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Additive impact of diabetes and Helicobacter pylori infection on all-cause mortality, diabetic mortality, and cardiovascular mortality: a longitudinal nationwide population-based study

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Abstract

Background Diabetes mellitus (DM) and Helicobacter pylori infection (HPI) pose increasing public health challenges in aging societies, sharing common pathophysiological mechanisms, and linked to significant health risks. Our study examines their respective impacts on all-cause and cardiovascular mortalities in a comprehensive longitudinal population-based analysis.

Methods The study analyzed data from the National Health and Nutrition Examination Survey (NHANES) database conducted between 1999 and 2019, which included information on Diabetes mellitus status and Helicobacter pylori infection status. Mortality data were obtained from the same database mentioned above.

Results Among the 2719 participants, 1362 (50.1%) were free of both diabetes mellitus (DM) and Helicobacter pylori infection (HP) (DM −/HP −), 140 (5.1%) had DM alone (DM +/HP −), 1011 (37.2%) had HP alone (DM −/HP +), and 206 (7.6%) had both DM and HP (DM +/HP +). Compared to the DM −/HP − group, the DM +/HP − and DM + /HP + groups demonstrated increased all-cause mortality with adjusted hazard ratios (HRs) of 1.40 (95% [CI] 1.07–1.78) and 1.46 (95% CI 1.15–1.84), respectively. For diabetic mortality, DM +/HP− group and DM + /HP + group showed increased HR of 6.30 (95% CI 1.30–30.43) and 8.56 (95% CI 1.98–36.94), respectively. For cardiovascular mortality, the DM + /HP− group and DM + /HP + group exhibited increased HR of 1.75 (95% CI 1.14–2.69) and 1.98 (95% CI 1.40–2.79), respectively. The DM + /HP + cohort displayed the highest risk of overall mortality (p for trend = 0.003), diabetic mortality (p for trend < 0.0001), an6d cardiovascular mortality (p for trend < 0.0001).

Conclusions The concurrent presence of DM and Helicobacter pylori infection significantly amplifies the risk of all-cause, cardiovascular, and diabetic mortality. Individuals with either condition may necessitate heightened management to prevent the onset of the other ailment and reduce mortality rates.

Keywords Diabetes mellitus, Helicobacter pylori infection, NHANES, Population-based study, Mortality

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Introduction

The incidence and prevalence of diabetes mellitus (DM) have been increasing sharply worldwide [1]. The prevalence of diabetes in China, the USA, and globally was reported as 11.7%, 11.6%, and 6.1%, respectively [2], resulting in global health expenditure of Us$966 billion globally [3]. Helicobacter pylori (H. pylori), a Gram-negative bacterium, colonizes the human stomach and exhibits a strong correlation with a spectrum of gastric disorders, encompassing gastritis, peptic ulcer disease, and gastric cancer [4]. Helicobacter pylori (H. pylori) infections impact nearly half of the global population, with a progressively rising incidence observed in developed nations [5]. Intriguingly, there is growing evidence of a bidirectional relationship between diabetes and H. pylori infection, with each condition potentially exacerbating the risk of the other [6, 7].

Research conducted over the past two decades has indicated potential links between H. pylori infection and various extra gastric conditions, including idiopathic thrombocytopenic purpura, iron deficiency anemia, and atherosclerotic disease [8, 9]. Additionally, associations with cardiovascular disease, diabetes mellitus (DM), nonalcoholic fatty liver disease, and other metabolic syndromes have been suggested [10]. Several studies have indicated a heightened prevalence of H. pylori infection [6, 11], lower eradication rates [12, 13], and increased reinfection rates [14] among diabetic individuals compared to controls. To date, no longitudinal studies have investigated the cumulative impact of diabetes and H. pylori infection on cardiovascular or all-cause mortality. Given the widespread prevalence and adverse health consequences associated with both conditions, assessing their combined effects on mortality in the general population could provide valuable insights.

Therefore, this study aimed to assess the influence of both diabetes and H. pylori infection on overall and cardiovascular mortality among American adults, utilizing nationally representative data.

Materials and methods

Study design and population

The study utilized data from the NHANES (National Health and Nutrition Examination Survey) database, administered by the Centers for Disease Control and Prevention (CDC) in the United States. This comprehensive program gathers information on individuals' health and nutritional status through interviews, physical assessments, and laboratory analyses. Participants were chosen employing a two-stage stratified cluster sampling method, utilizing population and housing census information. Data collection involved household interviews and standardized physical assessments. Prior to the survey, written informed consent was obtained from each participant, and secondary anonymized data were utilized for analysis. The study focused on data from the survey conducted between 1999 and 2019, during which participants underwent testing for H. pylori infection. The NHANES database is publicly available at https://www.cdc.gov/nchs/nhanes/index.htm.

The NHANES database comprised a total of 3419 participants from 1999 to 2019. Among them, individuals who underwent H. pylori infection testing and had available data on blood glucose were included. After excluding participants with missing data on metabolic parameters or survival status, 2719 participants were deemed eligible for the final analysis.

Assessment of diabetes status

Blood samples were collected from participants after a minimum 8 h fast. Enzymatic assays were employed to measure fasting blood glucose (FBG), lipid profile, and creatinine levels using the Hitachi Automatic Analyzer 7600 (Hitachi, Ltd., Tokyo, Japan). Vitamin D levels were assessed using a radioimmunoassay (PerkinElmer, Turku, Finland). Diabetes mellitus (DM) was defined as FBG levels $\geq$ 126 mg/dL, the use of antidiabetic medication, or a physician's diagnosis of DM.

Helicobacter pylori status

NHANES employed an enzyme-linked immunoassay (ELISA) to assess H. pylori exposure through IgG antibody detection [15]. However, specific IgG results were not included in the NHANES datasets. The ELISA method exhibited comparable sensitivity, specificity, and reproducibility to other antibody serological tests, such as immunofluorescence, complement fixation, hemagglutination, and radioimmunoassays. Standard ELISA cut-offs were applied to classify participants as H. pylori seropositive (optical density (OD) value $\geq$ 1.1) or seronegative (OD value < 0.9) [16]. Equivocal values (0.9–1.1) were excluded from the analysis to ensure precise statistical outcomes in this study.

Participant grouping

Based on these definitions, the participants were grouped into the following four groups according to the presence of diabetes and H. pylori infection: (1) no diabetes or H. pylori infection (DM −/HP −), (2) with diabetes but no H. pylori infection (DM +/HP −), (3)no diabetes but with H. pylori infection (DM −/HP +), and (4) with both diabetes and H. pylori infection (DM +/HP +).

Covariates

The survey questionnaire collected various participant data, encompassing age, gender, race, education level,

smoking and alcohol consumption habits, hypertension status, BMI, waist circumference, hemoglobin level, platelet count, HbA1c level, total bilirubin, triglycerides (TG), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), urinary albumin-to-creatinine ratio (UACR), mortality status, and family income. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, or as having received antihypertensive treatment. Smoking status was stratified into three categories: non-smokers, former smokers, and current smokers. Non-smokers comprised individuals who had either never smoked or had smoked fewer than 100 cigarettes in their lifetime. Former smokers were individuals who had previously smoked at least 100 cigarettes but had ceased smoking. Current smokers were participants who had smoked at least 100 cigarettes in their lifetime and reported consuming cigarettes within the past 30 days [17]. Alcohol consumption patterns were categorized into four groups. Never drinkers reported consuming less than 12 drinks in their lifetime. Former drinkers had consumed more than 12 drinks in their lifetime but had abstained from alcohol for at least one year. Current drinkers were further subdivided into mild, moderate, or heavy drinkers. Heavy current drinkers were women who consumed three or more drinks per day or men who consumed four or more drinks per day, with at least five or more binge drinking episodes per month. Moderate drinkers were women who consumed two or more drinks per day or men who consumed three or more drinks per day. Moreover, the educational level was categorized into 5 groups: College Graduate or above, some college or AA degree, high school Grad/GED or equivalent, 9-11th Grade and less than 9th Grad. Family income is classified into three categories: high income, moderate income, and low income.

Study endpoint and outcomes

The main outcomes investigated in this study comprised mortality rates associated with all causes, diabetes, and cardiovascular conditions. Vital status data were sourced from the National Death Index, supplied by the National Center for Health Statistics (NCHS), encompassing comprehensive records up to December 2019.

Statistical analysis

R version 3.4.0 was used to perform the data analysis (R Foundation for Statistical Computing, Vienna, Austria; available at http://www.R-project.org). Continuous variables are expressed as means ± standard deviations, while categorical variables are presented as frequencies with weighted percentages. The Cox proportional hazard model was employed to estimate the hazard ratio (HR) and 95% confidence interval (CI) for mortality based on the presence of diabetes mellitus (DM) and Helicobacter pylori (HP) infection. The crude model included only group 3, while model 1 was adjusted for age and sex. Model 2 was further adjusted for age, sex, ethnicity, marital status, and family income, and model 3 additionally incorporated adjustments for BMI, waist circumference, triglycerides (TG), total cholesterol, high-density lipoprotein (HDL), total bilirubin, smoking status, urine albumin-to-creatinine ratio (UACR), and alcohol use. To ensure the reliability of our results, sensitivity analyses were conducted by excluding participants with a history of death within 2 years for any reason and those under 40 years old. We also conducted corresponding subgroup analysis, dividing participants into different subgroups based on age, gender, and presence of hypertension, to study the impact of Diabetes mellitus (DM) and Helicobacter pylori infection (HPI) on mortality.

Results

Baseline characteristics

Among the 2719 participants, 1362 (50.1%) were free of both diabetes mellitus (DM) and Helicobacter pylori infection (HP) (DM−/HP−), 140 (5.1%) had DM alone (DM+/HP−), 1011 (37.2%) had HP alone (DM−/HP+), and 206 (7.6%) had both DM and HP (DM+/HP+). Table 1 outlines the baseline characteristics of participants across the four groups. Participants in the DM+/HP+group had significantly higher BMI compared to the other groups (27.4 vs 30.0 vs 27.7 vs 30.3, $p < 0.001$). Moreover, TG and UACR levels were notably elevated in the DM+/HP+group compared to the other groups (all $p < 0.001$). Additionally, the prevalence of hypertension and dyslipidemia was higher in participants with DM or HP compared to those without DM or HP (all $p < 0.001$). Hypertension was more prevalent among participants with DM or HP compared to those without either condition. ($p < 0.001$).

All-cause, cardiovascular, and diabetic mortality according to DM and HP status

We observed that the group with both DM and HP exhibited the lowest survival rate. Kaplan–Meier survival analysis curves indicated that the groups without DM or HP infection had the highest survival rate, followed by the group with HP alone, then the group with DM alone. The survival rates followed a descending order, with the group having both DM and HP infection displaying the lowest survival rate, followed by the group with DM but without HP infection, then the group without DM but with HP infection, and finally, the group without both DM and HP infection exhibiting the highest survival rate (P-log rank < 0.001, Fig. 1).

Table 1 Demographic and clinical characteristics of study participants

	[ALL] N = 2719	H_pylori−/DM− N = 1362	H_pylori−/ DM + N = 140	H_pylori + / DM− N = 1011	H_pylori + / DM + N = 206	p.overall
hp	1.20 (1.11)	0.31 (0.19)	0.38 (0.23)	2.31 (0.71)	2.24 (0.70)	0.000
Age	50.5 (18.3)	46.5 (18.3)	64.2 (12.7)	51.6 (17.8)	63.0 (12.0)	< 0.001
Sex						0.327
Female	1350 (49.7%)	698 (51.2%)	65 (46.4%)	483 (47.8%)	104 (50.5%)	
Male	1369 (50.3%)	664 (48.8%)	75 (53.6%)	528 (52.2%)	102 (49.5%)	
Eth1						
Mexican American	736 (27.1%)	220 (16.2%)	29 (20.7%)	398 (39.4%)	89 (43.2%)	
Non-hispanic black	454 (16.7%)	171 (12.6%)	23 (16.4%)	210 (20.8%)	50 (24.3%)	
Non-Hispanic white	1273 (46.8%)	877 (64.4%)	78 (55.7%)	279 (27.6%)	39 (18.9%)	
Other hispanic	183 (6.73%)	62 (4.55%)	7 (5.00%)	95 (9.40%)	19 (9.22%)	
Other race-including multi-racial	73 (2.68%)	32 (2.35%)	3 (2.14%)	29 (2.87%)	9 (4.37%)	
Marital						< 0.001
Living with partner	117 (4.30%)	53 (3.89%)	3 (2.14%)	55 (5.44%)	6 (2.91%)	
Married	1569 (57.7%)	764 (56.1%)	86 (61.4%)	595 (58.9%)	124 (60.2%)	
Never married	427 (15.7%)	280 (20.6%)	7 (5.00%)	130 (12.9%)	10 (4.85%)	
Other	606 (22.3%)	265 (19.5%)	44 (31.4%)	231 (22.8%)	66 (32.0%)	
Edu						< 0.001
9-11th grade (includes 12th grade with no diploma)	534 (19.6%)	192 (14.1%)	32 (22.9%)	244 (24.1%)	66 (32.0%)	
College graduate or above	430 (15.8%)	323 (23.7%)	12 (8.57%)	87 (8.61%)	8 (3.88%)	
High school grad/GED or equivalent	615 (22.6%)	337 (24.7%)	45 (32.1%)	212 (21.0%)	21 (10.2%)	
Less than 9th grade	503 (18.5%)	102 (7.49%)	26 (18.6%)	293 (29.0%)	82 (39.8%)	
Some college or AA degree	637 (23.4%)	408 (30.0%)	25 (17.9%)	175 (17.3%)	29 (14.1%)	
BMI	27.8 (5.52)	27.4 (5.53)	30.0 (5.84)	27.7 (5.25)	30.3 (5.62)	< 0.001
Waist_circumference	95.5 (14.0)	93.9 (14.1)	105 (13.5)	94.9 (13.3)	104 (12.4)	< 0.001
Hemoglobin_g.dl	14.4 (1.47)	14.5 (1.43)	14.4 (1.50)	14.4 (1.51)	14.1 (1.55)	0.002
PLT	263 (65.1)	263 (65.9)	249 (62.7)	266 (63.5)	254 (67.7)	0.009
HbA1c	5.60 (1.13)	5.22 (0.36)	7.68 (1.92)	5.36 (0.35)	7.86 (1.89)	0.000
Total_bilirubin	9.88 (4.96)	10.1 (5.24)	9.33 (4.79)	9.80 (4.69)	9.28 (4.44)	0.067
TG	1.98 (1.69)	1.80 (1.49)	2.62 (2.06)	1.99 (1.68)	2.75 (2.30)	< 0.001
Total_cholesterol	5.28 (1.04)	5.23 (0.99)	5.26 (1.06)	5.34 (1.06)	5.37 (1.18)	0.053
HDL	1.31 (0.40)	1.36 (0.41)	1.16 (0.35)	1.29 (0.39)	1.18 (0.35)	< 0.001
LDL	3.07 (0.89)	3.05 (0.88)	2.90 (0.87)	3.14 (0.91)	2.95 (0.87)	0.001
UACR	57.3 (481)	23.4 (117)	202 (759)	26.5 (132)	335 (1547)	< 0.001
Hypertension						< 0.001
No	1597 (58.7%)	897 (65.9%)	44 (31.4%)	589 (58.3%)	67 (32.5%)	
Yes	1122 (41.3%)	465 (34.1%)	96 (68.6%)	422 (41.7%)	139 (67.5%)	
Mortstat	0.32 (0.47)	0.24 (0.43)	0.64 (0.48)	0.31 (0.46)	0.62 (0.49)	< 0.001
Smoke						< 0.001
Former	747 (27.5%)	342 (25.1%)	61 (43.6%)	268 (26.5%)	76 (36.9%)	
Never	1378 (50.7%)	729 (53.5%)	62 (44.3%)	491 (48.6%)	96 (46.6%)	
Now	594 (21.8%)	291 (21.4%)	17 (12.1%)	252 (24.9%)	34 (16.5%)	
Alcohol.user						< 0.001
Former	528 (19.4%)	191 (14.0%)	48 (34.3%)	207 (20.5%)	82 (39.8%)	
Heavy	548 (20.2%)	270 (19.8%)	17 (12.1%)	234 (23.1%)	27 (13.1%)	
Mild	888 (32.7%)	499 (36.6%)	42 (30.0%)	298 (29.5%)	49 (23.8%)	
Moderate	373 (13.7%)	222 (16.3%)	9 (6.43%)	129 (12.8%)	13 (6.31%)	
Never	382 (14.0%)	180 (13.2%)	24 (17.1%)	143 (14.1%)	35 (17.0%)	
Family_income						< 0.001

Table 1 (continued)

	[ALL] N = 2719	H_pylori−/DM− N = 1362	H_pylori−/ DM + N = 140	H_pylori + / DM− N = 1011	H_pylori + / DM + N = 206	p.overall
High	884 (32.5%)	582 (42.7%)	39 (27.9%)	230 (22.7%)	33 (16.0%)	
Low	818 (30.1%)	294 (21.6%)	42 (30.0%)	393 (38.9%)	89 (43.2%)	
Medium	1017 (37.4%)	486 (35.7%)	59 (42.1%)	388 (38.4%)	84 (40.8%)	

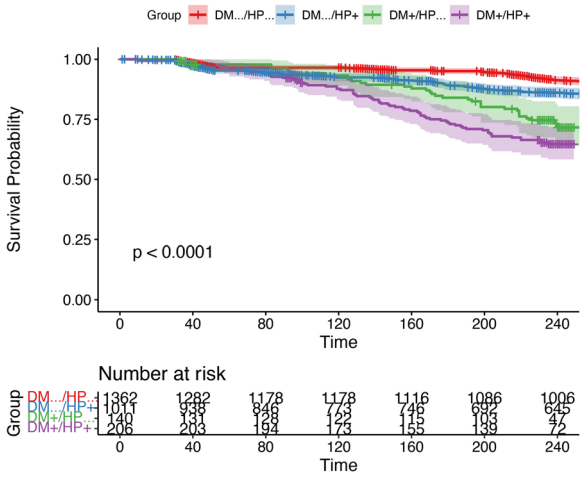

Fig. 1 Survival curves were plotted for the following four groups: individuals without diabetes mellitus or Helicobacter pylori infection (DM −/HP −), those with diabetes mellitus alone (DM + / HP −), individuals with Helicobacter pylori infection alone (DM −/ HP +), and those with both diabetes mellitus and Helicobacter pylori infection (DM + /HP +)

In all models, patients with DM alone, HP alone, or both DM and HP were associated with a higher risk of all-cause mortality compared to those without DM and HP (Table 2). Hazard ratios (HRs) for all-cause mortality, cardiovascular disease (CVD) mortality, and diabetes-related mortality among different groups of patients based on diabetes mellitus (DM) and Helicobacter pylori (HP) infection status. HRs are presented with their corresponding 95% confidence intervals (CI). The reference group is patients without both DM and HP infection. Adjusted models include age, gender, and other relevant covariates. In the fully adjusted model, we included the following factors for adjustment: age, sex, eth1, marital status, family income, education level (edu), BMI, waist circumference, TG (triglycerides), total cholesterol, HDL (high-density lipoprotein), total bilirubin, HbA1c, smoking status, UACR (urine albumin-to-creatinine ratio), hypertension, and history of cardiovascular disease (CVD). Individuals with DM alone had a 40% higher risk of all-cause death (HR 1.40; 95% CI 1.07–1.78), those with HP alone had a 10% higher risk (HR 1.08; 95% CI 0.85–1.16), and those with both DM and HP had a 56% higher risk (HR 1.46; 95% CI 1.15–1.84). Similarly, the risk of CVD death was 75% higher in individuals with DM alone (HR 1.75; 95% CI 1.14–2.69), and 98% higher in patients with both DM and HP (HR 1.98; 95% CI 1.40–2.79). Furthermore, the risk of death related to diabetes exhibited a comparable trend, showing a 6.30-fold higher risk among individuals with DM alone (HR 6.30 95% CI 1.30–30.43), and an 8.56-fold higher risk among patients with both DM and HP (HR 8.56 95% CI 1.98–36.94) (Tables 3 and 4).

Table 2 Survival rates and hazard ratios for all-cause mortality by diabetes mellitus (DM) and helicobacter pylori (HP) infection status

hp5 ~ ~ permth_int,mortstat	Group3							
	Crude model		Model 1		Model 2		Model 3	
Character	95%CI	P	95%CI	P	95%CI	P	95%CI	P
H_pylori−/DM−	Ref.		Ref.		Ref.		Ref.	
H_pylori−/DM +	3.69 (2.92,4.66)	< 0.0001	2.53 (2.25,2.88)	< 0.001	1.70 (1.53,1.88)	0.001	1.48 (1.17,1.88)	0.005
H_pylori + /DM−	1.33 (1.14,1.55)	< 0.001	1.05 (0.90,1.23)	0.56	1.02 (0.87,1.20)	0.85	1.10 (0.87,1.19)	0.27
H_pylori + /DM +	3.35 (2.73,4.10)	< 0.0001	2.56 (2.23,2.97)	< 0.0001	2.00 (1.68,2.41)	< 0.0001	1.56 (1.25,1.95)	0.01
p for trend(character2integer)		< 0.0001		< 0.0001		< 0.0001		0.003

Group3

Crudel model: group3

Model 1: group3, age, sex

Model 2: group3, age, sex, eth1, marital, Family_income

Model 3: group3, age, sex, marital, Family_income, BMI, waist_circumference, TG, total_cholesterol, HDL, Total_bilirubin, smoke, UACR, alcohol.user

Table 3 Hazard ratios for all-cause mortality, cardiovascular disease mortality, and diabetes-related mortality by DM and HP status with 95% confidence intervals

Subset (hp5, ucod_leading %in% c(Diabetes, no)) ~ ~ permth_int,mortstat	Group3							
	Crudemodel		Model 1		Model 2		Model 3	
Character	95%CI	P	95%CI	P	95%CI	P	95%CI	P
H_pylori−/DM−	Ref.		Ref.		Ref.		Ref.	
H_pylori−/DM +	68.86 (19.21,246.85)	< 0.0001	18.68 (5.16,67.60)	< 0.0001	13.05 (6.38, 26.71)	< 0.0001	6.83 (1.36,34.36)	0.02
H_pylori + /DM−	2.46 (0.59, 10.28)	0.22	1.47 (0.35, 6.18)	0.60	1.29 (0.35, 4.71)	0.72	1.05 (0.23, 4.82)	0.95
H_pylori + /DM +	65.23 (19.00,223.89)	< 0.0001	18.36 (5.32,63.45)	< 0.0001	15.81 (8.10, 30.86)	< 0.0001	9.17 (2.11,39.88)	0.003
p for trend(character2integer)		< 0.0001		< 0.0001		< 0.0001		< 0.0001

Group3

Crudel model: group3

Model 1: group3, age, sex

Model 2: group3, age, sex, eth1, marital, Family_income, edu

Model 3: group3, age, sex, eth1, marital, Family_income, edu, BMI, waist_circumference, TG, total_cholesterol, HDL, Total_bilirubin, HbA1c, smoke, UACR

Table 4 Adjusted hazard ratios for all-cause mortality, cardiovascular disease mortality, and diabetes-related mortality in relation to DM and HP infection status

Subset (hp5, ucod_leading %in% c(heart, Cerebrovascular, no)) ~ ~ permth_int,mortstat	Group3					
	Crude model		Model 1		Model 2	
Character	95%CI	P	95%CI	P	95%CI	P
H_pylori−/DM−	Ref.		Ref.		Ref.	
H_pylori−/DM +	5.75 (4.07,8.12)	< 0.0001	1.89 (1.33,2.67)	< 0.001	1.73 (1.13,2.63)	0.01
H_pylori + /DM−	1.54 (1.16,2.05)	0.003	1.14 (1.02,1.27)	0.02	1.01 (0.74,1.39)	0.93
H_pylori + /DM +	6.25 (4.21,9.27)	< 0.0001	2.03 (1.36,3.01)	< 0.001	2.02 (1.37,2.97)	< 0.001
p for trend (character2integer)		< 0.0001		< 0.0001		< 0.0001

Group3

Crudel model: group3

Model 1: group3, age, sex

Model 2: group3, age, sex, eth1, marital, Family_income, edu

Subgroup analysis

When participants were stratified by age, gender, and hypertension status, the relative risk of all-cause mortality was highest among those with both diabetes and HP infection compared to those without either condition, particularly among females and in the age groups between 20 to 60. (all $p < 0.05$). Among individuals aged between 20 and 60, mortality rates were higher among diabetic individuals in the DM−/HP + , DM + /HP − , and DM + /HP + groups compared to the DM − /HP − group, with respective hazard ratios (HRs) of 1.58 (95% CI 1.141–2.187), 2.255 (95% CI 1.110–4.581), and 2.253 (95% CI 1.130–4.493) (p-for-trend = 0.002). For females, mortality rates were elevated among diabetic individuals in the DM−/HP + , DM + /HP − , and DM + /HP + groups compared to the DM − /HP − group, with respective hazard ratios (HRs) of 1.164 (95% CI 0.913–1.484), 2.316 (95% CI 1.582–3.390), and 2.555 (95% CI 1.643–3.973) (p-for-trend < 0.0001). However, when stratified by hypertension, there was no significant difference in mortality between the subgroups.

The risk of diabetic mortality was highest among individuals with both diabetes and HP infection compared to those without either condition when stratified by age, gender, and hypertension status, particularly among males, females, and patients with hypertension. In patients with hypertension, diabetic mortality was elevated among individuals in the DM−/HP + , DM + /HP − , and DM + /HP + groups compared to the DM − /HP − group, with respective hazard ratios (HRs) of 1.951 (95% CI 0.347, 10.956), 14.084 (95% CI 2.307, 85.988), and 24.975 (95% CI 4.775, 130.631) (p-for-trend < 0.001). In male patients, diabetic mortality was elevated among individuals in the DM − /HP + , DM + /HP − , and DM + /

HP + groups compared to the DM − /HP − group, with respective hazard ratios (HRs) of 3.375 (p = 0.334), 59.224 (p = 0.004), and 65.417 (p < 0.001), (p-for-trend < 0.001). In female patients, diabetic mortality was elevated among individuals in the DM − /HP + , DM + /HP − , and DM + /HP + groups compared to the DM − /HP − group, with respective hazard ratios (HRs) of 1.749 (p = 0.673), 18.728 (p < 0.001), and 23.848 (p < 0.001), (p-for-trend < 0.001).

The risk of cardiovascular disease (CVD) mortality was greatest among individuals with both diabetes and HP infection compared to those without either condition when stratified by age, gender, and hypertension status, particularly among females. For females, CVD mortality rates were elevated among individuals in the DM − /HP + , DM + /HP − , and DM + /HP + groups compared to the DM − /HP − group, with respective hazard ratios (HRs) of 1.757 (95% CI 1.112–2.776), 4.563 (95% CI 2.348–8.864), and 4.466 (95% CI 2.016–9.895) (p-for-trend < 0.0001). When participants were stratified by age and hypertension status, none of the p-values for trend reached significance. Specifically, among individuals aged 20–60, the p-value for trend was 0.075, and among those aged 60–85, it was 0.74. Among individuals with hypertension, the p-value for trend was 0.132, while among those without hypertension, it was 0.117. The results of the subgroup analysis are presented in Supplementary Table 1.

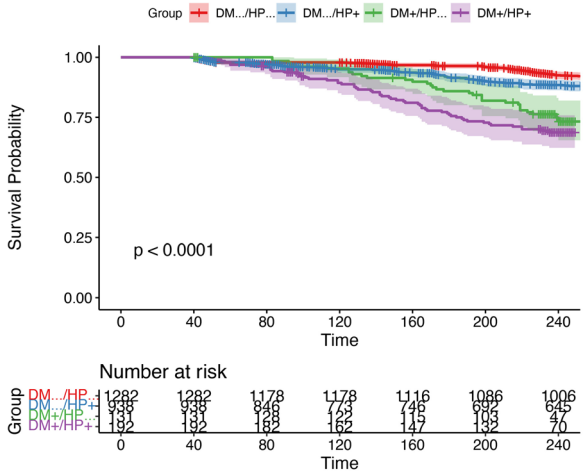

Fig. 2 Following the exclusion of deaths within a two-year timeframe, survival curves were generated for the following four groups: individuals without diabetes mellitus or Helicobacter pylori infection (DM − /HP −), those with diabetes mellitus alone (DM + /HP −), individuals with Helicobacter pylori infection alone (DM − /HP +), and those with both diabetes mellitus and Helicobacter pylori infection (DM + /HP +)

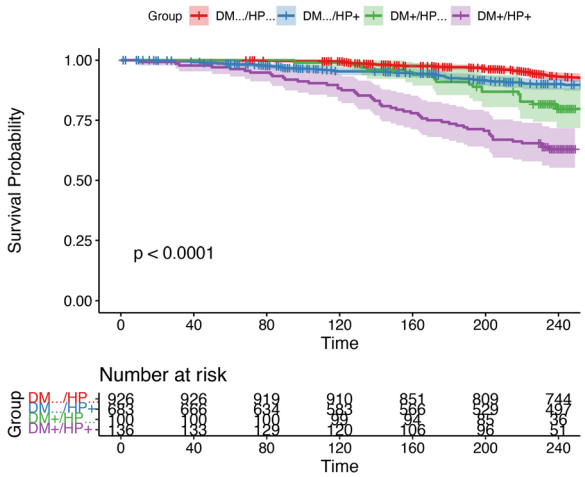

Fig. 3 After excluding participants under the age of 40, survival curves were plotted for the following four groups: individuals free of both diabetes mellitus and Helicobacter pylori infection (DM − /HP −), those with diabetes mellitus alone (DM + /HP −), individuals with Helicobacter pylori infection alone (DM − /HP +), and those with both diabetes mellitus and Helicobacter pylori infection (DM + /HP +)

Sensitivity analyses

Sensitivity analysis was performed by excluding deaths within two years and participants under the age of 40. The decision to exclude those under 40 was based on research showing Helicobacter pylori infection, a chronic inflammation, affects groups with higher survival rates regardless of H. pylori status or diabetes. Younger age groups often have higher survival rates, potentially masking impacts of these conditions. In both scenarios, the group with both DM and HP infection demonstrated the lowest survival rate, followed by the group with DM but without HP infection, then the group without DM but with HP infection, and finally, the group without both DM and HP infection had the highest survival rate (P-log rank < 0.001, Fig. 2; P-log rank < 0.001, Fig. 3). After excluding deaths within two years, the DM − /HP + and DM + /HP − groups demonstrated elevated risks of all-cause mortality compared to the DM − /HP − group in the crude model, with respective HRs of 1.32 (95%CI 1.13–1.55), 3.30 (95%CI 2.67–4.07), and 3.54 (95%CI 2.78–4.52), and a significant trend (p < 0.0001).After full adjustment, the DM − /HP + and DM + /HP − groups exhibited increased risks of all-cause mortality compared to the DM − /HP − group, with respective HRs of 1.09 (95%CI 0.93–1.27), 1.30 (95%CI 1.04–1.63), and 1.35 (95%CI 1.05–1.74), with a significant trend (p = 0.01). Similarly, mortality among diabetic individuals was elevated in the DM − /HP + , DM + /HP − , and DM + /HP + groups compared to the DM − /HP − group. The respective HRs in the fully adjusted model were 1.09 (95% CI 0.28–4.20), 6.82 (95% CI 1.34–34.67), and 8.33 (95% CI 1.88–36.87) (p-for-trend < 0.001). Additionally, cardiovascular disease

(CVD) mortality showed an increase in the DM−/HP+, DM+/HP−, and DM+/HP+groups compared to the DM−/HP−group. In the fully adjusted model, the corresponding hazard ratios (HRs) were 1.03 (95% CI 0.68–1.57), 1.63 (95% CI 1.04–2.54), and 2.08 (95% CI 1.40–3.10), respectively (p-for-trend < 0.001).

Sensitivity analysis, which excluded participants under the age of 40, yielded consistent findings. In the crude model, the DM−/HP+and DM+/HP−groups showed elevated risks of all-cause mortality compared to the DM−/HP−group, with respective hazard ratios (HRs) of 1.05 (95% CI 0.89–1.22), 1.89 (95% CI 1.54–2.32), and 2.13 (95% CI 1.68–2.70), indicating a significant trend (p < 0.0001). Following full adjustment, the DM−/HP+and DM+/HP−groups continued to exhibit increased risks of all-cause mortality compared to the DM−/HP−group, with respective HRs of 1.14 (95% CI 0.97–1.34), 1.29 (95% CI 1.04–1.62), and 1.37 (95% CI 1.07–1.76), maintaining a significant trend (p = 0.02). Similarly, mortality rates among diabetic individuals were elevated in the DM−/HP+, DM+/HP−, and DM+/HP+groups compared to the DM−/HP−group. In the fully adjusted model, the respective hazard ratios (HRs) were 1.05 (95% CI 0.41–2.72), 6.81 (95% CI 3.32–13.96), and 9.11 (95% CI 4.66–17.78) (p-for-trend < 0.03). Furthermore, cardiovascular disease (CVD) mortality displayed an increase in the DM−/HP+, DM+/HP−, and DM+/HP+groups compared to the DM−/HP−group. In the fully adjusted model, the corresponding HRs were 1.05 (95% CI 0.76–1.46), 1.55 (95% CI 1.00–2.39), and 1.92 (95% CI 1.30–2.84), respectively (p-for-trend < 0.001). The results of the sensitivity analysis, including risk models after excluding deaths within two years and participants under the age of 40, are presented in Supplementary Table 2 and Supplementary Table 3.

Discussion

DM and Hp infection are widespread globally, presenting significant challenges to public health. This longitudinal study aimed to evaluate the effects of DM and Hp infection on all-cause, cardiovascular, and diabetic mortality. In our study, conducted through a nationwide population-based survey and utilizing data from the National Death Registry, we found that the coexistence of DM and Hp infection significantly elevates the risk of all-cause, cardiovascular, and diabetic mortality. After adjusting for various confounding factors, participants with both DM and Hp infection exhibited a 1.33-fold increased risk of all-cause mortality, a 1.92-fold increased risk of cardiovascular mortality, and a 15.81-fold increased risk of diabetic mortality compared to those without DM or Hp infection.

Our study of 2719 participants revealed significant associations between Diabetes Mellitus (DM), Helicobacter pylori infection (HP), and adverse health outcomes. Participants were categorized as follows: 50.1% were free of both DM and HP (DM−/HP−), 5.1% had DM alone (DM+/HP−), 37.2% had HP alone (DM−/HP+), and 7.6% had both DM and HP (DM+/HP+). Compared to the DM−/HP−group, the DM+/HP−and DM+/HP+groups showed increased risks of all-cause mortality with hazard ratios (HRs) of 1.40 (95% CI 1.07–1.78) and 1.46 (95% CI 1.15–1.84), respectively. Specifically, the DM+/HP−and DM+/HP+groups had higher risks of diabetic mortality with HRs of 6.30 (95% CI 1.30–30.43) and 8.56 (95% CI 1.98–36.94), and cardiovascular mortality with HRs of 1.75 (95% CI 1.14–2.69) and 1.98 (95% CI 1.40–2.79), respectively. The DM+/HP+cohort exhibited the highest overall mortality, diabetic mortality, and cardiovascular mortality risks. Other studies from various perspectives have provided supplementary support for our research findings. Diabetes and Hp infection pose significant global health challenges due to their widespread occurrence in the general population [18, 19]. Many previous studies have indicated a certain correlation between them. Prior investigations have indicated a heightened prevalence of Hp infection among diabetic patients [20]. In a meta-analysis conducted by Feng Wang, which encompassed 39 eligible studies spanning from 1997 to 2012, a notable correlation emerged between Hp infection and elevated risks of both T1DM and T2DM [21]. In a study conducted in 2024 [22], a noteworthy correlation was identified between Hp infection and T1DM ([OR] 1.77, 95% [CI] 1.47–2.12, p < 0.0001). As per the findings of Xin et al., individuals with type 2 DM (T2DM) exhibit a greater risk of Hp eradication failure compared to non-diabetic individuals (odds ratio [OR] = 2.59, 95% confidence interval [CI] 1.82–3.70) [23]. In addition to a higher prevalence of Helicobacter pylori infection in diabetic patients, Hp infection can also lead to elevated glycated hemoglobin levels, thereby contributing to an increased incidence of diabetes. A study conducted in 2023 revealed that compared to the persistent Helicobacter pylori infection-negative group, individuals in the persistent Hp infection and new infection groups exhibited significantly higher levels of HbA1c (p < 0.05). Conversely, HbA1c levels decreased following Hp eradication [24]. Another study conducted in 2019 [25] found that patients with Helicobacter pylori infection exhibited significantly higher levels of glycated hemoglobin A compared to those without infection (WMD = 0.50, 95% CI 0.28–0.72, p < 0.001). Subgroup analysis based on diabetes subtype demonstrated a correlation between Helicobacter pylori infection and increased glycated hemoglobin A levels in both type 1

diabetes (p < 0.001, 95% CI 0.12–0.80) and type 2 diabetes (p < 0.001, 95% CI 0.28–0.90).

Previous studies [26, 27] indicated a significant correlation between long-term Hp infection and elevated HbA1c levels, particularly among older individuals (> 65 years old). Higher prevalence of Hp infection was observed in patients with elevated HbA1c levels and in those diagnosed with type 2 diabetes. Impaired insulin secretion was noted in subjects with Hp infection, especially in those under 45 years old, after adjusting for sex, age, BMI, and family history of diabetes. Helicobacter pylori infection has been reported to independently contribute to insulin resistance in a large asymptomatic population [28]. Many of the metabolic phenotypes associated with insulin resistance, such as BMI and HOMA-IR, as well as plasma triglyceride and HDL levels, are correlated with each other. Some studies [14, 29] have suggested that eradication of HP infection can improve metabolic control. These findings collectively underscore the beneficial impact of eradicating Hp (HP) on patient prognosis and survival. These results closely align with the findings of our own research.

There are several underlying mechanisms that could elucidate the association between Hp infection and diabetes. Firstly, Hp infection initiates the production of proinflammatory cytokines, potentially disrupting glycemic control [30]. Secondly, emerging evidence supports the notion that inflammation may play a pivotal role in the pathogenesis of type 2 diabetes, akin to an autoinflammatory disorder. This process involves inflammatory cytokines inducing the phosphorylation of serine residues on the insulin receptor substrate, impeding its interaction with insulin receptors and compromising insulin function [22, 31]. Thirdly, Hp infection-induced inflammation can impact pancreatic β cells, leading to reduced insulin secretion. Notably, cag + strains of Hp may exacerbate this effect by influencing somatostatin production [32]. Moreover, research indicates that Hp can promote insulin resistance by inducing chronic inflammation and modulating insulin regulation of gastrointestinal hormones [33]. Additionally, gastritis caused by Hp may disrupt the secretion of gastric-related hormones such as leptin, growth hormone-releasing hormone, gastrin, and somatostatin, potentially affecting susceptibility to diabetes [34, 35]. Furthermore, studies have reported a positive correlation between Hp infection and impaired insulin secretion. Lastly, compromised nonspecific immunity in diabetic patients may increase the risk of Hp infection. The mechanisms proposed above elucidate the potential link between Hp infection and the risk of diabetes. Furthermore, the impact of Helicobacter pylori infection on blood glucose and diabetes may outweigh the influence of blood glucose levels on Hp presence. This observation clarifies why, in our study, although patients in the DM + / HP + group exhibited a higher risk of all-cause mortality, diabetes-related mortality, and CVD mortality compared to those in the DM − /HP − group, the simultaneous occurrence of diabetes and Hp infection presented the most pronounced elevation in the risk of diabetes-related mortality. While a synergistic effect between the two diseases is plausible, further extensive research is required to substantiate these findings.

When exploring the interactions between diabetes, Helicobacter pylori infection, and their interplay, it becomes crucial to discuss gastric cancer-related death. This includes understanding their potential mutual influences and complexities, which involve chronic inflammation and immune responses. Pathophysiological mechanisms linking chronic conditions like diabetes and the inflammatory nature of H. pylori infection to gastric cancer risk are also significant [36]. Additionally, examining epidemiological correlations and conducting risk assessments among diabetes patients with H. pylori infection regarding gastric cancer-related mortality is essential. Furthermore, understanding these relationships has profound clinical and public health implications for developing targeted prevention and treatment strategies. Therefore, it is essential to investigate the incidence of gastric cancer-related deaths in these populations. Unfortunately, our study's data from the NHANES database lacks specific records of gastric cancer-related deaths among its mortality data, thus preventing direct presentation of these findings in our results. This underscores the need for future research to address this gap, highlighting the urgency for studies focusing on this critical aspect.

Our study holds a unique advantage as it is the first cohort investigation to delineate long-term mortality trends among populations with diabetes and Hp status. This analysis was conducted utilizing a representative population-based database, thereby enhancing the robustness of our findings. The conclusions of this study align with previous research findings, offering valuable insights into the eradication treatment of Helicobacter pylori in patients with diabetes. To control for potential confounding effects of various covariates, this study designed models to adjust for confounding factors, thereby enhancing the reliability of the results.

This study had several limitations. Firstly, the present study exclusively utilized data from the NHANES database population, limiting the generalizability of the results to populations worldwide. Secondly, due to the lack of specific data in the NHANES database, the study could not differentiate between types of diabetes (type 1 or type 2). Hp infection is a treatable condition known to impact various health outcomes. Assessing

whether the duration of Hp infection exposure affects prognosis is crucial in studies of this nature [37]. However, our analysis did not incorporate the exposure period to Hp infection due to limitations in the available data. This represents a notable limitation of our study, which we acknowledge here to ensure transparency in interpreting our findings. Future research should explore the potential influence of varying exposure durations to better understand the comprehensive impact of Hp infection on patient outcomes.

Therefore, it was not possible to separately analyze the effects of Hp infection on mortality in patients with type 1 or type 2 diabetes. Thirdly, cross-sectional studies do not establish causality. To elucidate causality further, additional prospective cohort studies and randomized controlled trials are warranted.

Conclusion

In conclusion, the concurrent presence of DM and H. pylori infection substantially elevates the risk of all-cause, diabetic, and cardiovascular mortalities compared to either condition alone. These findings underscore the importance of vigilant monitoring and proactive measures to mitigate the risk of mortality in patients with DM or H. pylori infection, highlighting a novel approach to disease management and prevention.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01437-2.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Author contributions
Di Zeng: conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); writing—original draft (lead); writing—review & editing (lead). Qingyue Zeng: conceptualization (equal); formal analysis (equal); investigation (equal); writing—review & editing (equal). Shaofeng Wang: investigation (equal); writing—review & editing (equal). Shuangqing Li: methodology (lead); supervision (lead).

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Availability of data and materials
All data generated or analyzed during this study are included in this published article. All figures in our study are original and have not been previously published. No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
In accordance with the guidelines provided by the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC), this study utilized data from the National Health and Nutrition Examination Survey (NHANES). NHANES is conducted by the CDC and follows strict ethical guidelines to protect participant confidentiality and ensure informed consent. All data used in this study were obtained from publicly available NHANES datasets, which are anonymized and do not contain identifiable personal information. Therefore, this research is exempt from human subjects review and informed consent requirements. The use of NHANES data in this study was conducted in compliance with the ethical standards outlined by the CDC and NCHS. Human Ethics and Consent to Participate declarations: not applicable.

Consent for publication
All authors unanimously agreed to submit this manuscript for publication in *Frontiers in Endocrinology*. Not applicable.

Competing interests
The authors declare that they have no competing interests. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors declare no competing interests.

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