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# Aspirin use for primary prevention among US adults with and without elevated Lipoprotein(a)

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ABSTRACT

*Objective:* Lipoprotein(a) [Lp(a)] is an atherogenic and prothrombotic lipoprotein associated with atherosclerotic cardiovascular disease (ASCVD). We assessed the association between regular aspirin use and ASCVD mortality among individuals *with* versus *without* elevated Lp(a) in a nationally representative US cohort.
*Methods:* Eligible participants were aged 40–70 years without clinical ASCVD, reported on aspirin use, and had Lp(a) measurements from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994), the only cycle of this nationally representative US cohort to measure Lp(a). Regular aspirin use was defined as taking aspirin ≥30 times in the previous month. Using NHANES III linked mortality records and weighted Cox proportional hazards regression, the association between regular aspirin use and ASCVD mortality was observed in those *with* and *without* elevated Lp(a) (≥50 versus <50 mg/dL) over a median 26-year follow-up.
*Results:* Among 2,990 persons meeting inclusion criteria (~73 million US adults), the mean age was 50 years, 86% were non-Hispanic White, 9% were non-Hispanic Black, 53% were female, and 7% reported regular aspirin use. The median Lp(a) was 14 mg/dL and the proportion with elevated Lp(a) was similar among those *with* versus *without* regular aspirin use (15.1% versus 21.9%, $p = 0.16$). Among individuals with elevated Lp(a), the incidence of ASCVD mortality per 1,000 person-years was lower for those *with* versus *without* regular aspirin use (1.2, 95% CI: 0.1–2.3 versus 3.9, 95% CI: 2.8–4.9). In multivariable modeling, regular aspirin use was associated with a 52% lower risk of ASCVD mortality among individuals with elevated Lp(a) (HR=0.48, 95% CI: 0.28–0.83), but not for those without elevated Lp(a) (HR=1.01, 95% CI: 0.81–1.25; *p*-interaction=0.001).
*Conclusion:* Regular aspirin use was associated with significantly lower ASCVD mortality in adults without clinical ASCVD who had elevated Lp(a). These findings may have clinical and public health implications for aspirin utilization in primary prevention.

## 1. Introduction

The 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease recommends an individualized approach to prescribing aspirin for individuals aged 40–70 years who are at higher atherosclerotic

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**Table 1**
Characteristics of United States adults aged 40–70 years without clinical ASCVD with available measures of Lp(a), stratified by aspirin use.

| Characteristics | Estimated US Population [a] | Total Number in Current NHANES III Sample | All [c] | Without Regular Aspirin Use [c] | Regular Aspirin Use [c] | *P*-Value |
|---|---|---|---|---|---|---|
| Total Population | 73,047,156 | 2,990 | 2,990 | 2,773 | 217 | – |
| Age, years, median (Q1, Q3) | – | – | 50.2 (43.5, 58.6) | 49.8 (43.3, 58.0) | 52.4 (44.8, 61.7) | 0.006 |
| Female,% (95% CI) | 38,788,040 | 1,676 | 53.1 (50.7, 55.5) | 55.4 (54.6, 56.2) | 32.2 (28.9, 35.5) | <0.001 |
| Race/Ethnicity,% (95% CI) | | | | | | <0.001 |
| Non-Hispanic White / Other [b] | 63,039,695 | 1,357 | 86.3 (82.8, 89.8) | 85.4 (84.8, 86.0) | 94.6 (93.1, 96.0) | |
| Non-Hispanic Black | 6,866,433 | 833 | 9.4 (6.6, 12.3) | 10.1 (9.7, 10.6) | 3.1 (1.8, 4.4) | |
| Mexican American | 3,141,028 | 800 | 4.3 (2.5, 6.1) | 4.5 (4.1, 4.9) | 2.4 (2.0, 2.7) | |
| Post-High School Education,% | 31,848,560 | 852 | 43.6 (42.1, 45.0) | 42.9 (41.2, 44.6) | 49.2 (46.4, 52.0) | 0.003 |
| Family Hx of MI <50 years old,% (95% CI) | 12,052,781 | 391 | 16.5 (13.8, 19.2) | 16.4 (15.7, 17.2) | 17.1 (13.9, 20.3) | 0.66 |
| Current Cigarette Smoking,% | 17,239,129 | 754 | 23.6 (20.5, 26.6) | 23.1 (21.4, 24.8) | 27.7 (24.5, 30.9) | 0.004 |
| Body Mass Index, kg/m$^2$, mean (95% CI) | – | – | 27.7 (27.3, 28.1) | 27.7 (27.5, 27.8) | 27.7 (27.3, 28.0) | 0.98 |
| Systolic Blood Pressure, mmHg, mean (95% CI) | – | – | 125.8 (124.6, 127.0) | 125.5 (125.0, 126.0) | 128.5 (127.4, 129.6) | 0.09 |
| Antihypertensive Medication,% (95% CI) | 12,052,781 | 613 | 16.5 (14.1, 18.8) | 15.9 (14.9, 16.9) | 21.4 (20.1, 22.7) | <0.001 |
| Diabetes,% (95% CI) | 4,601,971 | 308 | 6.3 (4.9, 7.6) | 6.2 (5.5, 7.0) | 6.7 (6.3, 7.1) | 0.13 |
| Total Cholesterol, mg/dL, mean (95% CI) | – | – | 214.2 (211.8, 216.6) | 213.9 (212.3, 215.5) | 216.6 (213.9, 219.2) | 0.49 |
| HDL-Cholesterol, mg/dL, mean (95% CI) | – | – | 50.0 (48.9, 51.2) | 50.1 (49.8, 50.4) | 49.4 (48.8, 50.0) | 0.62 |
| Triglycerides, mg/dL, median (Q1, Q3) | – | – | 127.7 (87.8, 188.8) | 126.8 (87.3, 189.9) | 131.1 (92.4, 183.6) | 0.32 |
| Cholesterol-Lowering Medication,% (95% CI) | 3,141,028 | 127 | 4.3 (3.0, 5.5) | 3.6 (3.3, 4.0) | 9.7 (7.4, 12.0) | <0.001 |
| Lp(a), mg/dL, median (Q1, Q3) | – | – | 14.0 (3.4, 31.5) | 13.5 (3.4, 31.2) | 18.6 (4.2, 35.2) | 0.16 |
| Lp(a) ≥50 mg/dL | 11,468,404 | 612 | 15.7 (14.7, 16.6) | 15.1 (14.3, 15.8) | 21.0 (18.1, 23.9) | 0.16 |
| eGFR, mL/min/1.73m$^2$, mean (95% CI) | – | – | 73.9 (72.7, 75.1) | 74.1 (73.7, 74.5) | 72.4 (71.9, 72.8) | 0.17 |

Source of Data: National Center for Health Statistics: The Third National Health and Nutrition Examination Survey.
eGFR=estimated glomerular filtration rate; Hx=history; Lp(a)=lipoprotein(a); MI=myocardial infarction.
[a] based on 1990 US Census Counts.
[b] also includes persons other than non-Hispanic Black or Mexican American.
[c] all values are presented as weighted estimates, except for total population row.

cardiovascular disease (ASCVD) risk [1]. Beyond advanced subclinical atherosclerosis [2], the early identification of individuals who may benefit from aspirin therapy for primary prevention remains challenging. Lipoprotein(a) [Lp(a)] is a prothrombotic lipoprotein causally associated with ASCVD; approximately 1 in 5 individuals have elevated Lp(a) [3]. Emerging evidence suggests that individuals with high-risk Lp(a) genotypes or elevated Lp(a) may benefit from aspirin therapy for primary prevention. [4–6] However, prior data has been limited to young female or older adults, has not consistently included measurements of serum Lp(a), and/or has not included ASCVD mortality as an outcome [4–6]. We sought to assess whether the association between aspirin use and ASCVD mortality differed by Lp(a) level in a nationally representative sample of United States (US) adults.

## 2. Methods

The National Health and Nutrition Examination Survey (NHANES) includes a series of national, stratified, multistage probability surveys to select a representative sample of noninstitutionalized adults living in the US. The Third National Health and Nutrition Examination Survey (NHANES III) was collected in two phases (1988–1991 and 1991–1994) and is the only cycle of this nationally representative cohort to measure Lp(a) [7,8]. For the current analysis (**Supplemental Figure 1**), eligible participants were 1) aged 40–70 years with available measures of Lp(a), 2) reported on aspirin use, 3) did not report a previous history of myocardial infarction or stroke, and 4) had available information on covariables and follow-up through National Death Index (NDI) records.

Study protocols for NHANES were approved by the National Center for Health Statistics Ethics Review Board. All adult participants provided signed, informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cohort studies. This activity was conducted consistent with applicable federal law and CDC policy.

The public NHANES III Linked Mortality File, which includes NDI searches through December 31, 2019, provided mortality follow-up data. Using the *International Classification of Diseases, Tenth Revision* codes, ASCVD mortality is defined as when “Diseases of the Heart” (I00-I09, I11, I13, I20-I51) or “Cerebrovascular Diseases” (I60-I69) are the underlying cause of death [9]. Participants who had multiple causes of death due to hypertension or diabetes were not considered within the ASCVD mortality definition.

Lp(a) was measured (mg/dL) among participants in the second phase of NHANES III using an enzyme-linked immunosorbent assay specific for apolipoprotein(a) (Strategic Diagnostics Inc., Newark, DE) [10]. Elevated Lp(a) was defined using a threshold of ≥50 mg/dL [3]. Aspirin use was measured using two questions, “In the past month have you taken any aspirin?” and “How often did you use aspirin during the past month?” Participants qualified for regular aspirin use if they reported taking aspirin ≥30 times in the month before the interview. To account for possible every other day dosing regimens, secondary analyses

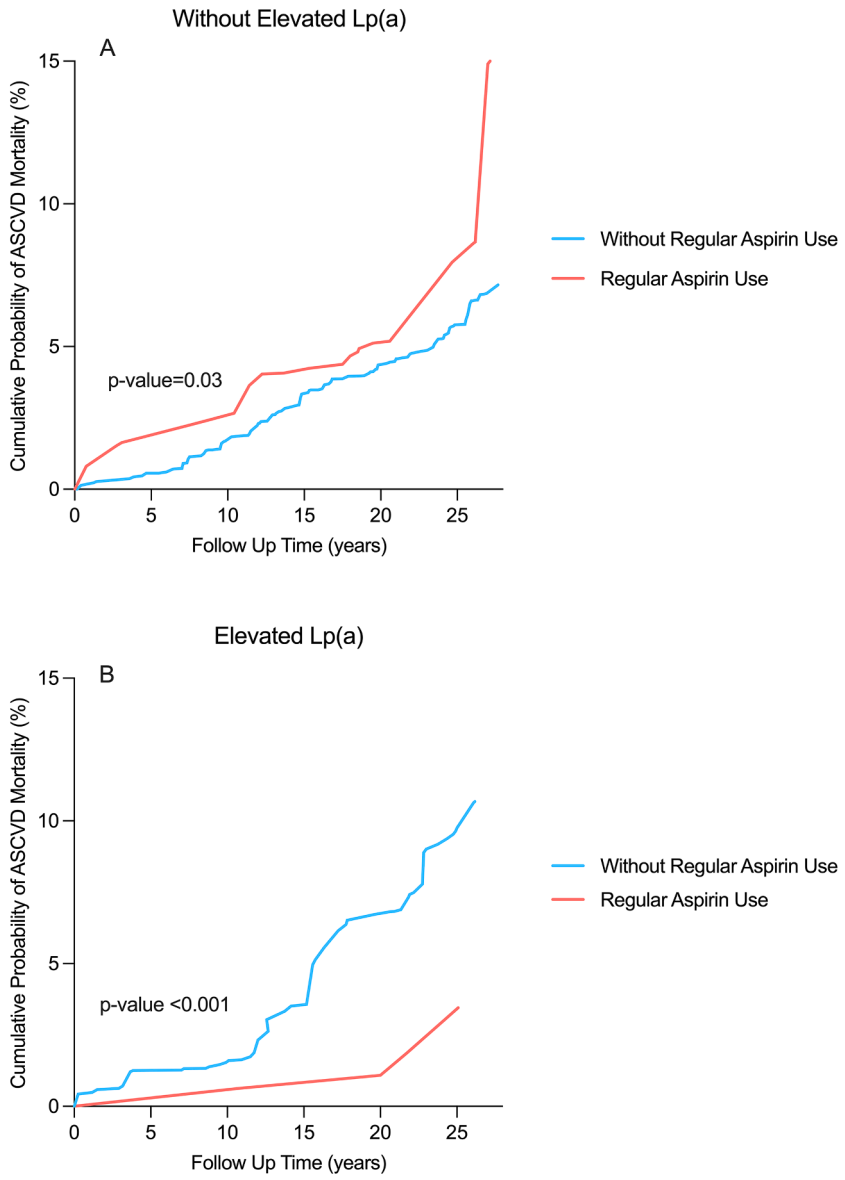


**Fig. 1.** Cumulative probability of ASCVD mortality according to aspirin use, stratified by normal (A) versus elevated Lp(a) (B).
*Among individuals with elevated Lp(a), those reporting regular aspirin use had a significantly lower crude cumulative probability of ASCVD mortality.

defined regular aspirin use as taking aspirin ≥15 times in the month before the interview [11].

Analyses were performed using NHANES III sample weights and considering the complex survey design. Because NHANES III population estimates derived from 1990, US Census estimates were only available for non-Hispanic White, non-Hispanic Black, and Mexican-American race ethnicity groups; persons belonging to other racial and ethnic groups were combined with non-Hispanic White. Participant characteristics were stratified according to regular aspirin use versus without regular aspirin use. The Student's *t*-test and Wilcoxon signed-rank test were used to assess differences in normally and non-normally distributed continuous variables, respectively. Differences between categorical variables were evaluated through the Chi-square test. The cumulative probability of ASCVD mortality according to aspirin groups was graphed across time for individuals with and without elevated Lp(a). Differences in the cumulative probability of ASCVD mortality between aspirin groups were assessed through bivariable Cox proportional hazards regression modeling. In multivariable Cox proportional hazards regression modeling, the association between regular aspirin use and ASCVD mortality was assessed among individuals *with* and *without* elevated Lp (a). The median follow-up time was 26 years.

Covariates adjusted for in regression models included age, sex, race/ethnicity (non-Hispanic Black, non-Hispanic White, and Mexican-American), education (post high school versus high school or below), family history of myocardial infarction at age <50 years, current cigarette smoking, body mass index, systolic blood pressure, total cholesterol, HDL-cholesterol, triglycerides, diabetes, estimated glomerular filtration rate, lipid-lowering medication use, and antihypertensive medication use. Diabetes was defined according to self-report or the utilization of glucose-lowering medication. Statistical analyses were performed using SAS 9.4 (Cary, NC).

## 3. Results

Among 2,990 participants meeting study inclusion criteria (representing 73 million people), mean age was 50 years, 9% were non-Hispanic Black people, 53% were female, and 7% reported regular aspirin use (Table 1). Individuals reporting regular aspirin use were older, more likely to be male, and more likely to be of non-Hispanic White race and ethnicity compared to participants without regular

**Table 2**
Association of regular aspirin use with ASCVD mortality among United States adults aged 40–70 years without clinical ASCVD, stratified by Lp(a).

| | Number of ASCVD Deaths (n) | Hazard Ratio (95% CI) | *P*-Value | *P*-Interaction [a] |
|---|---|---|---|---|
| **Model 1** [b] | | | | |
| Normal Lp(a) ($n$ = 2,378) | | | | |
| No Regular Aspirin Use ($n$ = 2,208) | 153 | Ref | – | 0.001 |
| Regular Aspirin Use ($n$ = 170) | 22 | 1.01 (0.81, 1.25) | 0.96 | |
| Elevated Lp(a) ($n$ = 612) | | | | |
| No Regular Aspirin Use ($n$ = 565) | 53 | Ref | – | |
| Regular Aspirin Use ($n$ = 47) | 4 | 0.48 (0.28, 0.83) | 0.01 | |
| **Model 2** [c] | | | | |
| Normal Lp(a) ($n$ = 2,378) | | | | |
| No Regular Aspirin Use ($n$ = 2,158) | 151 | Ref | – | 0.004 |
| Regular Aspirin Use ($n$ = 220) | 24 | 0.82 (0.61, 1.10) | 0.17 | |
| Elevated Lp(a) ($n$ = 612) | | | | |
| No Regular Aspirin Use ($n$ = 560) | 53 | Ref | – | |
| Regular Aspirin Use ($n$ = 52) | 4 | 0.43 (0.26, 0.72) | 0.005 | |

Sources of Data: Source of Data: National Center for Health Statistics: The Third National Health and Nutrition Examination Survey and Linked Mortality File.
All models adjusted for age, sex, race/ethnicity, education, family history of myocardial infarction <50 years old, cigarette smoking, body mass index, systolic blood pressure, total cholesterol, HDL-cholesterol, triglycerides, diabetes, estimated glomerular filtration rate, lipid-lowering medication use, and antihypertensive medication use.

[a] p-interaction value refers to Lp(a) (normal versus elevated) x regular aspirin use (yes versus no).

[b] regular aspirin use defined as having taken aspirin ≥30 times in the previous month.

[c] regular aspirin use defined as having taken aspirin ≥15 times in the previous month, to account for possible alternate day dosing regimens.

aspirin use. Median Lp(a) values between aspirin groups were similar. Participants with Lp(a) ≥50 were more likely to be female and of non-Hispanic Black race compared to those with Lp(a) <50 mg/dL (**Supplemental Table 1**).

In unadjusted models, among individuals with elevated Lp(a), those reporting regular aspirin use had a significantly lower crude cumulative probability of ASCVD mortality (Fig. 1A-B) and lower ASCVD mortality rate per 1000 person years versus those without regular aspirin use (**Supplemental Figure 2**). Contrastingly, the cumulative probability of ASCVD was significantly higher for individuals reporting regular versus non-regular aspirin use among persons without elevated Lp(a).

In multivariable modeling, regular aspirin use was significantly associated with a 52% lower risk of ASCVD mortality among individuals with elevated Lp(a) (HR=0.48, 95% CI: 0.28–0.83), but not for those without elevated Lp(a) (HR=1.01, 95% CI: 0.81–1.25; *p*-interaction=0.001). Similar findings were observed using an alternate day dosing definition for regular aspirin use (Table 2).

## 4. Discussion

Among a nationally representative sample of US adults without clinical ASCVD, regular aspirin use was independently associated with a 52% lower risk of ASCVD mortality for those with elevated Lp(a) but not those without elevated Lp(a) over a median 26-year follow-up. This is the first study to observe an ASCVD mortality benefit associated with aspirin therapy for primary prevention for individuals with elevated Lp(a).

Given the high prevalence of elevated Lp(a) (approximately 20% across populations), which is predominantly genetically determined [3], these findings may have substantial public health implications for the utilization of aspirin for primary prevention. Our results build on previous propensity-matched results from the Multi-Ethnic Study of Atherosclerosis that observed a 46% lower risk of coronary heart disease events with regular aspirin use for those with Lp(a) ≥50 mg/dL[6]. Earlier findings have also identified a 45–55% lower risk of index major adverse cardiovascular events for regular aspirin use among individuals carrying the rs3789220 *LPA* gene variant, but not for non-carriers [4,5].

Certain limitations should be considered. First, NHANES III survey data are subject to healthy volunteer bias and were collected three decades ago, as the current landscape of US demographics and preventive medications (increase in statins, antihypertensive, glucose-lowering medications) has changed. However, there have been no Food and Drug Administration-approved pharmacotherapies for Lp(a) lowering since NHANES III. Therefore, it is unlikely that current lower background ASCVD risk from non-Lp(a) risk lowering therapies would have affected our observed association between aspirin and ASCVD mortality among those with elevated Lp(a). Second, similar to several additional observational cohort studies [12,13], NHANES III utilized a mass-based (mg/dL) assay for quantifying Lp(a), which may be prone to measurement bias at the extremes of Lp(a) values [14]. While both mass (mg/dL) and particle (nmol/L) measurements are acceptable, particle-based measurement is preferred and efforts are ongoing to facilitate laboratory standardization [15]. Information on aspirin use was only collected at study baseline and also self-reported, subject to recall bias and misclassification [16]. In addition, regular aspirin use was not randomized across Lp(a) groups; however, NHANES III participants were taking aspirin therapy without prior knowledge of Lp(a) values. We sought to minimize these limitations by using two different definitions of regular aspirin use and adjusting for a multitude of risk factors, including kidney function, to mitigate residual confounding. Lastly, information on aspirin safety, including major bleeding events, was unavailable and deaths from others causes were not censored. Future net clinical benefit (benefit-harm) analyses involving the interaction of aspirin and Lp(a) with incident ASCVD and major bleeding events are needed.

## 5. Conclusion

Regular aspirin use was associated with a 52% lower risk of ASCVD mortality among adults without clinical ASCVD who had elevated Lp(a). These findings suggest that measurement of Lp(a) may help identify individuals who benefit from aspirin therapy for primary prevention.

## Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The authors have no conflicts of interest to disclose.

## CRediT authorship contribution statement

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Project administration. **Omar Dzaye:** Writing – review & editing, Validation, Methodology. **Harpreet S. Bhatia:** Writing – review & editing, Validation, Methodology, Conceptualization. **Anurag Mehta:** Writing – review & editing, Validation, Methodology. **Arshed A. Quyyumi:** Writing – review & editing, Validation, Methodology. **Viola Vaccarino:** Writing – review & editing, Validation, Methodology. **Matthew J. Budoff:** Writing – review & editing, Validation, Methodology. **Khurram Nasir:** Writing – review & editing, Validation, Methodology. **Sotirios Tsimikas:** Writing – review & editing, Validation, Methodology, Conceptualization. **Seamus P. Whelton:** Writing – review & editing, Validation, Methodology. **Michael J. Blaha:** Writing – review & editing, Validation, Methodology. **Roger S. Blumenthal:** Writing – review & editing, Validation, Methodology. **Laurence S. Sperling:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100674.

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