



# Long-Term Aspirin Use and 5-Year Survival in Healthy Adults: A Population-Based Cohort Study in South Korea

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**Purpose:** We investigated whether long-term aspirin use is associated with 5-year all-cause mortality.

**Materials and Methods:** Participants were individuals aged  $\geq 40$  years who were registered in the 2010 sample cohort database of the National Health Insurance Service in South Korea. Aspirin users were divided into three groups: continuous users (2006–2010), previous users (2006–2009), and new users (2010). Individuals with a history of coronary artery disease and cerebrovascular disease were excluded. Five-year all-cause mortality was defined as mortality due to any cause from January 1, 2011 to December 31, 2015. Data were analyzed by multivariable Cox regression.

**Results:** In total, 424444 individuals were included. Five-year all-cause mortality was 9% lower in continuous aspirin users than in unexposed individuals [hazard ratio (HR): 0.91, 95% confidence interval (CI): 0.86–0.97;  $p=0.003$ ]. Five-year all-cause mortality rates in the new aspirin users (HR: 1.00, 95% CI: 0.90–1.11;  $p=0.995$ ) and previous aspirin users (HR: 1.01, 95% CI: 0.94–1.09;  $p=0.776$ ) were not significantly different from that in unexposed individuals. In the 40–60-year age group, 5-year all-cause mortality in the continuous aspirin users was 24% lower (HR: 0.76, 95% CI: 0.64–0.90;  $p=0.002$ ) than that in unexposed individuals. However, in the  $>60$ -year age group, there was no significant association between aspirin use and 5-year all-cause mortality (HR: 0.96, 95% CI: 0.90–1.02;  $p=0.199$ ).

**Conclusion:** Long-term aspirin use is associated with reduced 5-year all-cause mortality in healthy adults, especially those aged  $<60$  years.

**Key Words:** Aspirin, mortality, neoplasm, cohort study

## INTRODUCTION

Aspirin, derived from salicylic acid, is one of the most frequently prescribed drugs worldwide for the primary and secondary prevention of cardiovascular diseases.<sup>1</sup> A recent study reported that over 30% of adults aged  $\geq 40$  years were prescribed as-

pirin to prevent cardiovascular diseases.<sup>2</sup> Despite its popularity, the usefulness of aspirin for the primary prevention of cardiovascular diseases remains controversial.<sup>3</sup>

Based on the evidence that aspirin use might prevent the development of both cancer and fatal cardiovascular events,<sup>4–8</sup> it is expected that aspirin could improve mortality rates in healthy adults. A meta-analysis of aspirin use for the primary prevention of cardiovascular disease showed that it was beneficial for the prevention of all-cause mortality.<sup>9</sup> However, a recent study, the Aspirin in Reducing Events in the Elderly (ASPREE) trial, reported that aspirin use did not prolong disability-free survival in healthy older adults; moreover, all-cause mortality was higher in apparently healthy older adults who received aspirin daily than in individuals in the placebo group.<sup>10,11</sup> Additionally, cancer-related death was increased in the low-dose daily aspirin group.<sup>10</sup> Although the ASPREE trial was a well-designed, large, population-based, randomized clinical trial, it comprised only

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healthy individuals aged 65 years or older. Thus, the effect of aspirin use on long-term mortality in the general adult population continues to be controversial and warrants further research. Accordingly, the aim of this population-based cohort study was to investigate whether long-term aspirin use is associated with 5-year all-cause mortality in the adult population in South Korea.

## MATERIALS AND METHODS

### Design and ethics statements

This population-based cohort study was conducted according to the Reporting of Observational Studies in Epidemiology guidelines,<sup>12</sup> and population, exposure, control, and outcomes were defined.<sup>13</sup> The study protocol was approved by the Institutional Review Board (X-1903-529-903) and the Health Insurance Review and Assessment Service (NHIS-2019-2-170).

### Data source

The National Health Insurance Service (NHIS) has developed a sample cohort database to provide data for academic health-care-related research in the general population in South Korea. The database includes a stratified random sample of one million individuals registered with the agency since 2002. It was designed to be representative of the national population in terms of demographic and socioeconomic variables. The cohort was dynamic, and the patients were followed up until the end of 2015. These data were supplemented with additional data, including data on infants, to make-up for attrition due to follow-up loss and death.<sup>14</sup>

### Study population

Individuals of the general adult population (aged  $\geq 40$  years) registered in the 2010 cohort database of the NHIS were included in this study. Individuals who died in 2010 and those who had a history of cerebrovascular or coronary artery diseases were excluded from analysis because we focused on the primary preventive effect of aspirin on 5-year mortality. These exclusions were performed based on the registered International Statistical Classification of Diseases (ICD)-10 codes from 2009 to 2010 in the NHIS database, such as I21\*, I22\*, and I25.2\* for coronary artery disease and G45\*, G46\*, H34.0, and I60\*–I69\* for cerebrovascular disease.

### Main exposure variable: aspirin use

To define aspirin exposure, prescription data for aspirin for 2006–2010 (5 years) were extracted. Using these prescription data, we defined individuals who had been prescribed aspirin for  $>30$  days regularly and continuously as aspirin users. The aspirin users were divided into three groups (continuous, previous, and new aspirin users). Continuous aspirin users were prescribed to take aspirin continuously for 5 years from 2006 to 2010. Previous aspirin users were defined as individuals who

were prescribed aspirin from 2006 to 2009, but did not use aspirin in 2010. New aspirin users were defined as individuals who were newly prescribed to take aspirin in 2010, but were not prescribed aspirin from 2006 to 2009. In addition, individuals who used aspirin from 2007 and 2008 to 2010 continuously were classified as continuous aspirin users, whereas those who used aspirin from 2009 to 2010 were classified as new aspirin users.

### Reference population of unexposed individuals

The reference population (unexposed individuals) in this study comprised individuals who did not use aspirin from 2006 to 2010 among the population in the 2010 NHIS cohort.

### Study endpoints

The primary endpoint of this study was 5-year all-cause mortality, and the secondary endpoints were 5-year cardiovascular mortality and cancer mortality. Five-year all-cause mortality was defined as mortality from any cause between January 1, 2011 and December 31, 2015. Five-year cardiovascular mortality was defined as mortality due to a cardiovascular disease (ICD-10: I00–I99, Q20–Q28), and 5-year cancer mortality was defined as mortality due to cancer (ICD-10: C00–D48).

### Confounders

Data on the following variables were collected as confounders in this study: 1) demographic information (age and sex); 2) annual income level (0–20%, 20–40%, 40–60%, 60–80%, and 80–100%); 3) residence in 2010 (capital city, metropolitan city, and others); 4) the Charlson comorbidity index (CCI), which was calculated based on ICD-10 codes from 2009 to 2010, as shown in Supplementary Material (only online); 5) comorbidities that were registered using ICD-10 codes from 2009 to 2010; 6) exposure to clopidogrel; and 7) number of outpatient clinic visits in 2010 (days). Individuals in the cohort who were prescribed regular clopidogrel in 2010 were considered exposed to clopidogrel.

### Statistical analysis

The baseline characteristics are presented as means with standard deviations for continuous variables and numbers with percentages for categorical variables. We fitted the multivariable Cox regression model for 5-year all-cause mortality to the entire cohort. All covariates were included in the multivariable model for adjustment, except CCI, to avoid multicollinearity with individual underlying diseases used to calculate CCI. In the multivariable model, the risk of 5-year all-cause mortality in continuous, previous, and new aspirin users was investigated in comparison to that in the unexposed individuals. We then performed a competing risk analysis of 5-year cardiovascular mortality and 5-year cancer mortality using the same methods of the main analysis (multivariable Cox regression model). For these competing risk analyses, death due to cardiovascular disease or cancer was set as an event in the Cox model, and the duration

from January 1, 2011 to the date of death was used as the time to event. We performed a subgroup analysis according to age (>60-year and 40–60-year age groups). All covariates were included in the subgroup analyses for multivariable adjustment.

To enhance the robustness of our main findings, we performed propensity score (PS) matching, which is known to reduce confounders in cohort studies,<sup>15</sup> using the nearest neighbor method with a 1:3 ratio, without replacement, and a caliper width of 0.1. The continuous aspirin users and unexposed individuals were included in this PS modeling, not new aspirin users or previous aspirin users. A logistic regression analysis was performed to calculate the PS values as a logistic model, and all covariates were included in the PS model. The absolute value of the standardized mean difference (ASD) was used to determine the balance between the aspirin and control groups before and after PS matching. The ASDs between the two groups before and after PS matching were set to <0.1 to determine if the two groups were well balanced through PS matching. In addition, we used C-statistics as a measure of the ability of the PS to control confounding.<sup>16</sup> After confirming good balance between the two groups (continuous aspirin users and the unexposed individuals), we performed a stratified Cox regression analysis of 5-year all-cause mortality in the PS-matched cohort.

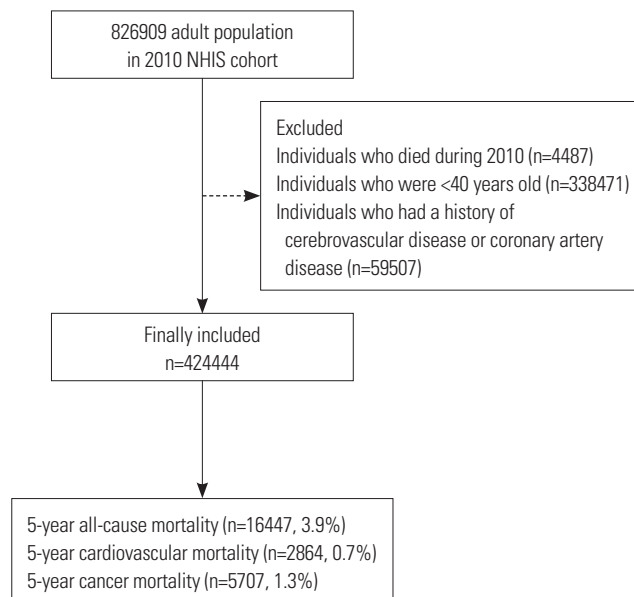
The results of the Cox regression models are presented as hazard ratios (HRs) with 95% confidence intervals (CIs); it was confirmed that there was no multicollinearity in all multivariable models of the entire cohort with a variance inflation factor <2.0. C-statistics were used to identify the C-index of the multivariable Cox regression models. All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), and results with  $p < 0.05$  were considered statistically significant.

## RESULTS

The 2010 NHIS sample cohort comprised 826909 individuals. Of these, we excluded 4487 individuals who died in 2010. Furthermore, 338471 individuals who were <40 years of age and 59507 individuals who had a history of cerebrovascular or coronary artery diseases were excluded from the analysis. Finally, 424444 individuals were included in the analysis. Of these, 16447 individuals (3.9%) died within 5 years, among which 2864 (0.7%) and 5707 (1.3%) deaths corresponded to (5-year) cardiovascular and cancer mortality, respectively (Fig. 1). The baseline characteristics of the study subjects are presented in Table 1. Among the individuals, the numbers of continuous aspirin users, previous aspirin users, and new aspirin users were 18482 (4.4%), 9332 (2.2%), and 5311 (1.1%), respectively.

### Survival analysis for the entire cohort

Table 2 shows the results of the survival analysis for the entire cohort. The 5-year all-cause mortality was 9% lower in the con-



**Fig. 1.** Flow chart showing the participant selection process. NHIS, National Health Insurance Service.

tinuous aspirin users than in unexposed individuals (HR: 0.91, 95% CI: 0.86–0.97;  $p=0.003$ ). However, 5-year all-cause mortality in new aspirin users (HR: 1.00, 95% CI: 0.90–1.11;  $p=0.995$ ) and previous aspirin users (HR: 1.01, 95% CI: 0.94–1.09;  $p=0.776$ ) was not significantly different from that in the unexposed individuals. The C-index of the multivariable model was 0.81 (95% CI: 0.80–0.81).

Table 3 shows the results of competing risk analysis of 5-year cancer and cardiovascular mortality. The 5-year cancer mortality in continuous aspirin users was 14% lower (HR: 0.86, 95% CI: 0.77–0.96;  $p=0.002$ ) than that in unexposed individuals. However, 5-year cardiovascular mortality in the continuous aspirin users did not show a significant association (HR: 1.01, 95% CI: 0.88–1.15;  $p=0.940$ ), compared to that in unexposed individuals.

Table 4 shows the results of subgroup analysis of 5-year all-cause mortality according to age. In the >60-year age group ( $n=111072$ ), there was no significant association between 5-year all-cause mortality and aspirin use (HR: 0.96, 95% CI: 0.90–1.02;  $p=0.199$ ). However, in the 40–60-year age group, 5-year all-cause mortality in the continuous aspirin users was 24% lower (HR: 0.76, 95% CI: 0.64–0.90;  $p=0.002$ ) than that in the unexposed individuals.

### Survival analysis after propensity score matching

The characteristics of the continuous aspirin users and unexposed individuals before and after PS matching are presented in Supplementary Table 1 (only online). All covariates were well balanced, as indicated by their ASDs, which were below 0.1, and the C-index of the PS model was 0.83 (95% CI: 0.82–0.83). Table 5 shows the results of the survival analysis after PS matching. After PS matching, the 5-year all-cause mortality in the continuous aspirin users was 7.0% (1289/18482), whereas that in

**Table 1.** Baseline Characteristics of the Participants (n=424444)

Variable	n (%)	Mean (SD)
Age (yr)		54.3 (10.9)
Sex: male (vs. female)	205021 (48.3)	
Income level		
0–20% (lowest)	60128 (14.2)	
20–40%	62016 (14.6)	
40–60%	87134 (20.5)	
60–80%	89719 (21.1)	
80–100% (highest)	125447 (29.6)	
Residence		
Capital city (Seoul)	85872 (20.2)	
Metropolitan city	109186 (25.7)	
Other area	229386 (54.0)	
Charlson comorbidity index		1.3 (1.7)
Hypertension	100095 (23.6)	
DM with chronic complication	20594 (4.9)	
DM without chronic complication	55429 (13.1)	
Congestive heart failure	7725 (1.8)	
Chronic pulmonary disease	111465 (26.3)	
Dementia	825 (0.2)	
Hemi- or paraplegia	1145 (0.3)	
Renal disease	2911 (0.7)	
Mild liver disease	81239 (19.1)	
Severe liver disease	3557 (0.8)	
Peptic ulcer disease	117864 (27.8)	
Rheumatic disease	16721 (3.9)	
Peripheral vascular disease	42086 (9.9)	
Clopidogrel user in 2010	1166 (0.3)	
Outpatient clinic visit in 2010, day		
0–7	224272 (52.8)	
8–30	176367 (41.6)	
30–90	23390 (5.5)	
>90	415 (0.1)	
Aspirin users		
Unexposed individuals	391319 (92.2)	
New aspirin users (2010)	5311 (1.3)	
Previous aspirin users (2006–2009)	9332 (2.2)	
Continuous aspirin users (2006–2010)	18482 (4.4)	

SD, standard deviation; DM, diabetes mellitus. Presented as numbers with percentages or means with standard deviations.

the unexposed individuals was 7.5% (4046/53675). We also found that the 5-year all-cause mortality was 7% lower in the continuous aspirin users (HR: 0.93, 95% CI: 0.87–0.98;  $p=0.014$ ) than in the unexposed individuals.

## DISCUSSION

The results of this population-based cohort study showed that long-term aspirin use is associated with reduced 5-year all-cause

**Table 2.** Multivariable Cox Regression Model for 5-Year All-Cause Mortality in the 2010 NHIS Sample Cohort

Variable	Multivariable model HR (95% CI)	p value
Age (yr)	1.11 (1.10–1.11)	<0.001
Sex: male (vs. female)	1.97 (1.91–2.04)	<0.001
Income level		
0–20% (lowest)	1	
20–40%	0.99 (0.93–1.05)	0.647
40–60%	1.08 (1.02–1.13)	0.004
60–80%	0.84 (0.80–0.88)	<0.001
80–100% (highest)	0.73 (0.69–0.76)	<0.001
Residence		
Capital city (Seoul)	1	
Metropolitan city	1.19 (1.13–1.25)	<0.001
Other area	1.16 (1.11–1.21)	<0.001
Comorbidities		
Hypertension	1.04 (1.00–1.08)	0.062
DM with chronic complication	1.34 (1.27–1.41)	<0.001
DM without chronic complication	1.27 (1.22–1.32)	<0.001
Congestive heart failure	1.59 (1.50–1.69)	<0.001
Chronic pulmonary disease	1.10 (1.06–1.14)	<0.001
Dementia	2.06 (1.81–2.35)	<0.001
Hemi- or paraplegia	2.38 (2.08–2.73)	<0.001
Renal disease	2.00 (1.82–2.19)	<0.001
Mild liver disease	1.16 (1.12–1.20)	<0.001
Severe liver disease	2.59 (2.37–2.84)	<0.001
Peptic ulcer disease	0.96 (0.93–1.00)	0.027
Rheumatic disease	1.03 (0.96–1.10)	0.432
Peripheral vascular disease	0.94 (0.93–1.10)	0.027
Clopidogrel user in 2010	1.06 (0.88–1.28)	0.527
Outpatient clinic visit in 2010, day		
0–7	1	
8–30	0.69 (0.66–0.71)	<0.001
30–90	0.65 (0.62–0.69)	<0.001
>90	0.83 (0.65–1.06)	0.137
Aspirin users		
Unexposed individuals	1	
New aspirin users (2010)	1.00 (0.90–1.11)	0.995
Previous aspirin users (2006–2009)	1.01 (0.94–1.09)	0.776
Continuous aspirin users (2006–2010)	0.91 (0.86–0.97)	0.003

NHIS, National Health Insurance Service; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus. C-index: 0.81 (95% CI: 0.80–0.81).

mortality in the adult population in South Korea. This association was more evident in aspirin users aged <60 years. Additionally, the results of competing risk analysis suggested that 5-year cancer mortality, but not cardiovascular mortality, might be reduced in continuous aspirin users. This result was similar to that of a recent cohort study, which reported that aspirin use is associated with a reduction in all-cause and cancer mortality.<sup>17</sup>

The results of this observational study should be interpreted

carefully. In this study, only continuous aspirin use was associated with a benefit in terms of 5-year all-cause and cancer mortality, compared to that for unexposed individuals. However, the comparison between the continuous aspirin users and unexposed individuals has some limitations. First, if the use of aspirin affects mortality shortly after treatment initiation, this is not captured in an analysis of continuous users. In addition, the

continuous aspirin users tended to be healthy adherers and represented those who would benefit from treatment, which could also affect the results. Compared to the continuous aspirin users, the new users or previous aspirin users might not be exhibiting good treatment adherence or the duration of aspirin exposure might not have been sufficient to yield a clinical benefit with respect to long-term mortality.

**Table 3.** Competing Risk Analyses of 5-Year Cancer Mortality and Cardiovascular Mortality

Variable	Multivariable model	
	HR (95% CI)	p value
5-year cancer mortality		
Unexposed individuals	1	
New aspirin users (2010)	0.98 (0.81–1.18)	0.833
Previous aspirin users (2006–2009)	0.88 (0.76–1.02)	0.079
Continuous aspirin users (2006–2010)	0.86 (0.77–0.96)	0.002
5-year cardiovascular mortality		
Unexposed individuals	1	
New aspirin users (2010)	1.25 (1.01–1.57)	0.052
Previous aspirin users (2006–2009)	1.18 (1.00–1.40)	0.051
Continuous aspirin users (2006–2010)	1.01 (0.88–1.15)	0.940

HR, hazard ratio; CI, confidence interval.

**Table 4.** Subgroup Analyses of 5-Year All-Cause Mortality According to Age

Variable	Multivariable model	
	HR (95% CI)	p value
Age >60, n=111072		
Unexposed individuals	1	
New aspirin users (2010)	1.00 (0.88–1.12)	0.929
Previous aspirin users (2006–2009)	1.04 (0.96–1.14)	0.324
Continuous aspirin users (2006–2010)	0.96 (0.90–1.02)	0.199
Age 40–60, n=313372		
Unexposed individuals	1	
New aspirin users (2010)	1.12 (0.89–1.42)	0.335
Previous aspirin users (2006–2009)	0.87 (0.71–1.08)	0.199
Continuous aspirin users (2006–2010)	0.76 (0.64–0.90)	0.002

HR, hazard ratio; CI, confidence interval.

Owing to this being an observational study, indication bias should also be considered.<sup>18</sup> In this study, aspirin might have been prescribed for the primary prevention of acute cardiovascular events in the healthy population without a history of cerebrovascular or coronary artery disease. However, the aspirin users in this study of older age or with higher CCI scores might have had a higher risk of acute cardiovascular events as shown in Supplementary Table 1 (only online). Although we controlled for confounders using multivariable adjustments and PS matching, the indication of aspirin might affect the results. For example, the association between 5-year cardiovascular mortality and aspirin use was not significant in the aspirin users, compared with that in unexposed individuals. However, considering indication bias, the results could have been influenced by the characteristics of aspirin users and not by the effect of aspirin itself.

The results of the present study are different from those of the ASPREE trial,<sup>10,11,19</sup> which reported higher all-cause mortality in the aspirin group than in the placebo group. As the ASPREE trial focused on healthy older individuals with a lower risk of mortality than older individuals who had chronic diseases, aspirin use was expected to prevent primary cardiovascular events and cancer development and not secondary events. In the AR-RIVE trial, the primary prevention of cardiovascular events in aspirin users was not significant (HR: 0.96, 95% CI: 0.81–1.13;  $p=0.60$ ) among 12546 men (aged  $\geq 55$  years) and women (aged  $\geq 60$  years) with moderate cardiovascular disease risk.<sup>20</sup> However, gastrointestinal bleeding was higher in participants who received aspirin [odds ratio (OR): 2.11, 95% CI: 1.36–3.28;  $p=0.007$ ], as a major complication of aspirin use.<sup>21</sup> In another recent trial of cardiovascular events in diabetes conducted with 15480 participants, the fatal vascular death rate did not differ

**Table 5.** Five-Year Mortality after PS Matching

Variables	Mortality (n, %)	HR (95% CI)	p value
After PS matching			
5-year all-cause mortality			
Unexposed individuals	4046 of 53675 (7.5)	1	
Continuous aspirin users	1289 of 18482 (7.0)	0.93 (0.87–0.98)	0.014
5-year cancer mortality			
Unexposed individuals	1270 of 53675 (2.4)	1	
Continuous aspirin users	406 of 18482 (2.2)	0.93 (0.83–1.04)	0.175
5-year cardiovascular mortality			
Unexposed individuals	800 of 53675 (1.5)	1	
Continuous aspirin users	283 of 18482 (1.5)	1.02 (0.89–1.17)	0.731

PS, propensity score; HR, hazard ratio; CI, confidence interval.

between the aspirin and placebo groups, and increased major bleeding (OR: 1.29, 95% CI: 1.09–1.52;  $p=0.003$ ) was reported in the aspirin group.<sup>22</sup> Furthermore, a recent meta-analysis concluded that aspirin was not associated with a reduction in the incidence of all-cause mortality; however, it was associated with an increased incidence of major bleeding.<sup>23</sup> The authors of the meta-analysis suggested that the routine use of aspirin for primary prevention should be reconsidered. Considering that the 5-year cardiovascular mortality in our competing risk analysis was not significantly associated with aspirin use, compared to that for unexposed individuals, the effect of aspirin use on the prevention of cardiovascular events might not be significant, as reported in previous clinical trials.<sup>19,21–23</sup>

Although our study was not a randomized clinical trial, we covered a much broader population, including the general adult population aged 40 years or above, who had no history of cerebrovascular or coronary artery diseases. Thus, the association with aspirin use might be applied to the primary prevention of cardiovascular disease or cancer. Additionally, we included many confounders in this analysis, such as comorbidities related to cardiovascular disease-related risk factors, frailty-related information, and socioeconomic status-related information. Therefore, the residual confounders were minimized in this study, despite the limitations of the study design.

The results of the competing risk analysis in our study were noteworthy. The association between exposure to aspirin and an improvement in 5-year mortality was more evident with respect to death due to cancer. A recent population-based cohort study, which was conducted in Hong Kong, reported that the long-term use of low-dose aspirin was associated with a decreased risk of cancer, except for breast cancer.<sup>24</sup> Other population-based cohort studies in South Korea and the United States have also reported that aspirin use was associated with a decreased risk of lung cancer.<sup>25,26</sup> However, another recent cohort study reported that low-dose aspirin use did not reduce cancer incidence and cancer mortality in older individuals (aged 60–85 years) in Japan.<sup>27</sup> Similarly, another population-based cohort study conducted on the Danish population reported that ovarian cancer mortality was not associated with aspirin use.<sup>28</sup> Thus, the relationship between the use of aspirin and risk of cancer or cancer mortality remains controversial.

The results of subgroup analyses indicated that the association between aspirin use and reduced 5-year all-cause mortality is more evident in individuals aged 40–60 years, not in those >60 years. This suggests that the effect of aspirin on reduced 5-year all-cause mortality is applicable to younger individuals and not older individuals. A previous study of the ASPREE trial focusing on older adults (70 years or older) reported that higher mortality was observed in the aspirin group than in the placebo group, and this is in contrast to the findings of our study.<sup>10</sup> Other studies also failed to demonstrate the effect of aspirin on primary prevention for serious and adverse cardiovascular events in older individuals.<sup>20,22</sup> Therefore, the primary preven-

tive effect of aspirin remains controversial, especially in older individuals,<sup>29</sup> and the results of the subgroup analyses validated this.

This study had some limitations. First, some important variables, such as body mass index, were not included in the statistical adjustment, because they were not included in the NHIS dataset. Second, we defined comorbidities using the ICD-10 codes registered in the NHIS database. The diseases specified by the ICD-10 codes might differ from the actual underlying diseases in all patients. Third, PS adjustment and multivariable adjustment could control for only known confounders; thus, there might be residual confounders that could affect the study results. Fourth, we based the analysis on aspirin prescription data and did not assess adherence or compliance in those classified as aspirin users. Lastly, indication bias might have affected the results of this study, as we previously mentioned.

In conclusion, the results of this population-based cohort study suggested that long-term aspirin use is associated with reduced 5-year all-cause mortality in the general population of adults ( $\geq 40$  years) with no history of cerebrovascular or coronary artery disease. This association was more evident in individuals aged <60 years and for 5-year cancer mortality. Therefore, the effect of aspirin use on long-term mortality remains controversial, and further studies are needed to clarify this issue.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Tak Kyu Oh and In-Ae Song. **Data curation:** Tak Kyu Oh. **Formal analysis:** Tak Kyu Oh. **Investigation:** In-Ae Song. **Methodology:** Tak Kyu Oh and In-Ae Song. **Project administration:** Tak Kyu Oh and In-Ae Song. **Resources:** Tak Kyu Oh and In-Ae Song. **Supervision:** In-Ae Song. **Validation:** Tak Kyu Oh and In-Ae Song. **Visualization:** Tak Kyu Oh and In-Ae Song. **Writing—original draft:** Tak Kyu Oh. **Writing—review & editing:** In-Ae Song. **Approval of final manuscript:** Tak Kyu Oh and In-Ae Song.

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