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Association of nonrefractive visual impairment with risk of all-cause and specific-cause mortality in the National Health and Nutrition Examination Survey, 1999 to 2008

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Abstract

Objective To investigate and describe the impact of nonrefractive visual impairment (NVI) and its severity on all-cause and cause-specific mortality, along with the latest estimations.

Methods Cox proportional hazards regression models with multiple covariate adjustments and Fine-Gray competing risk regression models assessed the risk of all-cause and specific-cause mortality. Propensity score matching (PSM) was employed to achieve covariate balance.

Results Among 7 961 participants (representing 171 383 125 non-institutionalized US individuals), baseline NVI was present in 350 participants (4.40%), with 313 (3.93%) having mild NVI and 37 (0.47%) having severe NVI. Both any NVI and Severe NVI were associated with increased all-cause and diabetes mellitus (DM)-related mortality. After PSM, the results remained consistent (for all-cause mortality: HR, 1.34; 95% CI, 1.05–1.70; for DM-related mortality: HR, 3.54; 95% CI, 1.15–10.97). Severity analysis demonstrated a significant trend between increasing NVI severity and elevated risks of all-cause and DM-specific mortality.

Conclusion Our findings confirm that NVI and its severity are independent risk factors for all-cause and DM-specific mortality among the US population. This highlights the importance of regular visual acuity examinations, particularly for NVI screening, especially in individuals with diabetes.

Keywords Visual impairment, All-Cause mortality, Specific-Cause mortality

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Introduction

Visual Impairments due to causes other than refractive error may be collectively referred to as "nonrefractive visual impairment (NVI)". While NVI in the US has been identified as a health issue that is both increasing in prevalence and producing growing impacts in terms of rising healthcare cost, declining work productivity.etc.[1, 2] The prevalence of VI in the U.S. population is estimated to be around 14 million individuals aged 12 years and above, with the majority (over 11 million) being correctable VI (CVI) cases [3]. In contrast to CVI, NVI has a lower prevalence but can result in irreversible residual VI [4]. Age-related macular degeneration (AMD), cataracts, diabetic retinopathy (DR), glaucoma, and other retinal diseases are among the most common causes of NVI [5–7]. Given that the increasing prevalence of NVI has been associated with risk factors such as diabetes mellitus (DM) [2], the relationship between NVI occurrence and mortality in diseases like diabetes remains insufficiently studied.

VI has served as a marker of declining physical function, with studies such as the Age-Related Eye Disease Study 2 (AREDS2), National Health Interview Survey, and the Beaver Dam Eye Study having reported associations between VI and increased mortality risk in U.S. populations [8–10]. However, few studies have distinguished and further categorized CVI and NVI, which may overlook the impact of NVI on mortality and disease-specific survival risk [11]. Moreover, inadequate or omitted adjustments for key confounders such as comorbidities of cardiovascular diseases (CVD), depression or walking difficulties, may have biased the results. Since observational studies are incapable of applying randomized grouping, most traditional research models fail to adequately adjust for the effects of important confounders between groups, resulting in potential imbalances in confounders and systematic biases that remain difficult to eliminate [12]. In addition, regarding studies on attributable mortality, many previous relevant studies might have overestimated absolute risk of specific-cause (e.g. DM, CVD) deaths by not considering competing mortality risks [13].

To the best of our knowledge, there is currently no evidence regarding the association of NVI with all-cause and specific-cause mortality in the U.S. population. Limited evidence from the Liwan Eye Study in China, involving 1,399 participants, demonstrated a nearly threefold higher mortality risk in NVI patients after ten years (HR: 2.72; 95% CI, 1.86–3.98), surpassing that of CVI [14]. Therefore, given the increased prevalence of NVI and related demographic/systemic risks (like diagnosed DM), there remains a lack of evidence from large NVI patient samples, especially within the US [2]. With substantial clinical NVI burden and limited interventions, it's crucial to clarify the exact impact of NVI on future mortality (especially CVD and DM) to understand whether NVI can be used as a key predictor for further development of early screening assessment and stratified risk management based on refractive error, vision screening, etc.

Methods

Study population

NHANES is an ongoing nationwide cross-sectional study that employs a complex, multistage, stratified sampling design, it updates health data biennially with approval from its Institutional Review Board and informed consent from participants (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). From 1999 to 2008, ultimately 7961 eligible adult participants completed at least one valid NHANES refraction examination, and they were included in the baseline study. The publicly available data used in this project were derived from the NHANES program, which was approved by the Ethics Review Board of the National Center for Health Statistics (NCHS), and in which all participants provided written informed consent to participate in the survey and agreed to the use of their data for health-related statistical research with links to vital statistics (e.g., the National Death Index), adhering to the principles of the Declaration of Helsinki. eFigure in the supplementary material provides the flowchart detailing the participant selection process for this study.

NVI assessment

Study participants underwent vision assessments during mobile examination center visits from 1999 to 2008. Relevant methods have been previously described.[3 15] Although the definition of NVI is not universal, several authoritative studies have clearly described the diagnostic criteria and definitions of NVI, on the basis of which we developed the inclusion criteria for this study [15–18]. Presenting visual acuity was measured for each eye with the participant's usual distance vision correction using an autorefractor (ARK-760, Nidek Co Ltd) equipped with visual acuity charts containing lines corresponding to 20/20, 20/25, 20/30, 20/40, 20/50, 20/60, 20/80, and 20/200. NVI was classified when presenting visual acuity was less than 20/40 and remained less than 20/40 when aided by autorefractor in the better-seeing eye [2]. Participants were categorized as no NVI (≤ 20/40), any NVI (≥ 20/40), mild NVI (20/40 – 20/200), and severe NVI (≥ 20/200). The study included participants aged 20 years and older who participated in household interviews and excluded those determined to be completely blind, bilaterally unseeing, or those with severe eye infections in one or both eyes.

Mortality data

As of 2019, mortality status information for each participant was obtained through the National Center for

Health Statistics (NCHS) linkage to the National Death Index using probabilistic matching algorithms [19–22]. Deaths were determined for all causes using the 10th revision of the International Classification of Diseases (ICD-10). Causes included CVD (I00–I09, I11, I13, I20–I51, and I60–I69), diabetes (E10-E14), Alzheimer's disease (AD) (G30), and cancers (C00–C97). Unattributed deaths were classified as deaths from other causes. Follow-up time ranged from the NHANES examination date to the death date or end of follow-up.

Participant characteristics and covariate assessment

Comprehensive demographic characteristics, health-related behaviors, and comorbidity information were obtained through interviews or examinations (physiological measurements, laboratory tests, etc.). Specifically, age was categorized into seven groups spanning each decade: 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥ 80. Race/ethnicity was classified into non-Hispanic White, non-Hispanic Black, Mexican American, or other. Depressive symptoms were assessed using the 9-item Patient Health Questionnaire (PHQ-9) [23]. Other systemic comorbidities or covariates were extracted and classified in line with prior research [24–26].

Statistical analysis

Given the complex sampling design of NHANES, all analyses incorporated sample weights, clustering, and stratification. Continuous variables were described using means and standard errors (SEs), and categorical variables were described using numbers and weighted percentages (%) to portray baseline characteristics of all participants, including matched baseline characteristics after propensity score matching (PSM). Design-adjusted paired t-tests were applied to continuous non-paired variables, and Rao-Scott Pearson χ^2 tests were used for categorical variables to compare data distribution and mortality characteristics.

Kaplan-Meier estimates were employed to present survival profiles for the presence (binary) and severity (tertiary) of NVI participants. Cox proportional hazard regression model incorporated covariates significantly associated with all-cause mortality and NVI. Interaction test results suggested no statistically significant interactions between covariates ($P > 0.05$). The proportionality hazards assumption for each covariate was verified by assessing interaction with follow-up time and graphical representation ($P > 0.05$). Multiple-adjusted Fine and Gray competing risk regression model was further employed to estimate the risk of specific-cause mortality. [25, 27] Moreover, accounting for the non-linear relationship between age and mortality, we conducted sensitivity analyses by additionally adjusting for age squared in the final models to assess model stability [25]. Collinearity effects among all covariates were tested using variance inflation factors (VIFs), which were all below 2 in this study (mean [SE], 1.11 [0.03]). PSM was employed to address the imbalance of intergroup covariates, thereby reducing confounding bias and achieving comparable effects to randomized controlled trials (RCTs) throughout the study design process [28–30]. The "MatchIt" package in R software was employed, baseline characteristics matched all participants (1:1) between NVI and non-NVI groups. eTable 1 confirms post-matching balance. To further explore differences in the impact of NVI presence and severity on all-cause mortality across different subgroups, we performed stratified subgroup analyses based on age (20–39, 40–59, 60–79, ≥ 80), sex, race/ethnicity, education level, poverty level, smoking history, alcohol consumption history, and history of baseline diseases including diabetes, hypertension, hyperlipidemia, heart attack and stroke.

Data analysis for this study was performed using R version 4.2.1 (2023-07-12) with statistical packages such as "nhanesR", "reshape2", "do", "survey", and "dplyr". *P*-values less than 0.05 were considered statistically significant.

Results

Initially, 35,090 participants aged ≥ 20 years from NHANES 1999–2008 were included. After excluding those with missing data, 7961 participants remained for analysis, representing a US population of 171,383,125 (eFigure in the supplementary material). Compared to excluded participants, those included in this study were more likely to be married or living with a partner (65.61% vs. 55.73%), higher education (82.17% vs. 66.57%), above-baseline income (88.16% vs. 84.05%), higher BMI (34.34% vs. 27.36%), history of DM (12.28% vs. 8.27%), hypertension (36.37% vs. 28.30%), and hyperlipidemia (72.10% vs. 61.58%) (eTable 2 in the supplementary material). Table 1 presents demographic characteristics, health-related behaviors, and general health comorbidities of participants categorized based on overall status and classification of NVI.

All-Cause mortality

eTable 3 presents the results indicating that among the 7,961 enrolled participants, 350 individuals (4.40%) were diagnosed with NVI, representing 5,305,730 individuals in the U.S. population. Of these, 313 individuals (3.93%) had mild NVI, and 37 individuals (0.47%) had severe NVI, representing 4,776,369 and 529,361 individuals in the U.S. population, respectively. As of December 31, 2019, after a median follow-up of 12.33 years (interquartile range, 11.33–13.67), a total of 1,429 participants were identified as deceased, with 1,270 cases having no NVI at baseline and 159 cases having NVI. Non-NVI patients had a significantly lower mean (SE) age at death (46.29

Table 1 Demographic, health behavior, and general health characteristics of participants by NVI

Characteristic	Study Participants [a]						
	All	No NVI < 20/40	NVI ≥ 20/40	*P*	Mild NVI 20/40 – 20/200	Severe NVI ≥ 20/200	*P* for trend
Participant sample cases, No	7961	7611	350		313	37	
Representative population, No	171,383,125	166,077,395	5,305,730		4,776,369	529,361	
Age, No. (%), y				< 0.0001			< 0.0001
20–29	1255(15.76)	1210(17.90)	45(17.09)		39(17.03)	6(17.68)	
30–39	1368(17.18)	1338(19.22)	30(9.99)		28(10.31)	2(7.12)	
40–49	1413(17.75)	1394(22.29)	19(6.15)		19(6.83)	0(0.00)	
50–59	1235(15.51)	1213(19.07)	22(9.78)		21(10.66)	1(1.81)	
60–69	1318(16.56)	1252(11.53)	66(16.40)		59(16.72)	7(13.55)	
70–79	904(11.36)	818(7.06)	86(20.02)		78(19.77)	8(22.32)	
≥ 80	468(5.88)	386(2.93)	82(20.57)		69(18.69)	13(37.51)	
Sex, No. (%)				0.04			0.13
Male	4047(50.84)	3880(49.47)	167(43.21)		152(43.29)	15(42.47)	
Female	3914(49.16)	3731(50.53)	183(56.79)		161(56.71)	22(57.53)	
Race/Ethnicity, No. (%)				0.41			0.51
Non-Hispanic White	4038(50.72)	3849(73.05)	189(73.86)		168(74.05)	21(72.08)	
Non-Hispanic Black	1650(20.73)	1591(10.32)	59(9.91)		52(9.61)	7(12.62)	
Mexican American	1426(17.91)	1357(7.70)	69(9.33)		64(9.82)	5(4.87)	
Other	847(10.64)	814(8.94)	33(6.90)		29(6.51)	4(10.43)	
Marital status, No. (%)				< 0.001			0.001
Unmarried or other	3048(38.29)	2871(34.02)	177(46.34)		156(45.82)	21(51.00)	
Married or living with a partner	4913(61.71)	4740(65.98)	173(53.66)		157(54.18)	16(49.00)	
Educational attainment, No. (%)				< 0.0001			< 0.0001
< High school	2208(27.74)	2051(17.35)	157(33.08)		138(32.05)	19(42.38)	
≥High school	5753(72.26)	5560(82.65)	193(66.92)		175(67.95)	18(57.62)	
Poverty income ratio, No. (%)				< 0.001			0.01
Below poverty line (< 1.00)	1451(18.23)	1357(11.65)	94(18.17)		85(18.09)	9(18.94)	
At or above poverty line (≥ 1.00)	6510(81.77)	6254(88.35)	256(81.83)		228(81.91)	28(81.06)	
Smoking history, No. (%)				0.08			0.19
Never	4084(51.3)	3912(51.25)	172(49.96)		154(50.19)	18(47.95)	
Former	2056(25.83)	1948(24.88)	108(31.33)		97(31.18)	11(32.65)	
Current	1821(22.87)	1751(23.87)	70(18.71)		62(18.63)	8(19.39)	
Alcohol consumption, No. (%)				< 0.0001			< 0.0001
Never	1073(13.48)	996(10.53)	77(22.11)		70(22.06)	7(22.55)	
Former	1660(20.85)	1547(16.70)	113(27.86)		99(27.22)	14(33.63)	
Mild	2473(31.06)	2396(34.81)	77(24.93)		69(24.98)	8(24.42)	
Moderate	1172(14.72)	1133(16.49)	39(12.24)		36(12.49)	3(9.95)	
Heavy	1583(19.88)	1539(21.47)	44(12.86)		39(13.24)	5(9.45)	
BMI, No. (%)				0.49			0.65
18.5–30.0	4958(62.28)	4727(64.13)	231(62.59)		207(62.91)	24(59.71)	
< 18.5	126(1.58)	117(1.53)	9(2.44)		8(2.57)	1(1.18)	
≥ 30.0	2877(36.14)	2767(34.34)	110(34.97)		98(34.51)	12(39.12)	
High C-reactive protein level, No. (%)				0.08			0.11
No	7101(89.2)	6792(90.40)	309(86.42)		278(87.11)	31(80.23)	
Yes	860(10.8)	819(9.60)	41(13.58)		35(12.89)	6(19.77)	
Diabetes mellitus, No. (%)				< 0.0001			< 0.0001
No	6594(82.83)	6354(88.23)	240(71.61)		217(72.09)	23(67.31)	
Yes	1367(17.17)	1257(11.77)	110(28.39)		96(27.91)	14(32.69)	
Hypertension, No. (%)				< 0.0001			< 0.0001
No	4621(58.05)	4473(64.14)	148(47.22)		135(49.07)	13(30.57)	
Yes	3340(41.95)	3138(35.86)	202(52.78)		178(50.93)	24(69.43)	
Hyperlipidemia, No. (%)				0.1			0.09

Table 1 (continued)

Characteristic	Study Participants [a]						
	All	No NVI < 20/40	NVI ≥ 20/40	*P*	Mild NVI 20/40 – 20/200	Severe NVI ≥ 20/200	*P* for trend
No	2147(26.97)	2070(28.03)	77(23.33)		73(24.75)	4(10.53)	
Yes	5814(73.03)	5541(71.97)	273(76.67)		240(75.25)	33(89.47)	
Depressive symptoms, No. (%)				0.27			0.48
No	7331(92.09)	7014(93.39)	317(91.79)		283(91.65)	34(93.00)	
Yes	630(7.91)	597(6.61)	33(8.21)		30(8.35)	3(7.00)	
Difficulty walking, No. (%)				< 0.0001			< 0.0001
No	7345(92.26)	7053(94.58)	292(82.73)		264(82.83)	28(81.83)	
Yes	616(7.74)	558(5.42)	58(17.27)		49(17.17)	9(18.17)	
Health status, No. (%)				< 0.0001			< 0.0001
Poor to fair	1814(22.79)	1691(15.73)	123(28.11)		110(28.13)	13(27.95)	
Good to excellent	6147(77.21)	5920(84.27)	227(71.89)		203(71.87)	24(72.05)	
History of congestive heart failure, No. (%)				< 0.001			< 0.001
No	7716(96.92)	7385(98.03)	331(94.85)		298(95.47)	33(89.23)	
Yes	245(3.08)	226(1.97)	19(5.15)		15(4.53)	4(10.77)	
History of coronary heart disease, No. (%)				< 0.001			< 0.001
No	7645(96.03)	7322(96.99)	323(92.66)		290(92.77)	33(91.66)	
Yes	316(3.97)	289(3.01)	27(7.34)		23(7.23)	4(8.34)	
History of angina, No. (%)				0.75			0.24
No	7745(97.29)	7407(97.90)	338(97.67)		303(98.08)	35(93.96)	
Yes	216(2.71)	204(2.10)	12(2.33)		10(1.92)	2(6.04)	
History of heart attack, No. (%)				0.01			0.01
No	7618(95.69)	7296(96.94)	322(93.98)		288(93.91)	34(94.56)	
Yes	343(4.31)	315(3.06)	28(6.02)		25(6.09)	3(5.44)	
History of stroke, No. (%)				< 0.0001			< 0.0001
No	7658(96.19)	7339(97.38)	319(91.60)		288(92.91)	31(79.76)	
Yes	303(3.81)	272(2.62)	31(8.40)		25(7.09)	6(20.24)	
History of cancer, No. (%)				0.02			0.03
No	7228(90.79)	6922(91.67)	306(87.38)		274(87.25)	32(88.51)	
Yes	733(9.21)	689(8.33)	44(12.62)		39(12.75)	5(11.49)	

Abbreviations: NVI, Nonrefractive Visual Impairment; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared)

[a] All proportions, means, and SEs are weighted estimates of the US population characteristics, taking into account the complex sampling design of the National Health and Nutrition Examination Survey

(0.44) years) compared to NVI patients (57.98 (1.68) years), as well as mild NVI (57.33 (1.80) years) and severe NVI (63.83 (4.45) years) (eTable 3). Furthermore, there was a statistically significant trend of shorter survival time with increasing severity of NVI.

Table 2 illustrates the correlations between covariates and all-cause mortality. HRs increased exponentially with every decade increase in age. Additionally, factors including smoking history (former: HR = 2.10; 95% CI: 1.74–2.54, current: HR = 1.38; 95% CI: 1.17–1.63), former alcohol consumption (HR = 1.37; 95% CI: 1.05–1.79), presence of diabetes (HR = 3.55; 95% CI: 3.09–4.08), etc. were significantly associated with increased all-cause mortality risk.

Severity analysis further indicated that patients with severe NVI had a higher risk of death (HR = 1.88; 95% CI: 1.18–2.98), with a statistically significant increasing trend (P for trend = 0.002) (Table 3). Figure 1 visually displays the Kaplan-Meier curves with multiple adjustments for all-cause mortality based on NVI.

In addition, after PSM, Cox proportional hazards models were reconstructed for two 1:1 matched participant groups. This involved 350 NVI participants (2,505,022 individuals) and 350 non-NVI participants (2,463,357 individuals). The findings confirmed higher all-cause mortality risk in NVI individuals (HR = 1.34; 95% CI: 1.05–1.70) compared to non-NVI participants (Table 4).

Subgroup analysis

Subgroup stratified analyses showed significant associations between all-cause mortality and any NVI or NVI severity observed in all subgroups, except for those aged under forty and over eighty years. No significant association was found between mild NVI and all-cause mortality in stroke patients. Similarly, the severity analysis indicated increased mortality risk with rising NVI severity

Table 2 Due to all causes mortality by demographic, health-Related behaviors and general health characteristics

Characteristics	Participants [a]		
	Survived	Died	HR (95% CI) [b]
Participant sample cases, No	6532	1429	
Representative population, No	149,777,086	21,573,947	
Age, No. (%), y			
20–29	1243(20.25)	12(1.43)	1 [Reference]
30–39	1332(21.07)	36(4.10)	2.72(1.22, 6.07)**
40–49	1339(23.84)	74(7.51)	4.34(1.95, 9.66)***
50–59	1094(19.59)	141(13.18)	9.11(4.40, 18.83)****
60–69	994(10.31)	324(21.21)	25.50(12.44, 52.26)****
70–79	450(4.25)	454(29.73)	67.32(32.79,138.23)****
≥ 80	80(0.69)	388(22.84)	175.52(85.49,360.38)****
Sex, No. (%)			
Male	3217(48.83)	830(52.39)	1 [Reference]
Female	3315(51.17)	599(47.61)	0.87(0.79,0.97)**
Race/Ethnicity, No. (%)			
Non-Hispanic White	3098(71.72)	940(82.46)	1 [Reference]
Non-Hispanic Black	1349(10.21)	301(10.97)	0.95(0.77,1.16)
Mexican American	1323(8.46)	103(2.83)	0.3q 1(0.25,0.40)****
Other	762(9.62)	85(3.73)	0.36(0.24,0.55)****
Marital status, No. (%)			
Unmarried or other	2368(32.73)	680(46.00)	1 [Reference]
Married or living with a partner	4164(67.27)	749(54.00)	0.59(0.52,0.66)****
Educational attainment, No. (%)			
< High school	1681(15.99)	527(30.61)	1 [Reference]
≥High school	4851(84.01)	902(69.39)	0.45(0.39,0.53)****
Poverty income ratio, No. (%)			
Below poverty line (< 1.00)	1176(11.55)	275(13.93)	1 [Reference]
At or above poverty line (≥ 1.00)	5356(88.45)	1154(86.07)	0.80(0.66,0.96)*
Smoking history, No. (%)			
Never	3533(53.07)	551(38.28)	1 [Reference]
Former	1491(23.28)	565(37.56)	2.10(1.74,2.54)****
Current	1508(23.65)	313(24.16)	1.38(1.17,1.63)****
Alcohol consumption, No. (%)			
Never	826(10.11)	247(16.34)	1 [Reference]
Former	1144(14.61)	516(33.94)	1.37(1.05,1.79)*
Mild	2063(35.24)	410(29.36)	0.53(0.40,0.71)****
Moderate	1047(17.29)	125(9.94)	0.37(0.26,0.53)****
Heavy	1452(22.76)	131(10.41)	0.30(0.22,0.41)****
BMI, No. (%)			
18.5–30.0	4034(64.14)	924(63.66)	1 [Reference]
< 18.5	94(1.50)	32(1.95)	1.27(0.75,2.14)
≥ 30.0	2404(34.35)	473(34.39)	1.00(0.85,1.19)
Diabetes mellitus, No. (%)			
No	5645(90.28)	949(69.90)	1 [Reference]
Yes	887(9.72)	480(30.10)	3.55(3.09,4.08)****
Hypertension, No. (%)			
No	4191(68.17)	430(32.00)	1 [Reference]
Yes	2341(31.83)	999(68.00)	4.12(3.47,4.89)****
Hyperlipidemia, No. (%)			
No	1860(29.06)	287(19.75)	1 [Reference]
Yes	4672(70.94)	1142(80.25)	1.63(1.37,1.93)****
PHQ9, No. (%)			
No	6026(93.72)	1305(90.75)	1 [Reference]

Table 2 (continued)

Characteristics	Participants [a]		
	Survived	Died	HR (95% CI) [b]
Yes	506(6.28)	124(9.25)	1.50(1.17,1.93)**
Difficulty walking, No. (%)			
No	6238(96.55)	1107(78.02)	1 [Reference]
Yes	294(3.45)	322(21.98)	6.09(5.09,7.28)****
Health status, No. (%)			
Poor to fair	1297(13.74)	517(32.61)	1 [Reference]
Good to excellent	5235(86.26)	912(67.39)	0.35(0.31,0.40)****
History of congestive heart failure, No. (%)			
No	6447(99.22)	1269(89.00)	1 [Reference]
Yes	85(0.78)	160(11.00)	9.85(8.23,11.79)****
History of coronary heart disease, No. (%)			
No	6394(98.16)	1251(87.78)	1 [Reference]
Yes	138(1.84)	178(12.22)	5.58(4.75,6.55)****
History of angina, No. (%)			
No	6426(98.69)	1319(92.32)	1 [Reference]
Yes	106(1.31)	110(7.68)	4.84(3.98,5.88)****
History of heart attack, No. (%)			
No	6389(98.21)	1229(87.40)	1 [Reference]
Yes	143(1.79)	200(12.60)	6.03(5.13,7.10)****
History of stroke, No. (%)			
No	6399(98.47)	1259(88.37)	1 [Reference]
Yes	133(1.53)	170(11.63)	6.30(4.80,8.26)****
History of cancer, No. (%)			
No	6117(93.41)	1111(78.53)	1 [Reference]
Yes	415(6.59)	318(21.47)	3.42(2.95,3.97)****

Abbreviations: NVI, nonrefractive visual impairment; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio

[a] All-cause mortality was assessed through December 31, 2020. All proportions, means, and SEs are weighted estimates of the US population characteristics, taking into account the complex sampling design of the National Health and Nutrition Examination Survey

[b] Adjusted for age and sex

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$

in all subgroups, except those aged under forty and over eighty years, maintaining a statistically significant trend (eTable 4).

Cause-Specific mortality

Among the 1429 deceased participants in the study, 337 individuals (4.23%) died from cancer, 520 individuals (6.53%) from CVD, 49 individuals (0.62%) from DM, 51 individuals (0.64%) from AD, and 472 individuals (5.94%) from other causes not specified above. After adjusting for covariates, Table 3 reveals that individuals with any NVI had over threefold higher DM-specific mortality risk (HR = 3.33; 95% CI: 1.29–8.65). Both severities of NVI were associated with an increased risk of DM-related mortality (mild NVI: HR = 2.61; 95% CI: 1.04–6.58, severe NVI: HR = 13.03; 95% CI: 3.92–43.34), with a statistically significant trend test (P for trend = 0.01). Further adjustment for the square of age demonstrated that the presence of any NVI (HR = 3.20; 95% CI: 1.10–9.35) and severe NVI (HR = 13.07; 95% CI: 3.98–42.87) remained significantly associated with an elevated risk of DM-specific mortality. However, neither the presence of NVI nor its severity exhibited any statistically significant correlation with mortality from causes other than DM. PSM analysis confirmed higher DM-specific mortality risk in NVI participants (HR = 3.54; 95% CI: 1.15–10.97). Similarly, no significant differences were observed in other cause-specific mortality (Table 4).

Sensitivity analysis

We included the square of age in the Cox proportional hazards regression model to correct for the nonlinear relationship between age and mortality rate. The observed results remained consistent with those in the main analysis, suggesting that the presence of NVI (of any degree) as well as severe NVI was significantly associated with all-cause as well as DM-specific deaths, and the test for trend also yielded statistically significant differences (Table 4).

Table 3 Cox proportional hazards models for all-cause mortality and specific-cause mortality by NVI status

Mortality		HR (95% CI)				
		No NVI	Any NVI < 20/40	Mild NVI ≥ 20/40	Severe NVI 20/40 – 20/200	*P* for trend
All-Cause	Model 1 [a]	1 [Reference]	1.27(1.06,1.53)**	1.19(0.97,1.46)	1.88(1.18,2.98)**	0.002**
	Model 2 [b]	1 [Reference]	1.26(1.01,1.57)*	1.13(0.92,1.40)	1.77(1.10,2.85)*	0.02*
Cancer-Specific	Model 1	1 [Reference]	1.40(0.83,2.36)	1.28(0.72,2.29)	2.80(0.96,8.17)	0.21
	Model 2	1 [Reference]	1.43(0.84,2.46)	1.31(0.73,2.37)	2.95(0.98,8.83)	0.19
CVD-Specific	Model 1	1 [Reference]	1.22(0.83,1.79)	1.10(0.71,1.73)	1.99(0.97,4.11)	0.31
	Model 2	1 [Reference]	1.16(0.78,1.73)	1.06(0.67,1.68)	1.82(0.88,3.76)	0.45
DM-Specific	Model 1	1 [Reference]	3.33(1.29, 8.65)**	2.61(1.04, 6.58)*	13.03(3.92,43.34)****	0.01*
	Model 2	1 [Reference]	3.20(1.10, 9.35)*	2.46(0.86, 7.04)	13.07(3.98,42.87)****	0.03*
AD-Specific	Model 1	1 [Reference]	0.79(0.31, 2.02)	0.33(0.11, 1.00)	3.59(0.97,13.22)	0.62
	Model 2	1 [Reference]	0.76(0.28, 2.03)	0.31(0.09, 1.07)	3.18(0.96,10.51)	0.58
Due to other causes	Model 1	1 [Reference]	1.33(0.96,1.84)	1.31(0.94,1.82)	1.88(0.58,6.07)	0.08
	Model 2	1 [Reference]	1.08(0.77,1.51)	1.07(0.76,1.50)	1.36(0.39,4.73)	0.64

Abbreviations: NVI, nonrefractive visual impairment; CVD, cardiovascular disease; DM, Diabetes mellitus; AD, Alzheimer's disease; HR, hazard ratio

[a] Adjusted for age, sex, race/ethnicity, educational attainment, marital status, body mass index, family income, smoking status, alcohol consumption, hypertension, hyperlipidemia, high C-reactive protein level, depressive symptoms, walking disability, self-rated health, history of coronary heart disease, congestive heart failure, heart attack, stroke, angina and cancer

[b] Adjusted for age, squared age, sex, race/ethnicity, educational attainment, marital status, body mass index, family income, smoking status, alcohol consumption, hypertension, hyperlipidemia, high C-reactive protein level, depressive symptoms, walking disability, self-rated health, history of coronary heart disease, congestive heart failure, heart attack, stroke, angina and cancer

*$P < 0.05$; **$P < 0.01$; ****$P < 0.0001$

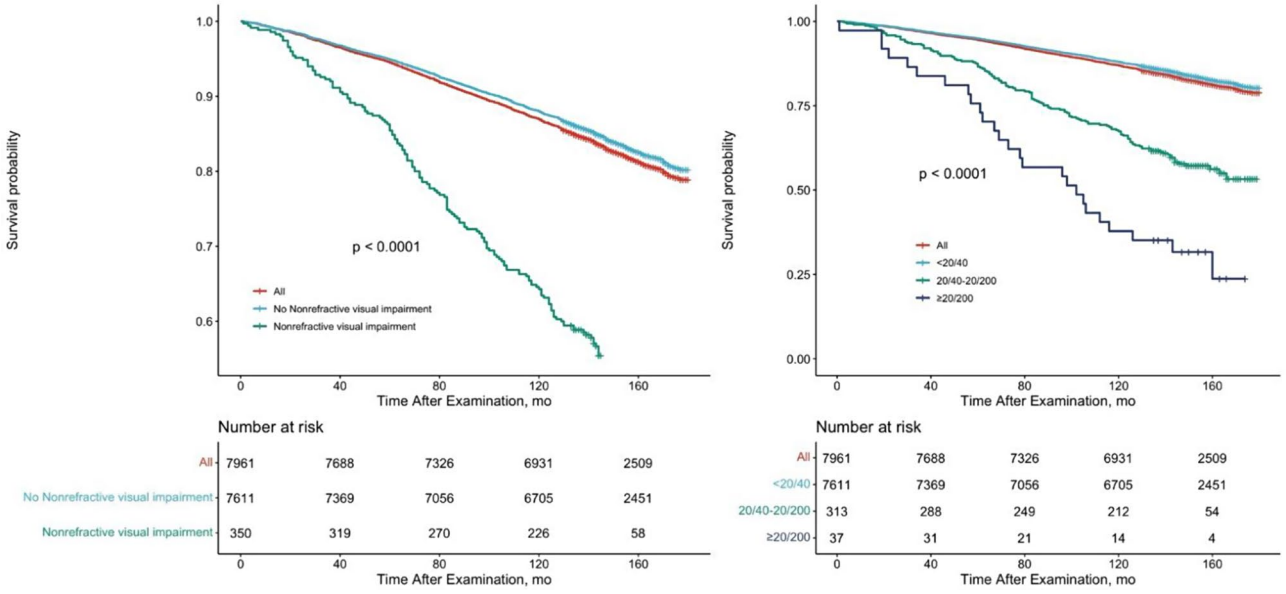

Fig. 1 Adjusted Kaplan-Meier Curve for All-Cause Mortality Rate by Nonrefractive Visual Impairment (NVI) Status. Study results were stratified according to the presence or absence of NVI (**A**) or NVI grading (**B**), using 1999–2008 National Health and Nutrition Examination Survey (NHANES) data. All-cause mortality was assessed through 31 December 2019

Discussion

In this study, we found an association between NVI and increased all-cause and DM-specific mortality risks in the U.S. population. After adjusting for confounders and using PSM, both any NVI and severe NVI correlated significantly with mortality. The severity analysis indicated a significant trend of increased risk of all-cause and DM-specific mortality as NVI severity increased. Particularly, DM-specific mortality notably surged exponentially as NVI worsened. Any NVI correlated with 1.3-fold all-cause mortality and over 3-fold DM-specific mortality. We elucidated that NVI may be a new risk factor for all-cause mortality, especially DM-specific mortality, independent of other risk factors such as CVD comorbidities, social determinants.

Table 4 Cox proportional hazards models for All-Cause mortality and fine and Gray competing risks regression models for Specific-Cause mortality by NVI status after propensity score matching (PSM)

NVI Status	All-Cause	Cancer-Specific	CVD-Specific	DM-Specific	AD-Specific	Due to other causes
Participant sample cases, No	294	52	117	14	11	100
Representative population, No	1,821,320	320,030	731,770	105,247	74,780	589,490
No NVI						
Participant sample cases, No (350)	135	24	59	5	6	41
Representative population, No (2 463 357)	847,734	143,529	361,647	25,419	36,061	254,576
HR (95% CI)	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
NVI						
Participant sample cases, No (350)	159	28	58	9	5	59
Representative population, No (2505022)	1,000,086	176,501	370,123	79,827	38,719	334,914
HR (95% CI)	1.34(1.05,1.70)*	1.38(0.68,2.80)	1.19(0.76,1.86)	3.54(1.15,10.97)*	1.26(0.43,3.66)	1.49(0.99,2.25)
P for trend	0.02*	0.37	0.44	0.03*	0.68	0.05

Abbreviations: NVI, Nonrefractive Visual Impairment; CVD, cardiovascular disease; DM, Diabetes mellitus; PSM, Propensity score matching; HR, hazard ratio

*$P < 0.05$

Our findings are similar to the results and conclusions of the Liwan Eye Study conducted in China, which is the only available existing longitudinal study analyzing NVI and mortality. Wang et al. conducted this survey of individuals aged 50 and above in Guangzhou, China, and found a significant association between NVI and decreased survival (HR: 2.72; 95% CI: 1.86–3.98), however, this study did not further refine the subgroups of NVI severity, nor did it further address the risk of NVI for attributable mortality [14]. The results of some of the other U.S. cohorts on VI and mortality resembled our findings on NVI.[10, 31, 32] NVI has long been unrecognized as a VI that cannot be eliminated by refractive correction in American adults [2], and our results emphasize once again the importance of regular examination of the visual acuity for VI and especially NVI screening.

On the one hand, VI could increase the likelihood of falls, accidents, and unintentional injuries.[33, 34] Additionally, VI has been found to affect physical function and psychological state, with implications for survival [8], which may contribute to varying degrees of mortality risk. On the other hand, systemic diseases such as endocrine, inflammatory, and autoimmune disorders are often reflected through ocular manifestations [35]. Notably, ocular symptoms of declining vision could serve as markers for systemic metabolic disorders such as DM (e.g., DR) [36]. However, Siersma et al. proposed a similar argument that the apparent association of impaired vision with all-cause mortality and diabetes-related mortality could be explained by confounding by comorbidities. [33, 37] Therefore, the possibility of common underlying pathogenesis between NVI associated with ocular and systemic diseases warrants further elucidation.

In our study, the majority of NVI patients were older, and the presence of age-related ocular diseases or NVI-related ocular diseases could be among the factors influencing patient survival. However, stratified subgroup analysis based on age revealed that NVI and its severity appeared to lack the significant association with all-cause mortality among patients aged over 80, which is consistent with the findings of Thompson et al. in their study of individuals aged 75 and older, where they did not observe a significant relationship between severe bilateral VI (defined as BCVA of 20/60 to 20/400) or blindness (below 20/400) and elderly mortality, the authors suggest that this may be explained by the fact that people with very poor vision or blindness, especially the elderly, generally receive better social care than those with moderate VI [38]. This implies that further research is warranted to explore the impact of NVI on the health and survival risks of elderly patients.

In contrast to previously published VI-related research within the U.S. population, our study did not detect a correlation between NVI and CVD-related mortality, indicating that NVI and VI might signify distinct physiological changes and disease progression characteristics. The National Health Interview Survey ($n = 116,796$) demonstrated that VI independently predicts increased CVD-related mortality (HR: 2.53; 95% CI: 1.68–3.81) in the US women [9]. Furthermore, the Kangbuk Samsung Health Study suggests potential connections between VI and CVD-related mortality [32]. Our study results contribute to bridging the evidence gap concerning the association between NVI and specific CVD-related mortality outcomes. Similarly, we found no significant association between NVI and AD or cancer-related mortality. The role of VI and NVI in the survival risk of AD and dementia remains largely unexplored, previous studies have demonstrated that VI is associated with several independent risk factors for mortality outcomes including dementia, depression and other major mental or social disorders [39]. However, the competing risk of death

events and the potential for bias in AD-related survival outcomes due to the therapeutic investment of elderly individuals in addressing VI might confound such findings.[40, 41] Overall, research on the association between VI (NVI) and AD-related and cancer-related mortality outcomes remains considerably limited and necessitates further exploration.

This study exhibits several strengths. Firstly, we confirmed that NVI and its severity are independent risk factors for all-cause and diabetes-specific mortality in the U.S. population. We used a representative sample of U.S. residents with comprehensive NHANES follow-up mortality data and standardized NVI assessment. Secondly, we employed Cox proportional hazards regression and competing risk models, adjusting for key confounders and using PSM to rectify them. Lastly, trend tests and subgroup analyses were conducted to clarify the impact of NVI on mortality across diverse population subsets. However, it's important to acknowledge the limitations in this study. Firstly, assessing visual acuity and NVI concurrently with confounding factors presents challenges in precisely evaluating changes during follow-up. Secondly, self-reported interviews and clinical data might omit mild cases, while NHANES excludes hospitalized patients, potentially losing severe cases. Treatment interventions or corrective status for visual impairment were not exhaustively documented in the NHANES survey data, which may have affected our interpretation of the definition of NVI and related outcomes. In addition, although we controlled for several potential confounders in our analyses, we were unable to completely exclude the influence of unmeasured variables (e.g., ophthalmic surgery, anti-vascular endothelial growth factor therapy, interventions) on the results. In addition, NHANES failed to clearly distinguish the relative contribution of multiple ophthalmic conditions (e.g., cataract, age-related macular degeneration, diabetic retinopathy) to NVI. Although NHANES provided information on participants' ophthalmic diagnoses, the inability to identify the primary source of visual impairment may result in incomplete identification of potential ophthalmic co-morbidities contributing to NVI, compromising our overall understanding of the relationship between NVI and mortality.

Conclusions

NVI has long been unrecognized as a vision impairment that cannot be eliminated by refractive correction in US adults, and our findings confirm, for the first time in this large, nationally representative cohort, substantiate NVI and its severity as independent risk factors for all-cause and diabetes-specific mortality among the US population, suggesting that the general middle-aged and older adult population may benefit from a routine refractive screening program. Given the expedience and convenience of vision assessments and NVI diagnoses, our results reiterate the significance of regular visual acuity screening, with particular emphasis on NVI identification. Vigilant and dynamic monitoring of visual changes and the onset and progression of NVI among individuals with diabetes may facilitate risk stratification and early intervention strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22249-7.

Supplementary Material 1

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Author contributions

SYG, XCW, QQW, LZ designed of the work. YYX and YRL directed the study's acquisition and analysis. JCQ, ZHH helped to interpret the data. HTL, JG and XDS have drafted the work and substantively revised it. FBT, CYH took responsible for the creation of new software used in the work. All authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analysed during the current study are available in the https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate

The publicly available data used in this project were derived from the NHANES program, which was approved by the Ethics Review Board of the National Center for Health Statistics (NCHS), adhering to the principles of the Declaration of Helsinki.

Consent for publication

All participants provided written informed consent to participate in the survey and agreed to the use of their data for health-related statistical research with links to vital statistics (e.g., the National Death Index).

Competing interests

The authors declare no competing interests.

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