroprevalence (Figure 16). The effects of these estimates (i.e. potential differences in the true seroprevalence rates) on the seroprevalence risk ratios (RRs) for ethnicity are presented in Table 15. For Pacific, it did not matter what combination of seroprevalence estimates were used, this group still had greater seroprevalence than European. Māori seroprevalence was also greater than European for all but the most unlikely seroprevalence combinations. Seroprevalence uncertainty had the greatest impact on RRs in the latter birth cohorts. RRs were relatively stable for the 1926-40 cohort.
Figure 16: Best estimates and assigned upper and lower estimates of H. pylori seroprevalence by ethnicity and year of birth. Figures are regionally weighted and adjusted for selection and measurement bias.
Table 15: Impact of upper and lower assigned seroprevalence estimates on the relative risk of *H. pylori* seropositivity between ethnic groups in each birth cohort, the ‘best est.’ is calculated from pooled New Zealand data with weighting for region and adjustment for some biases.

<table>
<thead>
<tr>
<th></th>
<th>Māori vs. European</th>
<th>Pacific vs. European</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>European seroprevalence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lowest est.</td>
<td>best est.</td>
</tr>
<tr>
<td>1926-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lowest est.</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>best est.</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>highest est.</td>
<td>51%</td>
</tr>
<tr>
<td>1941-55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lowest est.</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>best est.</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>highest est.</td>
<td>30%</td>
</tr>
<tr>
<td>1956-70</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lowest est.</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>best est.</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>highest est.</td>
<td>18%</td>
</tr>
<tr>
<td>1971-85</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lowest est.</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>best est.</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>highest est.</td>
<td>12%</td>
</tr>
</tbody>
</table>
Stomach cancer incidence

Māori and Pacific stomach cancer incidence was significantly greater than European/Other in all birth cohorts (rate ratios, Table 16). Age-standardised stomach cancer incidence was 2.76, 3.83 and 5.96 times greater for Māori compared to European/Other in the 1926-40, 1941-55 and 1956-70 birth cohorts respectively. For Pacific these rate ratios were similar with 3.11, 4.30 and 5.25 greater rates of stomach cancer compared to European/Other. When the analysis was restricted to non-cardia stomach cancer, the excess incidence among Māori and Pacific compared to European/Other was even greater, with observed RRs ranging from 4.7 to 10.2 (Table 16). Rates of stomach cancer incidence were largely similar between Māori and Pacific and small differences were possibly due to statistical uncertainty.

Relative differences in stomach cancer incidence (RRs) were greater in subsequent birth cohorts, similar to the trend shown in seroprevalence. It should be noted however that different birth cohorts correspond to different age groups and therefore are not directly comparable, because stomach cancer is less common in younger age groups.

Comparing seroprevalence and stomach cancer differences

The patterns of ethnic differences (RRs) in pooled *H. pylori* seroprevalence and stomach cancer incidence can be compared in Table 16. The relative risk of seroprevalence was never more than the relative rates of stomach cancer. Trends in seroprevalence differences across cohorts and ethnic groups largely reflect the trends in stomach cancer differences.
<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Ethnicity</th>
<th>Proportion H. pylori seropositive in pooled studies* (%)</th>
<th>H. pylori seropositivity risk ratio (sensitivity analysis range)</th>
<th>Person-time (years)</th>
<th>Standardised incidence rate of all stomach cancer (per 100,000)</th>
<th>Rate ratio of all stomach cancer incidence (95% C.I.)</th>
<th>Estimated incidence rate of non-cardia stomach cancer (per 100,000)^</th>
<th>Rate ratio of non-cardia stomach cancer incidence (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1926-40 (40-79yo)</td>
<td>European/Other</td>
<td>35</td>
<td>1</td>
<td>4,518,114</td>
<td>20.8</td>
<td>1</td>
<td>10.6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>57</td>
<td>1.65 (0.88-3.08)</td>
<td>413,188</td>
<td>57.4</td>
<td>2.76 (2.39-3.20)</td>
<td>49.9</td>
<td>4.71 (3.99-5.57)</td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>83</td>
<td>2.38 (1.39-4.00)</td>
<td>136,124</td>
<td>64.6</td>
<td>3.11 (2.49-3.89)</td>
<td>56.8</td>
<td>5.37 (4.21-6.85)</td>
</tr>
<tr>
<td>1941-55 (25-64yo)</td>
<td>European/Other</td>
<td>20</td>
<td>1</td>
<td>6,519,818</td>
<td>4.1</td>
<td>1</td>
<td>2.1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>42</td>
<td>2.08 (1.03-4.31)</td>
<td>805,226</td>
<td>15.6</td>
<td>3.83 (3.08-4.75)</td>
<td>13.6</td>
<td>6.53 (5.06-8.43)</td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>70</td>
<td>3.45 (2.00-6.38)</td>
<td>314,018</td>
<td>17.5</td>
<td>4.30 (3.20-5.77)</td>
<td>15.4</td>
<td>7.42 (5.32-10.3)</td>
</tr>
<tr>
<td>1956-70 (25-49yo)</td>
<td>European/Other</td>
<td>11</td>
<td>1</td>
<td>3,892,691</td>
<td>1.2</td>
<td>1</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>24</td>
<td>2.09 (0.83-6.80)</td>
<td>722,497</td>
<td>7.1</td>
<td>5.96 (4.00-8.90)</td>
<td>6.2</td>
<td>10.2 (6.16-16.8)</td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>55</td>
<td>4.89 (2.56-13.2)</td>
<td>283,584</td>
<td>6.2</td>
<td>5.25 (3.04-9.07)</td>
<td>5.5</td>
<td>9.06 (4.78-17.2)</td>
</tr>
</tbody>
</table>

Table 16: Comparison of cohort specific pooled seroprevalence risk ratios (*weighted by region and adjusted for selection and measurement bias) and stomach cancer age-standardised incidence rate ratios by ethnicity for the New Zealand population during study period 1981-2004 (^based on non-cardia stomach cancer proportions by ethnicity (Biggar et al., 2011))
Stomach cancer incidence rate ratios were adjusted for *H. pylori* to evaluate the remaining ethnic differences in stomach cancer. This was done by repeating the analysis; and instead of including the whole population, the analysis was restricted to the proportion of each ethnic group who were seropositive. Table 17 and Figure 17 show the results from adjusting stomach cancer incidence rate ratios (column C) for *H. pylori* (column D) and the adjustment for smoking prevalence with probabilistic bias analysis (column F in Table 17).

Based on the assumption that *H. pylori* is a necessary risk factor for all stomach cancer; the contribution of *H. pylori* to stomach cancer differences was substantial and relatively stable across all three birth cohorts. In all cases, estimates indicate that *H. pylori* was most important for the Pacific group contributing to 85%, 92% and 98% (in each subsequent cohort) of the relative difference in stomach cancer rates compared to

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Ethnicity</th>
<th>Age-standardised incidence RR of stomach cancer (95% C.I.)</th>
<th>RR&lt;sub&gt;HP&lt;/sub&gt; of stomach cancer adjusted for <em>H. pylori</em> (95% C.I.)</th>
<th>Stomach cancer differences attributable to <em>H. pylori</em> (% excess RR)</th>
<th>RR&lt;sub&gt;HP+smok&lt;/sub&gt; of stomach cancer adjusted for <em>H. pylori</em> &amp; smoking (95% U.I.)</th>
<th>Stomach cancer differences attributable to <em>H. pylori</em> &amp; smoking (% excess RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1926-40 (40-79yo)</td>
<td>European/Other</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>66%</td>
<td>1.60 (1.39 - 1.85)</td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>2.76 (2.39-3.20)</td>
<td>1.68 (1.45-1.94)</td>
<td>61%</td>
<td>1.60 (1.39 - 1.85)</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>3.11 (2.49-3.89)</td>
<td>1.31 (1.05-1.63)</td>
<td>85%</td>
<td>1.26 (1.00 - 1.57)</td>
<td>88%</td>
</tr>
<tr>
<td>1941-55 (25-64yo)</td>
<td>European/Other</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>74%</td>
<td>1.73 (1.39 - 2.13)</td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>3.83 (3.08-4.75)</td>
<td>1.85 (1.49-2.30)</td>
<td>70%</td>
<td>1.73 (1.39 - 2.13)</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>4.30 (3.20-5.77)</td>
<td>1.25 (0.93-1.68)</td>
<td>92%</td>
<td>1.21 (0.90 - 1.61)</td>
<td>94%</td>
</tr>
<tr>
<td>1956-70 (25-49yo)</td>
<td>European/Other</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>67%</td>
<td>2.62 (1.74 - 3.87)</td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>5.96 (4.00-8.90)</td>
<td>2.85 (1.91-4.25)</td>
<td>63%</td>
<td>2.62 (1.74 - 3.87)</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>5.25 (3.04-9.07)</td>
<td>1.08 (0.62-1.86)</td>
<td>98%</td>
<td>1.06 (0.61 - 1.85)</td>
<td>99%</td>
</tr>
</tbody>
</table>

Table 17: Differences in stomach cancer incidence by ethnicity in three birth cohorts, before (column C) and after column D) restricting the at risk population to those who are *H. pylori* seropositive (*assuming *H. pylori* is a necessary factor for stomach cancer cases) and using probabilistic sensitivity analysis to adjust for mediation by current smoking prevalence by cohort in 1981, in column F the uncertainty interval (U.I.) includes statistical uncertainty and systematic error from probabilistic bias analysis.
European/Other. For Māori the *H. pylori* contribution was estimated to be 61%, 70% and 63% of the relative differences.

Greater smoking prevalence in Māori and Pacific (particularly among Māori) compared to European accounted for a small additional proportion of the relative stomach cancer rates (column G). Again figures were relatively stable across cohorts with smoking making a 4-5% contribution to increased risk in Māori and a 1-3% contribution to increased risk in Pacific. These estimates assume that smoking exposure is the same in both seropositive and seronegative populations.

Assuming that *H. pylori* is necessary for all stomach cancer, estimates indicate that *H. pylori* and smoking came close to explaining all the excess stomach cancer among Pacific peoples compared to European/Other. That is, after adjusting for *H. pylori* seroprevalence and smoking status in each subsequent cohort, 88%, 94% and 99% of the differences between Pacific and European/Other were explained by *H. pylori* and smoking; and there was no statistical evidence of any remaining differences in stomach cancer incidence after adjusting for these two risk factors. The contribution of *H. pylori* was less substantial for Māori than it was for Pacific. RRs adjusted for *H. pylori* and smoking consistently explained two-thirds (61%, 70% and 63%) of the observed stomach cancer RR for Māori compared to European/Other (Table 6, column C) (Figure 17).
1926-40
(40-79yo)

RR

Māori

Pacific

RR

Māori vs. European/Other

RR(HP)
H. pylori adjusted

RR(HP+smok)
H. pylori & smoking adjusted

RR
Pacific vs. European/Other

RR(HP)
H. pylori adjusted

RR(HP+smok)
H. pylori & smoking adjusted

Māori

Pacific

RR

Māori

1941-55
(25-64yo)

RR

Māori vs. European/Other

RR(HP)
H. pylori adjusted

RR(HP+smok)
H. pylori & smoking adjusted

RR
Pacific vs. European/Other

RR(HP)
H. pylori adjusted

RR(HP+smok)
H. pylori & smoking adjusted

Māori

Pacific
Figure 17: Age-standardised stomach cancer incidence rate ratios (RR) comparing ethnic groups in three birth cohorts. RRs are adjusted for *H. pylori* by restricting the population at risk to those who are *H. pylori* seropositive. The RR was further adjusted using probabilistic sensitivity analysis to adjust for mediation by 1981 smoking prevalence. The conventional 95% confidence intervals are illustrated with a dash (except for in the smoking adjusted estimate where these are uncertainty intervals which include systematic error).
Sensitivity analysis

The impact of sensitivity analysis on results (Table 17) is presented in Table 18. Results were generally stable to changes in various input parameters. In fact changes were more likely to increase the contribution of *H. pylori* (or smoking) to excess Māori and Pacific stomach cancer than decrease its contribution. This was particularly true for the cohort for which we have the best data (1926-40) for which there were 1251 cases of stomach cancer from 1981-2004.

Sensitivity to seroprevalence was tested. When the lowest and highest assigned estimates of seroprevalence were separately imputed, the contribution of *H. pylori* to excess Pacific stomach cancer remained substantial across the cohorts ranging from 72-100%. For Māori in this instance, the contribution of *H. pylori* also remained close to the two-thirds estimate ranging from 53-80%.

When the analysis was restricted to non-cardia stomach cancer in the 1926-40, 1941-55 and 1956-70 birth cohorts, *H. pylori* and smoking (to a lesser degree) remained substantial contributors, attributable for more than half of the excess Māori non-cardia stomach cancer incidence (53%, 65%, 63% respectively) and approximately eight-tenths of excess Pacific non-cardia stomach cancer incidence (74%, 83%, 90% respectively). These are perhaps the best estimates of the true *H. pylori* contribution.
<table>
<thead>
<tr>
<th>Adjusted input parameters:</th>
<th>Birth cohort and ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1926-40 (40-79yo)</td>
</tr>
<tr>
<td></td>
<td>Māori</td>
</tr>
<tr>
<td>Principal estimates for comparison:</td>
<td>RR for stomach cancer (95% C.I.)</td>
</tr>
<tr>
<td>RR adjusted for <em>H. pylori</em> (95% C.I.)</td>
<td>1.68 (1.45-1.94)</td>
</tr>
<tr>
<td>Excess RR attributable to <em>H. pylori</em> (%)</td>
<td>61%</td>
</tr>
<tr>
<td>RR adjusted for <em>H. pylori</em> and smoking (95% U.I.)</td>
<td>1.60 (1.39-1.85)</td>
</tr>
<tr>
<td>Excess RR attributable to <em>H. pylori</em> &amp; smoking (%)</td>
<td>66%</td>
</tr>
<tr>
<td>Stomach cancer incidence parameters:</td>
<td></td>
</tr>
<tr>
<td>Non-cardia proportions (Biggar) applied to total stomach cancer incidence data: i.e. European (51%), Māori (87%), Pacific (88%)</td>
<td>RR for stomach cancer (95% C.I.)</td>
</tr>
<tr>
<td>RR adjusted for <em>H. pylori</em> (95% C.I.)</td>
<td>2.86 (2.42-3.39)</td>
</tr>
<tr>
<td>Incidence attributable to <em>H. pylori</em> (%)</td>
<td>50% L</td>
</tr>
<tr>
<td>RR adjusted for <em>H. pylori</em> and smoking (95% U.I.)</td>
<td>2.73 (2.32-3.18)</td>
</tr>
<tr>
<td>Incidence attributable to <em>H. pylori</em> and smoking (%)</td>
<td>53% L</td>
</tr>
<tr>
<td>Age standardisation using the cases as a reference population (&gt; contribution in older age groups)</td>
<td>RR for stomach cancer (95% C.I.)</td>
</tr>
<tr>
<td>RR adjusted for <em>H. pylori</em> (95% C.I.)</td>
<td>1.53 (1.29-1.82)</td>
</tr>
<tr>
<td>Incidence attributable to <em>H. pylori</em> (%)</td>
<td>65%</td>
</tr>
<tr>
<td>Smoking parameters:</td>
<td></td>
</tr>
<tr>
<td>Greater estimate of association between smoking and cancer, RR 1.74 (Gandini) instead of 1.42</td>
<td>RR adjusted for <em>H. pylori</em> and smoking (95% U.I.)</td>
</tr>
<tr>
<td>Incidence attributable to <em>H. pylori</em> and smoking (%)</td>
<td>68%</td>
</tr>
<tr>
<td>Association with smoking among seropositive only ie. RR 2.4 (Siman) instead of 1.42</td>
<td>RR adjusted for <em>H. pylori</em> and smoking (95% U.I.)</td>
</tr>
<tr>
<td>Incidence attributable to <em>H. pylori</em> and smoking (%)</td>
<td>72% H</td>
</tr>
</tbody>
</table>

* *H. pylori* adjusted for smoking and cancer.
Table continued….

<table>
<thead>
<tr>
<th>Birth cohort and ethnicity</th>
<th>1926-40 (40-79yo)</th>
<th>1941-55 (25-64yo)</th>
<th>1956-70 (25-49yo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Māori</td>
<td>Pacific</td>
<td>Māori</td>
</tr>
<tr>
<td><strong>Principal estimates for comparison:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR adjusted for <em>H. pylori</em> (95% C.I.)</td>
<td>1.68 (1.45-1.94)</td>
<td>1.31 (1.05-1.63)</td>
<td>1.85 (1.49-2.30)</td>
</tr>
<tr>
<td>Excess RR attributable to <em>H. pylori</em> (%)</td>
<td>61%</td>
<td>85%</td>
<td>70%</td>
</tr>
</tbody>
</table>

**Pooled seroprevalence parameters:**

<table>
<thead>
<tr>
<th>Lowest estimates for <em>H. pylori</em> seroprevalence (for European and for Māori/Pacific) – ↑relative ethnic diff.</th>
<th>RR adjusted for <em>H. pylori</em> (95% C.I.)</th>
<th>Incidence attributable to <em>H. pylori</em> (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.54 (1.33-1.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.10 (0.88-1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.62 (1.30-2.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.94 (0.70-1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.98 (1.33-2.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.58 (0.33-0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75% H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78% H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80% H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Highest estimates for <em>H. pylori</em> seroprevalence (for European and for Māori/Pacific) – ↓relative ethnic diff.</th>
<th>RR adjusted for <em>H. pylori</em> (95% C.I.)</th>
<th>Incidence attributable to <em>H. pylori</em> (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.83 (1.58-2.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.59 (1.27-1.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.06 (1.66-2.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.56 (1.16-2.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.15 (2.11-4.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.44 (0.83-2.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53% L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>57% L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>63% L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83% L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>57% L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional variation was allowed to vary by cohort when applying regional weighting</th>
<th>RR adjusted for <em>H. pylori</em> (95% C.I.)</th>
<th>Incidence attributable to <em>H. pylori</em> (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.60 (1.38-1.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.59 (1.37-1.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.71 (1.38-2.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.40 (1.05-1.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.18 (2.13-4.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.56 L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56% L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>64% L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>64% L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56% L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient data</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion of the Morris study with potentially low sensitivity to detect <em>H. pylori</em></th>
<th>RR adjusted for <em>H. pylori</em> (95% C.I.)</th>
<th>Incidence attributable to <em>H. pylori</em> (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.58 (1.37-1.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.71 (1.38-2.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.40 (1.05-1.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>67% H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>88%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion of two Fraser studies which sampled low socioeconomic areas</th>
<th>RR adjusted for <em>H. pylori</em> (95% C.I.)</th>
<th>Incidence attributable to <em>H. pylori</em> (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.59 (1.37-1.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.77 (1.43-2.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.58 (1.73-3.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>67% H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>73%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>82%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 18: Sensitivity analysis showing how excess stomach cancer incidence rates in Māori or Pacific (each compared to European/Other) change by variation in input parameters or methodology, during study period 1981-2004. Absolute changes of more than 5% in the contribution of *H. pylori* are highlighted in bold; where ‘H’ is higher than the principal estimate and ‘L’ is lower than the principle estimate. Where the rate ratio (RR) adjusted for *H. pylori* was less than one, the contribution was assigned the value of 100%. If the RR adjusted for *H. pylori* was greater than the unadjusted RR, then *H. pylori* did not contribute anything to the differences in stomach cancer and the value was assigned to be 0%.
Chapter 6: Discussion

Summary of key findings

Meta-analysis of studies adjusted for age and socioeconomic status, indicated that persons exposed to greater household crowding had on average 1.73 (CI: 1.48-2.03, n=28, $I^2 = 87\%$) times greater odds of *H. pylori* infection than those least exposed. The magnitude of risk was significantly greater ($p=0.0006$) for participants who experienced household crowding in childhood (OR 2.06, CI: 1.53-2.77, n=19) than in adulthood (OR 1.17, CI: 1.07-1.28, n=6). Quality scores of 9+/10 were associated with a greater association (OR). Unreported results, uncontrolled confounding, unexplained heterogeneity and outcome misclassification may have impacted these results.

Pooled *H. pylori* seroprevalence was greatest among Pacific (62%), followed by Māori (35%) and European (18%). Seroprevalence has declined in subsequent birth cohorts for all ethnic groups and absolute ethnic differences appear to have decreased. However, relative ethnic differences appear to have increased. Māori seroprevalence was 1.65 times greater than European seroprevalence in the 1926-40 cohort and 2.70 times greater in the 1971-85 cohort. The RRs for Pacific in these respective cohorts were 2.38 and 5.83 times greater than European.

Household crowding in children born 1971-85 was estimated to have contributed to *H. pylori* infection among 1 in 6 (95%CI: 12-21%) Pacific people, 1 in 15 (95%CI: 4.6-8.4%) Māori, and 1 in 57 (95%CI: 1.1-2.5%) European.

Māori and Pacific stomach cancer incidence was significantly greater than European/Other incidence in all three cohorts, and the differences were greater still for non-cardia stomach cancer. Total stomach cancer incidence rates (standardised for age) were 2.76, 3.83 and 5.96 times greater for Māori compared to European/Other in the 1926-40, 1941-55 and 1956-70 cohorts respectively. For Pacific these rate ratios were similar with 3.11, 4.30 and 5.25 times greater incidence compared to European/Other.
Our principal results estimate that *H. pylori* and smoking (to a lesser degree) contributed to almost all of the excess Pacific stomach cancer (88-98%) and approximately two-thirds (65-75%) of the excess Māori stomach cancer, compared to European/Other. It is most appropriate however to consider the results restricted to non-cardia stomach cancer, for which *H. pylori* is established as a necessary causal factor. For men in the 1926-40, 1941-55 and 1956-70 birth cohorts, *H. pylori* and smoking (to a lesser degree) contributed to more than half of excess non-cardia stomach cancer among Māori (53%, 65%, 63% respectively) and approximately eight-tenths of the excess non-cardia stomach cancer among Pacific (74%, 83%, 90% respectively).
Discussion of key findings

Ethnic trends in *H. pylori* infection and the role of household crowding

*H. pylori* seroprevalence varied substantially by ethnicity. In subsequent cohorts seroprevalence declined for all ethnic groups, and the relative differences between ethnic groups increased. Meta-analysis shows that household crowding is associated with twice the risk of infection among children in crowded households, making a substantial contribution to Pacific (44% of seroprevalence) and Māori seroprevalence (36%).

**Association with crowding**

Meta-analysis findings are consistent with reviews which have concluded that household crowding is one of the major risk factors for *H. pylori* infection (Brown, 2000) (Office of the Deputy Prime Minister London, 2004). Findings are further strengthened by their consistency with other meta-analyses which demonstrate how several close-contact infectious diseases are associated with household crowding (Baker et al., 2013).

Meta-analysis sub-group analysis showed that childhood household crowding was associated with greater *H. pylori* risk, consistent with the predominant acquisition of *H. pylori* infection in childhood (Lindkvist et al., 1996, Webb et al., 1994, Mitchell et al., 1992). Childhood is a particularly vulnerable age with high rates of most infectious disease compared with other age groups.

**Trends over time**

For all ethnic groups, pooled seroprevalence demonstrated a consistent decline in infection from between persons born in 1926-40 and 1971-85. Although the association of increasing seroprevalence with age has already been demonstrated in NZ this is the first analysis which pools NZ data and does so by cohort of birth. Adult acquisition of *H. pylori* may partially contribute to increased seroprevalence with age because earlier cohorts were tested at an older age. It has already been described however that year of
birth is likely to be the major contributor to decreasing seroprevalence and this appears likely to apply in the NZ context.

Trends in seroprevalence reflect substantial improvements in NZ 20\textsuperscript{th} century living standards. Increases in household income have occurred since the 1920s, substantial developments in house building occurred from the 1940s (e.g. urban-based state housing) and there has been reductions in household size with declining fertility rates (Statistics New Zealand, 2012b). During the 1950s and 1960s indoor toilets, bathrooms, and electricity became standard features of NZ homes (Statistics New Zealand, 2012b). Children born in subsequent birth cohorts have experienced substantial reductions in the acquisition of \textit{H. pylori} infection, demonstrating one of the many benefits of improved living standards. It is not possible to link the declines in \textit{H. pylori} with any specific aspect of living standard improvements, except perhaps overcrowding (Malaty et al., 1996).

\textit{Ethnic differences}

Pacific participants (and to a lesser extent Māori) had a particularly increased risk of \textit{H. pylori} infection. Ethnic differences in \textit{H. pylori} prevalence are consistent with other clinical studies in NZ, which were excluded because participants all had gastric symptoms. A cohort in South Auckland in 2012 (n=592) demonstrated that Māori (35\%) and Pacific (32\%) gastroscopy patients had approximately 5.0 and 4.6 times greater prevalence (respectively) of active \textit{H. pylori} infection compared to European (7\%) using a rapid urease test (unpublished: Hsiang & Patrick, 2013).

Our findings suggest that a reasonable proportion of Pacific and Māori \textit{H. pylori} infection was attributable to household crowding (Pacific 44\% and Māori 36\%). Pacific children particularly experience much greater exposure to severe household crowding in early childhood than European (RR 11.1, 95\%CI 10.6-11.5) (Baker et al., 2012b). However, factors other than household crowding density may also contribute to \textit{H. pylori} infection risk. Recent migration from the Pacific may be a contributor for Pacific seroprevalence. Many Pacific countries have high \textit{H. pylori} prevalence (Pandeya and Whiteman, 2011,
Watson et al., 1999, Nicholson et al., 1988). Other potential contributing socioeconomic factors (many of which overlap) for Pacific and Māori include rented homes, absence of hot water, bed sharing, large family size, single parent households, (Office of the Deputy Prime Minister London, 2004) and less than adequate consumption of fruit, vegetables and vitamin C, which appears to protect against infection with *H. pylori* (Brown, 2000).

The Pacific ethnic group comprises many different cultural backgrounds each with different exposures to household crowding. The proportion of children exposed to crowding ranges from 55% for Tongan, 45% for Samoan and 32% for Fijian peoples (2006 census) (Statistics New Zealand, 2012a). Reflecting these crowding differences, two NZ studies show Tongan seroprevalence was greater than Samoan seroprevalence (71% vs. 50% (Fraser et al., 1996), and 70% vs. 44% (Morris et al., 1986)). Pacific results in this analysis are based on an average for all Pacific peoples and do not account for the variation between groups.

**Mechanisms**

The contribution of household crowding to increased rates of *H. pylori* has a high degree of biological plausibility. Household crowding is expected to increase the number of contacts that household members have over a period of time and increase the risk of transmission per contact (Baker et al., 2013). In NZ, crowded households frequently consist of more than one family or a family plus other household members (Statistics New Zealand, 2012a). An additional adult in a household increases the chance that a household member has a chronic *H. pylori* infection and increases the risk that the infection is transmitted to a child in the household.

Crowding may also put greater strain on household hygiene measures. Exposure to gastroenteritis may contribute to *H. pylori* acquisition (Perry et al., 2006) through gastric-oral or faecal-oral spread. In a US study gastroenteritis was attributable for 75% of *H. pylori* acquisition (Perry et al., 2006). Gastroenteritis has also been found to be associated with household crowding (Baker et al., 2013) and it may be that
gastroenteritis and *H. pylori* infection are related due to common risk factors such as household crowding.

Household crowding may contribute to greater *H. pylori* seroprevalence through mechanisms other than simply acquisition. *H. pylori* seroprevalence tested in adulthood may not just be a measure of acquisition but may also indicate duration of infection, infection severity, the immune system’s ability to clear the infection and whether a person has had access to antibiotic treatment for other infectious diseases. Crowding may be associated with psychological stress (Evans, 2003) and increased competition for household resources such as adequate nutrition for growth (Montgomery et al., 1996) and immune function (Calder and Jackson, 2000). Crowded households may face increased barriers to accessing health care and antibiotics (Özen et al., 2006) such as the requirement to care for other siblings.

Furthermore, risk factors for *H. pylori* such as household crowding are likely to have an intergenerational effect that is not assessed here. A child is more likely to become infected if their parent has the infection, because most transmission occurs within families (Malaty, 2007). Historic differences in household crowding not measured here may also have contributed to excess *H. pylori* infection among Māori and Pacific peoples.
Ethnic trends in stomach cancer and the role of H. pylori

Māori and Pacific stomach cancer incidence was significantly greater than European/Other incidence, and this was substantial for non-cardia stomach cancer. H. pylori together with smoking was estimated to contribute to eight-tenths of the excess Pacific non-cardia stomach cancer incidence and more than half of excess Māori non-cardia stomach cancer incidence, compared to European/Other. These figures were consistent across cohorts.

Trends over time

The ethnic trends for stomach cancer were strikingly similar to the ethnic trends for H. pylori infection (Table 16). The decline in H. pylori infection among persons born in 1926-40 to persons born in 1971-85, is very similar to the decline in total NZ stomach cancer incidence between 1948 and 2008 (compare Figure 4 and Figure 14), supporting the idea that H. pylori plays an important role in the declining stomach cancer rates.

Environmental conditions are certainly more amenable to rapid change over time than genetic factors, and are therefore likely to be the major contributing factor to the decline in both stomach cancer and H. pylori infection in all ethnic groups. Declines are likely to reflect improvements in living standards such as improved housing quality and less household crowding. Neither the decline of H. pylori infection nor the decline in stomach cancer incidence in NZ is consistent (Howson et al., 1986) with a genetic influence, although gene-environment interactions are possible.

Ethnic differences

Ethnic differences in stomach cancer incidence were consistently present in all three birth cohorts and relative differences were greater in younger birth cohorts. Māori and Pacific stomach cancer incidence was approximately three times greater than European/Other in the 1926-40 cohort, four times greater in the 1941-55 cohort and more than five times greater in the younger 1956-70 cohort. Ethnic differences in
stomach cancer have already been documented in NZ (Blakely et al., 2010) however the trend over time has been more difficult to determine.

The trend of increasing relative differences in stomach cancer may be due to statistical chance, a true trend over time or the effect of age on relative ethnic differences. Māori and Pacific get stomach cancer at a younger age than European peoples and this may have contributed to greater relative differences in latter cohorts because these cohorts were restricted to younger adults.

A true trend of increasing relative ethnic differences in stomach cancer over time would reflect the trend seen in the pooled *H. pylori* seroprevalence data, with increases in relative ethnic differences over time. However more data are required to support this conclusion.

Statistical chance may have partially contributed to the apparent increase in relative differences. Figures in subsequent cohorts are less precise. Confidence intervals tended to overlap between adjacent cohorts and were particularly wide in the youngest cohort (1956-70) with the least stomach cancer cases and the least reliable data (30% had to be approximated from 20 year age groups and smoothed data).

**The *H. pylori* and smoking contribution**

It is commonly supposed that the high rates of stomach cancer among Māori are due to genetic factors (Blair et al., 2003) (Biggar et al., 2011) yet evidence for this perspective is not conclusive. Genetic-environment interaction cannot be ruled out by this data but we have demonstrated how more than half of the excess Māori non-cardia stomach cancer incidence among men can be explained by *H. pylori* and (to a lesser extent) smoking. For Pacific peoples, *H. pylori* and smoking explained eight-tenths of the increased stomach cancer risk, suggesting that a genetic predisposition is not necessary to explain the persistent ethnic differences in stomach cancer incidence.
Results can be applied to estimate the impact of reducing Māori and Pacific seroprevalence (and smoking) to the same as European levels. During the study period (1981-2004) for the three cohorts studied (born 1926-70), we would have expected 172 fewer non-cardia stomach cases among Māori men and 94 fewer non-cardia stomach cancer cases among Pacific men (Appendix 5).

**Remaining ethnic differences**

There are several overlapping factors which may contribute to the remaining ethnic differences in stomach cancer. The likely impact of diet on both *H. pylori* infection and stomach cancer has already been discussed. Salt, fruit and vegetable intake are significant risk factors for stomach cancer; however, there is little evidence that these are strongly associated with ethnicity in NZ adults either presently or in the past. Measurement bias from determining nutritional intake may have diluted estimates of the true differences between ethnic groups.

Other risk factors for stomach cancer shown in meta-analyses implicate pickled food (Ren et al., 2012), processed meat (Larsson et al., 2006) and heavy alcohol drinking (Tramacere et al., 2012). Neither of the latter two meta-analysis included studies which controlled for *H. pylori* status.

Protective factors may also contribute to the remaining ethnic differences in stomach cancer incidence, particularly if these factors are more prevalent in the European ethnic group and less prevalent in Māori or Pacific. Protective factors include soy-bean products and tofu (Tong et al., 2010), whole grains (Jacobs Jr et al., 1998) and the use of aspirin (randomised trials) (Rothwell et al., 2011).

While some of these factors may play a causal role in the aetiology of stomach cancer, there are problems with many studies that investigate them. Most importantly it is difficult to interpret meta-analysis results when the studies they include do not necessarily take into account potential confounding from *H. pylori* infection. Any study into risk factors for stomach cancer that does not adjust for *H. pylori* may be affected by
confounding bias. It may be difficult if not impossible (Tramacere et al., 2012) to adjust for *H. pylori* when most cases of stomach cancer have the infection. However studies restricted to participants who are *H. pylori* seropositive, will be able to estimate the independent effects of these other risk (and protective) factors.
Strengths and limitations

Broadly

This analysis is distinctive because it quantifies a two-step process from household crowding to *H. pylori* infection, and *H. pylori* infection to stomach cancer; and then distinguishes how this process differs by ethnicity. A combination of information sources enabled us to estimate the contribution of household crowding to Māori, Pacific and European *H. pylori* seroprevalence; and the contribution of *H. pylori* and smoking to ethnic differences in the incidence of stomach cancer in men. A birth cohort approach provides a platform that highlights the links between household crowding in early life, chronic *H. pylori* infection, sequelae of stomach cancer in adulthood and the ethnic differences in all three of these exposures and outcomes.

Strengths and weaknesses: meta-analysis of household crowding as a risk factor for *H. pylori* infection

To the author’s knowledge this is the first meta-analysis examining the association of household crowding with *H. pylori* and stomach cancer. The large number of eligible *H. pylori* studies allowed an important investigation into the reasons for differences between study results.

Individual study limitations and review level limitations are discussed in the Part A results section. Meta-analyses reliant on observational studies are considered low quality evidence for causality (Higgins and Green, 2011). Study quality, heterogeneity, incomplete retrieval and publication bias may have influenced results. Conclusions were strengthened however by a suggestion that improved study quality is associated with greater magnitude of association, heterogeneity is explained by some sub-group analyses and the narrative synthesis supports meta-analysis findings. Misclassification of past *H. pylori* infection may mean that meta-analysis has substantially underestimated the magnitude of the true association with household crowding density.
Strengths and weaknesses: comparing ethnic differences in seroprevalence and stomach cancer

This analysis is strengthened by bringing together a wealth of information sources that inform the best possible estimates for the contribution of *H. pylori* infection to excess Māori and Pacific stomach cancer incidence. Probabilistic bias analysis is underused in epidemiology and has allowed us to create a rigorous estimate for the mediating effect of smoking on the remaining ethnic differences in stomach cancer incidence. In this way we were able to incorporate systematic uncertainty from all the important input variables and maximise the accuracy of our best estimates.

The greatest limitation in this analysis was identifying accurate data on the prevalence of past *H. pylori* infection by age and ethnicity in NZ. *H. pylori* seroprevalence was a key input for calculating the contribution of *H. pylori* to ethnic differences in stomach cancer incidence. Ethnicity and stomach cancer incidence data were the most robust.

**Selection**

The generalizability of the seven pooled studies to the NZ population as a whole was limited because data was only available from two regions – the north and the south. However, regional bias was minimised by weighting the data according to each ethnic group’s geographical population distribution. It was an advantage to incorporate data from the two most contrasting regions.

Only three of seven studies included adequate numbers of all three ethnic groups and two of these included only participants born in 1971-85. We are interested in relative seroprevalence between ethnic groups but not all ethnic groups were present in every study. It was encouraging however that the studies which included three ethnic groups (all from the high seroprevalence North region) demonstrated substantial ethnic differences in *H. pylori* consistent with our overall estimates.
Measurement

This analysis depends on accurate measurement of several exposures and outcomes.

The data on stomach cancer incidence is perhaps the most rigorous, being sourced from a national population registry, linked to census data on ethnicity and age, and adjusted for linkage bias. The impact of adjustments to get cancer incidence rates in five-year age groups was mainly limited to the 1956-70 cohort.

Non-cardia cancer incidence however relied on subsite approximations (Biggar et al., 2011). Figures were not age-standardised and are from just one public hospital. Furthermore subsite approximations may be less accurate for the earliest cohorts because it appears ethnic differences in subsite have increased over time (Table 2) (reflecting the widening ethnic differences in H. pylori seroprevalence) (Stewart et al., 1982). However these proportions were our best estimates and substantially improved our analysis.

The precision of tests to detect past exposure to H. pylori infection is a particularly important source of potential bias. The sensitivity and the specificity of the seroprevalence test for detecting past infection is considered low. Our results are particularly sensitive to relative differences in seroprevalence by ethnicity (RRs). Misclassification of the H. pylori outcome is likely to underestimate the true RRs for Māori or Pacific vs. European seroprevalence, depending on the balance of the sensitivity and the specificity of the test. This bias means our analysis has likely underestimated the true contribution of H. pylori to excess Māori and Pacific non-cardia stomach cancer.

The ELISA test does not distinguish the length of exposure to chronic infection, the intensity of infection or the malignant potential of the sub-type of H. pylori acquired. This is unlikely to be important unless there is variation in these factors by ethnicity. For example, if H. pylori virulence is greater among European peoples (greater CagA proportion seroprevalence (Pérez-Pérez et al., 1997)) then we may have overestimated
the contribution of *H. pylori* infection to excess Māori and Pacific stomach cancer, or vice versa if other virulence factors are more prevalence for Māori and Pacific.

**Uncertainty and sensitivity analysis**

Incorporation of both the highest seroprevalence estimates and the lowest seroprevalence estimates in sensitivity analysis did not substantially change study results. When higher and then lower seroprevalence estimates were imputed, the contribution of *H. pylori* to excess Māori and Pacific stomach cancer remained approximately similar (up to 17% absolute difference).

The key assumption used in the analysis to calculate the contribution of *H. pylori* to ethnic differences is that the bacterium is a necessary factor for all stomach cancer. This assumption overestimates the contribution of *H. pylori* infection, because cardia cancer is included which is not associated with *H. pylori*. When analysis was more appropriately restricted to non-cardia stomach cancer incidence, *H. pylori* contributed less to the excess stomach cancer incidence. This is because ethnic differences in non-cardia stomach cancer incidence were greater than the ethnic differences for all stomach cancer. The excess stomach cancer incidence in Māori and Pacific is predominantly non-cardia stomach cancer.
**Implications**

The substantial contribution of *H. pylori* to stomach cancer in this analysis has important implications for practice, policy and research. It is encouraging that both *H. pylori* seroprevalence and stomach cancer incidence are declining in New Zealand, but concerning that relative ethnic differences in *H. pylori* infection appear to be increasing. Any increase in household crowding among children, particularly for Pacific and for Māori, has serious implications for the risk of *H. pylori* infection and future non-cardia stomach cancer. It is crucial that strategies taken to prevent stomach cancer are pro-equity.

There is a substantial time lag between *H. pylori* acquisition and non-cardia stomach cancer incidence. Current childhood household crowding is unlikely to impact stomach cancer incidence rates for at least thirty years, when the current population of children grow into adults of the susceptible age. Widening ethnic differences in childhood exposure to *H. pylori* in recent cohorts are particularly concerning for future ethnic differences in stomach cancer incidence. Widening differences are likely to exacerbate excess Māori and Pacific stomach cancer risk both in this decade and for many decades to come.

Results should inform the approach taken to reduce stomach cancer incidence in NZ, including whether interventions should focus on prevention of *H. pylori* acquisition, or screening and treating for infection that has already been acquired. There are advantages and disadvantages for each approach.

**Preventing acquisition of *H. pylori* infection**

The most effective intervention to prevent *H. pylori* acquisition and chronic infection may well be to focus on this infection’s association with household crowding density. The Asia-Pacific Guidelines suggest that eliminating *H. pylori* infection through improvements in public health will have the greatest impact in reducing the burden of stomach cancer for areas with high prevalence of both *H. pylori* infection and stomach cancer (Fock et al., 2009).
A broad approach that aims to prevent close-contact infection by reducing household crowding and improving socioeconomic living conditions should focus on children. Crowding in this study refers to crowding density that is measures of people per number of rooms. A well conducted household crowding reduction programme is expected to produce long-term benefits with reduced *H. pylori* acquisition and non-cardia stomach cancer, along with reductions in many other acute and chronic conditions associated with household crowding. Improved living standards are expected to both reduce *H. pylori* transmission and reduce the reservoir of infection (Goh et al., 2011).

Policies to improve housing affordability are also suggested in order to reduce household crowding in NZ. This includes increasing the number and proportion of social and affordable houses and their proportion of the housing stock, improving accessibility to social and affordable housing for all ethnic groups, and ensuring housing subsidies and supplements are available for low income households with the most need, particularly large families with children. Crowding reduction policies are likely to involve large upfront costs and substantial benefits over both the short- and the long-term. Negative impacts on health are unlikely.

The Housing NZ Corporation (HNZC) Healthy Housing Programme included crowding reduction as one of its specific goals. The programme involved house modifications to reduce overcrowding, insulation and ventilation improvements, and health and social service assessments, referrals and linkages (Jackson et al., 2011). Evaluations of the programme show that it has been highly successful at reducing hospitalisations in children, with suggestive evidence of a reduction in close-contact infectious diseases (Jackson et al., 2011, Baker et al., 2011). Inclusion of links to health and social services are important for health (e.g. for treatment of gastric symptoms or access to contraceptive choices). Barriers to accessing primary health care are likely to be greatest among the most disadvantaged population and should be addressed (Campbell et al., 2006).
**Equity**

Household crowding reduction is likely to have an important impact on reducing excess Māori and Pacific *H. pylori* acquisition because household crowding contributes substantially to infection in these groups. Conversely, the highly targeted nature of crowding reduction increases the risk that some disadvantaged households will miss out. A significant investment is required to ensure that the housing needs of all families are met.

**Treatment approach**

An alternative approach to prevent stomach cancer and reduce ethnic differences is to treat *H. pylori* infection in adults. The scope of this approach ranges from the status quo where we ‘test and treat’ only symptomatic patients; to a ‘screen and treat’ approach where we effectively screen the whole adult population or those groups at greatest risk.

**Current approach**

Historically the treatment of *H. pylori* has focussed on patients with gastric symptoms. Eradication treatment was first used for patients with peptic ulcer disease and it was not until the last fifteen years that treatment has been extended to patients presenting with dyspepsia in general practice (Fraser, 2004). NZ guidelines (2004) recommend testing (e.g. faecal antigen test) and treating *H. pylori* for persons who have dyspepsia and one of the following risk factors: originate from areas of high seroprevalence (>30%), persons with present or past history of peptic ulcer, with lymphoid tissue lymphoma or with a family history of stomach cancer (New Zealand Guidelines Group, 2004). There is little (or no) data on implementation of these guidelines, and retesting after eradication treatment is done infrequently.

The main problem with the current approach is that testing for *H. pylori* is opportunistic and confined to those who seek medical input for stomach complaints. This approach does not appear to be well focussed on the groups at highest risk of *H. pylori* infection, the same groups who face the greatest barriers to primary care. Only 20% of patients with *H. pylori* are likely to have gastric symptoms and it is possible that for the most
disadvantaged socioeconomic groups a smaller proportion will actually present to a clinician. Improvements in this scenario may occur if investments in primary care can provide wide spread access for Māori and Pacific (Tan et al., 2012).

**Evidence for effectiveness**

A recently updated meta-analysis studied the effectiveness of the ‘test and treat’ approach. *H. pylori* positive patients who were treated with eradication therapy had diagnoses ranging from superficial gastritis to dysplasia, with most having either gastric atrophy or intestinal metaplasia. The risk of neoplastic changes after eradication therapy was less (OR 0.65, CI: 0.43-0.98, n=6 RCTs), (Fuccio, 2012). Most trials were carried out in Asia where stomach cancer incidence is high. The median age of participants was 42-51 years old. The meta-analysis does not discuss the risk of oesophageal cancer or other harms from eradication treatment. The ‘test and treat’ approach may be effective in the context of the studies even among patients with mucosa changes. It is similar to what is used in NZ for symptomatic persons but evidence is limited particularly when applied to the New Zealand context.

One of the more recent trials included in the above meta-analysis, from a high risk region of China, investigated eradication treatment effectiveness in two sub-groups of patients (post-hoc analysis) - those with no precancerous lesions and those with lesions (gastric atrophy, intestinal metaplasia, or dysplasia) (Wong et al., 2004). Eradication treatment was more effective at preventing stomach cancer (in the 7.5 years of follow-up) for participants with no precancerous lesions on presentation (no cases among those treated and 6 cases among those on placebo, p=0.02). After offering first-line treatment and second-line treatment where required, the eradication rate in the treatment group was 83.7%. The trial supports the theory that there is a ‘point of no return’ and that *H. pylori* eradication is most beneficial before intestinal metaplasia changes are detectable (Wright, 1998) however in diffuse-type stomach cancer metaplastic changes are not required. More trial evidence is required to validate the results of the post hoc analysis in this trial.
The problem with trials of *H. pylori* eradication for the prevention of stomach cancer is that carcinogenesis is a long process and requires decades to follow-up (de Martel et al., 2013). There is also concern that the ‘point of no return’ may make it difficult to treat *H. pylori* early enough to prevent stomach cancer (de Martel et al., 2013).

**The alternative approach**

Asia-Pacific guidelines (Fock et al., 2008) (Fock et al., 2009) now recommend a risk reduction strategy for stomach cancer in populations with high *H. pylori* prevalence, where asymptomatic persons are screened and treated for *H. pylori*. The long-term risk reduction, and health and economic benefits of this approach require further study (Fock et al., 2009) however, even in a country with relatively low prevalence of gastric cancer (Canada), modelling suggests that a ‘screen and treat’ approach may be cost-effective at a level even greater than that of breast cancer and cervical cancer screening (Richard Hunt et al., 2004).

A more comprehensive approach to screening and treating high risk groups within NZ is likely to be particularly beneficial for reducing excess Māori and Pacific non-cardia stomach cancer. The highest risk groups include Māori and Pacific men living in the regions with the greatest household crowding. Any ‘screen and treat’ strategy is likely to have a long term impact on future generations with reduction in the reservoir of infection.

The advantage of the ‘screen and treat’ approach is that stomach cancer can be prevented for persons already at a susceptible age who can no longer benefit from childhood crowding reduction interventions. More evidence is required to evaluate the magnitude of likely effectiveness in NZ populations and the risk of potential harms (such as antibiotic resistance or oesophageal cancer). Risk of oesophageal cancer after eradication treatment has not been demonstrated and even if this was a causal association it would be far out-weighed by the number of stomach cancer cases prevented.
**Equity**

There may be a concern that implementing *H. pylori* screening for asymptomatic populations would exacerbate ethnic differences. This would be the case if disadvantaged groups were less likely to receive the screening test (e.g. faecal antigen test), fill the prescription or take the treatment. Targeting the ‘screen and treat’ approach to high risk populations or regions may improve equity and better prioritise resources to the populations with the highest risk of non-cardia stomach cancer.

**Further research**

Further research is required to evaluate crowding reduction interventions and ‘screen and treat’ approaches in high risk populations.

Intervention studies are required to determine if the findings consistently found here in observational studies, truly represent causality between household crowding in childhood and *H. pylori*. Randomised staggered interventions of crowding reduction interventions (plus or minus other measures) would provide the most robust form of evidence. NZ is well positioned to conduct such research and investigate outcomes not just for *H. pylori* infection and stomach cancer but for a host of other socioeconomically related close-contact infectious diseases and other health outcomes.

Two key factors could have substantially improved the precision of this analysis. Firstly, a more sensitive measure of past *H. pylori* infection is required which improves on the ELISA serology test. This would reduce misclassification bias and contribute to better understanding the true extent of the necessary causal factor proposition, and the true magnitude of the association between *H. pylori* infection and its risk factors, such as household crowding and ethnicity. For cervical cancer, it was not until application of improved detection techniques, including PCR and liquid-phase, immunocaptured hybridization, that HPV was able to be detected in 95-100% of adequate specimens of cervical cancer (Franco et al., 1999), thus supporting the claim that HPV is a necessary cause of cervical cancer.
Secondly, classification of stomach cancer by subsite should be improved. Cardia and non-cardia cancer are two pathological entities with different risk factor profiles and care should be taken to update registration data on which cancer is present wherever possible. In this way, clearer information will be available for trends in cancer incidence over time and the contribution of various risk factors such as \textit{H. pylori} infection.
Chapter 7: Conclusion

This analysis is distinctive because it quantifies a two-step process from household crowding to *H. pylori* infection, and *H. pylori* infection to stomach cancer; and then distinguishes how this process differs by ethnicity in NZ. Results are consistent with the view that household crowding is one of the key risk factors for *H. pylori* infection, and *H. pylori* is the major contributor to excess Māori and Pacific stomach cancer incidence among men in NZ. Children exposed to greater vs. less household crowding were more than twice as likely to be infected with *H. pylori*. *H. pylori* seroprevalence appears to be declining across all ethnic groups; however ethnic differences in subsequent birth cohorts have increased in relative terms. *H. pylori* and smoking (to a lesser extent) explained more than half of the excess non-cardia stomach cancer among Māori and eight-tenths of the excess non-cardia stomach cancer among Pacific.

It is therefore crucial that interventions to reduce stomach cancer take a pro-equity approach. Household crowding reduction programmes are recommended which address the greater risk of household crowding among Māori and Pacific children. A substantial investment is required to reach all families facing household crowding, and the impact is likely to be substantial in the long-term.

To benefit adults who might already be infected with *H. pylori*, a ‘screen and treat’ approach for asymptomatic persons in high risk populations should be evaluated, particularly for Pacific and Māori adults in NZ. The aim would be to identify active infection and treat it with a short course of antibiotics before damage to the stomach mucosa ensues. This approach is likely to be particularly cost-effective.

Crowding reduction and ‘screen and treat’ programmes should be evaluated in NZ. Research would benefit from wider application of more sensitive tests of past *H. pylori* infection and better classification of stomach cancer incidence by cardia and non-cardia subsites.
References


CPRONLINE. 2013. *Overcrowded Households: Private Occupied Dwellings>*


MOHER, D., PHAM, B., LAWSON, M. & KLASSEN, T. 2003. The inclusion of reports of randomised trials published in languages other than English in systematic reviews, Core Research.


PRODUCTIVITY COMMISSION 2012. Housing affordability inquiry.


an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for H pylori infection. *Can J Gastroenterol*, 18, 547.


### Appendix 1: Search strategies for Systematic Literature review

<table>
<thead>
<tr>
<th>Embase search 9th July 2012</th>
<th>Outcome: <em>H. pylori</em> infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Embase search 9th July 2012</strong></td>
<td><strong>Outcome: <em>H. pylori</em> infection</strong></td>
</tr>
<tr>
<td>Exposure Crowding</td>
<td>MeSH</td>
</tr>
<tr>
<td><strong>Crowding/</strong></td>
<td><strong>exp Communicable Diseases/ or exp bacterial infection/ or helicobacter infection/</strong></td>
</tr>
<tr>
<td>*<em>Or bed sharing/</em></td>
<td>Keywords</td>
</tr>
<tr>
<td><strong>Keywords</strong></td>
<td><strong>Keywords</strong></td>
</tr>
<tr>
<td><strong>or crowd</strong></td>
<td><strong>helicobacter</strong></td>
</tr>
<tr>
<td><strong>or overcrowd</strong></td>
<td><strong>or overcrowd</strong></td>
</tr>
<tr>
<td><strong>or per room</strong></td>
<td><strong>or per room</strong></td>
</tr>
<tr>
<td><em><em>or ((People or person or persons or child</em> or adult or adults or resident or residents or member</em>) adj3 (room* or bed* or area or m2 or square meter* or square metre* or ft2 or square feet*))**</td>
<td><em><em>or ((People or person or persons or child</em> or adult or adults or resident or residents or member</em>) adj3 (room* or bed* or area or m2 or square meter* or square metre* or ft2 or square feet*))**</td>
</tr>
<tr>
<td><em><em>or ((bed</em> or room</em>) adj3 (sharing or share))**</td>
<td><em><em>or ((bed</em> or room</em>) adj3 (sharing or share))**</td>
</tr>
<tr>
<td><em><em>or ((hous</em> or home) adj3 (area or m2 or square meter</em> or square metre* or ft2 or square feet* or size or density))**</td>
<td><em><em>or ((hous</em> or home) adj3 (area or m2 or square meter</em> or square metre* or ft2 or square feet* or size or density))**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Embase search 14th March 2013:</th>
<th>Outcome: Stomach cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure Crowding</td>
<td>MeSH</td>
</tr>
<tr>
<td><strong>Crowding/</strong></td>
<td><strong>stomach cancer/ or stomach carcinoma/</strong></td>
</tr>
<tr>
<td>*<em>Or bed sharing/</em></td>
<td>Keywords</td>
</tr>
<tr>
<td><strong>Keywords</strong></td>
<td><strong>Keywords</strong></td>
</tr>
<tr>
<td><strong>or crowd</strong></td>
<td><strong>((carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or cyst$ or growth$ or adenocarcin$ or malig$) adj3 (Intestin$ or Digest$ or Gastr$ or gut or epigastr$ or stomach$))</strong></td>
</tr>
<tr>
<td><strong>or overcrowd</strong></td>
<td><strong>or overcrowd</strong></td>
</tr>
<tr>
<td><strong>or per room</strong></td>
<td><strong>or per room</strong></td>
</tr>
<tr>
<td><em><em>or ((People or person or persons or child</em> or adult or adults or resident or residents or member</em>) adj3 (room* or bed* or area or m2 or square meter* or square metre* or ft2 or square feet*))**</td>
<td><em><em>or ((People or person or persons or child</em> or adult or adults or resident or residents or member</em>) adj3 (room* or bed* or area or m2 or square meter* or square metre* or ft2 or square feet*))**</td>
</tr>
<tr>
<td><em><em>or ((bed</em> or room</em>) adj3 (sharing or share))**</td>
<td><em><em>or ((bed</em> or room</em>) adj3 (sharing or share))**</td>
</tr>
<tr>
<td><em><em>or ((hous</em> or home) adj3 (area or m2 or square meter</em> or square metre* or ft2 or square feet*))**</td>
<td><em><em>or ((hous</em> or home) adj3 (area or m2 or square meter</em> or square metre* or ft2 or square feet*))**</td>
</tr>
<tr>
<td>SCOPUS search: 14&lt;sup&gt;th&lt;/sup&gt; March 2013</td>
<td>Outcome: <em>H. pylori</em></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Exposure: Crowding</td>
<td><strong>ABS</strong> (crowd* or overcrowd* or ((People or person or persons or child* or adult or adults or resident or residents or member*) W/3 (room* or bed* or area or m2 or &quot;square meter&quot;* or &quot;square metre&quot;* or ft2 or &quot;square feet&quot;<em>)) or &quot;per room&quot; or ((bed</em> or room*) W/3 (sharing or share)) or ((hou* or home) W/3 (area or m2 or &quot;square meter&quot;* or &quot;square metre&quot;* or ft2 or &quot;square feet&quot;* or size or density)) )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCOPUS search: 9&lt;sup&gt;th&lt;/sup&gt; July</th>
<th>Outcome: Stomach cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure: Crowding</td>
<td><strong>ABS</strong> (crowd* or overcrowd* or ((People or person or persons or child* or adult or adults or resident or residents or member*) W/3 (room* or bed* or area or m2 or &quot;square meter&quot;* or &quot;square metre&quot;* or ft2 or &quot;square feet&quot;<em>)) or &quot;per room&quot; or ((bed</em> or room*) W/3 (sharing or share)) or ((hou* or home) W/3 (area or m2 or &quot;square meter&quot;* or &quot;square metre&quot;* or ft2 or &quot;square feet&quot;* or size or density)) )</td>
</tr>
</tbody>
</table>

**OR**

TITLE (crowd* or overcrowd* or ((People or person or persons or child* or adult or adults or resident or residents or member*) W/3 (room* or bed* or area or m2 or "square meter"* or "square metre"* or ft2 or "square feet"*)) or "per room" or ((bed* or room*) W/3 (sharing or share)) or ((hou* or home) W/3 (area or m2 or "square meter"* or "square metre"* or ft2 or "square feet"* or size or density)) )

**OR**

TITLE (Communicable or infection* or infectious or microorgan* or micro-organis* or bacteria* or helicobacter)
**WEB OF SCIENCE/COCHRANE search 9th July**

**Exposure: Crowding**

**TS = (crowd* or overcrowd* or ((People or person or persons or child* or adult or adults or resident or residents or member*) NEAR/3 (room* or bed* or area or m2 or “square meter**” or “square metre**” or ft2 or “square feet**”)) or "per room" or ((bed* or room*) NEAR/3 (sharing or share)) or ((hous* or home) NEAR/3 (area or m2 or “square meter**” or “square metre**” or ft2 or “square feet**” or size or density)) )

**B Outcome: H. pylori**

TS=(Communicable or infection* or infectious or microorgan* or micro-organis* or bacteria* or virus or viral or parasit* or fungi or fungal or fungus or mould* or mycoses or helminth or Mening* or encephalitis or sepsis or tuberculosis or “rheumatic fever” or Haemophilus or pneumonia or otitis or “respiratory syncytial virus” or bronchiolitis or bronchitis or “respiratory tract infection” or gastroenteritis or diarrhea or vomiting or gastritis or helicobacter or “skin infect*” or cellulitis or conjunctivitis or Hepatitis or “Pediculosis capitis” or “head lice” or rotavirus or Influenza or Staphylococc* or Streptococc* or Pneumococc*) 2.5m

**WEB OF SCIENCE/COCHRANE search 9th July**

**Exposure: Crowding**

**TS = (crowd* or overcrowd* or ((People or person or persons or child* or adult or adults or resident or residents or member*) NEAR/3 (room* or bed* or area or m2 or “square meter**” or “square metre**” or ft2 or “square feet**”)) or "per room" or ((bed* or room*) NEAR/3 (sharing or share)) or ((hous* or home) NEAR/3 (area or m2 or “square meter**” or “square metre**” or ft2 or “square feet**” or size or density)) )

**B Outcome: Stomach cancer**

TS=((carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malig*) NEAR/3 (Intestin* or Digest* or Gastr* or gut or epigastr* or stomach*))
Appendix 2: Newcastle Ottawa Scale Adaption

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT/CROSS-SECTIONAL STUDIES

Selection
1) Representativeness of the exposed cohort
   a) truly representative of the population at risk ★
   b) somewhat representative of the population at risk ★
   c) selected group of users e.g. only certain socio-economic groups/areas
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort ★
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (e.g. health care records) ★
   b) structured interview/questionnaire ★
   c) written self-report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ★
   b) no

Comparability
5) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for age and socioeconomic status (income, occupation, housing, education) ★
   b) smoking or additional ses variables were adjusted for ★

Outcome
6) Assessment of outcome
   a) independent blind assessment (lab diagnosis) ★
   b) record linkage ★
   c) self-report, symptoms only
   d) no description

7) Was follow-up long enough for outcomes to occur
   a) yes adequate follow up period for outcome of interest e.g. >= 6 months ★
   b) no (e.g. cross-sectional study)

8) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ★
   b) subjects lost to follow up unlikely to introduce bias - small number lost - <=20% to follow up, or description provided of those lost) ★
   c) follow up rate < 80% (select an adequate %) and no description of those lost
   d) no statement

9) All results are reported
a) relevant crowding & infectious disease associations are reported as intended in study design

b) some variables, categories or subcategories not reported on
Appendix 3: Table illustrating more detailed information about included studies

<table>
<thead>
<tr>
<th>Year of study and id</th>
<th>Study sample</th>
<th>Serology test</th>
<th>Seroprevalence with age and ethnicity stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1985</strong> (Morris et al., 1986)</td>
<td>n=483 15-60yo, b 1925-70 Blood donors sample with known ethnicity from the Blood Transfusion Centre, Auckland</td>
<td>Enzyme-linked immunosorbent assay using pooled whole organism antigen from 14 C pyloridis isolates, the Marshall strain and C pyloridis type organism (NCTC 11637). Cut-off absorbance selected as 3.5.</td>
<td>Overall 185/564 (33%) Māori 41/192 (21%) [Pacific 129/270 (48%)]: Cook Island 33/85 (39%), Samoan 57/129 (44%), Tongan 39/56 (70%) Unknown ethnicity 15/102 (15%) - no European group specified</td>
</tr>
<tr>
<td><strong>1988-1990</strong> (Scragg et al., 1996)</td>
<td>n=579 40-64yo, b 1926-50 Randomly selected sample from worksites in Auckland and Tokoroa (Fraser et al., 2010)</td>
<td>H. pylori antibody response by enzyme immunoassay (Roche Diagnostics).</td>
<td>Overall 56% European 35.8% Māori 57.4% Pacific Island 73.2% 40-49 yo (b 1940-1949) 48.0% 50-64 yo (b 1926-1939) 63.4%</td>
</tr>
<tr>
<td><strong>1988-1990</strong> (Fraser et al., 1996)</td>
<td>n=324 11-12yo, b 1976-79 Three schools selected from South Auckland with a high proportion of Māori and Pacific students. Only 6% of students were European.</td>
<td>Enzyme immunoassay (Roche Diagnostics)</td>
<td>Overall 33.6% European 7%, (4/1) Māori/part Māori 21% (102) Cook Is 41% (9/22), Samoan 50% (49/98), Tongan 71% (10/14), Nuiean 26% (5/19), [Pacific Island 48% (73/153)] Compared with Europeans the increased relative risk of seropositivity for H.pylori in Māori and Pacific Island participants was significant after adjusting for age and socio-economic status (1.43 [1.13, 1.80] and 1.76 [1.43, 2.18] respectively.</td>
</tr>
<tr>
<td><strong>1997-1998</strong> (Fraser et al., 2010)</td>
<td>n=792 16yo mean, b 1979-83 Year 11-13 female students</td>
<td>Enzyme immunoassay using commercially available kits</td>
<td>Overall 278/792 = 35.1% European (14%; CI 6–21) Māori (27%; CI 17–36)</td>
</tr>
</tbody>
</table>
From seven schools in Auckland with >15% Pacific pupils (decile 1-3) - low socioeconomic status study population

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Details</th>
<th>Sample Details</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986-Feb 1988</td>
<td>Auckland, random sample from electoral role – frequency matched to cases which had had an MI. Māori and Pacific were excluded.</td>
<td>n=831, 35-64yo</td>
<td>In 1997, serum antibodies measured using the Premier enzyme-linked immunosorbent assay (ELISA) test (Meridian Scientific, Cincinnati, OH, USA). Cut-off according to the manufacturer’s recommendation.</td>
<td>35-44yo: 21.0%</td>
</tr>
<tr>
<td>1986-Feb 1988</td>
<td>Dunedin Multidisciplinary Health and Development Study (DMHDS) (Fawcett et al., 1998)</td>
<td>n=561, b 1972-73</td>
<td>Commercially available second generation anti-(H. pylori) (IgG) enzyme immunoassay (CobasB Core Anti-(H. pylori) EIA; Roche Diagnostic Systems, Auckland, New Zealand)</td>
<td>11yo: 6.6% - 37/561</td>
</tr>
<tr>
<td>1998-1999 DMHDS (Fawcett et al., 2005)</td>
<td>n = 871, 26yo, b 1972-73</td>
<td>Two tests used: Cobas® Switzerland[11] Core Anti-(H. pylori) EIA (Roche SA, Basel, and the (H. pylori) DTect ELISA (Diagnostic Technology, Australia))</td>
<td>26yo: 6.3%</td>
<td>Not stratified by ethnicity.</td>
</tr>
<tr>
<td>1996 (Collett et al., 1999)</td>
<td>Random sample from the</td>
<td>Roche method using Cobas Core anti-(H. pylori) EIA KITSET (Hoffmann-La Roche</td>
<td>Overall: 24%</td>
<td>NZ European 22% - 217/984</td>
</tr>
</tbody>
</table>

\(H. pylori\) infection was associated with iron deficiency.
<table>
<thead>
<tr>
<th>Christchurch electoral roll AG, Basel, Switzerland</th>
<th>Māori 35% - 8/23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainly European population</td>
<td>Polynesian 38% - 3/8</td>
</tr>
<tr>
<td></td>
<td>Asian 40% - 2/5</td>
</tr>
<tr>
<td></td>
<td>Other 40% - 2/5</td>
</tr>
<tr>
<td></td>
<td>[Non-European 48.7% (OR 4.46 adj for income, smoking, age – all signf)]</td>
</tr>
</tbody>
</table>

Summary of eight articles measuring *H. pylori* seroprevalence in seven New Zealand studies
### Appendix 4: Table of the characteristics of other stomach cancer risk factors

<table>
<thead>
<tr>
<th>Risk factors (male adults)</th>
<th>Ever smoking vs. never Smoking</th>
<th>Fruit and vegetable intake 5+ vs. &lt;5 per day</th>
<th>Sodium &gt; 2300mgs vs. ≤2300mgs per day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk of stomach cancer (irrespective of H. pylori status)</strong></td>
<td>RR <strong>1.62</strong> (1.50-1.75) males (Ladeiras-Lopes et al., 2008)</td>
<td>RR <strong>0.85</strong>, Cohort: 15% decreased risk per 50 g total vegetables/day (n=10, ccs n=45) *3 recommended</td>
<td>RR <strong>1.18</strong> per g sodium a day (n=21) (World Cancer Research Fund and American Institute for Cancer Research, 2007)</td>
</tr>
<tr>
<td></td>
<td>RR <strong>1.44</strong> (1.17–1.78), males (Trédaniel et al., 1998)</td>
<td><strong>RR 0.83</strong>, CCS: 17 per cent decreased risk per 50 g fruits per day (n=51) *2 recommended (World Cancer Research Fund and American Institute for Cancer Research, 2007)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR 1.36 (1.15-1.60) NZ (adj age, ethn, ses) (Dockerty et al., 1991)</td>
<td><strong>RR 0.82</strong> (0.73-0.93, n=13) highest vs. lowest fruit (=1.22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>RR 0.88</strong> (0.69–1.13, n=8) highest vs. lowest vegetables (=1.14) (Lunet et al., 2005)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Risk of stomach cancer in H. pylori seropositive | Suggestive positive interaction, possibly multiplicative (González and López-Carrillo, 2010) | Potential protective effect of dietary antioxidants such as vitamins C and E and β-carotene seems to be stronger in those infected by H. pylori (González and López-Carrillo, 2010) | Asian populations: subjects infected by H. pylori and with high dietary salt intake may have a higher risk of GC than subjects without H. pylori infection and with a low salt intake. (González and López-Carrillo, 2010) |

| Prevalence by ethnicity in New Zealand | Vast differences in smoking prevalence between ethnic groups (Hill et al., 2003) | Māori MALES 2008/09 age-std: 3+ vege: 51.8(45.58.5)%, RR 0.90 cf. non-Māori n.s. 2+ fruit: Māori 50.4(43.9-56.9)%, RR 0.94 cf. non-Māori n.s. (Ministry of Health, 2012c) Pacific MALES 2008/09 age-std: 3+ vege: 40.9(34.4-47.4)%, RR 0.68 cf. non-Pacific **p<0.05** 2+ fruit: Pacific 54.3(47.5-61.1)%, RR 1.02 cf. non-Pacific n.s. (Ministry of Health, 2012d) No difference by prioritised ethnicity or level of deprivation in 2008/2009 [But differences by age and sex] (McLean, 2011b) (McLean, 2011a) Spot urines used to calculate 24-hour urinary sodium excretion to get g/day in 15+ yo n = 3315 Mean 3544mg/day by spot urine equivalent to 8.9g salt excreted a day and 9.8g intake | |

*Risk factors for stomach cancer, the effect of the presence of H. pylori on the association and whether the prevalence of the risk factor varies by ethnicity in New Zealand*
Appendix 5: Population attributable fraction calculations for all stomach cancer and restricted to non-cardia stomach cancer

<table>
<thead>
<tr>
<th>A</th>
<th>Outcome, birth cohort, and age</th>
<th>B</th>
<th>Ethnicity</th>
<th>C</th>
<th>Standardised incidence rate of stomach cancer (per 100,000)</th>
<th>D</th>
<th>RR_{HP+smok} of stomach cancer adjusted for H. pylori* &amp; smoking (95% U.I.)</th>
<th>E</th>
<th>Incidence rate of stomach cancer if Euro seroprevalence (per 100,000)</th>
<th>F</th>
<th>PAR incidence rate of stomach cancer attributable to H. pylori &amp; smoking (per 100,000)</th>
<th>G</th>
<th>PAF % = (C-E)/C</th>
<th>H</th>
<th>Estimated cases that could be prevented if H. pylori &amp; smoking was at European levels = F x PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stomach cancer 1926-40 (40-79yo)</td>
<td>European/Other</td>
<td>20.8</td>
<td>1</td>
<td>20.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>57.4</td>
<td>1.60 (1.39 - 1.85)</td>
<td>33.3</td>
<td>24.1</td>
<td>42%</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>64.6</td>
<td>1.26 (1.00 - 1.57)</td>
<td>26.2</td>
<td>38.4</td>
<td>59%</td>
<td>52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stomach cancer 1941-55</td>
<td>European/Other</td>
<td>4.1</td>
<td>1</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>15.6</td>
<td>1.73 (1.39 - 2.13)</td>
<td>7.1</td>
<td>8.6</td>
<td>55%</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>17.5</td>
<td>1.21 (0.90 - 1.61)</td>
<td>4.9</td>
<td>12.6</td>
<td>72%</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stomach cancer 1956-70</td>
<td>European/Other</td>
<td>1.2</td>
<td>1</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>7.1</td>
<td>2.62 (1.74 - 3.87)</td>
<td>3.1</td>
<td>4.0</td>
<td>56%</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>6.2</td>
<td>1.06 (0.61 - 1.85)</td>
<td>1.3</td>
<td>5.0</td>
<td>80%</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardia stomach cancer 1926-40 (40-79yo)</td>
<td>European/Other</td>
<td>10.6</td>
<td>1</td>
<td>10.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>49.9</td>
<td>2.73 (2.32 - 3.18)</td>
<td>28.9</td>
<td>21.0</td>
<td>42%</td>
<td>87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>56.8</td>
<td>2.14 (1.72 - 2.77)</td>
<td>22.7</td>
<td>34.1</td>
<td>60%</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardia stomach cancer 1941-55</td>
<td>European/Other</td>
<td>2.1</td>
<td>1</td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>13.6</td>
<td>2.96 (2.28 - 3.75)</td>
<td>6.2</td>
<td>7.4</td>
<td>55%</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>15.4</td>
<td>2.08 (1.48 - 2.85)</td>
<td>4.3</td>
<td>11.1</td>
<td>72%</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardia stomach cancer 1956-70</td>
<td>European/Other</td>
<td>0.6</td>
<td>1</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Māori</td>
<td>6.2</td>
<td>4.38 (2.72 - 7.17)</td>
<td>2.7</td>
<td>3.5</td>
<td>57%</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pacific</td>
<td>5.5</td>
<td>1.78 (0.89 - 3.34)</td>
<td>1.1</td>
<td>4.4</td>
<td>80%</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TOTAL Māori: 172, Pacific: 94