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Association of prophylactic low-dose aspirin use with all-cause and cause-specific mortality in cancer patients

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The long-term use of aspirin for preventing cardiovascular disease has been recommended for decades. However, there is currently uncertainty regarding the long-term effects of aspirin use on the risk of all-cause, cardiovascular, and cancer mortality in cancer patients. The aim of this work was to analyze the connection between the prophylactic use of low-dose aspirin and the risk of all-cause death, cardiovascular death, and carcinoma death in carcinoma patients in the United States. A cohort study was conducted using National Health and Nutrition Examination Survey (NHANES) data (2011–2012, 2013–2014, 2015–2016, and 2017–2018) and associated mortality data. The 95% confidence intervals (CIs) and hazard ratios (HRs) between non-aspirin use and prophylactic low-dose aspirin use and the risk of death were measured via Cox proportional hazard regression models. A total of 1819 participants were included in the present research, of whom 945 were nonaspirin users and 874 were prophylactic aspirin users. Compared with non-aspirin users, prophylactic low-dose aspirin users had a decreased risk of all-cause death (HR = 0.647, 95% CI = 0.489–0.857). There was no statistically significant difference in the risk of cardiovascular death (HR = 0.623, 95% CI = 0.362–1.074) or cancer death (HR = 0.709, 95% CI = 0.410–1.226). Prophylactic use of low-dose aspirin may lower all-cause mortality in individuals with cancer but does not have a substantial effect on cardiovascular risk or cancer-specific mortality in this patient population.

Keywords NHANES, Aspirin, Cancer, Mortality

Although the pathogenesis of cancer is well known, the global burden of cancer has not decreased, and cancer continues to be a primary contributor to the global mortality rates associated with cancer[1]. It is estimated that 9 out of 10 deaths per year are cancer deaths[2]. Furthermore, the American Cancer Society estimates that in 2024, there will be approximately 2,001,140 new cancer cases and 611,720 fatalities due to cancer in the United States. This number equates to approximately 5,480 diagnoses and 1,680 deaths on a daily basis[3], indicating that cancer affects a substantial segment of the population. It is imperative to reduce the global burden of cancer.

Aspirin, also known as acetylsalicylic acid, which is known for its antipyretic and analgesic properties, is a widely used nonprescription drug suitable for the bulk of the global population[4]. With further research on the biological effects of aspirin[5], the relationship between aspirin and survival has also begun to gain widespread attention. A study conducted on a cohort of 10,854 individuals in the United States who were over 40 years old concluded that the preventive use of low-dose (75–100 mg/day) aspirin did not have a substantial effect on mortality from any cause[6]. A growing body of evidence shows that it is also linked to cancer[7]. Researchers believe that aspirin has the potential to impede cancer progression by directly targeting and disrupting cyclooxygenase (COX), inhibiting crucial enzymes associated with cancer cell proliferation, and intervening in cancer-related inflammation as well as platelet-induced cancer-promoting activity[8]. A nationwide study in Sweden revealed that aspirin use during follow-up in colon cancer patients was associated with an increased risk of death (hazard ratio [HR] = 1.09, 95% confidence interval [CI]: 1.04–1.15)[9], whereas a Danish study of endometrial cancer reported no association between low-dose aspirin use and mortality (HR = 1.10, 95% CI: 0.90–1.33)[10]. Thus,

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The relationship between aspirin use and death in patients with cancer remains uncertain. According to the Patient Mortality Detection, Epidemiology, and End Results (SEER) program, cardiovascular disease mortality within one year of cancer diagnosis is extremely high[11]. Moreover, cardiovascular disease accounts for 11% of cancer patient deaths. Therefore, whether aspirin, a cardiovascular prevention agent[12], can also improve cardiovascular events in cancer patients warrants further study.

Therefore, in this survey, we utilized the National Health and Nutrition Examination Survey (NHANES) and related mortality data bank to examine the relationships between the prophylactic use of low-dose aspirin and the risk of all-cause, cardiovascular, and cancer-related death among United States sufferers with carcinoma.

Materials and methods

Study population

A total of 39,156 participants from 4 periods of the NHANES (2011–2012, 2013–2014, 2015–2016, and 2017–2018) were used and linked with subsequent mortality data (NHANES Mortality Public Use File, 2011–2018). We excluded 36,984 participants who did not have cancer or who were uncertain about whether they had cancer, 2 participants who had unqualified or undisclosed mortality data, 318 participants who had unclear aspirin use, and 33 participants whose diabetes or hypercholesterolemia data were unclear. Ultimately, 1819 participants were included in this research (Fig. 1). The research protocol was approved by the Institutional Review Board of the National Center for Health Statistics (NCHS), and informed agreement was signed by all participants. All studies were conducted in strict accordance with the Declaration of Helsinki.

Assessing exposure

The independent variables for this study were derived from questionnaires that reported aspirin use for prophylaxis and recommended low-dose aspirin use. A trained interviewer, through a computer-aided personal interview (CAPI) system, asked about aspirin use-related issues to determine aspirin use. "Doctors and other health care providers sometimes recommend taking low-dose aspirin daily to prevent heart attacks, strokes, or cancer. Were you told to do so?" and "Are you currently taking low-dose aspirin as recommended?"

Cancer status

In the NHANES, the Medical Conditions section provides information on self-reported health conditions. The diagnosis of cancer was made by a trained interviewer at home via the CAPI system. These methods are based on the following two questions: (1) "Have you ever been told by a doctor or other health professional that you have cancer or any malignancy?" (2) "What kind of cancer is this? When was it diagnosed?"

Death status

The National Center for Health Statistics released the NHANES Public Use Associated Mortality Archive for 1999–2018, providing follow-up data on fatality status, cause of death, and fatality from the date of the participant's investigation through December 31, 2019. We categorized the reasons for death on the basis of the International Statistical Classification of Diseases, 10th Revision (ICD-10) code. The major events of our research were all-cause mortality, cardiovascular illness (codes I00-I09, I11, I13, and I20-I51), cancer (codes C00-C97), and mortality for other reasons.

Other covariates

The relevant covariates were extracted from the four data blocks of the NHANES database (demographic data, examination data, laboratory data and questionnaire data), which included the following two categories of

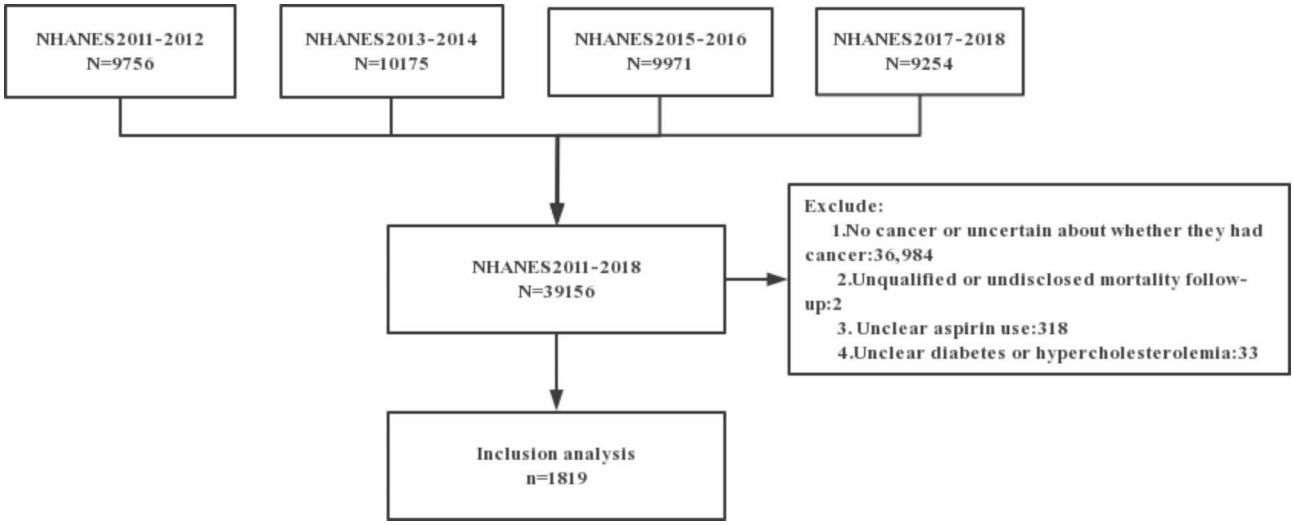

Fig. 1. Flow chart of the study.

covariates. The first type of continuous variable included age, BMI, total cholesterol, and glycosylated hemoglobin. Category 2 Categorical variables: sex, race, education, marital status, alcohol consumption status (no alcohol consumption, low to moderate alcohol consumption: < 1 drink/day for females, < 2 drinks/day for males, high alcohol intake or alcohol abuse: ≥1 drink/day for women, ≥2 drinks/day for men or history of alcohol abuse, not recorded), hypertension status (no, yes: 3 systolic or diastolic blood pressures ≥ 140/90 mmHg, or treatment with antihypertensive drugs), hypercholesterolemia status (no, yes: TC ≥ 6.2 mmol/L or use of hyperlipidemic drugs), diabetes status (no, yes: HBA1c ≥ 6.5% or uninterrupted usage of insulin or hypoglycemic pharmaceuticals), physical activity status (inactive: no moderate exercise and vigorous exercise per week, not too active: vigorous activity ≤ 75 min per week or moderate exercise ≤ 150 min per week, active: vigorous activity > 75 min per week or moderate exercise > 150 min per week, not recorded), smoking status (smoking from the questionnaire data - cigarette use asking "Do you currently smoke" was divided into never smoking, occasional smoking, daily smoking, not recorded).

Statistical analysis

The data used in this research are accessible at https://www.cdc.gov/nchs/nhanes/.

The participants were divided into two groups according to their aspirin use status: no aspirin use and prophylactic low-dose aspirin use. For normally distributed data, the median (interquartile distance) was used, whereas for normally distributed data, the mean ± standard deviation was considered, and differences between two groups were compared via t tests. Count data are expressed as frequencies (weighted percentages), and the $\chi 2$ test was used to compare differences between two sets. The results were compared between the two sets via hazard ratios (HRs) (95% CIs). Cox proportional hazard regression models were used to calculate the percentages of all-cause death, cardiovascular disease death (CVD), and carcinoma death. Two patterns were created: Model 1 was revised for gender, age, race and BMI; Model 2 was revised for gender, race, education, marital status, alcohol use, hypertension status, hypercholesterolemia status, diabetes status, physical activity, smoking status and the continuous variables of age, BMI, HBA1c, and total cholesterol. Additionally, we performed subgroup analyses for age, sex, hypertension status, hypercholesterolemia status, diabetes status, physical activity level, and smoking status via Model 2. Given aspirin's susceptibility to cardiovascular disease, participants with preexisting heart failure, coronary artery disease, angina, myocardial infarction, or cerebrovascular accidents were excluded from the sensitivity analysis. If $P < 0.05$ for both sides, the difference was considered statistically significant, and all the statistical analyses were performed with Stata Statistical Software version 17 (StataCorp., T.X., USA). We can obtain the software at https://www.stata.com/.

Results

Baseline data of the participants

A combined sample of 1,819 participants participated in the research, of whom 945 were not treated with aspirin, and 874 were treated with low-dose aspirin prophylaxis. The mean age of the overall research population was 65.75 years, and the sample included 874 men and 945 women. Compared with the non-aspirin group, the prophylactic aspirin group had a greater mean age (62.39 ± 11.55 vs. 69.75 ± 9.22 years, $P < 0.0001$) and elevated HBA1c levels (5.74 ± 0.69 vs. 6.04 ± 0.93 mmol/L) but also had lower total cholesterol levels (5.22 ± 1.09 vs. 4.81 ± 1.03 mmol/L, $P < 0.0001$). Males, non-Hispanic whites, those with a senior high school degree, those who were less active, those who were not smokers and who occasionally had HBP, hypercholesterolemia, diabetes, and heart disease were more likely to use low-dose aspirin (Table 1).

Association between prophylactic low-dose aspirin use and mortality

We used the number of person-months of follow-up from the beginning of the interview to the date of death or the end of the follow-up period. The number of person-years of follow-up was 7856 (median follow-up, 4.5 years) in the group with no aspirin use and 7848 (median follow-up, 5.08 years) in the group with prophylactic low-dose aspirin use. After adjusting for potential confounders of sex, age, race, and BMI, the risk of all-cause death was lower in cancer patients treated with prophylactic low-dose aspirin than in patients not treated with aspirin (HR = 0.647, 95% CI: 0.489–0.857), but the risks of cardiovascular death (HR = 0.623, 95% CI: 0.362–1.074) and cancer death (HR = 0.709, 95% CI: 0.410–1.226) were not substantially different between the two groups. After adjusting for all factors, prophylactic administration of low-dose aspirin was associated with a decreased risk of all-cause mortality in cancer patients (HR = 0.604, 95% CI: 0.455–0.800), and neither the risk of death from cardiovascular disease (HR = 0.577, 95% CI: 0.323–1.020) nor the risk of cancer death (HR = 0.712, 95% CI: 0.447–1.133) had a significant effect. In addition, we found that the number of cancer deaths per 1000 person-years was slightly lower in the low-dose aspirin group (6.881 vs. 7.383) than in the non-aspirin group, but the difference was not statistically significant (Table 2).

Subgroup analysis

In addition, subgroup percentages of all-cause death, cardiovascular disease, and carcinoma death among cancer patients were analyzed for sex, age, alcohol consumption, smoking status, physical activity, and the presence of hypertension, hypercholesterolemia, and diabetes. Our study revealed that prophylactic use of low-dose aspirin was associated with a decreased risk of all-cause death in patients in all cancer subgroups. There was no significant difference in the incidence of cardiovascular death or cancer death between the subgroups (Fig. 2).

Sensitivity analysis

Considering the sensitivity of cardiovascular disease to aspirin[13], we excluded 444 participants and 3 unrecorded participants with preexisting cardiac failure, ischemic heart disease, stenocardia, heart attack or stroke; ultimately, 1372 participants were included in the sensitivity analysis. Consistent with these results, compared with non-

No.	Total ($N=1819$)	Non-aspirin use ($N=945$)	Low-dose aspirin use ($N=874$)	P
Age (Mean ± SD)	65.75 ± 11.17	62.39 ± 11.55	69.75 ± 9.22	< 0.0001
BMI (Mean ± SD)	29.39 ± 6.45	29.14 ± 6.64	29.68 ± 6.21	0.0756
TC (Mean ± SD)	5.04 ± 1.08	5.22 ± 1.09	4.81 ± 1.03	< 0.0001
HbA1c (Mean ± SD)	5.88 ± 0.82	5.74 ± 0.69	6.04 ± 0.93	< 0.0001
Gender				< 0.0001
Male	874(44.05)	389(38.78)	485(50.31)	
Female	945(55.95)	556(61.22)	389(49.69)	
Race				0.017
Mexican American	123(2.61)	74(3.03)	49(2.11)	
Non-Hispanic White	1128(85.04)	549(83.00)	579(87.47)	
Non-Hispanic Black	289(5.29)	145(5.16)	144(4.45)	
Non-Hispanic Asian	82(1.68)	56(2.15)	26(1.14)	
Other	197(5.37)	121(6.66)	76(3.83)	
Education				0.0017
Less than high school	345(9.69)	158(7.98)	187(11.72)	
High school	379(19.51)	196(17.71)	183(21.64)	
More than high school	109(70.70)	590(74.28)	501(66.45)	
Not recorded	4(0.10)	1(0.03)	4(0.19)	
Marital status				0.1471
Married	1653(91.85)	840(90.82)	813(93.07)	
Separated	162(8.08)	101(9.06)	61(6.93)	
Not recorded	4(0.07)	4(0.13)	0(0.00)	
Alcohol drinking				0.1022
Non-drinker	301(11.59)	146(10.56)	155(12.81)	
Low to moderate drinker	478(31.59)	245(30.83)	233(32.49)	
Heavy drinker	607(37.42)	333(39.84)	274(34.54)	
Not recorded	433(19.4)	221(18.76)	212(20.16)	
HBP				< 0.0001
No	578(37.33)	381(46.75)	197(26.14)	
Yes	1241(62.67)	564(53.25)	677(73.86)	
Hypercholesterolemia				< 0.0001
No	789(44.26)	509(53.97)	260(32.72)	
Yes	1030(55.74)	436(46.03)	594(67.28)	
Diabetes				< 0.0001
No	1306(77.92)	753(85.53)	553(68.87)	
Yes	513(22.08)	192(14.47)	321(31.13)	
Heart attack				< 0.0001
No	1372(79.82)	802(87.53)	570(70.66)	
Yes	444(20.04)	142(12.45)	302(29.06)	
Not recorded	3(0.14)	1(0.02)	2(0.27)	
Physical activity				< 0.0001
Inactivity	1152(57.80)	587(55.72)	565(60.28)	
Less active	174(10.97)	79(9.87)	95(12.29)	
Dynamic	489(31.06)	276(34.2)	213(27.33)	
Not recorded	4(0.16)	3(0.21)	1(0.11)	
Smoking status				0.0008
Not at all	728(38.89)	338(25.94)	390(42.40)	
Some days	40(2.03)	20(1.45)	20(2.72)	
Every day	214(11.87)	129(13.84)	85(9.53)	
Not recorded	837(47.21)	458(48.78)	379(45.35)	

Table 1. Weighted baseline characteristics of all study participants and non-aspirin users and low-dose aspirin users. SD: standard deviation; BMI: body mass index; TC: total cholesterol; HbA1c: glycated hemoglobin a1c; HBP: high blood pressure.

	Non-aspirin use($N=945$)	Low-dose aspirin use($N=874$)
Person-years of follow-up	7856	7848
Median follow-up (years)	4.500	5.083
All-cause death		
No. of deaths	162	179
Mortality, per 1,000 person-years	20.621	22.808
Model1 HR (95% CI)	1 (Reference)	0.647(0.489,0.857)
Model2 HR (95% CI)	1 (Reference)	0.604(0.455,0.800)
CVD death		
No. of deaths	31	43
Mortality, per 1,000 person-years	3.946	5.479
Model1 HR (95% CI)	1 (Reference)	0.623(0.362,1.074)
Model2 HR (95% CI)	1 (Reference)	0.577(0.323,1.029)
Cancer death		
No. of deaths	58	54
Mortality, per 1,000 person-years	7.383	6.881
Model1 HR (95% CI)	1 (Reference)	0.709(0.410,1.226)
Model2 HR (95% CI)	1 (Reference)	0.712(0.447,1.133)

Table 2. Association between prophylactic low-dose aspirin use and mortality. Model 1: Revised for gender, age, race, and BMI; Model 2: Revised for gender, race, education, marriage, alcohol use, hypertension status, hypercholesterolemia, diabetes, physical activity, smoking, age, BMI, HBA1c, and total cholesterol. HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease death.

aspirin use, prophylactic low-dose aspirin was a protective factor against all-cause death but had no statistically significant effect on the risk of cardiovascular death or cancer death. Cancer mortality per 1000 person-years (5.566 vs. 7.993) was slightly lower in the prophylactic aspirin status group than in the non-aspirin status group, but the difference was not statistically significant (Table 3).

Discuss

In this cohort study based on a cancer population in the United States, we observed that the prophylactic use of low-dose aspirin was correlated with a decreased risk of all-cause mortality in cancer patients but was not significantly associated with cardiovascular death or carcinoma death in cancer patients. Sensitivity analyses that excluded participants with a record of cardiac failure, ischemic heart disease, stenocardia, heart attack or apoplexy did not change the results. This finding also shows the reliability and stability of the results of this study on the basis of the NAHNES 2011–2018 cancer population in the United States.

In 1981, a comprehensive prospective study was carried out to explore the potential link between the use of aspirin and the likelihood of fatal prostate cancer (PC), as well as postdiagnosis survival following PC, among a cohort of 22,071 healthy male physicians who were randomly allocated to receive either aspirin or placebo. As of 2009, a total of 502 instances of fatal PCs had been identified. The utilization of aspirin on a regular basis, whether in the present or past, is linked to a reduced likelihood of developing fatal PC compared with individuals who never used aspirin. Subsequent survival analysis revealed that the use of aspirin following diagnosis was linked to a decreased risk of fatal PC (HR = 0.68, 95% CI: 0.52–0.90) and gross mortality (HR = 0.72, 95% CI: 0.61–0.9)[14]. A systematic review of aspirin usage in populations eligible for CVD primary prevention revealed that both primary and secondary prevention trials demonstrated a reduction in colon cancer mortality over 20 years with aspirin (RR = 0.67; 95% CI: 0.52, 0.86). Furthermore, the initiation of aspirin therapy resulted in a decrease in the incidence of colon cancer, with an RR of 0.60 (95% CI: 0.47, 0.76) after a period of 10–19 years[15]. A meta-analysis of 118 studies on aspirin and 18 cancer types revealed that aspirin was associated with a decrease in all-cause mortality in carcinoma patients (HR = 0.80, 95% CI: 0.74–0.76)[16]. This study is consistent with these results, and our subgroup analysis also revealed that prophylactic low-dose aspirin use was involved in all-cause mortality in patients with carcinoma effects. Those with carcinoma who were ≥ 70 years of age; women; those with occasional alcohol use; those with no history of smoking or inactivity; and those with no history of hypertension, hypercholesterolemia, or diabetes were more likely to benefit from preventive low-dose aspirin use. A study of breast cancer revealed that aspirin can regulate M1/M2 macrophage subtypes by inhibiting crosstalk between 4T1 and RAW 264.7 cells and regulating angiogenesis and the production of inflammatory mediators to achieve adjuvant therapeutic effects[17]. Therefore, we believe that aspirin may increase cancer survival and thus affect all-cause death in the cancer population.

Previous studies have shown that aspirin can reduce the risk of cardiovascular death[18,19]. However, no significant impact of aspirin use on the risk of cardiovascular death was detected in healthy older adults ≥ 70 years old or adults ≥ 40 years old in the United States[6,20]. The study also revealed no statistically significant association between aspirin and cardiovascular death in the carcinoma population, including subsequent subgroup analyses that did not change this finding. This may be due to the decreased efficacy of low-dose aspirin in inhibiting platelet function in the cancer population[21].

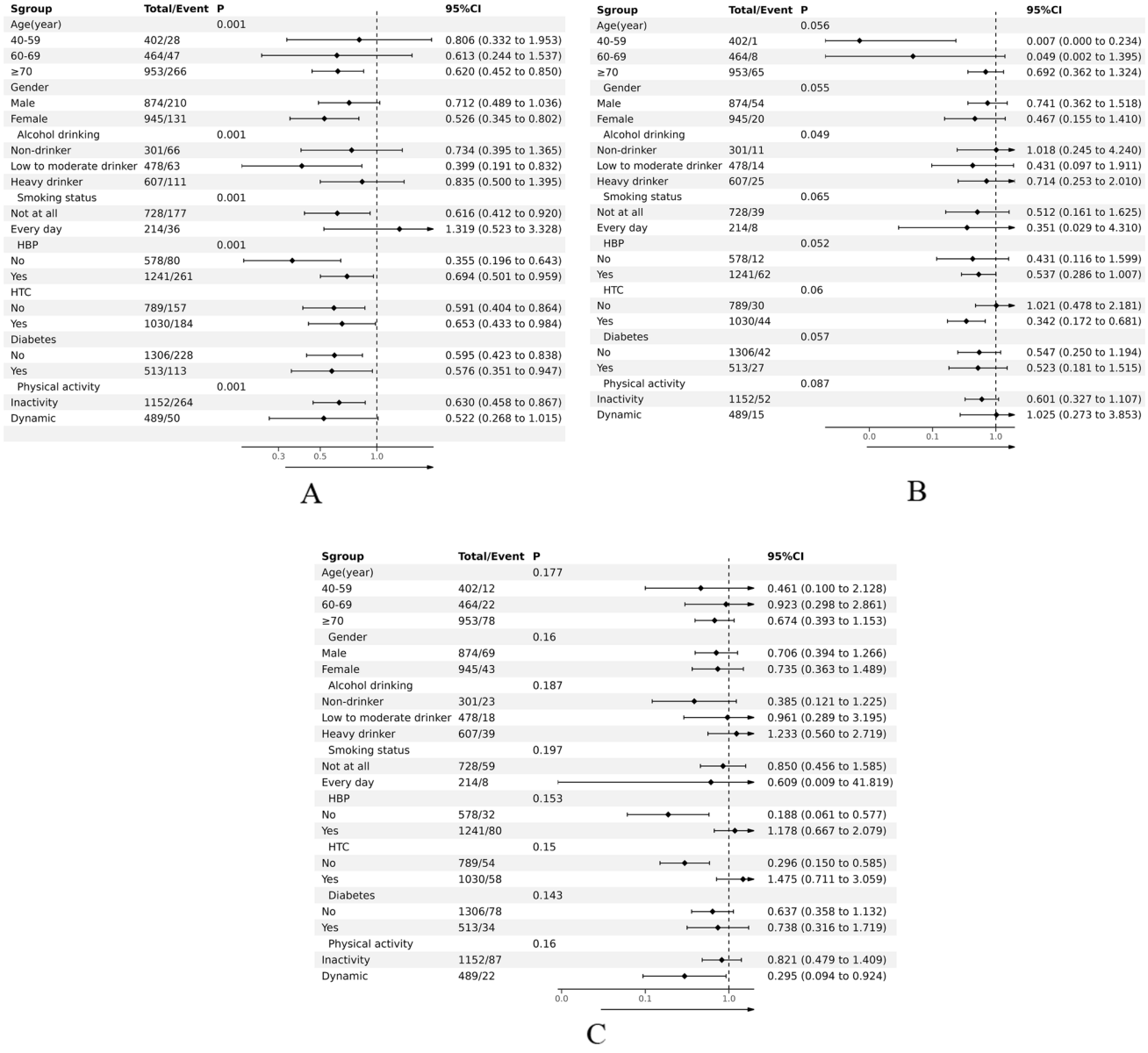

Fig. 2. Forest plots analyzed by subgroup. (**A**) Risk of all-cause death. (**B**) Cardiovascular death risk. (**C**) Risk of death from cancer.

It is currently believed that aspirin can inhibit the upregulation of COX-2 in carcinoma cells for anticancer purposes[22]. However, studies at the cellular level[23,24] have shown that aspirin impedes cell propagation and initiates cell cycle progression and apoptosis in multiple carcinoma cell lines, regardless of whether cancer cells express COX-2. There is also evidence of other potential targets for aspirin in the treatment of cancer[25]. In conclusion, the specific mechanism of the biological effects of aspirin in cancer is still not well understood. However, this study revealed that prophylactic low-dose aspirin use had no significant effect on cancer mortality and was not statistically significant in any subgroup. This is consistent with the results obtained by Elwood et al.[26]. In addition, our study revealed that prophylactic aspirin use may affect cancer mortality per 1000 person-years; even though this reduction was not statistically significant in this trial, it can be further observed in an expanded study population.

This research also has several limitations. First, the research was observational, and no causal relationship could be established between prophylactic low-dose aspirin use and mortality in carcinoma patients. Second, the identification of cancer patients and the use of aspirin were obtained through questionnaires, which may have resulted in certain memory bias. Finally, in our study, we did not explore aspirin-related deaths from side effects.

Overall, prophylactic use of low-dose aspirin diminishes the risk of all-cause death in carcinoma sufferers, specifically those who are aged more than 70 years, are female, have a history of occasional alcohol consumption, have no history of smoking, are inactive, and have no history of hypertension, hypercholesterolemia, or diabetes.

	Non-aspirin use($N=802$)	Low-dose aspirin use($N=570$)
Person-years of follow-up	6130	6109
All-cause death		
No. of deaths	116	99
Mortality, per 1,000 person-years	18.923	16.206
Model1 HR (95% CI)	1 (Reference)	0.706(0.537,0.930)
Model2 HR (95% CI)	1 (Reference)	0.706(0.533,0.936)
CVD death		
No. of deaths	14	16
Mortality, per 1,000 person-years	2.284	2.619
Model1 HR (95% CI)	1 (Reference)	0.764(0.372,1.570)
Model2 HR (95% CI)	1 (Reference)	0.772(0.367,1.622)
Cancer death		
No. of deaths	49	34
Mortality, per 1,000 person-years	7.993	5.566
Model1 HR (95% CI)	1 (Reference)	0.634(0.405,0.994)
Model2 HR (95% CI)	1 (Reference)	0.664(0.418,1.054)

Table 3. Sensitivity analysis of the connection between low-dose aspirin use and mortality in subjects who had cardiovascular disease at baseline. Model 1: Revised for gender, age, race, and BMI; Model 2: Revised for gender, race, education, marriage, alcohol use, hypertension status, hypercholesterolemia, diabetes, physical activity, smoking, age, BMI, HBA1c, and total cholesterol. HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease death.

Data availability

The data used in this research are obtainable at https://www.cdc.gov/nchs/nhanes.

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Author contributions
H.H. and J.-p.X. conceived and designed the study. W.-j.C. and C.S. collected and evaluated the data. H.H., W.-j.C., Z.-y.X. and L.-f.L. analyzed and interpreted the data, and H.H. wrote the manuscript. H.H. and J.-p.X. revised the manuscript. All authors read and approved the final manuscript.

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Declarations

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Ethics and Consent Statements
The research protocol was espoused by the Institutional Review Board of the National Center for Health Statistics (NCHS), and informed consent was signed by all participants.

Consent for publication
All authors agree to publish this work.

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