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Abstract

Background: In the US, the percentage of adults with diagnosed diabetes are higher in members of racial and ethnic minority groups compared to non-Latino Whites. Understanding why such disparities exist has been less forthcoming.

Methods: Secondary data analysis was conducted using the National Health and Nutrition Examination Survey (NHANES) 1999-2000 cross-sectional data.

Results: *H.pylori* seropositivity was highest in Mexican Americans (43.7%), lowest in non-Hispanic Whites (18.1%). Diabetes was highest in non-Hispanic Blacks (5.9%); lowest in non-Hispanic whites (4.3%). *H.pylori* seropositivity was associated with greater likelihood of having type 2 diabetes (1.927, 95% CI 1.142, 3.257) compared to *H.pylori* negative in unadjusted model. After adjustment, *H.pylori* seropositivity was no longer associated with diabetes. Obesity (aOR 4.94, 95% CI 2.672,9.133) was associated with having type 2 diabetes compared to normal weight. Non-Hispanic Blacks (2.436, 95% CI 1.489,3.984) and Mexican Americans (1.896, 95% CI 1.002,3.587) had greater odds of diabetes compared to Whites. For nearly all stratified analyses, *H.pylori* did not have a significant association with type 2 diabetes although several other noteworthy findings emerged. A chance finding, where *H.pylori* was associated with greater likelihood of diabetes in Mexican Americans, 60-85, >25 BMI, may be worth a closer look.

Conclusion: Findings indicate weight status, obesity in particular, is the strongest predictor of diabetes followed by Black race. Stratified analyses suggest increasing racial disparities over the course of the life span.

Keywords

H.pylori; diabetes; health disparities; Mexican Americans; Blacks

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Exploring H.pylori Seropositivity as a Risk Factor for Type 2 Diabetes

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ABSTRACT

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Conclusion: Findings indicate weight status, obesity in particular, is the strongest predictor of diabetes followed by Black race. Stratified analyses suggest increasing racial disparities over the course of the life span.

Keywords: H.pylori; diabetes; health disparities; Mexican Americans; Blacks

INTRODUCTION

In the US, the percentage of adults with diagnosed diabetes has steadily increased over time and rates are higher in members of racial and ethnic minority groups compared to non-Latino Whites (Centers for Disease Control and Prevention, 2015). Understanding why such health disparities exist has been less forthcoming. To our knowledge, no one has proposed *Helicobacter pylori* (*H.pylori*) infection as a risk factor to explain such disparities. *H.pylori* is a gram-negative, spiral-shaped pathogenic bacterium that is recognized as playing an etiologic role in chronic gastritis, peptic ulcer disease and gastric cancer. More recently, there is now a growing debate as to whether *H.pylori* is associated with diabetes, which could provide new insight to explain disparities in diabetes prevalence. Some studies investigated whether risk factors such as obesity and acculturation might help explain the existing disparity in Mexican Americans, for example (Garcia et al., 2012; Nguyen, Nguyen, Lane, & Wang, 2011; O'Brien, Alos, Davey, Bueno, & Whitaker, 2014). Other factors including age, ethnicity, socio-economic status (SES) and education have been linked to type 2 diabetes (Hanni, Ahn, & Winkleby, 2013). Studies using the National Health and Nutrition Examination Survey (NHANES) datasets attempted to elucidate clues to help explain ethnic and racial disparities. In the NHANES 1999-2008 datasets Garcia et al. found prevalence of diabetes higher in Mexican Americans (11.4%) compared to non-Latino Whites (9.6%), but analyses comparing the prevalence of overweight, obesity, pre-diabetes and diabetes by different levels of acculturation for Mexican Americans indicated acculturation was not associated with diabetes or pre-diabetes in adjusted models (Garcia et al., 2012). Conversely another study using NHANES 2007-2010 data found acculturation was associated with a higher risk of diabetes among Latinos but this risk was only partly explained by body mass index (BMI) (O'Brien et al., 2014). Perhaps one of the most interesting analyses involved four different NHANES datasets to compare diabetes rates across ethnicities and weight status (Zhang, Wang, & Huang, 2009). In that study, disparities varied according to BMI groups, where increasing disparities were noted over time in the normal weight and overweight groups suggesting that other mechanisms beyond those explained by obesity alone are at play in development of diabetes. We explore *H.pylori* seropositivity as a biologically plausible risk factor for type 2 diabetes. We build on a previous NHANES study that found *H.pylori* was associated with glycated hemoglobin (HbAIc) levels, but not with diabetes (Chen & Blaser, 2012). Our study examines *H.pylori* as a potential risk factor to explain existing disparities specifically in type 2 diabetes using a larger NHANES 1999-2000 sample and series of stratified analyses to control for confounders.

Mechanisms have been hypothesized to explain development of type 2 diabetes. A review examining the impact of ethnicity on type 2 diabetes cited several studies that support the hypothesis that neither obesity nor fat distribution explains excess insulin resistance and type 2 diabetes in Asian Indians, Hispanic and African American populations (Abate & Chandalia, 2003). The authors propose that there may be genetic factors that interact with obesity and fat distribution. Moreover, excessive insulin resistance found in ethnic groups is likely a result of an interaction between acquired factors, related to "western" lifestyle and genetic predisposition (Abate & Chandalia, 2003). In another review focusing on immunology, authors present evidence that inflammation participates in the pathogenesis of type 2 diabetes (Donath & Shoelson, 2011). Specifically, immunological changes include altered levels of specific cytokines and chemokines, changes in the number and activation state of various leukocytes and increase apoptosis and tissue

fibrosis with the most apparent changes occurring in adipose tissue, the liver, pancreatic islets, the vasculature and circulating leukocytes.

Like type 2 diabetes, demographic factors including age, socioeconomic status and race/ethnicity are associated with *H.pylori* prevalence. In one study where two sets of NHANES data (1998-1991 and 1999-2000) compared *H.pylori* infection by age and race/ethnicity, seroprevalence levels in US adults increased with age in all racial/ethnic groups, with significantly higher levels in Mexican Americans (64%, 95% CI 58.8,69.2) and non-Hispanic Blacks (52%, 95% CI 48.3, 55.7) compared to non-Hispanic Whites (21.2%, 95% Ci 19.1, 23.2) (Grad, Lipsitch, & Aiello, 2012). Specifically, Mexican Americans were 2.79-3.05 times more likely to be *H. pylori* positive compared to whites (Grad et al., 2012). Only one study to date has demonstrated a temporal relationship between *H. pylori* and development of type 2 diabetes. That is, a prospective study of Latino elderly men demonstrated for the first time that individuals who were seropositive for *H. pylori* were 2.7 times more likely to develop diabetes than seronegative individuals (hazard ratio 2.69, 95% CI 1.10-6.60) (Jeon et al., 2012). Authors examined markers of inflammation (HOMA-IR, IL-6, C-reactive protein) as potential mediators but found these did not change the effect of *H. pylori*. The latter study provides impetus for further exploration of *H. pylori* as a potential predictor of type 2 diabetes in ethnic minorities.

There are generally two theories surrounding the link between *H. pylori* and diabetes (He, Yang, & Lu, 2014; Zhou, Zhang, Wu, & Zhang, 2013). The first school of thought is that diabetes mellitus, as a systemic metabolic disease, predisposes individuals to *H. pylori* infection. The other school of thought is that *H. pylori* infection may contribute to the development of diabetes particularly type 2 diabetes. The latter may be more likely considering *H. pylori* is generally acquired early in life, preceding the development of type 2 diabetes that typically occurs in adulthood; and accumulating evidence suggest that *H. pylori* infection is associated with pathogenic mechanisms characteristic of development of diabetes (He et al., 2014). For example, a 2011 review identified nine studies (7 cross-sectional, 2 longitudinal) to evaluate the association between *H. pylori* infection and insulin resistance (Polyzos, Kountouras, Zavos, & Deretzi, 2011). Six of these studies reported a positive association between *H. pylori* and homeostatic model of assessment insulin resistance (HOMA-IR) (Polyzos et al., 2011). In addition, a 2014 review paper summarizes empirical evidence suggesting *H. pylori* may cause insulin resistance and chronic inflammation that contribute to disease development (He et al., 2014). Alternatively, evidence is cited to suggest *H. pylori* induced gastritis can also potentially affect secretion of gastric hormones and inflammatory cytokines. The latter has accumulating evidence to indicate cytokines play an important role in pancreatic β-cell failure. While there are studies to support the link between *H. pylori* and diabetes, there are also studies that have not found an association between the two. A meta-analysis pooled data from 41 studies, which included 13 studies that reached significance level for detecting a difference in *H. pylori* infection between patients with diabetes and controls, and 28 studies lacking evidence to support any difference in prevalence between groups. Results pooled from data of 14,080 patients ultimately showed prevalence of *H. pylori* infection in patients with diabetes was significantly higher than in controls (Zhou et al., 2013). Moreover, a subgroup analysis indicated this held true only for type 2 diabetes and not type 1 diabetes. As this was a meta-analysis of observational studies, temporal relationships could not be determined to establish which came first, *H. pylori* or type 2 diabetes.

Undoubtedly the pathophysiology of type 2 diabetes is complex and unlikely to result from a single cause. However, in light of the aforementioned evidence, investigating whether *H. pylori*

is associated with increased risk of type 2 diabetes appears worth a closer look. The objective of this study is to investigate whether *H.pylori* seropositivity is an independent risk factor for type 2 diabetes using secondary data analysis of a nationally representative sample. Evidence of such could help explain why established demographic characteristics are associated with increased risk of type 2 diabetes.

METHODS

The National Health and Nutrition Examination Survey (NHANES) is conducted each year by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). The NHANES provides cross-sectional data designed to assess the health and nutritional status of adults and children in the United States. The survey examines a nationally representative stratified, multistage probability sample of the civilian non-institutionalized population with oversampling of Mexican Americans and non-Hispanic Black participants. The survey combines an extensive health information interview, a complete physical examination, and extensive laboratory testing. NHANES 1999-2000 was the last release of this cross-sectional national survey that includes laboratory data on *H. pylori* status.

Variables of interest

Data files extracted for this study included demographic data, questionnaire data, examination data, and laboratory data. Participants were considered to have type 2 diabetes mellitus type 2 if they were told by their doctor they have diabetes, and age >5 when first told, or if they reported taking medication for diabetes. *H. pylori* seropositivity was determined using the Wampole Laboratories *H. pylori* IgG enzyme linked immunosorbent assay (ELISA). Specimens with a value of $\geq$ than 1.10 indicates the presence of detectable IgG antibody (*H. pylori* positive). Height, weight and waist circumference were measured as part of the physical examination using standardized protocols. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). In this study, a BMI < 25 was categorized as *normal weight*; a BMI between 25.0-29.9 was categorized as *overweight*; and a BMI $\geq$ 30 was categorized as *obese*. Socioeconomic indicators included education level, poverty to index ratio (PIR) and income category. Although the NHANES sample included a total of 9965 participants, sample sizes are reported for all variables to reflect available *H. pylori* and diabetes data as well as missing demographic data. In addition, sample sizes differed for stratified analyses and are provided in respective tables for reference.

Statistical analysis

All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, North Carolina). Descriptive statistics were compared across three racial/ethnic groups: non-Hispanic Whites, non-Hispanic Blacks and Mexican Americans. Sampling weights were used to adjust for nonresponse and oversampling in NHANES. Logistic regression modeling (using PROC SURVEYLOGISTIC) was used to compute odds ratio of having diabetes while adjusting for various confounders including age, race/ethnicity, BMI, waist circumference, education, PIR, income, birthplace and *H. pylori* status. Similarly, odds ratios were computed for *H. pylori* seropositivity adjusting for various confounders including age, race/ethnicity, education, PIR, income and birthplace. Subsequent modeling was run in four phases to explore whether *H. pylori* is an independent risk factor for diabetes. Modeling phases were stratified by: three age groups (60-85 year olds, 40-59 year olds and < 40 year olds); three race/ethnic groups; conditional

analyses stratified by both age group and racial/ethnic group; and finally, conditional analyses stratified by age group, racial/ethnic group and BMI group (<25 and ≥ 25).

RESULTS

Table 1 illustrates significant demographic differences across all ethnic/racial groups. A larger majority of non-Hispanic Blacks (73.6%,70.4%) and Mexican Americans (75.1%,78.2%) in this sample were under 40 years of age and had less than a high school education compared to non-Hispanic Whites, respectively (55.2%,37.2%). Indicators of socio-economic status (SES) followed education level trends, where non-Hispanic Blacks (36.7%) and Mexican Americans (39.2%) had more than one third of the sample population with incomes below $25,000 compared to non-Hispanic Whites (21.9%). *H.pylori* seropositivity was highest in Mexican American (43.7%), and lowest in non-Hispanic Whites (18.1%). Type 2 diabetes was lowest in non-Hispanic whites (4.3%) compared to non-Hispanic Blacks (5.9%).

Table 1. Demographic characteristics between ethnic/racial groups for NHANES 1999-2000 sample

	No. (%) White	No.(%) Black	No.(%) Mexican American	p value
Age category				
<40	1857 (55)	1639 (73.6)	2992 (75.1)	<.0001
40-59	560 (16.6)	285 (12.8)	451 (11.3)	<.0001
60-85	950 (28.2)	304 (13.6)	539 (13.5)	<.0001
Total n =	3367	2228	3982	
BMI category				
<25	1491 (51.4)	1146 (58.3)	1821 (55.5)	<.0001
25-29.9	744 (25.6)	382 (19.4)	860 (26.2)	<.0001
≥30	668 (23)	439 (22.3)	602 (18.3)	<.0001
Total n =	2903	1967	3283	
Education level				
Less than HS	1101 (37.2)	1325 (70.4)	2536 (78.2)	<.0001
Completion of HS	678 (22.9)	225 (11.9)	334 (10.3)	<.0001
Associates/College Degree	1177 (39.8)	333 (17.7)	373 (11.5)	<.0001
Total n =	2956	1883	3243	
PIR category				
≤.84	699 (20.8)	931 (41.8)	1692 (42.5)	<.0001
.85-1.45	425 (12.6)	359 (16.1)	932 (23.4)	<.0001
1.46-2.59	614 (18.2)	418 (18.8)	687 (17.3)	<.0001
≥2.60	1629 (48.4)	520 (23.3)	671 (16.9)	<.0001
Total n =	3367	2228	3982	
Income category				
<$25,000	630 (21.9)	639 (36.7)	1200 (39.2)	<.0001
$25,000-$64,999	1109 (38.5)	708 (40.7)	1365 (44.5)	<.0001

>$65,000	1143 (39.7)	392 (22.5)	500 (16.3)	<.0001
Total n =	2882	1739	3065	
Place of birth				
United States	3198 (99.9)	2055 (100)	2537 (69)	<.0001
Mexico	2 (0.1)	0 (0)	1141 (31)	<.0001
Total n =	3200	2055	3678	
H.pylori status				
Positive	461 (18.1)	662 (38.9)	1309 (43.7)	<.0001
Negative	2084 (81.9)	1038 (61.1)	1687 (56.3)	<.0001
Total n =	2545	1700	2998	
Diabetes status				
No diabetes	3067 (94.7)	2009 (93.4)	3521 (94.5)	<.0001
Type I diabetes	8 (0.2)	5 (0.2)	8 (0.2)	0.6514
Type II diabetes	138 (4.3)	126 (5.9)	181 (4.9)	0.0036
Borderline	26 (0.8)	12 (0.6)	16 (0.4)	0.0556
Total n =	3239	2152	3726	
Other	Mean±SD	Mean±SD	Mean±SD	p value
Waist circumference	88.313 (0.383)	81.596 (0.5)	83.449 (0.337)	<.0001
H. pylori values	0.648 (0.017)	1.091 (0.025)	1.150 (0.02)	<.0001

Table 2 displays odds ratio of having type 2 diabetes with unadjusted and adjusted models. Unadjusted model indicates *H.pylori* seropositivity was associated with nearly a 2-fold greater likelihood of having type 2 diabetes (1.927, 95% CI 1.142, 3.257) compared to those who were *H.pylori* negative. Other risk factors associated with having diabetes included Black race, overweight and obese status, and lower income ranges. Model 1 adjustments include all potentially confounding variables and Model 2 eliminates confounding variables that are not statistically significant in Model 1 or those that exhibit collinearity. After adjusting for confounding variables, *H.pylori* seropositivity was no longer associated with diabetes. Obese participants (BMI ≥30) were nearly 5 times (aOR 4.94, 95% CI 2.672, 9.133) more likely to have type 2 diabetes compared to those with BMI <25. Having an income less than $65,000 was associated with over two and half times increased odds of having diabetes compared to those with an income of at least $65,000. Non-Hispanic Blacks (2.436, 95% CI 1.489,3.984) were nearly two and half times more likely and Mexican Americans (1.896, 95% CI 1.002,3.587) had nearly twice the odds of having diabetes compared to Whites. Age also increased the odds of diabetes 5.5% each year.

Table 2. Odds ratio of having type II diabetes, NHANES 1999-2000

	Unadjusted odds ratio	95% CI	Adjusted* odds ratio	95% CI	Adjusted** odds ratio	95% CI
Age	1.054	(1.048, 1.059)	1.052	(1.041, 1.064)	1.055	(1.048, 1.062)
Race/ethnicity						
White	referent		referent		referent	
Black	1.813	(1.180, 2.786)	2.877	(1.359, 6.092)	2.436	(1.489, 3.984)
Mexican American	1.324	(0.651, 2.693)	2.112	(0.862, 5.176)	1.896	(1.002, 3.587)
BMI category						
Normal <25	referent		referent		referent	
Overweight 25-29.9	3.052	(1.627, 5.726)	0.699	(0.280, 1.747)	1.851	(0.948, 3.616)
Obese ≥30	7.622	(4.194, 13.852)	0.594	(0.206, 1.707)	4.94	(2.672, 9.133)
Education level						
Less than HS	1.385	(0.907, 2.114)	0.961	(0.517, 1.788)		
Completion of HS	1.578	(0.846, 2.945)	1.071	(0.522, 2.197)		
Associates/College Degree	referent		referent		referent	
PIR	0.856	(0.754, 0.973)	1.169	(0.951, 1.436)		
Income category						
<$25,000	4.658	(2.307, 9.406)	4.664	(1.255, 17.328)	2.605	(1.240, 5.471)
$25,000-$64,999	3.65	(1.869, 7.126)	3.493	(1.161, 10.507)	2.737	(1.330, 5.632)
>$65,000	referent		referent		referent	
H.pylori status						
Positive	1.927	(1. 142, 3.257)	0.975	(0.477, 1.992)	0.930	(0.536, 1.614)
Negative	referent		referent		referent	
Place Born						
US	referent		referent		referent	
Mexico	0.79	(0.406, 1.538)	1.616	(0.820, 3.175)		

PIR Poverty income ratio

*Model 1 Adjusted for age, race/ethnicity, BMI, waist circumference, education, PIR, income, birthplace, H.pylori status

**Model 2 Adjusted for age, race/ethnicity, BMI, income, H.pylori status

Table 3 demonstrates unadjusted and adjusted odds ratio of having *H.pylori* seropositivity where ethnicity is the biggest predictor. Non-Hispanic Blacks (3.693, 95% CI 2.832, 4.816) and Mexican Americans (3.512, 95% CI 2.418, 5.101) are more than three and a half times more likely to be positive for *H.pylori* than non-Hispanic Whites. Birthplace (in Mexico), lower levels of education and age were all associated with greater odds of *H.pylori* seropositivity. Both type 2 diabetes and *H.pylori* seropositivity were significantly associated with a set of the same covariates. This provides an explanation of why *H.pylori* was significantly associated with type 2 diabetes in

the unadjusted model, but not the case when the model for type 2 diabetes was adjusted by the variables related to *H.pylori.*

Table 3. Odds ratio of having positive *H.pylori* status, NHANES 1999-2000

	Unadjusted odds ratio	95% CI	Adjusted* odds ratio	95% CI	Adjusted** odds ratio	95% CI
Age	1.026	(1.020, 1.031)	1.041	(1.034, 1.048)	1.041	(1.035, 1.048)
Race/ethnicity						
White	referent		referent		referent	
Black	3.128	(2.441, 4.008)	3.481	(2.375, 5.100)	3.693	(2.832, 4.816)
Mexican American	3.591	(2.591, 4.976)	3.481	(2.737, 4.893)	3.512	(2.418, 5.101)
BMI category						
Normal <25	referent		referent		referent	
Overweight 25-29.9	1.354	(1.110, 1.652)	0.993	(0.707, 1.396)		
Obese ≥30	1.596	(1.288, 1.977)	1.047	(0.698, 1.571)		
Education level						
Less than HS	2.267	(1.750, 2.935)	2.063	(1.557, 2.735)	2.058	(1.562, 2.712)
Completion of HS	1.77	(1.242, 2.522)	1.44	(1.037, 2.000)	1.466	(1.049, 2.048)
Associates/College Degree	referent		referent		referent	
PIR category	0.788	(0.730, 0.852)	0.806	(0.714, 0.910)	0.8	(0.715, 0.895)
Income category						
<$25,000	2.456	(1.879, 3.211)	0.604	(0.386, 0.945)	0.579	(0.385, 0.873)
$25,000-$64,999	1.582	(1.047, 2.391)	0.718	(0.481, 1.071)	0.689	(0.441, 1.075)
>$65,000	referent		referent		referent	
Place Born						
US	referent		referent		referent	
Mexico	6.993	(4.975, 9.901)	2.681	(1.880, 3.817)	2.674	(1.855, 3.846)

BMI Body mass index

PIR Poverty income ratio

*Model 1 Adjusted for age, race/ethnicity, BMI, waist circumference, education, PIR, income, birthplace

**Model 2 Adjusted for age, race/ethnicity, education, PIR, income, birthplace

Our first series of stratified analyses by age groups is demonstrated in Table 4. Because *H. pylori* seropositivity and age are positively correlated, stratified analyses by age groups provides an alternative adjustment for age in examining *H. pylori* as an independent risk factor for diabetes. Note that for all age groups, *H.pylori* still did not have a significant impact on type 2 diabetes in adjusted models. The first model explored adjusted odds ratio of having diabetes among 60-85 year olds. Non-Hispanic Blacks (aOR 2.571, 95% CI 1.451, 4.556) and obese individuals (aOR 2.565, 95% CI 1.620, 4.061) are two and a half times more likely to have diabetes than non-

Hispanic Whites and normal weight (BMI <25) counterparts, respectively, in this age category. Similarly, among 40-59 year olds, non-Hispanic Blacks (aOR 2.55, 95% CI 1.116, 5.824) are two and half times more likely, while obese individuals (aOR 4.126, 95% Ci 1.223, 13.914) are four times more likely to have diabetes than non-Hispanic Whites and normal weight individuals, respectively. Additionally, those with mid-range incomes ($25,000-$64,999) were at higher risk (aOR 3.651, 95% CI 1.394, 9.565) of type 2 diabetes compared to those with the highest incomes (≥$65,000). In the <40-year-old age group, higher BMIs and lower income categories were strong predictors of having type 2 diabetes. Specifically, compared to having BMI category <25, being overweight (143.244, 95% CI 11.161, >999) or obese (415.145, 95% 43.642, >999) significantly increased the odds of having type 2 diabetes. Income level also significantly increased the likelihood of having type 2 diabetes for those with income ranges <$25,000 (29.265, 95% CI 2.204, 388.529) and $25,000-$64,999 (14.727, 95% CI 1.815, 119.476) compared to those with incomes >$65,000.

Table 4. Odds ratio of having type II diabetes stratified by age groups, NHANES 1999-2000

	Model 1: Age group 60-85		Model 2: Age group 40-59		Model 3: Age group <40	
	Adjusted* odds ratio	95% CI	Adjusted* odds ratio	95% CI	Adjusted* odds ratio	95% CI
Race/ethnicity	n = 1092		n = 936		n = 3505	
White	referent		referent		referent	
Black	2.571	(1.451, 4.556)	2.55	(1.116, 5.824)	0.897	(0.401, 2.006)
Mexican American	1.258	(0.481, 3.289)	2.659	(0.964, 7.333)	0.736	(0.245, 2.213)
BMI category						
Normal <25	referent		referent		referent	
Overweight 25-29.9	1.264	(0.667, 2.394)	1.428	(0.353, 5.787)	143.244	(11.161, >999)
Obese ≥30	2.565	(1.620, 4.061)	4.126	(1.223, 13.914)	415.145	(43.642, >999)
Education level						
Less than HS	1.833	(0.865, 3.882)	1.039	(0.603, 1.791)	0.594	(0.107, 3.298)
Completion of HS	1.362	(0.552, 3.362)	0.409	(0.160, 1.050)	2.862	(0.456, 17.973)
Associates/College Degree	referent		referent		referent	
Income category						
<$25,000	1.711	(0.708, 4.134)	2.381	(0.775, 7.321)	29.265	(2.204, 388.529)
$25,000-$64,999	1.68	(0.610, 4.630)	3.651	(1.394, 9.565)	14.727	(1.815, 119.476)
>$65,000	referent		referent		referent	
H.pylori status						
Positive	0.859	(0.383, 1.927)	1.107	(0.574, 2.137)	0.414	(0.161, 1.067)
Negative	referent		referent		referent	

CI Confidence Interval

BMI Body mass index

* Adjusted for race/ethnicity, BMI, education, income, H.pylori status

Another series of stratified analyses by race/ethnic group is depicted in Table 5. *H.pylori* was not significant in any of the three ethnic group models. In the first model examining non-Hispanic Whites only, those with older age ranges, obese BMI status and lower income categories had greater likelihood of diabetes compared to their respective reference groups. The adjusted odds ratio of having diabetes was highest for 60-85 year olds (8.538, 95% CI 5.248, 13.891) and also increased for 40-59 year olds (3.351, 95% CI 1.544, 7.275) compared to those <40 years of age. Having a BMI ≥30 or income <$65,000 increased the likelihood of having diabetes compared to those with BMI <25 and incomes > $65,000, respectively. Similar patterns emerged for age and obesity in the stratified analyses for non-Hispanic Blacks and Mexican Americans (Table 5) although the adjusted odds ratios were markedly higher for age in these racial/ethnic groups.

Table 5. Odds ratio of having type II diabetes stratified by race/ethnic groups, NHANES 1999-2000

	Model 1: White		Model 2: Black		Model 3: Mexican American	
	Adjusted* odds ratio	95% CI	Adjusted* odds ratio	95% CI	Adjusted* odds ratio	95% CI
Age category	n = 2100		n = 1247		n = 2186	
<40	referent		referent		referent	
40-59	3.351	(1.544, 7.275)	11.504	(3.242, 40.829)	19.809	(8.708, 45.062)
60-85	8.538	(5.248, 13.891)	34.651	(8.048, 149.196)	22.957	(9.364, 56.282)
BMI category						
Normal <25	referent		referent		referent	
Overweight 25-29.9	1.68	(0.648, 4.355)	2.062	(0.611, 6.965)	2.084	(0.891, 4.874)
Obese ≥30	4.583	(2.153, 9.757)	5.843	(2.178, 15.680)	3.574	(2.183, 5.850)
Education level						
Less than HS	1.003	(0.560, 1.796)	0.779	(0.344, 1.760)	2.417	(1.657, 3.525)
Completion of HS	1.014	(0.421, 2.440)	0.522	(0.198, 1.377)	1.085	(0.413, 2.346)
Associates/College Degree	referent		referent		referent	
Income category						
<$25,000	4.198	(1.484, 11.879)	1.878	(0.936, 3.768)	1.088	(0.352, 3.365)
$25,000-$64,999	4.015	(1.479, 10.903)	2.041	(0.942, 4.425)	1.069	(0.378, 3.023)
>$65,000	referent		referent		referent	
H.pylori status						
Positive	0.813	(0.327, 2.020)	1.399	(0.573, 3.413)	0.893	(0.488, 1.637)
Negative	referent		referent		referent	

CI Confidence Interval

BMI Body mass index

* Adjusted for age, BMI, education, income, H.pylori status

Finally, conditional analyses examining the association between *H.pylori* and diabetes were not significant for all age groups crossed by race/ethnicity groups (data not shown). However, when we further stratified these groups by BMI category, there was a significant relationship only in the conditional analysis for Mexican American, 60-85 age group, ≥25 BMI. In this subset of the NHANES population, the adjusted odds ratio of having type 2 diabetes was higher for participants who were *H.pylori* positive (6.10, 95% CI 2.98-12.45) compared to those who were *H.pylori* negative.

Table 6. Odds ratio of type II diabetes in participants with *H.pylori* (+) compared to *H.pylori* (-) seropositivity: 18 models, stratified by race/ethnic, age & BMI, NHANES 1999-2000

		Mexican American			**Black**			**White**		
		n	Adjusted* odds ratio	95% CI	n	Adjusted* odds ratio	95% CI	n	Adjusted* odds ratio	95% CI
Age 60-85	BMI < 25	261	0.87	(0.36-2.06)	132	0.72	(0.3-1.76)	399	1.05	(0.39-2.78)
	BMI ≥25	64	6.10	(2.98-12.45)	35	0.57	(0.12-2.75)	205	0.62	(0.8-4.9
Age 40-59	BMI < 25	256	1.31	(0.48-3.59)	137	1.27	(0.56-2.90)	285	1.32	(0.48-3.65)
	BMI ≥25	63	0.27	(0.08-0.85)	53	na	na	142	na	na
Age <40	BMI < 25	610	0.16	(0.01-1.70)	324	2.75	(0.11-70.25)	401	na	na
	BMI ≥25	1059	na	na	na	na	na	na	na	na

CI Confidence Interval

BMI Body mass index

* Adjusted for income

na Cells are suppressed or incomplete because all observations have the same response.

DISCUSSION

The prevalence of diabetes in this NHANES 1999-2000 sample was consistent with similar estimates provided by the National Health Interview Survey (NHIS). Specifically, CDC's Division of Diabetes Translation reports the percentage of U.S. population with diagnosed diabetes was 4.0% in 1999 and 4.4% in 2000, with incremental increases over time (Centers for Disease Control and Prevention, 2015). Our findings indicate prevalence of diabetes ranged from 4.5% for non-Hispanic Whites to 6.1% for Blacks for the same time frame, 1999-2000. Our initial exploration to determine whether *H.pylori* plays a role in explaining racial and ethnic disparities in diabetes diagnosis indicated that those with *H.pylori* seropositivity were nearly two times as likely to have diabetes compared to *H.pylori* negative individuals. Indeed, we showed that increased age, Black *or* Mexican American race/ethnicity and lower education levels were all significantly associated with having *H.pylori*. However, after adjusting for such significant confounders in models examining the odds ratio of having type 2 diabetes, *H.pylori* was no longer statistically significant. Hence, *H.pylori* does not appear to be an independent risk factor for type 2 diabetes, and to that end, does not help to explain the racial disparities so typically witnessed in such datasets.

Not surprisingly, age, minority race/ethnicity, obese status, and lower incomes all independently increased the odds ratio of having diabetes. With regards to age, this nationally representative sample depicted a relatively young and uneducated Black and Mexican American population, where roughly three-quarters were under the age of 40 and had less than a high school education. This has huge implications for future diabetes forecasts, healthcare costs and quality of life, particularly for disadvantaged ethnic minority groups. It has been estimated that 1 in 3 individuals will have diabetes by 2050, largely attributable to an aging US population, increasing numbers of higher-risk minority groups and people with diabetes living longer (Boyle, Thompson, Gregg, Barker, & Williamson, 2010). Diagnosis, treatment, education and support of these populations will need a concerted national effort to reach the masses to provide quality healthcare and health promotion strategies in a timely and sustainable manner. Current estimates of people with type 2 diabetes receiving diabetes self-management education (DSME), ongoing support (DSMS) or medical nutrition therapy (MNT) is low and has been understudied as indicated by the dearth of literature. For example, only 4% of Medicare participants received DSME/S and/or MNT within 12 months of diagnosis (Duncan et al., 2009). Similarly, only 6.8% of individuals with newly diagnosed type 2 diabetes with private health insurance participated in DSME/S within 12 months of diagnosis (Li et al., 2014).

Because age and race/ethnicity are not modifiable, we explored these risk factors more closely by stratifying age groups and race/ethnicity groups to better understand relative contributions of modifiable risk factors and whether *H. pylori* may play a role in certain subgroups, such as Mexican Americans or in 60-85 year olds for example. Although *H. pylori* was not associated with increased odds of having diabetes in nearly all of our analyses, stratifying by age groups yielded other noteworthy findings in adjusted models. In the under-40 age group, obese and overweight status drastically increased the odds of having diabetes compared to normal weight. Similarly, incomes below $65,000 had drastic increases in the likelihood of having diabetes compared to those with incomes above $65,000. Under-40 is the only age category where race/ethnicity did not increase the odds of having diabetes. However, these findings should be interpreted with caution since diabetes self-report in this sample may be a reflection of racial/ethnic disparities in health care access and diagnosis of diabetes. In older age groups, income became less significant and race/ethnicity became more consequential as risk factors for diabetes. Specifically, in both 40-59 year olds and 60-85 year olds, being Black increased the likelihood of having diabetes two and half times over Whites. Similarly, obesity, but not overweight status, was associated with increased odds of diabetes compared to normal weight in both older age groups.

Overall, these models seem to indicate that across the life span, weight status, obesity in particular, is the strongest predictor of having diabetes followed by Black race. Income, although significant in some instances for younger age groups, may in part explain the circumstances contributing to weight status and thus, play a mediating and/or moderating role in development of diabetes. Interestingly, compared to Whites, Mexican American ethnicity was not statistically significant for diabetes in any of the stratified age groups. This finding was a bit surprising, but considering the reported prevalence of diabetes (4.9%) in this sample of Mexican Americans it is possible there was underreporting or undiagnosed diabetes in this group. The finding that Black race was a significant independent risk factor across older age groups causes one to consider the cumulative life experiences and stressors that may very well be contributing to the development of diabetes apart from those mechanisms related to weight status.

When examining independent risk factors stratified by race/ethnic groups, there appear to be notable racial disparities of having diabetes by age. Compared to the under-40 age group, Blacks and Mexican Americans have disproportionately higher odds of having diabetes in 40-59 year olds and 60-85 year olds relative to Whites making the same comparisons. These findings are independent and markedly higher than a comparable trend noted across groups for obesity status. Moreover, for whites only, incomes below $65,000 were associated with a greater likelihood of having diabetes, similar to that seen with obesity. Taken together, this may suggest that for Whites, experiences related to poverty are associated with greater likelihood of having diabetes, while for Blacks and Mexican Americans it may be related to a genetic predisposition or their cumulative experiences as members of a minority group in the US, or some other unknown factor or any a combination of these factors. Scholars examining the influence of various forms of stress on health, including poverty, migration, segregation, racism and discrimination, have provided empirical evidence that its effects are real and thus, should be considered with greater conscientiousness in unraveling the mechanisms related to development of type 2 diabetes in ethnic minority groups (Williams & Mohammed, 2009; Williams, Mohammed, Leavell, & Collins, 2010). On the other hand, studies investigating the association between work-related stress and type 2 diabetes have not supported such a link, although too few studies and considerable methodological weakness of studies have been identified (Cosgrove, Sargeant, Caleyachetty, & Griffin, 2012). Similarly, a longitudinal study in 9,222 Australian adults did not find an association between work-related stress and diabetes (Renzaho, Houng, Oldroyd, Nicholson, D'Esposito, & Oldenburg, 2013). However, personal stress (indicated by a 'yes' to experiencing separation from spouse or long-term partner, victim of physical violence and being detained in jail or correctional facility) increased the likelihood of type 2 diabetes (OR=1.47, $p<0.05$) in the same study. Still, others suggest that number and nature of life events (such as death of a spouse or moving from a house) are important to consider in relation to diabetes risk (Mooy, deVries, Grootenhuis, Boutner, & Heine, 2000).

Although our findings generally do not demonstrate an association between *H. pylori* seropositivity and type 2 diabetes, there were findings to suggest that this may be the case in a subgroup of the population, namely, in 60-85 year old Mexican Americans with a BMI $\geq$25. This would typically be written off as a chance finding, except that it supports a seminal study with a similar demographic makeup (Jeon et al., 2012). Interestingly, Jeon et al. demonstrated for the first time that *H.pylori* infection leads to an increased rate of incident diabetes in a prospective cohort of Latino elderly in California. Future studies should focus on this subgroup to delineate whether the association between *H.pylori* infection and type 2 diabetes is real, while carefully considering measurement of potential mediating and moderating variables relevant to this ethnic group.

In addition, there are study limitations to bear in mind. First, diabetes diagnosis was based on self-report. Some estimates for the sensitivity of self-reported diabetes ranged from 66.7% to 85.2% in other studies, which may lead to a bias toward the null (Bowlin, Morrill, Nafziger, Lewis, & Pearson, 1996; The Italian Longitudinal Study on Aging Working Group, 1997; Goldman, Lin, Weinstein, & Lin, 2003; Molenaar, Van Ameijden, Grobbee, & Numans, 2007). A diabetes biomarker, such as HbAIc, ideally would be included in the analysis, but in this study that would have decreased the sample size even further since such measures were not collected on all NHANES participants. Second, it is important to note that *H. pylori* status was not determined by histologic detection of organisms in mucosal biopsy specimens, which is considered the golden

standard (He et al., 2014). Such a procedure is not feasible in a nationally representative survey sample of this nature. In addition, NHANES use of serum *H. pylori*-specific IgG antibodies may include false-positives or false-negatives, which may also skew findings toward the null. Finally, as this study is based on secondary data analysis, selection and construction of variables was limited to those available through NHANES datasets.

Future research should consider prospective study designs to examine the temporal nature of H. pylori and type 2 diabetes if this relationship truly exists. In addition, research designs should consider gold standard procedures alongside other valid (and more feasible) measures for clinical diagnosis and delineation of disease development and progression for type 2 diabetes and *H.pylori* colonization. This could provide better insight of disease progression (or lack thereof) among individuals as a function of genetic and lifestyle variations and interactions. Moreover, more attention should focus on the physiological response to various forms of stress experienced by different groups and its effect on health. For example, a research design focused solely on pregnant women at risk for development of gestational diabetes (which would inherently include members of ethnic minority groups) could provide a perfect milieu of stressors in a shortened timeline to examine interrelationships of such variables on the development of gestational diabetes. Much remains to be explored to explain health disparities related to type 2 diabetes, where arguably the effects of various types of stress on health over the course of the lifespan need greater consideration and support in the world of diabetes research.

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