Helicobacter pylori colonization and obesity – a Mendelian randomization study

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Obesity is associated with substantial morbidity, costs, and decreased life expectancy, and continues to rise worldwide. While etiological understanding is needed for prevention, epidemiological studies indicated that colonization with *Helicobacter pylori* (H. pylori) may affect body mass index (BMI), but with inconsistent results. Here, we examine the relationship between *H. pylori* colonization and BMI/obesity. Cross-sectional analyses were performed in two independent population-based cohorts of elderly from the Netherlands and Germany (n = 13,044). Genetic risk scores were conducted based on genetic loci associated with either *H. pylori* colonization or BMI/obesity. We performed a bi-directional Mendelian randomization. Meta-analysis of cross-sectional data revealed no association between anti-*H. pylori* IgG titer and BMI, nor of *H. pylori* positivity and BMI. Anti-*H. pylori* IgG titer was negatively associated with obesity (OR 0.99972; 95% CI 0.99946-0.99997, p = 0.03) and with obesity classes (Beta = −6.91 • 10⁻⁶; 95% CI −1.38•10⁻⁵, −5.49•10⁻⁶, p = 0.048), but the magnitude of these effects was limited. Mendelian randomization showed no causal relation between *H. pylori* genetic risk score and BMI/obesity, nor between BMI or obesity genetic risk scores and *H. pylori* positivity. This study provides no evidence for a clinically relevant association between *H. pylori* and BMI/obesity.

The prevalence of obesity rises worldwide. This is associated with significant morbidity, costs, and decreased life expectancy. The latter can be reduced with 8-13 years¹, which results in a huge economic burden². The causes of obesity are diverse and include excessive energy intake, lack of physical activity, but also culprits such as stress, lack of sleep, or exposure to chemical endocrine disruptors³. There is increasing evidence from mouse as well as human studies that shows that the gut microbiome may play an important role in energy balance⁴. Modern lifestyle, and the widespread use of antibiotics may affect the composition of our microbiome, which may have consequences for our health⁵.

In this context, *Helicobacter pylori* (H. pylori), is of relevance. This Gram-negative, spiral-shaped, gastric bacterium is gradually disappearing in Western populations⁶. *H. pylori* colonization is virtually always associated with chronic active gastritis, which can have various effects. This includes interference with gastric hormone regulation, including ghrelin and leptin. Both have multiple roles in energy homeostasis⁷. Disturbance of their normal regulation interferes with metabolism and our energy household. *H. pylori* eradication increases serum ghrelin levels⁸.

For these reasons, several epidemiological studies have focused on the correlation between *H. pylori* colonization and BMI and obesity. They showed contrasting results, which were based on *H. pylori* status and BMI data.

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but did not include genetic information. A recent genome-wide association study (GWAS) identified two genetic loci associated with anti-\(H.\) \(pylori\) IgG titer\(^6\). Numerous GWAS have identified many genetic loci associated with BMI variation and/or obesity risk\(^9\). Combining these results into risk scores enables a Mendelian randomization (MR) technique that aims at unbiased detection of causal effects\(^10\).

We aimed to assess the relationship between \(H.\) \(pylori\) seroprevalence and obesity using both epidemiological and genetic data of two population-based cohort studies. Results of cross-sectional and genetic analyses were compared. In addition, we performed a meta-analysis of data derived from both cohorts.

### Results

#### Baseline characteristics.

In total, 13,044 participants were initially included in this study. Table 1 summarizes the baseline characteristics of each cohort. In 220 subjects (1.7%) no data on BMI was available. Data on \(H.\) \(pylori\) titer was lacking in 252 individuals (1.9%) of SHIP. The total population included in the cross-sectional analyses consisted of 12,572 (96.4%) subjects. According to the predefined phenotypic seroprevalence, a total of 3,147 (25.0%) subjects were considered as cases, and 9,425 (75%) as controls.

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| Cohort | RS-I and RS-II | SHIP | SHIP-TREND |
|--------|----------------|------|-------------|
| Total number (n) | 7,977 | 4,081 | 986 |
| Age (years), mean (sd) | 69.0 (9.3) | 49.7 (16.3) | 50.1 (13.7) |
| Female sex (%) | 4,391 (55.0) | 2,073 (50.8) | 554 (56.2) |
| \(H.\) \(pylori\) titer distribution, median (range) | 24.3 (6.2–5587.4) | 30.4 (5–500) | 16.1 (5–500) |
| \(H.\) \(pylori\) positive (cut-off), % | 4,372 (54.8) | 2,275 (59.4) | 440 (44.8) |
| \(H.\) \(pylori\) positive (highest 25% IgG titer), % | 1,994 (25.0) | 958 (25.0) | 246 (25.0) |
| \(H.\) \(pylori\) antigen distribution, median (range) | NA | NA | −0.004 (−0.151, 3.983) |
| \(H.\) \(pylori\) antigen (cut-off), % | NA | NA | 255 (26.9) |
| BMI (kg/m\(^2\)), mean (sd) | 26.7 (3.9) | 27.3 (4.7) | 27.4 (4.6) |
| Missing, n (%) | 209 (2.6) | 11 (0.3) | 0 (0.0) |
| Obesity (BMI ≥ 30), % | 1,343 (17.3) | 1,042 (25.6) | 252 (25.6) |
| Overweight (BMI ≥ 25), % | 5,027 (64.7) | 2,690 (66.1) | 660 (66.9) |
| Obesity classes (BMI), % | | | |
| Lean, <18.5 | 79 (1.0) | 42 (1.0) | 2 (0.2) |
| Normal weight, 18.5–24.9 | 2,662 (34.3) | 1,338 (32.9) | 324 (32.9) |
| Overweight, 25.0–29.9 | 3,684 (47.2) | 1,648 (40.5) | 408 (40.5) |
| Class I obesity, 30.0–34.9 | 1,110 (14.3) | 775 (19.0) | 200 (20.3) |
| Class II obesity, 35.0–39.9 | 203 (2.6) | 217 (5.3) | 42 (4.3) |
| Class III obesity, >40.0 | 30 (0.4) | 50 (1.2) | 10 (1.0) |
| BMI risk score, mean (sd) | 43.22 (3.98) | | |
| Missing, n (%) | 1,094 (13.7) | 257 (6.3) | 3 (0.3) |
| Obesity risk score, mean (sd) | 42.58 (3.94) | | |
| Missing, n (%) | 1,094 (13.7) | 257 (6.3) | 3 (0.3) |
| \(H.\) \(pylori\) risk score, mean (sd) | 3.34 (0.65) | | |
| Missing, n (%) | 1,094 (13.7) | 257 (6.3) | 3 (0.3) |

Table 1. Baseline characteristics (total cohort n = 13,044). \(^1\)According to manufacturer's definition. \(^2\)According to phenotype definition. NA, not applicable.

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**Cross-sectional analyses.** Cross-sectional analyses revealed an association between \(H.\) \(pylori\) titer and BMI in RS and SHIP (Supplementary Table S1), however with opposite direction. Meta-analysis of all three cohorts showed no association between \(H.\) \(pylori\) titer and BMI, nor between \(H.\) \(pylori\) positivity and BMI (Table 2). \(H.\) \(pylori\) titer, adjusted for age and sex, was negatively associated with obesity (OR 0.99; 95% CI 0.99–1.00, p = 0.03) and with obesity classes (Beta = −6.91 \(\times\) 10\(^{-5}\); 95% CI −1.38 \(\times\) 10\(^{-4}\), −5.49 \(\times\) 10\(^{-5}\), p = 0.048) (Table 2).

Cross-sectional analyses regarding fecal \(H.\) \(pylori\) status and BMI/obesity showed no association (Supplementary Table S2).
founders such as age. Age is an important confounder as it is positively correlated with H. 
suggest that either negative12, or positive 13,14, or no association15,16 between 
titer were positive, this association did not remain statistically significant after adjustment for age and sex. So, the 
class II obesity: BMI ≥ 35 and < 40 kg/m², class III obesity: BMI ≥ 40 kg/m². 1−1 means a negative Beta or 

A clinical trial from Japan randomized 1,558 H. pylori-positive adults to either antibiotic treatment or placebo with a subsequent follow-up of 6 months. H. pylori eradication was associated with a mean weight gain of 0.6 kg (95% CI 0.31, 0.88) and an increase in BMI of 0.2 kg/m²19. The simultaneous improvement of dyspepsia symptoms in the eradication group may have stimulated the appetite and subsequently caused the weight gain by increased food intake. Others have suggested that circulating meal-associated leptin and ghrelin levels, which changed after H. pylori eradication, gave rise to the increased BMI. US investigators observed an increase in both post-prandial levels of leptin and ghrelin a median seven months following H. pylori eradication in a group of 21 patients25. In addition, BMI significantly increased after over 18 months of follow-up, while no change was observed in those who were H. pylori-negative at baseline. Although these studies provided evidence that H. pylori eradication may result in weight gain, it does not imply that there is an absolute difference in BMI between H. pylori-negative and positive subjects. Both our cross-sectional as well as Mendelian randomization results suggest that H. pylori-colonized and H. pylori-negative subjects have similar BMI. The congruence between the

| Model | Cohort | Meta-analysis |
|-------|--------|--------------|
|       |        | BMI kg/m² (95% CI) | p-value |
| H. pylori titer - crude | SHIP | 1.19±0.09 (1.01–1.38) | 0.03 |
| H. pylori titer - adjusted | SHIP | 3.09±0.06 (2.81–3.37) | 0.007 |
| H. pylori positivity – crude | SHIP | 0.37 (0.48–2.22) | 0.40 |
| H. pylori positivity - adjusted | SHIP | 0.04 (0.34–0.41) | 0.84 |

Table 2. Cross-sectional analyses regarding serologic H. pylori status and BMI/obesity – meta-analysis.

1Adjusted for sex and age. 2Obesity defined as BMI ≥ 30 kg/m²; lean: BMI < 18.5 kg/m²; normal-weight: BMI ≥ 18.5 and < 25 kg/m²; overweight: BMI ≥ 25 and < 30 kg/m²; class I obesity: BMI ≥ 30 and < 35 kg/m²; class II obesity: BMI ≥ 35 and < 40 kg/m²; class III obesity: BMI ≥ 40 kg/m². 1−1 means a negative Beta or OR < 1. 1+1 means a positive Beta or OR > 1.

Mendelian randomization. The BMI gene score was not associated with H. pylori titer or positivity (Table 3). Supplementary Table S3 shows the results of each cohort. Crude analysis showed a positive association between obesity gene score and H. pylori titer (Beta 0.76; 95% CI 0.02–1.50, p = 0.04) (Table 3). H. pylori gene score was not associated with BMI, neither with obesity nor obesity classes (Table 4 and Supplementary Table S4). Also, no associations were observed regarding fecal H. pylori status and the BMI or obesity gene score (Supplementary Table S5).

Discussion

This study included a meta-analysis of 13,044 subjects from two large population-based cohorts. This analysis did not demonstrate an association between H. pylori colonization and BMI, neither when examined by means of serology, nor by fecal antigen, or Mendelian randomization. H. pylori serology, adjusted for age and sex, was negatively associated with obesity (BMI ≥ 30 kg/m²), and obesity classes. However, these effects were small. Active H. pylori colonization, determined by a positive fecal antigen test, was also not positively or negatively associated with obesity. While the unadjusted and adjusted effect estimates for the obesity gene score on anti-H. pylori IgG titer were positive, this association did not remain statistically significant after adjustment for age and sex. So, the use of a Mendelian randomization method did not show a causal bi-directional link between H. pylori serology and BMI or obesity.

Our meta-analysis of H. pylori status as determined by serology showed a small negative association with both obesity and obesity classes. Considering both the small effect estimates, and opposite directions in the individual cohorts, we consider these associations as clinically irrelevant. Prior epidemiological studies have shown either negative15, or positive18,19, or no association16,17 between H. pylori and BMI or obesity. The latter findings are most in line with our findings. A recent review of studies reporting data on H. pylori and obesity prevalence rates in developed countries, showed an inverse correlation (r = −0.29, p < 0.001) between H. pylori colonization and obesity and overweight18. In total, data of 99,463 subjects from 49 studies were pooled. Prevalence rates for H. pylori, but also for overweight and obesity were highly variable between included studies. Nevertheless, no additional analyses were performed to examine whether this correlation was related to potential significant founders such as age. Age is an important confounder as it is positively correlated with H. pylori colonization18, and negatively with obesity18. This may explain the negative correlation between H. pylori and obesity reported in the systematic review. Other studies have observed weight gain following successful H. pylori eradication16–23. A clinical trial from Japan randomized 1,558 H. pylori-positive adults to either antibiotic treatment or placebo with a subsequent follow-up of 6 months. H. pylori eradication was associated with a mean weight gain of 0.6 kg (95% CI 0.31, 0.88) and an increase in BMI of 0.2 kg/m²19. The simultaneous improvement of dyspepsia symptoms in the eradication group may have stimulated the appetite and subsequently caused the weight gain by increased food intake. Others have suggested that circulating meal-associated leptin and ghrelin levels, which changed after H. pylori eradication, gave rise to the increased BMI. US investigators observed an increase in both post-prandial levels of leptin and ghrelin a median seven months following H. pylori eradication in a group of 21 patients25. In addition, BMI significantly increased after over 18 months of follow-up, while no change was observed in those who were H. pylori-negative at baseline. Although these studies provided evidence that H. pylori eradication may result in weight gain, it does not imply that there is an absolute difference in BMI between H. pylori-negative and positive subjects. Both our cross-sectional as well as Mendelian randomization results suggest that H. pylori-colonized and H. pylori-negative subjects have similar BMI. The congruence between the
results of our cross-sectional and Mendelian randomization analyses is important, as the latter is based on an unbiased approach\textsuperscript{11}.

One of the strengths of this study was the use of different methods to detect \textit{H. pylori} colonization, by means of both serology and stool antigen. The latter is a reliable method to identify active \textit{H. pylori} colonization. While most prior studies reported data on serology, we were able to show that results for serology and fecal antigen did not differ. In addition, the use of SNP typing data with genetic risk scores for BMI, obesity, and \textit{H. pylori} colonization is unique in this field. The Mendelian randomization method is a powerful control for reverse causation and confounding, which otherwise affects epidemiological studies\textsuperscript{11}. It is based on the common disease, common variant hypothesis, which argues that common variants with modest effects underlie many complex traits\textsuperscript{25}.

As any method, the Mendelian randomization has its limitations. Although many genetic variants are discovered, these common variants only explain a small proportion of the estimated trait heritability. Regarding the \textit{H. pylori}-gene risk score, we were only able to include two genetic variants, due to the fact that no others (as far as we know) have been discovered so far, and these explain only 0.5% of the variance. Similarly, a recent large-scale consortium study estimates that 97 GWAS loci account for \(\sim 2.7\%\) of BMI variation\textsuperscript{26}. Data on \textit{H. pylori} eradication was not available in the RS and SHIP cohort. Nevertheless, given the selective indications for this both in The Netherlands and in Germany, we can safely assume that this was a small minority of the total population. Finally, we did not account for socio-economic status in the cross-sectional analyses. Although both populations are similar regarding ethnicity and age distribution, differences in socio-economic status are associated with both \textit{H. pylori} colonization and BMI, and may therefore have influenced our outcome.

In conclusion, this study provides no evidence for a cross-sectional association between \textit{H. pylori} colonization and BMI or obesity in adults. Mendelian randomization revealed no causal relation between \textit{H. pylori} and BMI or obesity.

**Methods**

**Study cohorts.** The Rotterdam Study is a large, population based prospective study of elderly individuals of European ancestry consisting of three cohorts (RS-I, RS-II, RS-III), who are residing in a suburb of Rotterdam, the Netherlands. The study design has been described in detail previously\textsuperscript{27,28}. Baseline recruitment and measurements for the RS-I study were obtained between 1990 and 1993. The second cohort, RS-II, was set-up in 2000–2001. A third cohort, RS-III, started in 2006 and recruitment ended in December 2008.

The SHIP study comprises two independent prospectively recruited population-based cohorts in Northeastern Germany: SHIP and SHIP-TREND. The study design of SHIP has been described in detail previously\textsuperscript{29,30}. Participants were recruited between October 1997 and May 2001. SHIP-TREND is an independent cohort from the same region. Individuals were recruited between September 2008 and summer 2012\textsuperscript{31}. An important characteristic of SHIP is that it attempts to describe health-related conditions with the widest focus possible.

Data from SHIP, SHIP-TREND, RS-I, and RS-II (RS from now on) were used in this study. Written informed consent was obtained from all participants. Both the medical ethics committee of the Erasmus MC University Medical Center Rotterdam and University Medicine Greifswald approved the study. All methods were performed in accordance with the relevant guidelines and regulations, approved by the medical ethics committee.

**Phenotype definition.** Serologic \textit{H. pylori} colonization in individuals from SHIP, SHIP-TREND, and RS was defined by measuring IgG antibody levels in serum using commercial enzyme-linked immunosorbent assay (Pyloriset EIA-G III ELISA; Orion). Seropositivity was defined as an anti-\textit{H. pylori} IgG titer of \(\geq 20\) U/mL.
and binary) in our analyses. A genotype score (GS) was calculated by summing the alleles of BMI / obesity / (lean BMI < 18.5 kg/m²; normal-weight: BMI ≥ 18.5 and < 25 kg/m²; overweight: BMI ≥ 25 and < 30 kg/m²; class I obesity: BMI ≥ 30 and < 35 kg/m²; class II obesity: BMI ≥ 35 and < 40 kg/m², class III obesity: BMI ≥ 40 kg/m²). ‘−’ means a negative Beta or OR < 0.1. ‘+’ means a positive Beta or OR > 0.1.

Table 4. Mendelian randomization regarding BMI/obesity and H. pylori gene score – meta-analysis.

| Model | Cohort | Meta-analysis |
|-------|--------|--------------|
| BMI–H. pylori gene score | RS | SHIP | SHIP-TREND | Beta (95% CI) | p-value |
| Hp gene score – crude | − | − | − | −0.05 (−0.16; 0.07) | 0.43 |
| Hp gene score – adjusted | − | − | − | −0.06 (−0.17; 0.05) | 0.31 |
| Hp gene score – adjusted | − | − | − | −0.05 (−0.17; 0.06) | 0.37 |

Obesity3–H. pylori gene score

| Obesity classes1–H. pylori gene score | OR (95% CI) |
|--------------------------------------|-------------|
| Hp gene score – crude | 0.98 (0.92; 1.05) | 0.60 |
| Hp gene score – adjusted | 0.98 (0.91; 1.04) | 0.47 |
| Hp gene score – adjusted | 0.98 (0.91; 1.05) | 0.56 |

Genetic risk score conduction. For the creation of the genetic risk scores (BMI risk score, obesity risk score, H. pylori risk score), we first searched the literature for publications of genome-wide association studies (GWAS) for these traits. A list of SNPs that reached genome-wide significance (P < 5 × 10−8) with BMI or binary obesity status in populations of European ancestry was established. Three different strategies were used to optimize the SNP selection procedure using a key word search (e.g. BMI) on i) the National Human Genome Research Institute (NHGRI) GWAS Catalog (www.genome.gov/gwastudies/) ii) the HuGE Navigator GWAS Integrator (www.hugenavigator.net/HuGENavigator/gwAHitStartPage.do) iii) the PubMed database (www.ncbi.nlm.nih.gov/pubmed). Using this strategy, 45 independent loci were found to be associated with BMI variation and 48 with binary obesity status. We chose to analyze risk scores for BMI and obesity separately. BMI is a phenotype which results in a relatively clean risk score. In contrast, various different definitions have been used to define obesity, like BMI ≥ 18.5 kg/m²; normal-weight: BMI ≥ 18.5 and < 25 kg/m²; overweight: BMI ≥ 25 and < 30 kg/m²; class I obesity: BMI ≥ 30 and < 35 kg/m²; class II obesity: BMI ≥ 35 and < 40 kg/m², class III obesity: BMI ≥ 40 kg/m²). ‘−’ means a negative Beta or OR < 0.1. ‘+’ means a positive Beta or OR > 0.1.

Statistical analysis. In total, we used three different approaches to assess the relationship between H. pylori status and BMI/obesity. First, cross-sectional analyses were performed to assess the relationship between H. pylori colonization and BMI/obesity at time of inclusion, by using linear and logistic regression. Outcomes were defined as continuous BMI, binary obesity (BMI ≥ 30 kg/m², with BMI < 30 kg/m² as reference group), and obesity classes (lean BMI < 18.5 kg/m²; normal-weight BMI ≥ 18.5 and < 25 kg/m²; overweight BMI ≥ 25 and < 30 kg/m²; class I obesity BMI ≥ 30 and < 35 kg/m²; class II obesity BMI ≥ 35 and < 40 kg/m², class III obesity BMI ≥ 40 kg/m²). The latter outcome was defined as a continuous variable with value ‘0’ for lean, and value ‘5’ for class III obesity. Unadjusted effects of H. pylori titer or antigen (continuous) and H. pylori positivity (binary phenotype) were assessed for each outcome. We additionally adjusted for sex and age. All analyses were done separately for RS, SHIP, and SHIP-TREND. A meta-analysis was performed to observe the combined effect of H. pylori colonization on BMI/obesity.

Second, a Mendelian randomization approach was carried out to explore a bi-directional link between H. pylori colonization and BMI. Linear regression analysis was used to assess the relationship between BMI gene score and H. pylori titer and H. pylori positivity. Analyses were first adjusted for sex, age, and additionally for BMI at baseline. The same analyses were done regarding the obesity gene score. Linear regression analysis was...
also used to examine the effect of the *H. pylori* gene score with BMI, binary obesity status, and obesity classes, all defined at baseline. Analyses were adjusted for sex, and age, and additionally for *H. pylori* status (binary phenotype). Data of the three cohorts were combined and examined by using meta-analysis approach. A p-value < 0.05 was considered to be statistically significant.

All measures of associations are presented as Odds Ratios (OR) or Beta's with their 95% confidence intervals (CI). Statistical analyses were performed using IBM SPSS Statistics 21.0 for Windows (SPSS IBM, Armonk, New York, USA). Meta-analyses were done with R library meta (R Core Team (2014), R Foundation for Statistical Computing, Vienna, Austria).

**Data availability.** Due to ethical restrictions data are available upon request. Interested researchers may contact our data management team (secretariat.epi@erasmusmc.nl) for access to sensitive data.

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