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***Helicobacter pylori* is associated with lower androgen activity among men in NHANES III**

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To the editor

Chen et al., using a nationally representative sample of the US population from the National Health and Nutrition Examination Survey III (NHANES III), intriguingly suggest infection with *Helicobacter (H.) pylori* may have positive health effects in addition to a causal role in gastric cancer.[1] *H. pylori* has a long history of co-existence with humans. Research on the human microbiome has also highlighted the symbiotic relation of gut microorganisms with their hosts. Animal biology suggests immune defense trades-off against reproductive success, such that infections suppresses androgens.[2] Correspondingly, changing the gut microbial environment in mice changes mice testosterone levels.[3] The same mechanisms may also apply to humans, particularly at older ages when the immune system is less effective. *H. pylori* could modulate androgen production and thereby affect health, because androgens, and similarly endocrine disruptors, may play a role in chronic diseases.

Two androgen biomarkers (serum testosterone and androstenediol glucuronide (3- α -diol-G) (AAG)) were assayed for a male sub-sample (12+ years) from NHANES III, who attended a morning examination session (n=2205) in phase 1 (1988–91) and had surplus sera available,[4] using a competitive electrochemiluminescence immunoassay for serum testosterone and an enzyme immunoassay for AAG.[4] *H. pylori* antibodies, assayed using ELISA, and antigens to *cagA* positive *H. pylori* strains were also obtained from surplus sera. [1] NHANES III was approved by the US Centers for Disease Control and Prevention's Institutional Review Board and all participants provided written informed consent.

Of 1445 men (18+ years) with an androgen and clearly negative or positive *H. pylori* status, 50.9% were *H. pylori* positive. *H. pylori* was associated with older age, less education, other than non-Hispanic white ethnicity and higher body mass index (BMI).[1] *H. pylori* was negatively associated with AAG, adjusted for age, race/ethnicity, education, BMI and smoking (model 2) using linear regression adjusted for the complex sample and weighted back to the US population (Table 1). Somewhat similar associations occurred for joint *H*

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Competing interests

None

pylori/cagA status among men aged 20+ years, where the associations did not appear to differ for *cagA*⁺ (Table 1). The association of *H. pylori* with AAG, but not with testosterone, varied with age, such that *H. pylori* was more strongly associated with lower AAG among older men (Figure 1).

H. pylori was most clearly associated with lower AAG, although testosterone had non-significant associations in the same direction. AAG was weakly positively correlated with testosterone (0.13), which may not capture all androgen activity,[5] consistent with anti-androgens treating prostate cancer effectively at castrate levels of serum testosterone.[5;6] AAG also had the biologically expected positive association of an androgen with higher hemoglobin (0.06 g/L per ng/mL AAG, 95% confidence interval (CI) 0.002 to 0.12 in model 2) whereas testosterone did not (0.22 g/L per ng/mL testosterone, 95% CI -0.17 to 0.62 in model 2).

These findings are consistent with some ecological observations. Some populations with high levels of stomach cancer, such as in China,[7] also have lower androgen related parameters, such as testicular weight,[8] than Caucasians, and lower rates of prostate cancer. [7] The association of *H. pylori* with lower androgens may also shed light on other observations. *H. pylori* is positively associated with type 2 diabetes;[9] lower androgens is a possible mechanism, as androgen deprivation increases vulnerability to diabetes. Antibiotic use is associated with prostate cancer,[10] for which raising androgens by eliminating *H. pylori* is a speculative mechanism. Clearly, these findings need to be confirmed or refuted in other study designs capable of establishing causality. *H. pylori* is currently very common; ongoing eradication could have widespread health consequences, particularly for older men, via altered androgens, such as increasing hormonally modulated cancers or affecting other chronic diseases.

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Figure 1.

Association of *H. pylori* (positive men compared to negative) with AAG by age-group using a multivariable linear regression model among 1,427 men from NHANES III phase 1 (1988–1991), adjusted for age (continuous), race/ethnicity, educational attainment, body mass index and smoking.

Table 1

Adjusted association of *H. pylori* and joint *H. pylori* and *cagA* status with serum testosterone and AAG using multivariable linear regression models among 1,435 men from NHANES III phase 1 (1988–1991).

		<i>H. pylori</i> positive compared with <i>H. pylori</i> negative					Joint status of <i>H. pylori</i> and <i>cagA</i> compared to <i>H. pylori</i> ⁺ <i>cagA</i> ⁻						
					Difference by age p-value*	<i>H. pylori</i> ⁺ <i>cagA</i> ⁻			<i>H. pylori</i> ⁺ <i>cagA</i> ⁺ †			Difference by age p-value*	
		mean (standard deviation)	Model	n	b	95% CI	n	b	95% CI	n	b	95% CI	
Testosterone (ng/mL)	5.3	1	1425	-0.08	-0.50 to 0.33	0.18	1399	-0.24	-0.62 to -0.14	-0.12	-0.47 to 0.22	0.05	
	(2.04)	2	1416	-0.18	-0.50 to 0.13	0.08	1390	-0.40	-0.65 to -0.14	-0.16	-0.47 to 0.15	0.02	
Androstanediol glucuronide (ng/mL)	13.3	1	1435	-1.85	-3.22 to -0.48	0.04	1409	-2.46	-4.28 to -0.64	-1.53	-3.35 to 0.29	0.06	
	(11.6)	2	1427	-1.66	-3.13 to -0.20	0.03	1401	-2.28	-4.06 to -0.50	-1.45	-3.43 to 0.52	0.08	

Model 1 adjusted for age (continuous) and race/ethnicity (Non-Hispanic white, Non-Hispanic black, Mexican-American and other)

Model 2 additionally adjusted for educational attainment (years), body mass index (<25,>25, missing) and smoking (never, past, current)

* p-value for the interaction of *H. pylori* status with age

[†] as previous publications *H. pylori*⁺ *cagA*⁺ includes anyone *cagA*⁺ regardless of the results of the *H. pylori* assay, [1] including those with equivocal *H. pylori* status [1]