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Association of aspirin, metformin, and statin use with gastric cancer incidence and mortality: A nationwide cohort study

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Running Title

Cardiovascular drugs and gastric cancer

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Conflict of Interest Statement

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ABSTRACT

Anticancer effects of aspirin, metformin, and statins against gastric cancer, one of the most common cancers in the world, have been reported. This retrospective cohort study aimed to investigate independent associations of aspirin, metformin, and statin use with gastric cancer incidence and mortality after adjustment for concomitant use of other drugs, using pooled cohort data extracted from the Korean National Health Insurance claim database. Follow-up started on January 1, 2004 and ended at the date of gastric cancer diagnosis, death, or December 31, 2013. Exposures to drugs were defined as cumulative duration of use for aspirin and cumulative defined daily dose for metformin and statin and were entered as time-dependent variables in Cox analysis models to avoid immortal time bias. Use of aspirin longer than 182.5 and 547.5 days during two-year interval was associated with reduced risks of gastric cancer incidence and mortality, respectively. Diabetic patients were at higher risk of gastric cancer incidence and mortality than non-diabetic people, regardless of metformin treatment. However, metformin use among diabetic patients was associated with a reduction in gastric cancer mortality in a dose-response manner. Statin use was also associated with a reduction of gastric cancer mortality in the general population but not with gastric cancer incidence. In conclusion, long-term use of aspirin was independently associated with reduced incidence and mortality of gastric cancer in the general population, but metformin or statin use was only associated with a reduction of gastric cancer mortality in diabetic patients and in the general population, respectively.

Keywords

Gastric cancer; Aspirin; Metformin; Statin

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INTRODUCTION

Although the incidence of gastric cancer has decreased over time, gastric cancer remains the fifth most frequently diagnosed cancer worldwide, responsible for over 1,000,000 new cancer patients, and was the third leading cause of cancer-related death in 2018 (1). Asian countries have the highest incident rate of gastric cancer (2). In Korea, patients with newly diagnosed gastric cancer numbered 229,180 people in 2016 and a total of 78,194 patients died due to gastric cancer (3).

Cardiovascular disease (CVD) is a major health problem contributing to one-third of deaths worldwide (4). A number of shared risk factors between CVD and cancer have been reported, suggesting biological mechanisms common to CVD and cancer (5). Chronic inflammation, a key biological mechanism for both CVD and cancer (6, 7), is induced by shared risk conditions, such as hyperglycemia, obesity, and smoking, so controlling CVD risk factors may help reduce cancer risk (8).

Aspirin, metformin, and statins are commonly prescribed to treat CVD and diabetes in clinical practice. Many previous studies have suggested the anticancer effects of aspirin (9–12), metformin (13–15), and statin (16, 17) in addition to their intended therapeutic effects. Multiple epidemiologic studies investigated cancer risk associated with use of aspirin (18–21), metformin (22, 23), or statin (24–26) for various cancers, including colorectal, esophageal, gastric, and breast cancer. Several studies reported that the incidence of gastric cancer was reduced with regular (27) and cumulative use (28) of aspirin. In a recent meta-analysis, the pooled relative risk (RR) of gastric cancer with aspirin use was 0.75 (95% confidence interval (CI) 0.65–0.86) (21). Metformin use was also associated with lower incidence of gastric cancer among diabetic patients when used on a regular, long-term basis (23, 29). And in a recent meta-

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analysis, the pooled risk of gastric cancer with metformin use in diabetic patients was 0.76 (95% CI 0.64–0.91) compared to non-metformin therapies (30). Statin use was also related to lower gastric cancer incidence in a dose-response manner in case control studies (31, 32), and the pooled risk estimate was 0.68 (95% CI 0.51–91) in a meta-analysis (33).

Aspirin, metformin, and statins are often prescribed concomitantly because cardiovascular disease, diabetes, and dyslipidemia are common metabolic diseases. Therefore, failure to adjust for concomitant use of other drugs to evaluate associations of aspirin, metformin, and statin use with gastric cancer incidence and mortality could lead to false conclusion. For example, if we assume that aspirin use reduces gastric cancer incidence and statin users are more likely to be prescribed aspirin than statin non-users, statin use might erroneously appear to be associated with lower gastric cancer risk if the data are not adjusted to account for aspirin use. However, most previous studies have not considered concomitant use of other medication (27–29) or have done so only crudely by implementing a dichotomized variable (i.e., use vs. non-use) (31). A previous aspirin study did not adjust for metformin or statin use (27), and a previous metformin study did not adjust for aspirin or statin use (29). Cardiovascular drug use which was crudely defined as a dichotomous variable (use vs. non-use) or according to duration of use cannot reflect amount taken per day (29, 31, 34, 35). In addition, many previous studies are limited by case-control design, which is subject to selection or recall bias (31, 32); numbers of study subjects in these studies were not large enough to conclude a dose-response relationship between drugs and gastric cancer-related risks (31, 32, 35). Furthermore, few studies of the putative anticancer effects of cardiovascular drugs have included data regarding gastric cancer mortality (18, 23, 36).

Thus, in this population-based cohort study, our primary objective was to investigate independent associations of aspirin, metformin, and statin use with gastric cancer incidence

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and mortality in the general population, using adjustment of concomitant use of other medications, to determine the potential of these cardiovascular drugs as chemopreventive agents in clinical practice.

MATERIALS AND METHODS

Data source and study population

The Korean National Health Insurance (KNHI) provides several sets of sample cohort data that are extracted from the claims database for research purposes; for this study, we pooled three cohorts to increase statistical power. First, the National Health Insurance Service (NHIS)-Senior Cohort was randomly selected to represent 10% of the Korean population aged ≥ 60 years in 2002 (n = 558,147). Second, the NHIS-Health Screening Cohort (NHIS-HealS) was randomly selected to represent 10% of the Korean population aged 40–79 years in 2002 who received national health screening examinations during 2002–2003 (n = 514,866). Finally, the NHIS-National Sample Cohort (NHIS-NSC) comprised 2.2% of the all-age Korean population covered by the KNHI program in 2002 (n = 1,025,340). The design and use of these databases are described in detail elsewhere (37, 38).

As we used a two-year interval to define drug exposure for time-dependent analysis (see below for details), we excluded patients who died from any cause (n = 23,823) or made claims for any cancer (n = 55,529) before January 1, 2004. People aged < 20 years in 2002 (n = 278,026) were also excluded from the study. Finally, we identified 1,740,975 study participants drawn from the NHIS-Senior, NHIS-HealS, and NHIS-NSC databases (Figure 1). Among them, 811,862 subjects participated in health screenings during 2002–2003, and these were classified as the screening subset population. Data for the health behaviors and health

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screening results of these individuals were included in this study. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB number: E-1612-007-809). Due to the anonymity of the NHIS data, the requirement for informed consent from individual subjects was waived.

Follow-up and case ascertainment

Gastric cancer incidence was determined using the registered gastric cancer diagnosis code (International Classification of Diseases (ICD)-10 code C16) that matched the KNHI claim data for treatments (surgical operation, radiation therapy, or use of chemotherapeutic agents) for gastric cancer. Gastric cancer mortality data were obtained from the Korean National Death Registry. Follow-up started on January 1, 2004 (the index date) and ended at the date of gastric cancer diagnosis (incidence), death from gastric cancer (mortality), death from any other cause, or December 31, 2013, whichever came first.

Exposure to cardiovascular drugs (aspirin, metformin, and statins)

Cumulative use of cardiovascular drugs was analyzed within a two-year latent period and was entered as a time-dependent variable in models to avoid immortal time bias (Supplementary Figure S1). Time-dependent exposure to cardiovascular drugs was defined in two ways: 1) for aspirin, cumulative duration of use, defined as the total number of days of drug exposure, and 2) for metformin and statins, cumulative defined daily dose (cDDD), which uses the defined daily dose (DDD) system, a validated unit of drug consumption defined by the World Health Organization (WHO) to standardize the dosage of drugs across multiple types (39). Since acetylsalicylic acid with any dose or frequency in a single day has independent strength for anti-platelet use, aspirin use for a day is equivalent to 1 DDD of aspirin. All aspirin prescribed

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as a cardiovascular drug in Korea is low dose aspirin. The cumulative duration of aspirin use was categorized as never use, <182.5, 182.5–365.0, 365.0–547.5, and 547.5–730.0 days. The cDDD for metformin and statins represents the total dose of each drug prescribed during the study period and was categorized as never use, < 182.5, 182.5–365.0, 365.0–547.5, and 547.5–730.0 cDDD-days.

Potential confounders

Data for potential confounders available from the KNHI claims database included sex, age, income level, Charlson comorbidity index (CCI), and metabolic risk factors such as smoking status, alcohol consumption, body mass index (BMI), and history of hypertension. The study sample was grouped into 5-year age categories based on age in 2002. We used monthly insurance premiums as proxies for economic status because they are imposed according to income level in Korea.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics of the study population and cumulative duration of use (aspirin) / cDDD (metformin, statin). Cox proportional hazards models were used with time-dependent covariates for cardiovascular drug exposure. First, we assessed associations between the cumulative dose of each cardiovascular drug and the incidence or mortality of gastric cancer in separate analyses. Second, we performed the same Cox regression analyses with all cardiovascular drug use as covariates in one Cox model (the concurrent model). All models were adjusted for the following variables measured during 2002–2003: 1) Model 1 was adjusted for age, sex, income, and CCI, and 2) Model 2 included the same variables as Model 1 and was additionally adjusted for BMI, smoking status, alcohol

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consumption, and hypertension using a screening subset population (about half of the study population who received national health screening examinations during 2002–2003). We also conducted subgroup analyses according to sex, age, BMI, smoking status, and alcohol consumption. All statistical analyses were conducted using STATA version 14.1 (StataCorp, College Station, TX, USA). All results were considered significant at two-sided p value <0.05.

RESULTS

Baseline characteristics

Baseline sociodemographic characteristics, health behaviors, and medical conditions of the total study population and subgroups depending on use of aspirin, metformin, and statin are presented in **Table 1**. In the pooled cohort, ever-users of aspirin and statin comprised 158,446 (9.10%) and 80,271 (4.61%) individuals, respectively. Patients with type 2 diabetes comprised 113,208 (6.50%) individuals, and metformin ever-users numbered 62,801 (55.5%) among diabetic patients. **Table 2** shows the cumulative doses of aspirin, metformin, and statin for every 2 years during follow-up. As the total numbers of cardiovascular drug users increased, proportions of long-term users (for aspirin use ≥ 547.5 days and for metformin or statin use ≥ 547.5 cDDD-days) gradually increased over time (**Table 2)**.

Use of cardiovascular drugs and gastric cancer incidence and mortality

Risks of gastric cancer incidence and mortality from separate analyses and concurrent analyses are presented in **Table 3** and **Table 4**, respectively. During the observation period, patients who were diagnosed with gastric cancer numbered 16,843 (incidence rate (IR) 103.83 per 10^5 person-year) in Model 1 and 9,250 (IR 118.84 per 10^5 person-year) in Model 2 **(Table 3).** A

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total of 9,250 and 3,206 deaths related to gastric cancer were observed over the follow-up years in Model 1 and Model 2, respectively **(Table 3).**

Aspirin use ≥ 182.5 days showed significant beneficial effects on gastric cancer incidence in the separate analysis **(Table 3).** Risks of gastric cancer mortality significantly decreased in people with aspirin use ≥ 547.5 days (adjusted hazard ratio (aHR) 0.68, 95% CI 0.63–0.74 in Model 1 and aHR 0.62, 95% CI 0.54–0.72 in Model 2) in the separate analysis **(Table 3).** Results were consistent after adjusting for cDDDs of metformin and statin use in the concurrent model **(Table 4).** *P* values for trend of gastric cancer incidence and mortality were < 0.001 in both analytical models, suggesting dose-dependent relationships.

For metformin use, diabetic patients were at higher risk of gastric cancer incidence than non-diabetic people, regardless of metformin treatment **(Table 3)**. Metformin use among diabetic patients did not show significant benefits on gastric cancer mortality compared with that in non-diabetic people **(Table 3)**. However, although there was no statistical significance, risk of gastric cancer mortality was reduced among diabetic patients with metformin use ≥ 547.5 cDDD-days (aHR 0.82, 95% CI 0.57–1.19 in Model 1 and aHR 0.67, 95% CI 0.35–1.29 in Model 2), even compared with that in non-diabetic people **(Table 3)**. In the additional analysis with only diabetic patients, gastric cancer mortality decreased with metformin use in a dose-response manner (*P* for trend <0.001 in both models) **(Table 5)**. Such results remained similar after adjustments for aspirin and statin use **(Table 4)**.

Gastric cancer incidence was not associated with statin use in the general population **(Table 3)**. On the other hand, gastric cancer mortality decreased in a dose-response manner in people even with statin use < 182.5 cDDD-days (aHR 0.71 95% CI 0.64–0.78 in Model 1 and aHR 0.67, 95% CI 0.35–1.29 in Model 2) (*P* for trend < 0.001 in both models) **(Table 3).** While results were generally consistent after additional adjustments, estimate risk of gastric cancer

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mortality was attenuated in the concurrent analysis model **(Table 4)**.

Subgroup analyses

Supplementary tables showed aHRs of gastric cancer incidence and mortality in subgroup analysis stratified by sex (Supplementary Table S1), age (Supplementary Table S2), body mass index (Supplementary Table S3), smoking status (Supplementary Table S4), and alcohol consumption (Supplementary Table S5). Although statistical significance differed depending on drug, results of subgroup analysis showed consistent tendencies.

DISCUSSION

In this population-based cohort study, we investigated independent associations of aspirin, statin, and metformin use with gastric cancer incidence and mortality in the general population after adjustment for concomitant use of other cardiovascular drugs. Long-term use of aspirin was independently associated with reduced incidence and mortality of gastric cancer in the general population. However, metformin use was positively associated with reduction of gastric cancer mortality only in diabetic patients. Statin use was also associated with a reduced risk of gastric cancer mortality, but not with that of gastric cancer incidence in the general population. Strengths of our study are 1) inclusion of a large representative sample (~1.7 million) in a region with high gastric cancer incidence, which reduces selection bias and enhances statistical power; 2) use of a reliable prescription database obtained through a compulsory, single, national insurance system and use of validated units of drug consumption; and 3) simultaneous examination of common cardiovascular drugs in a single analytical model with adjustment for the effects of each.

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Carcinogenesis of gastric cancer involves multiple factors (40), and several studies suggest that the cyclooxygenase-2 (COX-2) genes are one of the risk factors of gastric cancer (41). Since aspirin, an antiplatelet agent to prevent cardiovascular diseases, is a COX-1 and COX-2 inhibitor, this drug has potentially antineoplastic effects against gastric cancer by blocking the COX pathway and by inducing apoptosis (9–12). Consistent with previous studies, our results support the hypothesis that aspirin exerts chemopreventive effects against gastric cancer incidence in a dose-dependent manner (27, 28, 34). The aHRs of gastric cancer incidence among aspirin users in our study are higher than estimates from a previous meta-analysis (RR 0.75, 95% CI 0.65–0.86) (21). This is probably because low-dose aspirin can be purchased without a prescription in Korea and was quite widely used in the early 2000s (42), so low-dose aspirin users might be underestimated in our study. Our findings also suggest that gastric cancer mortality decreases with increasing duration of aspirin use. While gastric cancer incidence was reduced by 16% in our results, gastric cancer mortality decreased up to 40% in aspirin user groups. Possible reasons for the lower gastric cancer mortality compared to non-aspirin users are 1) lower cancer incidence due to aspirin use and 2) potential survival benefits of aspirin in patients even after diagnosis with gastric cancer.

Multiple previous studies suggested that diabetes is associated with higher risks of gastric cancer incidence (34, 43, 44) and mortality (44), which is consistent with our finding that diabetes patients were at elevated risks for gastric cancer incidence and mortality compared with non-diabetic patients. Metformin has been shown to inhibit proliferation of gastric cancer cell (15) and promote apoptosis, leading to anticancer effects (13, 14). Previous meta-analyses studies reported the chemopreventive effects of metformin use on gastric cancer incidence (30) and survival benefits in diabetic patients treated with metformin therapy (36). In a previous study with type 2 diabetes patients, gastric cancer risk was marginally lowered with regular

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metformin use (aHR 0.73, 95% CI 0.53–1.01), and the decrease became significant with metformin use ≥ 3 years (aHR 0.57, 95% CI 0.37–0.87) in the insulin non-user group (29). However, we did not find an association between metformin use and gastric cancer incidence even in diabetic patients in this study. This discrepancy may be because previous studies did not consider concomitant use of other cardiovascular drugs (29, 30) or because medical conditions seen in diabetic patients, such as diabetes duration or disease severity, were not considered in the present study. On the other hand, metformin use among diabetic patients showed linear dose-response effects on gastric cancer mortality in this study. This finding is consistent with previous study conducted in gastric cancer patients, reporting that longer cumulative duration of metformin use was associated with lower risks of recurrence and gastric cancer-specific and all-cause mortality (i.e., HR=0.86–0.87 for each outcome, with six additional cumulative months of metformin use after gastrectomy) (35).

Statins are widely used to treat hypercholesterolemia. The basic mechanism of the anticancer effect of statins is inhibition of the rate-limiting step of the mevalonate pathway (16, 17). The mevalonate pathway produces mevalonic acid, acting as a precursor to produce multiple end-products, and some of these products, such as *Ras* and *Rho*, regulate various signal processes related to cellular proliferation, angiogenesis, and anti-apoptosis (16, 45). However, in our study, statin use was not associated with reduction of gastric cancer incidence. This is not consistent with results from a previous meta-analysis reporting a dose-response chemopreventive effect of statin use on reduction of gastric cancer risk (aOR 0.35, 95% CI 0.16–0.76 for long duration of use vs. aOR 0.73, 95% CI 0.51–1.05 for short duration of use) (33). However, although the meta-analysis of all studies suggested positive associations, results from subgroup analyses varied, depending on study design and setting (33). Also, because concurrent use of aspirin and metformin was not considered in previous studies, this could be

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a reason for the discrepancy seen. Thus, further research is needed to determine the chemopreventive effects of statin use against gastric cancer. In contrast, statin use was associated with lower gastric mortality even at cDDD < 182.5 in the present study. Better survival outcomes among gastric cancer patients with statin use were previously reported in a small case-control study from Korea (34) and in cancer registry studies from Denmark (24) and England-Scotland (46). Given that gastric cancer incidence was not reduced with statin use, it is probable that the anticancer effects of statin use are more beneficial for gastric cancer patients compared to the general population.

One notable distinction of our study is simultaneous inclusion of aspirin, metformin, and statin use in a single analysis model. In clinical practice, cardiovascular drugs (aspirin, metformin, and statin) are often prescribed together. However, many previous studies about anticancer effects of cardiovascular drugs have been conducted without considering concurrent use of other drugs. Since the biological mechanisms of cardiovascular drugs may interact with each other to create positive or negative synergetic effects on gastric cancer, effects of cardiovascular drugs would be over- or underestimated without considering simultaneous administration of cardiovascular drugs. In this study, tendencies for anticancer effects against gastric cancer remained after adjustments for other drug use. However, the degree of antineoplastic effects in each cardiovascular drug was slightly attenuated when the models were simultaneously adjusted for use of other drugs. Such results suggest that estimates from previous studies that did not account for other cardiovascular drug use might have overestimated preventive effects, especially when the results showed marginal effects.

There are several limitations of our study. First, as we used secondary data-based claims reimbursement data, we were unable to take into account clinical information, such as stages, histological types, and anatomical locations of gastric cancer, and other known risk

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factors of gastric cancer, such as *H. pylori* infection and medical history of gastric ulcer or other precancerous disease. Further studies considering theses additional factors are needed to determine clinical applications of cardiovascular drugs to reduce risks of gastric cancer. Second, for analysis of metformin use, it is important to consider clinical details of diabetes, such as disease severity and diabetes duration, which were not considered in this study due to the nature of reimbursement data. Third, we may have underestimated gastric cancer incidence because we identified it using a disease code and reimbursement data representing cancer treatment. Thus, untreated gastric cancer could not be counted as gastric cancer in this study. However, since universal health coverage is provided to almost all Koreans, and the proportion of early gastric cancer among gastric cancer patients is high due to gastric cancer screening provided by the National Cancer Screening Program every two years, untreated gastric cancer may not be common unless people are very old or have other serious health problems. Thus, there is no reason to believe that untreated gastric cancer is generally common among cardiovascular drug users. Fourth, aspirin can be purchased over the counter without a prescription. Thus, aspirin use might be underestimated in this study. Finally, regarding mortality, we may have overestimated the anticancer effects due to screening effects. It is possible that cardiovascular drug users have more frequent contact with health care professionals and receive more cancer screening examinations than the general population (47, 48). In this case, they are likely to be diagnosed at an early stage of gastric cancer, leading to lower mortality.

In summary, the results of the present study suggest that aspirin use was independently associated with reduced incidence and mortality of gastric cancer in the general population, but metformin or statin use was only associated with a reduction of gastric cancer mortality in diabetic patients and in the general population in a dose-response manner, respectively. Further

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studies are needed to determine clinical applications of these cardiovascular drugs as chemopreventive agents in public health and clinical practice.

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Table 1. Baseline characteristics of the study population, classified by history of cardiovascular drug use during 2002–2003

	Total	Aspirin			Metformin				Statin		
		Never user	Ever user	*p* value	Non-DM	Never user	Ever user	*p* value	Never user	Ever user	*p* value
N (%)	1,740,975 (100.0)	1,582,529 (90.90)	158,446 (9.10)		1,627,777 (93.50)	50,397 (2.89)	62,801 (3.61)		1,660,704 (95.39)	80,271 (4.61)	
Age, years, n (%)											
20 – 29	170,111 (9.77)	169,570 (10.72)	541 (0.34)		169,765 (10.43)	229 (0.45)	117 (0.19)		169,833 (10.23)	278 (0.35)	
30 – 39	185,906 (10.68)	184,464 (11.66)	1,442 (0.91)		184,225 (11.32)	771 (1.53)	910 (1.45)		184,528 (11.11)	1,378 (1.72)	
40 – 49	397,281 (22.82)	385,036 (24.33)	12,245 (7.73)		385,696 (23.69)	5,037 (9.99)	6,548 (10.43)		386,987 (23.30)	10,294 (12.82)	
50 – 59	233,813 (13.43)	212,851 (13.45)	20,962 (13.23)		216,794 (13.32)	7,323 (14.53)	9,696 (15.44)		218,932 (13.18)	14,881 (18.54)	
60 – 69	489,256 (28.10)	413,425 (26.12)	75,831 (47.86)		433,466 (26.63)	24,210 (48.04)	31,580 (50.29)		450,606 (27.13)	38,650 (48.15)	
70 – 79	206,239 (11.85)	166,933 (10.55)	39,306 (24.81)		182,980 (11.24)	10,858 (21.54)	12,401 (19.75)		192,906 (11.62)	13,333 (16.61)	
≥ 80	58,369 (3.35)	50,250 (3.18)	8,119 (5.12)		54,851 (3.37)	1,969 (3.91)	1,549 (2.47)		56,912 (3.43)	1,457 (1.82)	
Sex, n (%)				<0.01				<0.01			<0.01
Male	834,739 (47.95)	765,494 (48.37)	69,245 (43.70)		780,871 (47.97)	25,082 (49.77)	28,786 (45.84)		803,784 (48.40)	30,955 (38.56)	
Female	906,236 (52.05)	817,035 (51.63)	89,201 (56.30)		846,906 (52.03)	25,315 (50.23)	34,015 (54.16)		856,920 (51.60)	49,316 (61.44)	
Income, n (%)				<0.01				<0.01			<0.01
Rank 1–3	692,465 (39.77)	619,437 (39.14)	73,028 (46.09)		641,763 (39.43)	22,976 (45.59)	27,726 (44.15)		653,866 (39.37)	38,599 (48.09)	
Rank 4–6	470,362 (27.02)	430,599 (27.21)	39,763 (25.10)		441,160 (27.10)	12,771 (25.34)	16,431 (26.16)		450,134 (27.11)	20,228 (25.20)	
Rank 7–10	513,399 (29.49)	468,435 (29.60)	44,964 (28.38)		480,803 (29.54)	14,302 (28.38)	18,294 (29.13)		492,204 (29.64)	21,195 (26.40)	
Medical aid	64,749 (3.72)	64,058 (4.05)	691 (0.44)		64,051 (3.93)	348 (0.69)	350 (0.56)		64,500 (3.88)	249 (0.31)	
CCI, mean (SD)	0.65 (0.92)	0.56 (0.83)	1.54 (1.26)	<0.01	0.56 (0.81)	1.84 (1.37)	2.02 (1.34)	<0.01	0.60 (0.88)	1.59 (1.26)	<0.01
Smoking status, n (%) †				<0.01				<0.01			<0.01
Never	562,566 (69.29)	506,474 (68.60)	56,092 (76.29)		525,270 (69.10)	16,425 (71.76)	20,871 (72.45)		530,572 (68.90)	31,994 (76.56)	
Former < 20 years	35,137 (4.33)	32,616 (4.42)	2,541 (3.46)		33,348 (4.39)	859 (3.75)	950 (3.30)		33,590 (4.36)	1,567 (3.75)	
Former ≥ 20 years	23,914 (2.95)	20,691 (2.80)	3,223 (4.38)		21,818 (2.87)	990 (4.33)	1,106 (3.84)		22,336 (2.90)	1,578 (3.78)	
Current < 20 PY	123,101 (15.16)	116,539 (15.78)	6,562 (8.92)		117,374 (15.44)	2,567 (11.22)	3,160 (10.97)		119,269 (15.49)	3,832 (9.17)	
Current ≥ 20 PY	67,124 (8.27)	62,016 (8.40)	5,108 (6.95)		62,356 (8.20)	2,047 (8.94)	2,721 (9.45)		64,306 (8.35)	2,818 (6.74)	
Alcohol, g/day, n (%) †				<0.01				<0.01			<0.01
0 – 10	650,245 (80.09)	587,231 (79.53)	63,014 (85.70)		607,021 (79.85)	18,915 (82.64)	24,309 (84.38)		614,413 (79.79)	35,832 (85.75)	
10 – 20	91,683 (11.29)	85,977 (11.64)	5,706 (7.76)		87,351 (11.49)	2,019 (8.82)	2,313 (8.03)		88,432 (11.48)	3,251 (7.78)	
20 – 30	7,089 (0.87)	6,713 (0.91)	376 (0.51)		6,665 (0.88)	185 (0.81)	239 (0.83)		6,815 (0.88)	274 (0.66)	
30 – 40	25,827 (3.18)	24,000 (3.25)	1,827 (2.48)		24,389 (3.21)	684 (2.99)	754 (2.62)		24,823 (3.22)	1,004 (2.40)	
≥ 40	37,018 (4.56)	34,415 (4.66)	2,603 (3.54)		34,470 (4.57)	1,085 (4.74)	1,193 (4.14)		35,590 (4.62)	1,428 (3.42)	
Hypertension, n (%) †				<0.01				<0.01			<0.01
Yes	504,321 (62.12)	480,020 (65.01)	24,301 (33.05)		481,162 (63.30)	9,989 (43.64)	13,170 (45.72)		485,936 (63.10)	18,385 (43.99)	
No	307,541 (37.88)	258,316 (34.99)	49,225 (66.95)		279,004 (36.70)	12,899 (56.36)	15,638 (54.28)		284,137 (36.90)	23,404 (56.01)	
BMI, mean (SD)‡	23.88 (3.07)	23.79 (3.04)	24.82 (3.18)	<0.01	23.82 (3.05)	24.77 (3.13)	24.84 (3.17)	<0.01	23.81 (3.06)	25.18 (2.98)	<0.01

DM, diabetes mellitus; BMI (kg/m^2), body mass index; CCI, Charlson comorbidity index.

* Categorical variables were compared using the chi-square test, and continuous variables were compared using Student's t-test (aspirin or statin) or ANOVA (metformin).

† Sample size is 811,862 due to missing values of each independent variable.

‡ Sample size is 811,172 due to missing values of BMI.

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Table 2. Total dose of cardiovascular drugs among the study population

	2002–2003	2004–2005	2006–2007	2008–2009	2010–2011
N	1,740,975	1,740,975	1,698,800	1,652,451	1,606,151
Aspirin,					
Never use	1,582,529 (90.90)	1,496,164 (85.94)	1,399,726 (82.39)	1,329,776 (80.47)	1,279,451 (79.66)
Duration of aspirin use, day, n (%)					
< 182.5	81,515 (4.68)	106,421 (6.11)	102.908 (6.06)	96,772 (5.86)	93,160 (5.80)
182.5 – 365.0	28,916 (1.66)	38.464 (2.21)	43,379 (2.55)	42.982 (2.60)	42,184 (2.63)
365.0 – 547.5	20,001 (1.15)	32,342 (1.86)	39,689 (2.34)	41,777 (2.53)	41,849 (2.61)
≥ 547.5	28,014 (1.61)	67,584 (3.88)	113,098 (6.66)	141,144 (8.54)	149,507 (9.31)
Metformin,					
Non-DM	1,627,777 (93.50)	1,589,588 (91.30)	1,523,726 (89.69)	1,458,145 (88.24)	1,397,187 (86.99)
Never use among DM patients	50,397 (2.89)	61,214 (3.52)	61,874 (3.64)	57,673 (3.49)	45,649 (2.97)
cDDD of metformin use, n (%)					
< 182.5	43,165 (2.48)	56,011 (3.22)	64,985 (3.83)	76,462 (4.63)	85,298 (5.31)
182.5 – 365.0	14,591 (0.84)	23,920 (1.37)	32,480 (1.91)	39,009 (2.36)	48,259 (3.00)
365.0 – 547.5	3,898 (0.22)	7,507 (0.43)	10,902 (0.64)	13,713 (0.83)	17,032 (1.06)
≥ 547.5	1,147 (0.07)	2,735 (0.16)	4,833 (0.28)	7,449 (0.45)	10,726 (0.67)
Statins					
Never use	1,660,704 (95.39)	1,609,299 (92.44)	1,503,551 (88.51)	1,400,497 (84.75)	1,300,613 (80.98)
cDDD of statin use, n (%)					
< 182.5	66,192 (3.80)	93,331 (5.36)	112,264 (6.61)	128,999 (7.81)	136,440 (8.49)
182.5 – 365.0	11,407 (0.66)	26,963 (1.55)	48,141 (2.83)	64,584 (3.91)	94,764 (5.90)
365.0 – 547.5	2,345 (0.13)	8.695 (0.50)	23,946 (1.41)	35,725 (2.16)	39,433 (2.46)
≥ 547.5	327 (0.02)	2,687 (0.15)	10,898 (0.64)	22,646 (1.37)	34,901 (2.17)

cDDD, cumulative defined daily dose.

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Table 3. Associations of cardiovascular drug use with incidence and mortality of gastric cancer in separate analyses of aspirin, metformin, or statin

	Gastric cancer incidence				Gastric cancer mortality			
	Model 1 *		Model 2 †		Model 1 *		Model 2 †	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Case, N	16,843		9,250		8,463		3,206	
Person-years	16,221,786.25		7,783,607.32		16,284,456.7		7,819,859.90	
Crude incidence rates (per 10^5 person-year)	103.83		118.84		51.97		41.00	
Duration of aspirin use, day								
Never use	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
< 182.5	0.97 (0.91–1.03)	0.32	0.96 (0.89–1.04)	0.34	1.08 (1.01–1.17)	0.04	1.19 (1.06–1.34)	<0.01
182.5 – 365.0	0.87 (0.79–0.95)	<0.01	0.85 (0.74–0.96)	0.01	0.96 (0.86–1.08)	0.53	0.91 (0.74–1.10)	0.32
365.0 – 547.5	0.84 (0.76–0.93)	<0.01	0.78 (0.68–0.90)	<0.01	0.96 (0.85–1.09)	0.53	1.00 (0.82–1.21)	0.98
≥ 547.5	0.94 (0.89–0.99)	0.03	0.89 (0.82–0.96)	<0.01	0.68 (0.63–0.74)	<0.01	0.62 (0.54–0.72)	<0.01
P for trend	<0.01		<0.01		<0.01		<0.01	
cDDD of metformin use								
Non-DM	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
DM, never use	1.18 (1.10–1.27)	<0.01	1.23 (1.11–1.36)	<0.01	1.69 (1.55–1.83)	<0.01	2.15 (1.89–2.45)	<0.01
< 182.5	1.19 (1.11–1.28)	<0.01	1.11 (1.01–1.22)	0.03	1.33 (1.22–1.46)	<0.01	1.42 (1.23–1.64)	<0.01
182.5 – 365.0	1.25 (1.14–1.37)	<0.01	1.26 (1.12–1.43)	<0.01	1.20 (1.06–1.37)	0.010	1.43 (1.18–1.75)	<0.01
365.0 – 547.5	1.18 (1.01–1.38)	0.04	1.23 (0.99–1.52)	0.05	1.00 (0.78–1.27)	0.98	1.13 (0.77–1.64)	0.53
≥ 547.5	1.25 (1.01–1.55)	0.04	1.11 (0.82–1.50)	0.50	0.82 (0.57–1.19)	0.30	0.67 (0.35–1.29)	0.23
P for trend ‡	0.39		0.96		<0.01		<0.01	
cDDD of statin use								
Never use	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
< 182.5	1.00 (0.94–1.06)	1.00	0.92 (0.85–1.00)	0.05	0.71 (0.64–0.78)	<0.01	0.70 (0.60–0.82)	<0.01
182.5 – 365.0	1.07 (0.99–1.17)	0.09	1.02 (0.91–1.14)	0.75	0.74 (0.65–0.84)	<0.01	0.82 (0.67–0.99)	0.04
365.0 – 547.5	1.12 (1.00–1.26)	0.05	1.07 (0.91–1.25)	0.42	0.78 (0.65–0.93)	0.01	0.69 (0.51–0.94)	0.02
≥ 547.5	1.07 (0.93–1.23)	0.35	1.04 (0.86–1.26)	0.71	0.70 (0.56–0.88)	<0.01	0.58 (0.39–0.86)	0.01
P for trend	0.02		0.83		<0.01		<0.01	

HR, hazard ratio; CI, confidence interval; cDDD, cumulative defined daily dose; DM, diabetes mellitus
* Model 1: Adjusted for age (5-year group), sex, income, and Charlson comorbidity index (continuous).
† Model 2: Adjusted for age (5-year group), sex, income, Charlson comorbidity index (continuous), body mass index (continuous), smoking status, alcohol consumption, and hypertension.
‡ P for trend was calculated among diabetic patients only.

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Table 4. Associations of cardiovascular drug use with incidence and mortality of gastric cancer in concurrent analyses of aspirin, metformin, or statin

	Gastric cancer incidence				Gastric cancer mortality			
	Model 1 *		Model 2 †		Model 1 *		Model 2 †	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Duration of aspirin use, day								
Never use	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
< 182.5	0.95 (0.89–1.01)	0.08	0.95 (0.88–1.04)	0.26	1.09 (1.02–1.18)	0.02	1.20 (1.07–1.35)	<0.01
182.5 – 365.0	0.83 (0.76–0.92)	<0.01	0.83 (0.73–0.94)	<0.01	0.97 (0.86–1.10)	0.65	0.91 (0.74–1.10)	0.32
365.0 – 547.5	0.80 (0.73–0.89)	<0.01	0.76 (0.66–0.87)	<0.01	0.97 (0.86–1.10)	0.65	0.99 (0.82–1.21)	0.96
≥ 547.5	0.89 (0.84–0.94)	<0.01	0.85 (0.78–0.92)	<0.01	0.69 (0.63–0.75)	<0.01	0.62 (0.54–0.72)	<0.01
P for trend	<0.01		<0.01		<0.01		<0.01	
cDDD of metformin use								
Non-DM	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
DM, never use	1.20 (1.11–1.29)	<0.01	1.25 (1.13–1.39)	<0.01	1.81 (1.66–1.97)	<0.01	2.29 (2.01–2.61)	<0.01
< 182.5	1.21 (1.13–1.30)	<0.01	1.14 (1.04–1.26)	0.01	1.45 (1.32–1.58)	<0.01	1.52 (1.32–1.76)	<0.01
182.5 – 365.0	1.28 (1.16–1.40)	<0.01	1.31 (1.15–1.48)	<0.01	1.34 (1.18–1.53)	<0.01	1.60 (1.31–1.95)	<0.01
365.0 – 547.5	1.20 (1.03–1.41)	0.02	1.27 (1.03–1.58)	0.03	1.13 (0.89–1.44)	0.32	1.28 (0.88–1.86)	0.20
≥ 547.5	1.27 (1.03–1.57)	0.03	1.15 (0.85–1.55)	0.37	0.95 (0.65–1.37)	0.77	0.78 (0.40–1.50)	0.45
P for trend ‡	0.24		0.79		<0.01		<0.01	
cDDD of statin use								
Never use	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
< 182.5	1.00 (0.94–1.07)	0.96	0.93 (0.86–1.01)	0.08	0.67 (0.61–0.74)	<0.01	0.66 (0.56–0.77)	<0.01
182.5 – 365.0	1.08 (0.99–1.18)	0.06	1.04 (0.93–1.17)	0.47	0.73 (0.64–0.84)	<0.01	0.82 (0.67–0.99)	0.04
365.0 – 547.5	1.13 (1.00–1.27)	0.04	1.09 (0.93–1.28)	0.29	0.80 (0.67–0.96)	0.01	0.70 (0.52–0.96)	0.03
≥ 547.5	1.08 (0.94–1.25)	0.30	1.07 (0.88–1.30)	0.50	0.74 (0.59–0.93)	0.01	0.62 (0.41–0.92)	0.02
P for trend	0.02		0.46		<0.01		<0.01	

HR, hazard ratio; CI, confidence interval; cDDD, cumulative defined daily dose; DM, diabetes mellitus

* Model 1: Adjusted for age (5-year group), sex, income, Charlson comorbidity index (continuous), and concomitant use of other CVD drugs.

† Model 2: Adjusted for age (5-year group), sex, income, Charlson comorbidity index (continuous), body mass index (continuous), smoking status, alcohol consumption, hypertension, and concomitant use of other CVD drugs.

‡ P for trend was calculated among diabetic patients only.

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Table 5. Associations of metformin use with incidence and mortality of gastric cancer in diabetic patients

	Gastric cancer incidence				Gastric cancer mortality			
	Model 1 *		Model 2 †		Model 1 *		Model 2 †	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Case, N	2,449		1,287		1,482		614	
Person-years	1,529,524.25		740,447.96		1,540,026.80		746,205.82	
Crude incidence rates (per 10^5 person-year)	160.12		173.81		86.23		82.28	
Separate analyses of aspirin, metformin, or statin								
cDDD of metformin use								
DM, never use	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
< 182.5	0.99 (0.90–1.09)	0.89	0.91 (0.79–1.04)	0.15	0.76 (0.68–0.86)	<0.01	0.64 (0.54–0.77)	<0.01
182.5 – 365.0	1.06 (0.95–1.19)	0.29	1.03 (0.88–1.21)	0.87	0.68 (0.59–0.79)	<0.01	0.65 (0.51–0.81)	<0.01
365.0 – 547.5	1.00 (0.84–1.19)	0.97	1.00 (0.80–1.27)	0.97	0.56 (0.44–0.73)	<0.01	0.51 (0.34–0.75)	<0.01
≥ 547.5	1.07 (0.86–1.34)	0.54	0.91 (0.66–1.25)	0.56	0.46 (0.31–0.67)	<0.01	0.30 (0.15–0.58)	<0.01
P for trend	0.39		0.96		<0.01		<0.01	
Concurrent analyses of aspirin, metformin, or statin								
cDDD of metformin use								
DM, never use	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
< 182.5	1.00 (0.91–1.10)	0.95	0.92 (0.80–1.05)	0.22	0.76 (0.68–0.86)	<0.01	0.65 (0.54–0.78)	<0.01
182.5 – 365.0	1.08 (0.97–1.21)	0.18	1.05 (0.90–1.23)	0.53	0.71 (0.61–0.82)	<0.01	0.67 (0.54–0.85)	<0.01
365.0 – 547.5	1.02 (0.86–1.22)	0.79	1.03 (0.81–1.29)	0.83	0.59 (0.46–0.77)	<0.01	0.54 (0.36–0.80)	<0.01
≥ 547.5	1.09 (0.87–1.37)	0.44	0.93 (0.67–1.27)	0.63	0.49 (0.34–0.72)	<0.01	0.32 (0.17–0.63)	<0.01
P for trend	0.24		0.79		<0.01		<0.01	

HR, hazard ratio; CI, confidence interval; cDDD, cumulative defined daily dose; DM, diabetes mellitus

* Model 1: Adjusted for age (5-year group), sex, income, Charlson comorbidity index (continuous), and concomitant use of other CVD drugs.

† Model 2: Adjusted for age (5-year group), sex, income, Charlson comorbidity index (continuous), body mass index (continuous), smoking status, alcohol consumption, hypertension, and concomitant use of other CVD drugs.

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FIGURE LEGENDS

Figure 1. Study participants. The final pooled cohort includes the (a) NHIS-Senior cohort, (b) NHIS-HealS cohort, and (c) NHIS-NSC. NHIS, National Health Insurance Service; HealS, Health Screening Cohort; NSC, National Sample

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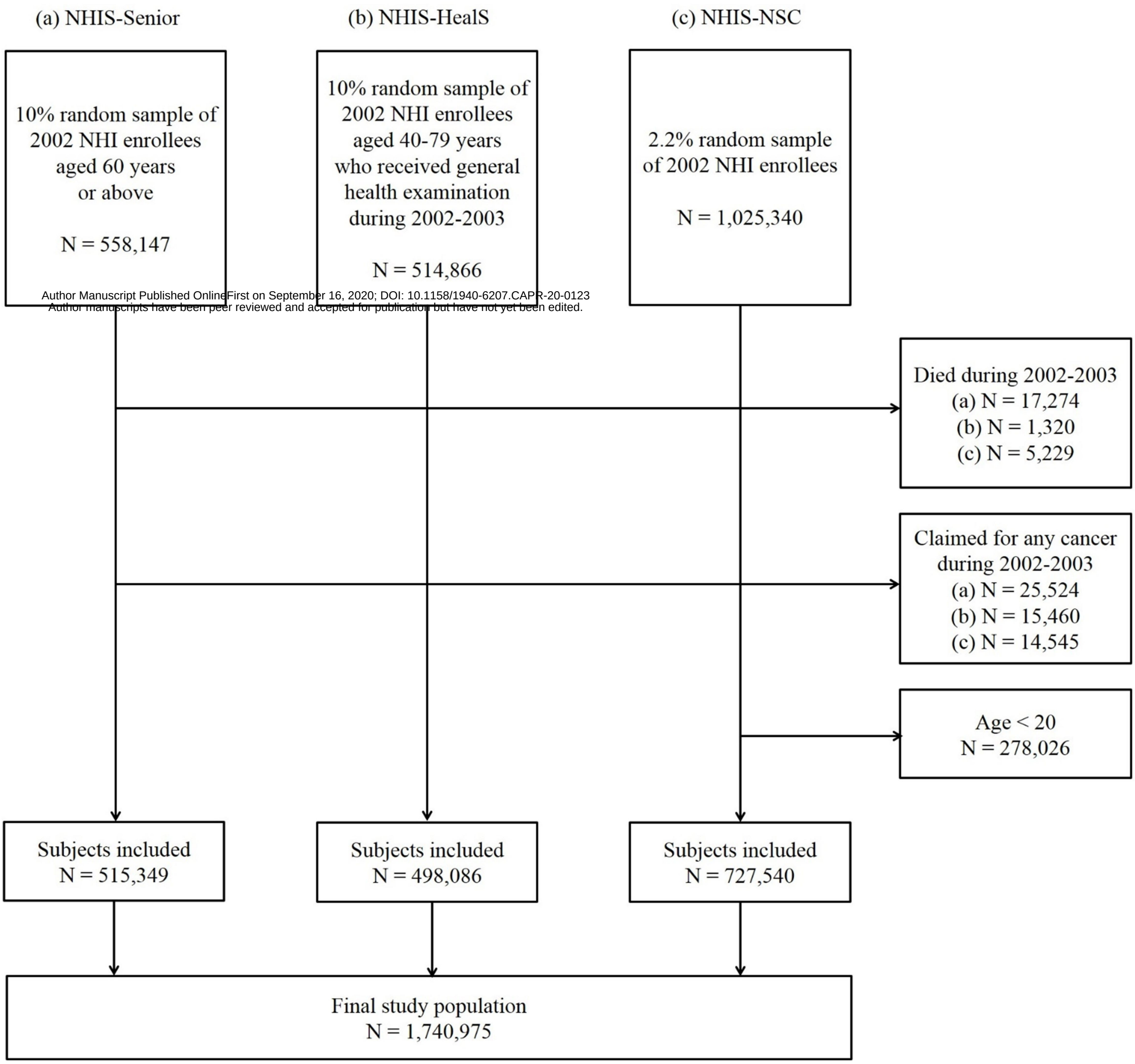

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Cancer Prevention Research

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Mi Hee Cho, Tae Gon Yoo, Su-Min Jeong, et al.

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