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Authors

Ness-Jensen, Eivind
Langhammer, Arnulf
Hveem, Kristian
et al.

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Helicobacter pylori in relation to asthma and allergy modified by abdominal obesity: The HUNT study in Norway

Eivind Ness-Jensen [a,b,c], Arnulf Langhammer [a], Kristian Hveem [a], Yunxia Lu [d,e,*]

[a] HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger, Norway
[b] Upper Gastrointestinal Research, Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[c] Medical Department, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway
[d] Program in Public Health, Susan and Henry Samueli College of Health Sciences, University of California Irvine, USA
[e] Clinical Genetics, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Objective: It is unknown whether the decreasing prevalence of *H. pylori* infections is associated with the increase in obesity and asthma and allergy. In this study, we assessed if obesity plays an intermediate role between *H. pylori* infections and allergy.

Design: A population-based, nested case-control study of 10,005 participants within the second Nord-Trøndelag Health Study (HUNT2), Norway, was performed in 1995–1997. The presence of *H. pylori* was tested by an enzyme immunoassay Pyloriset EIA-IgG, and weight, height, and waist circumference were measured. Body mass index (BMI) and waist circumference were used as measures of general and abdominal obesity, respectively. Self-reported asthma and allergic diseases were collected through questionnaires. The odds ratios of *H. pylori* relative to asthma and allergic diseases were estimated by logistic regression models stratified by waist circumference categories.

Results: H. pylori infection was present in 31%, ever asthma was reported in 10.4% and allergic rhinitis in 16.2%. The mean BMI was 26.4 kg/m^2 and the mean waist circumference was 86.6 cm. *H. pylori* infection was neither associated with asthma nor allergic diseases. However, when stratified by waist circumference, *H. pylori* infection was associated with 30–40% reduced odds of asthma and 25% reduced odds of allergic diseases in individuals with abdominal obesity (waist circumference ≥86 cm in women and ≥96 cm in men).

Conclusion: H. pylori infection is associated with reduced risk of asthma and allergy in individuals with abdominal obesity, suggesting a possible causal pathway from reduced *H. pylori* infections through obesity to increased risk of asthma and allergy.

Introduction

Infection with *Helicobacter pylori (H. pylori)* is common in humans and associated with socioeconomic status and living conditions in childhood.[1] In developed countries, the prevalence of *H. pylori* infections has rapidly decreased in parallel to economic improvement over the past decades.[2] This might be due to improved hygiene and sanitation, less salted food, and possibly increased use of antimicrobial agents.

Interestingly, as the prevalence of *H. pylori* has declined, there has been a rise in the prevalence of asthma and allergic diseases (e.g., hay fever and atopy) in developed countries.[3–5] Tobacco smoking, air pollution, allergens, microbial infection, and obesity are among the potentially attributable exposures that may cause the increase of asthma and allergic diseases.[6,7] As an indigenous microbiota, the decrease of *H. pylori* has been postulated to play a role in this increase.[8] There have been quite a few epidemiologic studies examining the association between *H. pylori* and asthma and allergic diseases. The results, however, are largely controversial.[9]

Parallel to the decrease in *H. pylori* infections, there has been a global increase of obesity during the past decades.[10,11] Obesity is associated with chronic inflammation which may be involved in the allergic response.[12] A positive association between obesity and asthma and

* Corresponding author. Program in Public Health, Susan and Henry Samueli College of Health Sciences, University of California, Irvine, 653 E. Peltason Drive, Irvine, CA, 92697-3957, USA.
E-mail addresses: eivind.ness-jensen@ntnu.no (E. Ness-Jensen), arnulf.langhammer@ntnu.no (A. Langhammer), Kristian.Hveem@ntnu.no (K. Hveem), yunxia.lu@uci.edu (Y. Lu).

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allergic diseases has been reported in many studies.[13,14] Moreover, lack of *H. pylori* infection has been associated with obesity in accumulating studies.[15,16] Thus, there could be an association between *H. pylori,* obesity, and asthma and allergic diseases, but so far this has not been studied. Whether lack of *H. pylori* infection leads to increased risk of asthma and allergic diseases and obesity, independent of each other, or the lack of *H. pylori* infection leads to increased obesity and then increased risk of allergic diseases, as a part of the same causal pathway, is unknown. In this large population-based Norwegian study, we examined the association between *H. pylori* infection, obesity, and asthma and allergic diseases.

Methods

Study design

In this nested case-control study, data from the second survey of the Nord-Trøndelag Health Study (HUNT2) was used.[17] In HUNT2, performed in 1995–1997, all residents of Nord-Trøndelag County aged 20 years and older were invited to answer questionnaires and interviews, participate in clinical examinations, and contribute with biological material. Among 65,237 participants in HUNT2 (69.5% of invited), serum from 10,005 randomly selected individuals were tested for *H. pylori.*

Study outcome

Asthma and allergy

Asthma and allergy were assessed through self-reported questionnaires in HUNT2. Asthma was defined as present if the participants reported to have or have had asthma (ever), or if they reported to use or have used asthma medication (definition I). To avoid misclassification with chronic obstructive pulmonary disease (COPD) due to tobacco smoking, we also defined asthma as for definition I, but excluding participants that had smoked for more than 10 years (definition II). The participants also reported age of onset of asthma. Allergic rhinitis was defined as present if the participants reported to have hay fever or nasal allergy.

Main exposures

H. pylori

Serological status of *H. pylori* IgG antibodies was analysed using the commercially available enzyme immunoassay Pylorisert EIA-IgG (Orion Diagnostica, Espoo, Finland) at Levanger Hospital, Norway. Assay for detection of *H. pylori* was performed in 1998. The cut-off level used for a positive *H. pylori* IgG was ≥300 U.[18]

General obesity and abdominal obesity

Trained personnel at the screening stations objectively measured height, weight, and waist circumference during HUNT2. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2) for estimation of general obesity. According to the World Health Organization's definitions, obesity was defined as BMI ≥30 and abdominal obesity as waist circumference ≥86 cm in women and ≥96 cm in men.

Other factors

The following factors were selected *a priori* and included in the analyses: sex, age, tobacco smoking, alcohol drinking (monthly frequency of drinking), physical activity (reported hours of physical activity [light and hard] per week in the last year), highest completed education, and family history of asthma and allergy. Except from sex and age, all factors were assessed through self-reported questionnaires. Family history of asthma or allergic rhinitis was reported on first degree relatives (parents, siblings, and children).

Statistical analysis

Logistic regression was used to assess odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between *H. pylori*, obesity, and asthma and allergy. Separate analyses were performed stratified for waist circumference categories based on the sex-specific intervals: <75, ≥75 to <86, and ≥86 for women; and <88, ≥88 to <96, and ≥96 for men. The fully adjusted analyses were performed with age as a continuous variable, while the other variables were categorized. Tobacco smoking was categorized as never, occasional, and daily. Alcohol drinking was categorized as never, infrequent (once a week or less), and frequent (more than once a week). Physical activity was categorized as inactive (no activity or less than one hour light activity a week), moderately active (1–2 hours light activity or less than 1 hour hard activity a week), and highly active (at least 3 hours light activity or at least 1 hour hard activity a week). Completed education was categorized as primary school, high school, and college/university. In order to entangle the complex relations between *H. pylori,* obesity and asthma and allergies, we performed a mediation analysis to estimate the indirect effect of obesity relative to the total effect of *H. pylori* on the outcome of interest. The SAS 9.4 for Window was applied for data management, descriptive statistical analysis and logistic regression. All statistical analysis were two sides with significant level at 0.05.

Ethical approval

The study has ethical approval through the Regional Committee for Medical and Health Research Ethics, Central Norway (2012/1878). In HUNT, all participants gave written informed consent when participating, stating that their data could be used in future medical research.

Results

Characteristics

In the study population, the mean age was 50 years, 54% were women, and 31% were *H. pylori* positive (Table 1). The mean BMI was 26.4 kg/m^2 (men:26.4; women; 26.3, respectively) and the mean waist circumference was 86.6 cm (men: 92.3; women: 81.6, respectively). Ever having had asthma was reported by 10.4% and after excluding those smoking >10 years, the figure was 5.7%. Hay fever or nasal allergies were reported by 15.1% and allergic rhinitis (including use of anti-allergy medication) were present in 16.2%. In total, 26.5% of the 10,005 participants had asthma or an allergic disease.

Associations

H. pylori infection was not associated with asthma or allergic diseases in general (Table 2), neither using the basic model, adjusting for sex and age, nor using the full model, also adjusting for BMI, tobacco smoking, alcohol drinking, physical activity, education, and family history of asthma and allergic diseases.

Effect modification analysis

However, when stratifying for waist circumference, *H. pylori* infection was associated with asthma and allergy in individuals with abdominal obesity (waist circumference ≥86 cm in women and ≥96 cm in men) (Table 3). In abdominal obesity, *H. pylori* infection was associated with a 40% reduced odds of asthma (definition I) with onset below 18 years of age (fully adjusted OR 0.61, 95% CI 0.37–0.99). *H. pylori* infection in abdominal obesity was not associated with asthma (definition I) with onset above 18 years of age (fully adjusted OR 0.98, 95% CI 0.71–1.35). Excluding those smoking for more than 10 years (definition II), *H. pylori* infection in abdominal obesity was associated with a 30% reduced odds of asthma (fully adjusted OR 0.70, 95% CI 0.50–0.97). *H. pylori* infection

Table 1
Basic characteristics of the randomly selected 10005 HUNT2 participants.

	Total		Asthma				Hay fever or nasal allergies		Allergic rhinitis		Asthma or allergic rhinitis	
			Definition I		Definition II							
Total	N	%	N	%	N	%	N	%	N	%	N	%
	10005	100	1041	10.40	569	5.69	1507	15.06	1620	16.19	2655	26.54
Sex												
Women	5414	54.11	576	55.33	334	58.70	882	58.53	951	58.70	1488	56.05
Men	4591	45.89	465	44.67	235	41.30	625	41.47	669	41.30	1167	43.95
Age												
Mean (SD)	50.11 (16.78)		50.11 (17.51)		46.31 (18.81)		46.30 (16.08)		46.54 (16.11)		49.03 (16.97)	
Median (IQR)	48.80 (27.00)		49.40 (29.30)		44.00 (31.30)		43.90 (23.70)		44.30 (24.05)		47.70 (27.20)	
<40	3166	31.64	339	32.56	251	44.11	610	40.48	642	39.63	925	34.84
40-	2046	20.45	189	18.16	87	15.29	317	21.04	342	21.11	526	19.81
50-	1796	17.95	165	15.85	74	13.01	242	16.06	270	16.67	439	16.53
≥60	2993	29.92	348	33.43	157	27.59	338	22.43	366	22.59	765	28.81
Missing	4	0.04										
***H. pylori* IgG**												
Negative	6924	69.21	711	68.30	418	73.46	1125	74.65	1201	74.14	1854	30.17
Positive	3081	30.79	330	31.70	151	26.54	382	25.35	419	25.86	801	69.83
Body mass index												
Mean (SD)	26.36 (4.06)		27.19 (4.51)		27.01 (4.40)		26.32 (4.15)		26.39 (4.15)		26.76 (4.31)	
Median (IQR)	25.80 (5.00)		26.50 (6.00)		26.45 (6.10)		25.80 (5.10)		25.90 (5.20)		26.20 (5.40)	
<20	273	2.73	22	2.13	14	2.47	41	2.73	44	2.73	64	2.42
20-	3666	36.64	313	30.24	177	31.27	560	37.31	594	36.80	887	33.57
25-	4362	43.60	440	42.51	237	41.87	651	43.37	701	43.43	1149	43.49
≥30	1656	16.55	260	25.12	138	24.38	249	16.59	275	17.04	542	20.51
Missing	48	0.48										
Waist circumference (cm)												
Mean (SD)	86.56 (11.86)		89.25 (12.95)		87.71 (12.47)		85.85 (12.10)		86.00 (12.10)		87.64 (12.56)	
Median (IQR)	86.00 (16.00)		89.00 (18.00)		87.00 (18.00)		85.00 (16.00)		86.00 (16.00)		87.00 (18.00)	
Women<75; Men<88	3095	30.93	253	24.56	156	27.76	474	31.83	499	31.17	739	28.14
75 ≤ Women <86; 88 ≤ Men<96	3493	34.91	315	30.58	180	32.03	535	35.93	575	35.92	885	33.70
Women≥86; Men≥96	3303	33.01	462	44.85	226	40.21	480	32.24	527	32.92	1002	38.16
Missing	114	1.14										
Tobacco smoking												
No smoking	4112	41.10	380	36.50	380	66.78	703	46.65	742	45.80	1048	39.47
Smoking occasionally	3057	30.55	355	34.10	140	24.60	452	29.99	488	30.12	822	30.96
Smoking daily	2831	28.30	306	29.39	49	8.61	352	23.36	390	24.07	785	29.57
Missing	5	0.05										
Alcohol drinking												
Never	2373	23.72	276	26.51	145	25.48	379	25.15	400	24.69	664	25.01
Infrequent	4572	45.70	454	43.61	259	45.52	724	48.04	776	47.90	1211	45.61
Frequent	1399	13.98	140	13.45	58	10.19	208	13.80	226	13.95	361	13.60
Missing	1661	16.60										
Physical activity												
Inactive	1709	17.08	195	18.73	83	14.59	224	14.86	249	15.37	464	17.48
Moderately active	2954	29.53	299	28.72	165	29.00	503	33.38	533	32.90	822	30.96
Highly active	4234	42.32	428	41.11	257	45.17	678	44.99	723	44.63	1111	41.85
Missing	1108	11.07										
Education												
Primary school	3241	32.39	363	34.87	158	27.77	417	27.67	450	27.78	859	32.35
High school	3191	31.89	322	30.93	169	29.70	457	30.33	500	30.86	829	31.22
College/university	3095	30.93	297	28.53	209	36.73	581	38.55	610	37.65	838	31.56
Missing	478	4.78										
Family history of asthma												
No	7963	79.59	636	61.10	299	52.55	599	39.75	1026	63.33	1805	67.98
Yes	2038	20.37	405	38.90	270	47.45	908	60.25	594	36.67	850	32.02
Missing	4	0.04										
Family history of allergic rhinitis												
No	6927	69.24	577	55.43	347	60.98	945	62.71	670	41.36	1411	53.15
Yes	3074	30.72	464	44.57	222	39.02	562	37.29	950	58.64	1244	46.85
Missing	4	0.04										

Asthma definition I: Asthma or medication for asthma.
Asthma definition II: Definition I, excluding those smoking for more than 10 years.
Allergic rhinitis: Hay fever or nasal allergies or use of anti-allergy medications.
SD: standard deviation.
IQR: interquartile range.

in abdominal obesity was also associated with a 25% reduced odds of hay fever or nasal allergies (fully adjusted OR 0.75, 95% CI 0.59–0.95).

Discussion

In the present study we found no association between *H. pylori* infection and asthma or allergic diseases in general. However, *H. pylori* infection was associated with a reduced risk of asthma and allergy in individuals with abdominal obesity, suggesting a possible causal pathway from reduced *H. pylori* infections through obesity to increased asthma and allergy.

The strengths of this study include the population-based design, large sample size, and random selection of participants where *H. pylori* status was assessed, reducing the risk of selection bias and chance findings. In

Table 2
Odds ratios (ORs) and 95% confidence intervals (CIs) of *H. pylori* infection relative to asthma and allergy.

	H. pylori infection			
	Negative	Positive	[d]Basic model	[e]Full model
	N	N	OR (95% CI)	OR (95% CI)
[a]Asthma (definition I)	711	330	1.01 (0.87,1.17)	1.00 (0.86,1.17)
Asthma (onset at age<18)	287	82	0.92 (0.70,1.20)	0.93 (0.71,1.22)
Asthma (onset at age≥18)	228	141	1.07 (0.85,1.34)	1.08 (0.85,1.36)
[b]Asthma (definition II)	418	151	0.90 (0.73,1.11)	0.94 (0.76,1.16)
Hay fever or nasal allergies	1125	382	0.91 (0.79,1.04)	0.93 (0.81,1.07)
[c]Allergic rhinitis	1201	419	0.93 (0.81,1.06)	0.95 (0.83,1.09)
Asthma or allergic rhinitis	1854	801	1.02 (0.92,1.13)	1.03 (0.92,1.14)

[a] Asthma definition I: Asthma or medication for asthma.
[b] Asthma definition II: Definition I, excluding those smoking for more than 10 years.
[c] Allergic rhinitis: Hay fever or nasal allergies or use of anti-allergy medications.
[d] Basic model: Adjusted for sex and age.
[e] Full model: Adjusted for sex, age, body mass index, tobacco smoking, alcohol drinking, physical activity, education, and family history of asthma or allergic rhinitis.

addition, the HUNT study assessed a number of high quality variables that made adjustments for important confounders possible. The objective measurements of BMI and waist circumference are of great importance when assessing obesity. One weakness in this study is the self-reported asthma and allergy. This might introduce misclassification, mainly towards COPD. This is partly avoided by using a definition of asthma excluding participants that had smoked for more than 10 years (definition II) and stratified asthma with onset below 18 years of age (childhood asthma). Another weakness is the lack of data on cagA status, which has been regarded as an important factor in *H. pylori* infection that is negatively associated with asthma and allergy.[19] As this is an observational study, causal associations cannot be claimed based on concurrent measurements of outcomes, exposures, and confounders.

A potential inverse relationship between *H. pylori* and asthma and allergy has been widely reported, although the results are controversial.[20–25] In the largest meta-analysis including 19 studies,[9] an inverse association between *H. pylori* and asthma was demonstrated based on nine cross-sectional studies (pooled OR 0.84, 95% CI 0.74–0.96), but the pooled OR was not statistically significant in seven case-control studies (pooled OR 0.82, 95% CI 0.53–1.27) or three prospective cohort studies (pooled OR 0.82, 95% CI 0.53–1.27). Interestingly, the meta-analysis showed an inverse association in children (pooled OR 0.81, 95% CI 0.72–0.91) but not in adults (pooled OR 0.88, 95% CI 0.71–1.08), which is partially consistent with our results. The benefit of *H. pylori* in early life has been observed in quite a few studies,[20–22,26,27] but at a late-in-life cost (e.g., *H. pylori* is a risk factor of peptic ulcer disease and stomach cancer).[28] However, in the present study, such an inverse association were only identified in abdominally obese persons who had asthma or allergic rhinitis in their early life. This result may indicate an intriguing and complex relationship between *H. pylori*, obesity, and asthma and allergy.

A possible inverse relationship between exposure to *H. pylori* and the occurrence of obesity has been addressed as well,[15,29–31] although the results are still controversial.[32] Moreover, whether *H. pylori* infection plays a role only in childhood or adult adiposity is unclear. As both *H. pylori* and obesity have been associated with asthma and allergic disease, the role of the two factors needs to be further clarified. Whether one factor is another factor's confounder, effect modifier or intermediate is unknown. In the present study, there was an association between *H. pylori* and asthma and allergic disease in abdominally obese participants, but this association disappeared in the non-abdominally obese population. This indicates that obesity may play a role as an effect modifier between *H. pylori* and asthma and allergy. As the analyses were based on cross-sectional data, potential obesity could be an intermediate in the pathway from *H. pylori* to asthma and allergy.

The underlying mechanisms between *H. pylori*, obesity, and asthma and allergy are plausible. *H. pylori* are one of the most common bacteria in humans, with prevalence rates of *H. pylori* in human populations ranging from 20 to 50%.[33,34] In the past decades, infection with *H. pylori* substantially declined due to improved living conditions and increased use of antibiotics. Individuals exposed to *H. pylori* in early childhood are prone to have a decreased appetite and food intake due to defective signalling of appetite- and satiety-related hormones in the stomach, e.g., ghrelin and leptin.[20,35] Hormone ghrelin exerts long-term appetite stimulating behaviour through its receptors in the hypothalamic paraventricular and arcuate nuclei.[36,37] Decreased exposure to *H. pylori* results in increased ghrelin and downregulated gastric leptin in children and in adults, thus increasing appetite stimulating behaviour and then leading to obesity. Interestingly, ghrelin has been associated with abdominal adiposity through regulation of lipid storage in abdominal white adipose tissue[38]; higher leptin levels has also been associated with abdominal obesity in quite a few studies.[39,40] In addition, *H. pylori* could be an indicator for changes in the gut microbiome. It reflects the complex interaction between microbes and the immune system.[41,42] When *H. pylori* are eradicated (other microbes will be influenced as well), the inner balance of microbes, appetite-related hormones, and the immune system will be broken, and then the person will become obese. The cytokines stimulated by chronic inflammation in the obese population will further trigger asthma and allergy. On the other hand, in obese persons, the cytokines may be supressed by infection with *H. pylori*. A protective association of *H. pylori* with asthma and allergic disease through obesity is plausible. This hypothesis aligns with the present study.

Another potential pathway is through Th1 and Th2 lymphocytes. A growing body of evidence indicates a preventive action of *H. pylori* to asthma and allergy probably through the gastric recruitment of regulatory T cells.[43] It is well recognized that infections with *H. pylori* can trigger a Th1-mediated immune response.[43] Activation of Th1 then suppresses the Th2 responses. The predominant activation of Th1 lymphocytes by *H. pylori* leads to the production of interferon gamma, interleukin 12, and tumor necrosis factor alpha in the stomach.[44] Eradication of *H. pylori* will lead to inadequate Th1 response that might result in an overactive Th2 response with production of cytokines, including interleukins 4, 5, and 13, which are associated with the promotion of IgE and eosinophilic responses, and eventually allergies. The inverse association between *H. pylori* and asthma and allergic disease was first observed in 1989 with the “hygiene hypothesis”.[45] It was based on observations of declining prevalence of allergic rhinitis with increasing number of older siblings. It suggested a preventive effect of transmitted infections in early childhood from older siblings. Exposure to infectious agents might educate the immune system and provide protection against allergic rhinitis. However, how obesity plays a role in this pathway is unclear. As the benefit of *H. pylori* was only shown in the obese population, the present study might suggest that the immune system educated by infection with *H. pylori* may be more alert to asthma and allergy in those obese.

Table 3
Odds ratios (ORs) and 95% confidence intervals (CIs) of *H. pylori* infection relative to asthma and allergy, stratified by waist circumference.

	Waist circumference (cm): women<75; men<88				Waist circumference (cm): 75 ≤ women<86; 88 ≤ men<96				Waist circumference (cm): women≥86; men≥96			
	H. pylori infection				*H. pylori* infection				*H. pylori* infection			
	Negative	Positive	Basic model[d]	Full Model	Negative	Positive	Basic model[d]	Full Model	Negative	Positive	Basic model[d]	Full Model
	N	N	OR (95%CI)	OR (95%CI)	N	N	OR (95%CI)	OR (95%CI)	N	N	OR (95%CI)	OR (95%CI)
Asthma (definition I)[a]	193	60	0.97 (0.70,1.34)	0.93 (0.67,1.30)	213	102	1.16 (0.90,1.52)	1.17 (0.89,1.53)	297	165	0.91 (0.73,1.14)	0.92 (0.73,1,15)
Asthma (onset at age<18)	102	24	0.97 (0.60,1.57)	0.97 (0.59,1.59)	87	31	1.19 (0.77,1.85)	1.24 (0.77,1.94)	90	24	0.58 (0.36,0.93)*	0.61 (0.37,0.99)*
Asthma (onset at age≥18)	37	25	1.55 (0.89,2.70)	1.46 (0.83,2.57)	67	36	1.02 (0.66,1.57)	1.00 (0.64,1.55)	119	80	0.99 (0.73,1.35)	0.98 (0.71,1.35)
Asthma (definition II)[b]	125	31	1.00 (0.65,1.54)	1.05 (0.67,1.63)	127	53	1.12 (0.79,1.59)	1.23 (0.85,1.77)	161	65	0.69 (0.50,0.94)*	0.70 (0.50,0.97)*
Hay fever or nasal allergies	378	96	0.97 (0.75,1.27)	0.98 (0.74,1.29)	388	147	1.07 (0.86,1.33)	1.09 (0.86,1.37)	346	134	0.72 (0.57,0.91)*	0.75 (0.59,0.95)*
Allergic rhinitis[c]	399	100	0.96 (0.74,1.25)	0.97 (0.74,1.27)	417	158	1.06 (0.85,1.31)	1.07 (0.86,1.34)	372	155	0.77 (0.62,0.96)*	0.80 (0.64,1.01)
Asthma or allergic rhinitis	571	168	0.99 (0.80,1.223)	0.99 (0.79,1.23)	617	268	1.09 (0.91,1.30)	1.10 (0.92,1.32)	644	358	0.96 (0.81,1.13)	0.98 (0.83, 1.16)

[a] Asthma definition I: Asthma or medication for asthma.
[b] Asthma definition II: Definition I, excluding those smoking for more than 10 years.
[c] Allergic rhinitis: Hay fever or nasal allergies or use of anti-allergy medications.
[d] Basic model: Adjusted for sex and age.
* $p < 0.05$.

In conclusion, this large population-based study found reduced risk of asthma and allergy with *H. pylori* infection in individuals with abdominal obesity. This suggests a possible protective effect of *H. pylori* infection in the development of asthma and allergy and possibly a causal pathway from reduced *H. pylori* infections through obesity to increased asthma and allergy.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YXL proposed the conception of the study, designed the study based on the HUNT cohort, performed the data analysis and wrote the paper; ENJ designed the study, collected the data and participated in the analysis and wrote the paper; AL contributed specifically to the definition of asthma and allergic diseases using data from the HUNT cohort. He also contributed to the results interpretation and wrote the paper; KH designed the study, collected the data and contributed to results interpretation and manuscript writing. All authors of this paper have directly participated in the planning, execution, or analysis of the study, and have read and approved the final version submitted.

Authors' information

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Results from the HUNTs have been published in numerous studies. Due to the current ethical issues, data was not supposed to be shared by the general public. Please contact the authors for data inquiry.

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