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Strongly increased risk of gastric and duodenal ulcers among new users of low-dose aspirin: results from two large cohorts with new-user design

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Summary

Background: Low-dose aspirin is a risk factor for peptic ulcer disease but previous, population-based cohort studies may have underestimated the low-dose aspirin risk because they did not use a new-user design. Gastrointestinal bleeding occurs more frequently early after initiation of low-dose aspirin therapy than in later years.

Aim: To assess the associations of low-dose aspirin with gastric and duodenal ulcer incidence in prevalent- and new-user design.

Methods: Multivariate Cox regression models in the German ESTHER study ($N = 7737$) and the UK Biobank ($N = 213{,}598$) with more than 10 years of follow-up.

Results: In the prevalent-user design, there was no significant association between low-dose aspirin and gastric ulcer observed in both cohorts. Furthermore, low-dose aspirin was weakly, statistically significantly associated with prevalent duodenal ulcer in the UK Biobank (hazard ratio [95% confidence interval]: 1.27 [1.07–1.51]) but not in the ESTHER study (1.33 [0.54–3.29]). When restricting the exposure to only new users, the hazard ratios for incident gastric and duodenal ulcer disease were 1.82 [1.58–2.11] and 1.66 [1.36–2.04] in the UK Biobank, respectively, and 2.83 [1.40–5.71] and 3.89 [1.46–10.42] in the ESTHER study, respectively.

Conclusions: This study shows that low-dose aspirin is an independent risk factor for both gastric and duodenal ulcers. The associations were not significant or weak in the prevalent-user design and strong and statistically significant in the new-user design in both cohorts. Thus, it is important to weigh risks against benefits when low-dose aspirin treatment shall be initiated and to monitor adverse gastrointestinal symptoms after the start of low-dose aspirin therapy.

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1 | BACKGROUND

Acetylsalicylic acid, commonly called by its brand name "aspirin," inhibits platelet aggregation through an irreversible acetylation process. At a low daily dose of 75–325 mg, it is used in the early treatment of myocardial infarction and unstable angina and in the primary and secondary prevention of atherosclerotic cardiovascular disease.[1,2] Additionally, recent studies provided evidence that low-dose aspirin might help in colorectal cancer and dementia prevention,[3–5] which would lead to a further increase in its use.

Low-dose aspirin therapy has been, however, shown to increase the risk of peptic ulcer disease. Even though the risk was modest for low-dose aspirin,[6] chronic use of aspirin was associated with a two to fourfold increased risk of upper gastrointestinal events.[7,8] The actual number of patients adversely affected by low-dose aspirin might be even higher than reported since 80% of endoscopy-confirmed gastroduodenal ulcer cases are asymptomatic.[9] Although the overall incidence of peptic ulcer disease has been decreasing over the past decades,[10] the incidence of complicated gastric ulcers and hospitalisation has remained stable, which in part was ascribed to the use of aspirin in ageing populations.[11]

Although the upper gastrointestinal toxicity of long-term low-dose aspirin has been well investigated before, to the best of our knowledge, no previous population-based cohort study has investigated the risks of new users. This is important because the previous studies with a prevalent-user design could have underestimated the risk of low-dose aspirin use for peptic ulcer disease because gastrointestinal bleeding more frequently occurs in the first year than in later years of chronic use. In a cohort of new low-dose aspirin users from the UK, the incidence of gastrointestinal bleeding during the first year of follow-up was 1.7 per 1000 person-years and during the remaining 7 years of follow-up, it was 0.9 per 1000 person-years.[12]

Therefore, in this analysis of two large, population-based cohort studies, we aim to investigate the association of low-dose aspirin use with gastric and duodenal ulcer disease incidence paying particular attention to the new-user design. Furthermore, we aim to evaluate the associations of other peptic ulcer risk factors suggested in the literature in these two studies.

2 | METHODS

2.1 | Study design and population

We used data from two prospective cohorts: the ESTHER study from Germany (German name: ***E**pidemiologische **S**tudie zu Chancen der Verhütung, Früherkennung und optimierten **TH**erapie chronischer **ER**krankungen in der älteren Bevölkerung*) and the primary care data of the UK Biobank from the United Kingdom.

The ESTHER cohort is an ongoing, population-based cohort study conducted in the federal state of Saarland, located in Southwest Germany. Details of the study design have been reported elsewhere.[13,14] In brief, 9940 individuals aged 50–75 years were recruited via their general practitioners during a routine health check-up between July 2000 and December 2002. After 2, 5, 8, 11, 14 and 17 years, participants and their general practitioners were contacted again and asked to complete questionnaires on health status, medical diagnoses and treatments.

For this project, we excluded participants who had missing drug assessment at either baseline (general practitioner reported) or 2-year follow-up (self-reported including over-the-counter drug purchase), had missing *Helicobacter pylori* or *cytotoxin-associated gene A* measurements, were *H. pylori* negative but *cytotxin-associated gene A* positive, had a self-reported history of ulcer before baseline, or were lost to follow-up and arrived at $N = 7737$ participants for inclusion in the prevalent-user design analysis (Figure S1). For the new-user design approach, we further excluded participants who reported the use of low-dose aspirin at baseline or 2-year follow-up and those with an incident ulcer prior to the starting date of low-dose aspirin use, leading to a sample size of $N = 6446$.

The UK Biobank is a large-scale, prospective cohort study. Between 2006 and 2010, 502,451 study participants aged 40–69 years who lived up to 25 miles from one of 22 study assessment centres in England, Scotland and Wales were recruited.[15] At the baseline assessment visit, participants completed a touchscreen questionnaire, a brief computer-assisted interview, had physical and functional measurements taken and biological samples collected.[16] Follow-up of health-related outcomes was enabled through linkage to routinely available data from the UK National Health Service (eg mortality, cancer registrations, hospital admissions, and primary care data). To date, primary care data have been gathered for roughly 45% of the UK Biobank cohort.

We included those $N = 213\,598$ participants with primary care and baseline assessment visit data who did not have peptic ulcer disease before baseline in the prevalent-user design analysis (Figure S1). For this analysis, participants who received at least one low-dose aspirin prescription before the baseline assessment date were considered to be prevalent users. For the new-user analysis, we excluded subjects who used low-dose aspirin at baseline and subjects with incident ulcers that had occurred before the starting date of low-dose aspirin intake, leaving $N = 189\,437$ participants in the new-user design analysis.

2.2 | Assessment of low-dose aspirin use

In ESTHER, assessment of low-dose aspirin use was made by linking information from the physicians' questionnaire at baseline and from the participants' questionnaire at 2-year follow-up to make use of the advantages of both drug assessment methods: high validity of prescribed aspirin reported by general practitioners and high completeness of aspirin use prevalence in self-reported data by including over-the-counter-drug use. In the prevalent-user analysis, a participant was considered a low-dose aspirin user when there was information on aspirin use at the dose of ≤300 mg/day either at baseline or at 2-year follow-up. The cohort entry date was then

set at the date of arrival of the 2-year follow-up questionnaire for all participants. For the new-user design, drug information from the 5-, 8-, 11- and 14-year follow-up questionnaires were used to identify low-dose aspirin users. For low-dose aspirin non-users, the cohort entry date was set at the date of arrival of the 2-year follow-up questionnaire and, for low-dose aspirin users, at the arrival date of the follow-up questionnaire in which low-dose aspirin use was reported for the first time.

In the primary care data of the UK Biobank, prescriptions were coded using Read v2, British National Formulary and dm+d and the low-dose aspirin prescriptions were identified by these codes (Tables S1–S3). The drug names were also available and were used to assist with interpretation when necessary. In the prevalent-user design, the baseline assessment date was used as the cohort entry date for all study participants. For the new-user design, the baseline assessment date was used for low-dose aspirin non-users. For low-dose aspirin users, the follow-up started at the date of the first low-dose aspirin prescription after the cohort's baseline assessment.

2.3 | Ascertainment of incident peptic ulcer disease

In ESTHER, self-reported incident peptic ulcer disease cases were validated by medical records obtained from the study participant's general practitioners. The locations of ulcers were determined from these records. A few fatal ulcer cases were identified from the death certificates of deceased study participants, which were obtained from local health authorities.

In the UK Biobank, incident peptic ulcer disease was obtained through the "first occurrence" data fields, which are provided to support researchers to identify individuals with respect to health outcomes not already covered by detailed algorithms or code lists available elsewhere.[17,18] These fields were generated by mapping READ code information in the primary care data, ICD-9 and ICD-10 codes in the hospital inpatient data, ICD-10 codes in death register records and self-reported medical condition codes reported at the UK Biobank assessment centre visits. However, we did not use incident peptic ulcer disease cases that were solely self-reported without further confirmation by primary care data or hospital inpatient data.

2.4 | Assessment of covariates

In ESTHER, study participants completed a standardised, comprehensive, self-administered questionnaire at baseline, providing information on socio-demographic characteristics, medical history, health status, family history of diseases and lifestyle factors. Their general practitioners completed a standardised health check-up form and documented current drug prescriptions. During the baseline assessment in ESTHER, serum samples were obtained from participants and stored at −80°C until analysis. An ELISA (enzyme-linked immunosorbent assay) technique was used to detect the presence of immunoglobulin G antibodies against *H. pylori* in general and specific to *cytotoxin-associated gene A* of *H. pylori* (*HP* screening ELISA and *HP* p120 [*cagA*] ELISA by ravo Diagnostika, Freiburg, Germany).[14]

For the UK Biobank, socio-demographics, lifestyle factors and medical history were obtained from the touchscreen questionnaire.[19] Self-reported diseases were complemented with information from the primary care data, which led to higher prevalences than with self-reported data only. Weight and height were measured during the assessment centre visit, and a blood sample was taken.[20] Since *H. pylori* antigen measurements in the UK Biobank were only available in a small sub-sample ($N \sim 10\,000$, which corresponds to ~2% of the total cohort), *H. pylori*-related covariates were not included in analyses done with the UK Biobank.[21]

In both studies, drug groups were identified from ATC-coded drugs using the following ATC codes or code groups: proton pump inhibitor or H_2-antagonists (A02BA, A02BC, B01AC56, B01AC86), warfarin or other anti-coagulants (B01AA, B01AB, B01AE, B01AF) and clopidogrel or other anti-platelet drugs, excl. low-dose aspirin (B01AC01-B01AC19, B01AC21-B01AC27, B01AC30, B01AC34, B01AC36).

2.5 | Statistical analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the longitudinal associations between low-dose aspirin and incident gastric as well as duodenal ulcers. The associations were tested both with prevalent-user and new-user design, and adjusted for the following demographic characteristics and ulcer risk factors in both cohorts: age, sex, education, body mass index, smoking status, alcohol consumption, coronary heart disease, hypertension, diabetes, history of stroke, use of lipid-lowering drugs, regular use of pain medication (differentiated into non-steroidal anti-inflammatory drugs [NSAIDs] and non-NSAIDs), use of proton pump inhibitors/H_2-antagonists, use of clopidogrel or other anti-platelet drugs (excl. low-dose aspirin) and use of warfarin or other anti-coagulant drugs. In sensitivity analysis, subjects who use drugs that could have affected the association between low-dose aspirin use and peptic ulcer disease (NSAIDs, warfarin or other anti-coagulants, clopidogrel or other anti-platelet drugs, and proton pump inhibitors or H_2-antagonists) were excluded.

As the variables "family history of peptic ulcer disease" and "*H. pylori* status" were not available in the UK Biobank, they have been included in the ESTHER cohort analysis in an additional model to quantify the extent of possible unconsidered confounding in the analysis of the UK Biobank.

The numbers of missing covariate values are shown in Table S4. To our knowledge, values of covariates were missing at random. Multiple imputation, generating five data sets, was undertaken to impute missing values in the UK Biobank and ESTHER study, which has been suggested to be a sufficient number to get reasonably accurate estimates.[22] The results of these imputed data sets were combined by the SAS procedure PROC MIANALYZE. All statistical

analyses were carried out with SAS v.9.4. All tests were performed two-sided using an α-level of 0.05.

3 | RESULTS

Table 1 shows the baseline characteristics of the included study participants of both cohorts. Both cohorts had a similar distribution of sex, with 56.6% females in ESTHER versus 55.4% in the UK Biobank. While the proportion of participants aged below 65 years was higher in the UK Biobank (81.4% vs 58.6% for ESTHER), ESTHER included more individuals aged 70 years or older (17.3% vs 0.4%). There were more participants in the ESTHER study than in the UK Biobank who smoked (current smoking: 15.4% vs 10.2% in the UK Biobank) but fewer participants with a moderate or high alcohol consumption: 6.7% vs 29.0%). As opposed to 47.7% in the UK Biobank, only 11.2% finished 12 years or more of school education. This, however, can be partly explained by the earlier school enrolment in the UK as well as the later recruitment period and younger age distribution in the UK Biobank. ESTHER participants had higher prevalences of coronary heart disease, hypertension, diabetes and stroke presumably due to the age difference. This higher morbidity with respect to coronary heart disease and stroke may explain the higher prevalence of low-dose aspirin use (16.4% vs 11.3%), of anti-coagulants use like warfarin (3.5% vs 1.1%) and other anti-platelet drugs use like clopidogrel (1.6% vs 0.9%) in the ESTHER study compared to the UK Biobank. However, ESTHER participants had a lower prevalence of lipid-lowering medication use, proton pump inhibitors/H_2-antagonists use and regular use of pain medication. One-quarter of the ESTHER participants had a family history of peptic ulcer disease, and approx. 50% were *H. pylori* positive, among whom half were infected with the highly virulent *cytotoxin-associated gene A-positive* strain.

3.1 | Prevalent-user analysis

The prevalent-user analysis included *N* = 7737 participants of the ESTHER study, who contributed 76 075 person-years during a median of 11.7 years of follow-up. Overall, 77 cases of gastric ulcer (incidence rate [IR] per 1000 person-years: 1.01) and 31 cases of duodenal ulcer (IR per 1000 person-years: 0.41) were observed. The UK Biobank included *N* = 213 598 participants who contributed 2 457 805 person-years for the gastric ulcer outcome and 2 463 256 person-years for the duodenal ulcer outcome during a median follow-up time of 11.7 years. Overall, 2398 cases of gastric ulcer (IR per 1000 person-years: 0.97) and 1323 cases of duodenal ulcer (IR per 1000 person-years: 0.54) were observed.

Table 2 shows the results of the longitudinal association between baseline low-dose aspirin use and other baseline characteristics with gastric ulcer disease in multivariate models. In the UK Biobank, factors statistically significantly associated with increased hazards for gastric ulcer incidence were age from 65 to 69 years, male sex, body mass index ≥30 kg/m^2, former or current

TABLE 1 Baseline characteristics of included study participants from the UK Biobank (*N* = 213,598) and the ESTHER study (*N* = 7737)

Characteristics	UK Biobank, *n* (%)	ESTHER, *n* (%)
Age (years)		
38–64	173,787 (81.4)	4533 (58.6)
65–69	38,844 (18.2)	1866 (24.1)
70–78	967 (0.4)	1338 (17.3)
Sex		
Female	118,376 (55.4)	4383 (56.6)
Male	95,222 (44.6)	3354 (43.4)
School education (years)		
≤9	49,685 (23.3)	5758 (74.4)
10–11	61,918 (29.0)	1110 (14.4)
≥12	101,995 (47.7)	869 (11.2)
Body mass index (kg/m^2)		
<25	69,064 (32.3)	2116 (27.3)
25 to <30	90,815 (42.5)	3644 (47.1)
≥30	53,719 (25.2)	1977 (25.6)
Smoking		
Never	118,704 (55.6)	4038 (52.2)
Former	72,989 (34.2)	2510 (32.4)
Current	21,905 (10.2)	1189 (15.4)
Alcohol consumption[a]		
None	67,147 (31.4)	2558 (33.1)
Low	84,604 (39.6)	4660 (60.2)
Moderate	36,392 (17.0)	408 (5.3)
High	25,455 (12.0)	111 (1.4)
Coronary heart disease	9845 (4.6)	908 (11.7)
Hypertension	57,135 (26.7)	4200 (54.3)
Diabetes	10,322 (4.8)	1129 (14.6)
History of stroke	2779 (1.3)	250 (3.2)
Use of lipid-lowering drugs	37,450 (17.5)	873 (11.3)
Regular use of pain medication		
None	125,625 (58.8)	7208 (93.2)
Non-NSAIDs	28,815 (13.5)	362 (4.7)
NSAIDs	59,158 (27.7)	167 (2.1)
Use of proton pump inhibitor or H_2-antagonists	24,090 (11.3)	522 (6.8)
Use of warfarin or other anti-coagulants	2384 (1.1)	267 (3.5)
Use of clopidogrel or other anti-platelet drugs, excl. low-dose aspirin	1889 (0.9)	125 (1.6)
Use of low-dose acetylic acid	24,058 (11.3)	1267 (16.4)
Family history of peptic ulcer disease	Not available	1950 (25.2)
Helicobacter pylori status	Not available	
H. pylori−/*CagA*−		3838 (49.6)
H. pylori+/*CagA*−		1913 (24.7)
H. pylori+/*CagA*+		1986 (25.7)

Abbreviations: CagA, cytotoxin-associated antigen A; *H. pylori*, *Helicobacter pylori*; NA, not available; NSAIDs, non-steroidal anti-inflammatory drugs.

[a]Definition of low alcohol consumption: women 0–19.99 g ethanol/day (g/d) or men 0–39.99 g/d; definition of moderate alcohol consumption: women 20–39.99 g/d or men 40–59.99 g/d; definition of high alcohol consumption: women ≥40–39.99 g/d or men ≥60 g/d.

TABLE 2 Associations of baseline characteristics with gastric ulcer incidence

Characteristics	UK Biobank (*N* = 213,598)		ESTHER study (*N* = 7737)		
	n_{cases} (%)[a]	HR (95% CI)[b]	n_{cases} (%)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Age (years)					
38–64	1721 (1.0)	Ref	48 (1.1)	Ref	Ref
65–69	663 (1.7)	**1.36 (1.24, 1.50)**	20 (1.1)	1.09 (0.64, 1.87)	1.05 (0.62, 1.80)
70–78	14 (1.5)	1.16 (0.68, 1.97)	9 (0.7)	0.85 (0.41, 1.77)	0.83 (0.40, 1.74)
Sex					
Female	1242 (1.1)	Ref	50 (1.1)	Ref	Ref
Male	1156 (1.2)	**1.10 (1.01, 1.19)**	27 (0.8)	0.74 (0.44, 1.26)	0.75 (0.44, 1.27)
School education (years)					
≤9	863 (1.7)	Ref	59 (1.0)	Ref	Ref
10–11	636 (1.0)	**0.73 (0.66, 0.82)**	12 (1.1)	0.94 (0.50, 1.77)	0.97 (0.52, 1.83)
≥12	899 (0.9)	**0.71 (0.64, 0.78)**	6 (0.7)	0.53 (0.21, 1.34)	0.53 (0.21, 1.33)
Body mass index (kg/m^2)					
<25	608 (0.9)	Ref	21 (1.0)	Ref	Ref
25 to <30	967 (1.1)	1.00 (0.90, 1.11)	34 (0.9)	0.95 (0.54, 1.66)	0.95 (0.54, 1.66)
≥30	823 (1.5)	**1.21 (1.08, 1.35)**	22 (1.1)	1.17 (0.62, 2.20)	1.16 (0.62, 2.20)
Smoking					
Never	1111 (0.9)	Ref	44 (1.1)	Ref	Ref
Former	951 (1.3)	**1.20 (1.10, 1.31)**	21 (0.8)	0.82 (0.47, 1.45)	0.84 (0.48, 1.49)
Current	336 (1.5)	**1.52 (1.34, 1.72)**	12 (1.0)	1.22 (0.63, 2.35)	1.25 (0.64, 2.42)
Alcohol consumption					
None	903 (1.3)	Ref	25 (1.0)	Ref	Ref
Low	877 (1.0)	**0.86 (0.78, 0.95)**	48 (1.0)	1.15 (0.68, 1.97)	1.17 (0.68, 1.99)
Moderate	340 (0.9)	**0.81 (0.71, 0.92)**	3 (0.7)	0.83 (0.24, 2.85)	0.86 (0.25, 2.96)
High	278 (1.1)	0.90 (0.78, 1.03)	1 (0.9)	1.16 (0.15, 8.74)	1.19 (0.16, 8.94)
Coronary heart disease					
No	2138 (1.1)	Ref	67 (1.0)	Ref	Ref
Yes	260 (2.6)	**1.19 (1.02, 1.38)**	10 (1.1)	0.83 (0.39, 1.77)	0.82 (0.39, 1.75)
Hypertension					
No	1475 (0.9)	Ref	29 (0.8)	Ref	Ref
Yes	923 (1.6)	**1.16 (1.06, 1.27)**	48 (1.1)	1.37 (0.83, 2.26)	1.37 (0.83, 2.27)
Diabetes					
No	2146 (1.1)	Ref	66 (1.0)	Ref	Ref
Yes	252 (2.4)	**1.33 (1.15, 1.54)**	11 (1.0)	1.01 (0.52, 1.99)	1.01 (0.51, 1.97)
History of stroke					
No	2331 (1.1)	Ref	74 (1.0)	Ref	Ref
Yes	67 (2.4)	1.14 (0.88, 1.48)	3 (1.2)	1.17 (0.35, 3.89)	1.17 (0.35, 3.87)
Use of lipid-lowering drugs					
No	1645 (0.9)	Ref	64 (0.9)	Ref	Ref
Yes	753 (2.0)	**1.22 (1.09, 1.37)**	13 (1.5)	1.47 (0.77, 2.79)	1.47 (0.77, 2.80)
Regular use of pain medication					
None	1048 (0.8)	Ref	75 (1.0)	Ref	Ref
Non-NSAIDs	428 (1.5)	**1.51 (1.35, 1.70)**	1 (0.3)	0.35 (0.05, 2.49)	0.34 (0.05, 2.42)
NSAIDs	922 (1.6)	**1.37 (1.23, 1.51)**	1 (0.6)	0.57 (0.08, 4.16)	0.58 (0.08, 4.21)

(Continues)

TABLE 2 (Continued)

Characteristics	UK Biobank (*N* = 213,598)		ESTHER study (*N* = 7737)		
	n_{cases} (%)[a]	HR (95% CI)[b]	n_{cases} (%)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Use of proton pump inhibitor or H_2-antagonists					
No	1860 (1.0)	Ref	72 (1.0)	Ref	Ref
Yes	538 (2.2)	**1.67 (1.51, 1.85)**	5 (1.0)	1.00 (0.40, 2.50)	1.04 (0.41, 2.60)
Use of warfarin or other anti-coagulants					
No	2352 (1.1)	Ref	76 (1.0)	Ref	Ref
Yes	46 (1.9)	1.25 (0.93, 1.69)	1 (0.4)	0.53 (0.07, 3.85)	0.53 (0.07, 3.86)
Use of clopidogrel or other anti-platelet drugs, excl. low-dose aspirin					
No	2345 (1.1)	Ref	74 (1.0)	Ref	Ref
Yes	53 (2.8)	1.13 (0.84, 1.51)	3 (2.4)	3.19 (0.96, 10.66)	3.06 (0.91, 10.21)
Use of low-dose aspirin					
No	1882 (1.0)	Ref	58 (0.9)	Ref	Ref
Yes	516 (2.1)	1.10 (0.97, 1.25)	19 (1.5)	1.66 (0.93, 2.96)	1.65 (0.93, 2.94)
Family history of peptic ulcer disease	Not available			Not included	
No			54 (0.9)		Ref
Yes			23 (1.2)		1.23 (0.75, 2.01)
Helicobacter pylori status	Not available			Not included	
H. pylori−/*CagA*−			33 (0.9)		Ref
H. pylori+/*CagA*−			18 (0.9)		1.17 (0.66, 2.08)
H. pylori+/*CagA*+			26 (1.3)		1.59 (0.94, 2.68)

Note: Statistically significant results at $p < 0.05$ are in bold.

Abbreviations: *CagA*, *cytotoxin-associated antigen A*; CI, confidence Interval; *H. pylori*, *Helicobacter pylori*; HR, hazard ratio; NSAIDs, non-steroidal anti-inflammatory drugs.

[a]Numbers of complete imputed data set 1.

[b]Hazard ratios are from the Cox regression model that includes all the variables listed except family history of peptic ulcer disease and *Helicobacter pylori* status.

[c]Hazard ratios are from the Cox regression model that includes all the variables listed.

smoking, coronary heart disease, hypertension, diabetes, use of lipid-lowering drugs, pain medication and proton pump inhibitor or H_2-antagonists. On the other hand, having more than 9 years of education and low or moderate alcohol consumption was statistically significantly associated with decreased hazards. For most factors, the results went in the same direction with similar hazard ratios in the ESTHER cohort but were not significant supposedly due to lower case numbers. Low-dose aspirin use had HRs >1 for gastric ulcer disease incidence, but the HRs were not statistically significant in both cohorts (HR [95% CI]: 1.10 [0.97–1.25] and 1.65 [0.93–2.94] for the UK Biobank and ESTHER, respectively). Models with and without adjustment for family history of peptic ulcer disease and *H. pylori* infection in the ESTHER study led to nearly identical results.

Results for the associations between baseline characteristics with duodenal ulcer disease are shown in Table 3. In the UK Biobank, age 65–69 years, male sex, current smoking, hypertension, diabetes, use of non-NSAIDs pain medication and proton pump inhibitor or H_2-antagonists were significantly associated with increased duodenal ulcer incidence. Having more than 9 years of education or consumption of low levels of alcohol was associated with a decreased risk. Low-dose aspirin use was significantly associated with duodenal ulcer incidence in the UK Biobank (HR [95% CI]: 1.27 [1.07–1.51]) and non-significantly in the ESTHER study (HR [95% CI]: 1.33 [0.54–3.29]). Similar to the gastric ulcer outcome, the results for all baseline characteristics and low-dose aspirin use did not differ much in the ESTHER study when the model was not adjusted for family history of peptic ulcer disease and *H. pylori* infection.

Table S5 shows the sensitivity analysis of the prevalent-user design analysis, excluding users of drugs that could have affected the association between low-dose aspirin use and peptic ulcer disease (NSAIDs, warfarin or other anti-coagulants, clopidogrel or other anti-platelet drugs, proton pump inhibitors or H_2-antagonists). The association between low-dose aspirin use and gastric ulcer became stronger than in the main analysis in both cohorts and was statistically significant in the UK Biobank (HR [95% CI]: 1.43 [1.11–1.84]). The point estimates for the association with duodenal ulcer also increased in the ESTHER study and remained the same in the UK Biobank. However, none of the associations with duodenal ulcer was statistically significant.

TABLE 3 Associations of baseline characteristics with duodenal ulcer incidence

Characteristics	UK Biobank (*N* = 213,598)		ESTHER study (*N* = 7737)		
	n_{cases} (%)[a]	HR (95% CI)[b]	n_{cases} (%)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Age (years)					
38–64	917 (0.5)	Ref	14 (0.3)	Ref	Ref
65–69	398 (1.0)	**1.54 (1.36, 1.75)**	10 (0.5)	2.05 (0.88, 4.77)	1.93 (0.83, 4.49)
70–78	8 (0.8)	1.25 (0.62, 2.51)	7 (0.5)	2.42 (0.94, 6.27)	2.27 (0.88, 5.88)
Sex					
Female	497 (0.4)	Ref	15 (0.3)	Ref	Ref
Male	826 (0.9)	**2.03 (1.80, 2.28)**	16 (0.5)	1.48 (0.67, 3.28)	1.51 (0.68, 3.38)
School education (years)					
≤9	456 (0.9)	Ref	25 (0.4)	Ref	Ref
10–11	374 (0.6)	**0.84 (0.73, 0.97)**	4 (0.4)	0.84 (0.29, 2.44)	0.88 (0.30, 2.58)
≥12	493 (0.5)	**0.74 (0.65, 0.85)**	2 (0.2)	0.46 (0.11, 1.96)	0.46 (0.11, 1.99)
Body mass index (kg/m^2)					
<25	315 (0.5)	Ref	9 (0.4)	Ref	Ref
25 to <30	606 (0.7)	1.10 (0.96, 1.27)	12 (0.3)	0.66 (0.27, 1.61)	0.66 (0.27, 1.62)
≥30	402 (0.8)	1.05 (0.90, 1.23)	10 (0.5)	1.05 (0.40, 2.73)	1.05 (0.40, 2.75)
Smoking					
Never	587 (0.5)	Ref	14 (0.4)	Ref	Ref
Former	501 (0.7)	1.10 (0.97, 1.24)	7 (0.3)	0.68 (0.26, 1.79)	0.69 (0.26, 1.83)
Current	235 (1.1)	**1.87 (1.60, 2.19)**	10 (0.8)	3.23 (1.35, 7.72)	3.26 (1.36, 7.81)
Alcohol consumption					
None	473 (0.7)	Ref	8 (0.3)	Ref	Ref
Low	463 (0.6)	**0.74 (0.65, 0.84)**	20 (0.4)	1.37 (0.53, 3.52)	1.41 (0.55, 3.64)
Moderate	215 (0.6)	0.93 (0.79, 1.10)	3 (0.7)	1.78 (0.35, 9.14)	2.01 (0.39, 10.37)
High	172 (0.7)	0.92 (0.77, 1.10)	0 (0.0)	N/A	N/A
Coronary heart disease					
No	1180 (0.6)	Ref	27 (0.4)	Ref	Ref
Yes	143 (1.5)	1.12 (0.91, 1.38)	4 (0.4)	0.54 (0.17, 1.73)	0.52 (0.16, 1.65)
Hypertension					
No	772 (0.5)	Ref	8 (0.2)	Ref	Ref
Yes	551 (1.0)	**1.39 (1.23, 1.57)**	23 (0.6)	2.17 (0.91, 5.16)	2.19 (0.92, 5.24)
Diabetes					
No	1181 (0.6)	Ref	24 (0.4)	Ref	Ref
Yes	142 (1.4)	**1.35 (1.11, 1.64)**	7 (0.6)	1.48 (0.60, 3.62)	1.41 (0.57, 3.47)
History of stroke					
No	1286 (0.6)	Ref	29 (0.4)	Ref	Ref
Yes	37 (1.3)	1.15 (0.82, 1.63)	2 (0.8)	1.52 (0.33, 6.94)	1.49 (0.33, 6.79)
Use of lipid-lowering drugs					
No	913 (0.5)	Ref	22 (0.3)	Ref	Ref
Yes	410 (1.1)	1.04 (0.89, 1.21)	9 (1.0)	2.67 (1.16, 6.14)	2.67 (1.16, 6.17)
Regular use of pain medication					
None	625 (0.5)	Ref	28 (0.4)	Ref	Ref
Non-NSAIDs	218 (0.8)	**1.41 (1.21, 1.65)**	1 (0.3)	0.84 (0.11, 6.28)	0.79 (0.10, 5.94)
NSAIDs	480 (0.8)	1.14 (0.99, 1.32)	2 (1.2)	3.24 (0.75, 13.94)	3.27 (0.75, 14.20)

(Continues)

TABLE 3 (Continued)

Characteristics	UK Biobank ($N = 213,598$)		ESTHER study ($N = 7737$)		
	n_{cases} (%)[a]	HR (95% CI)[b]	n_{cases} (%)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Use of proton pump inhibitor or H_2-antagonists					
No	1018 (0.5)	Ref	28 (0.4)	Ref	Ref
Yes	305 (1.3)	**1.82 (1.59, 2.08)**	3 (0.6)	1.37 (0.40, 4.62)	1.40 (0.41, 4.78)
Use of warfarin or other anti-coagulants					
No	1292 (0.6)	Ref	29 (0.4)	Ref	Ref
Yes	31 (1.3)	1.35 (0.93, 1.95)	2 (0.8)	1.94 (0.44, 8.62)	1.94 (0.44, 8.60)
Use of clopidogrel or other anti-platelet drugs, excl. low-dose aspirin					
No	1301 (0.6)	Ref	31 (100.0)	Ref	Ref
Yes	22 (1.2)	0.77 (0.50, 1.21)	0 (0.0)	N/A	N/A
Use of low-dose aspirin					
No	1016 (0.5)	Ref	23 (0.4)	Ref	Ref
Yes	307 (1.3)	**1.27 (1.07, 1.51)**	8 (0.6)	1.28 (0.52, 3.18)	1.33 (0.54, 3.29)
Family history of peptic ulcer disease		Not available		Not included	
No			22 (0.4)		Ref
Yes			9 (0.5)		1.36 (0.61, 3.01)
Helicobacter pylori status		Not available		Not included	
H. pylori-/CagA-			10 (0.3)		Ref
H. pylori+/CagA-			10 (0.5)		2.00 (0.82, 4.86)
H. pylori+/CagA+			11 (0.6)		2.18 (0.91, 5.21)

Note: Statistically significant results at $p < 0.05$ are in bold.

Abbreviations: *CagA*, *cytotoxin-associated antigen A*; CI, confidence Interval; *H. pylori*, *Helicobacter pylori*; HR, hazard ratio; NSAIDs, non-steroidal anti-inflammatory drugs.

[a]Numbers of complete imputed data set 1.

[b]Hazard ratios are from the Cox regression model that includes all the variables listed except the family history of peptic ulcer disease and *Helicobacter pylori* status.

[c]Hazard ratios are from the Cox regression model that includes all the variables listed.

3.2 | New-user analysis

The adjusted new-user design analyses for both outcomes are shown in Table 4. Among $N = 189\,437$ participants from the UK Biobank, there were 1819 cases of gastric ulcer (IR per 1000 person-years: 0.85) and 970 cases of duodenal ulcer (IR per 1000 person-years: 0.45) during a median of 11.6 follow-up years. Among $N = 6446$ participants from the ESTHER study, there were 48 cases of gastric ulcer (IR per 1000 person-years: 0.86) and 18 cases of duodenal ulcer (IR per 1000 person-years: 0.32) observed during a median follow-up time of 8.6 years. Low-dose aspirin use was associated with a 1.8-fold increased risk of gastric ulcer incidence among UK Biobank participants (HR [95% CI]: 1.82 [1.58–2.11]) and a 2.8-fold increased risk among ESTHER participants (HR [95% CI]: 2.83 [1.40, 5.71]). As for duodenal ulcer incidence, low-dose aspirin use was associated with a 1.7-fold increased risk in the UK Biobank (HR [95% CI]: 1.66 [1.36–2.04]) and with a 3.9-fold increased risk in the ESTHER study (HR [95% CI]: 3.89 [1.46, 10.42]). Although associations were stronger in the ESTHER study, it should be noted that the confidence intervals were wide and overlapped with those of the much larger UK Biobank.

Table S6 shows the sensitivity analysis of the new-user design analysis, excluding users of NSAIDs, warfarin or other anti-coagulants, clopidogrel or other anti-platelet drugs, proton pump inhibitors or H_2-antagonists. The associations between low-dose aspirin with a gastric ulcer in both cohorts and with duodenal ulcers in the UK Biobank did not change much and remained strong and statistically significant. Only the association of low-dose aspirin use with duodenal ulcer incidence in the ESTHER study lost statistical significance, but it needs to be mentioned that the number of duodenal ulcer cases was very low in this sensitivity analysis ($n = 11$).

4 | DISCUSSION

This analysis of two large cohort studies from the UK and Germany showed that low-dose aspirin use is an independent risk factor for both gastric and duodenal ulcers. Consistently in both cohorts, the

TABLE 4 Associations of low-dose aspirin use with gastric ulcer incidence and duodenal ulcer incidence in new-user design

Outcome	Use of low-dose aspirin	UK Biobank ($N = 189,437$)			ESTHER ($N = 6446$)			
		n_{total}	n_{case} (%)	HR (95% CI)[a]	n_{total}	n_{case} (%)	HR (95% CI)[a]	HR (95% CI)[b]
Gastric ulcer	No	172,844	1542 (0.89)	Ref	5088	35 (0.69)	Ref	Ref
	Yes	16,593	277 (1.67)	**1.82 (1.58, 2.11)**	1358	13 (0.96)	**2.73 (1.35, 5.49)**	**2.83 (1.40, 5.71)**
Duodenal ulcer	No	172,844	825 (0.48)	Ref	5088	10 (0.20)	Ref	Ref
	Yes	16,593	145 (0.87)	**1.66 (1.36, 2.04)**	1358	8 (0.59)	**3.79 (1.42, 10.14)**	**3.89 (1.46, 10.42)**

Note: Statistically significant results at $p < 0.05$ are in bold.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Hazard ratios are from the Cox regression model that includes all the variables listed in Table 2 except a family history of peptic ulcer disease and *Helicobacter pylori* status.

[b]Hazard ratios are from the Cox regression model that includes all the variables listed in Table 2.

associations were weak (and mostly not statistically significant) in the prevalent-user design and strong (and statistically significant) in the new-user design approach.

In a systematic review of observational studies from 2016, a meta-analysis of 24 studies found that the overall pooled estimate of the relative risk for upper gastrointestinal bleeding with low-dose aspirin was 2.3 (95% CI: 2.0–2.6).[23] Similarly, the relative risk for uncomplicated peptic ulcer disease was 2.9 (95% CI: 2.3–3.6), as reported by Rodriguez and Hernandez-Diaz.[24] Although the upper gastrointestinal toxicity of long-term low-dose aspirin use has been well investigated before, to the best of our knowledge, no previous population-based cohort study has investigated the risks of new users and has compared these to the risks of prevalent users. Our analysis of two independent cohort studies revealed a much stronger association between low-dose aspirin use and gastric and duodenal ulcer incidence when the new-user design was applied.

The lower gastrointestinal risk observed in prevalent users is presumably caused by either a physiological adaption to aspirin effects, the sick-stopper bias, or both. In our study example, prevalent users were individuals who were taking low-dose aspirin at baseline and in most cases have been taking them for some time before study follow-up began. These study participants are likely patients who adhere to their therapy and tolerate it well. Gastric adaptation to injury caused by chronic NSAIDs use has been described of which the development of resistance to programmed cell death seems to be a major contributor.[25] In addition, individuals who develop adverse gastrointestinal symptoms closely after initiation of low-dose aspirin therapy are more likely to discontinue the treatment because of the risk that these symptoms evolve into peptic ulcer disease. These subjects are then unlikely to be allocated to the low-dose aspirin group of prevalent-user design studies because these gastrointestinal problems have happened before baseline and are unknown to the investigators, which causes the sick-stopper bias.[26] In new-user design studies, follow-up starts with the initiation of therapy, and prevalent users are excluded from the study. The new-user design enabled us to capture early peptic ulcer disease events after first low-dose aspirin exposure and it is not affected by the sick-stopper bias.

Aspirin can induce mucosal damage in patients through both local and systemic mechanisms. The topical injury of aspirin is initiated by its weak acidic property, which enables aspirin to penetrate through the gastric mucus across plasma membranes into surface epithelial cells. The molecule is dissociated, resulting in trapping hydrogen ions within cells.[27] The systemic effect of aspirin, however, appears to play the predominant role, largely through the inhibition of the cyclooxygenase enzymes and the consequential reduction in the synthesis of gastroprotective prostaglandin. This leads to reduced bicarbonate and mucus secretion by the gastric epithelium, impaired blood flow in the gastric mucus and reduced epithelial cell proliferation, ultimately pre-disposing the gastric mucosa to harmful substances (eg stomach acid and pepsin). In addition, the anti-platelet property of aspirin makes the gastric intestinal tract vulnerable to bleeding once the injury has occurred.[28]

Aspirin, through its irreversible anti-thrombotic property, is the cornerstone of the well-established anti-platelet therapy recommended for the primary and secondary prevention of atherosclerotic cardiovascular disease. Additionally, recent evidence has emerged that long-term low-dose aspirin use might also benefit colorectal cancer and dementia prevention,[3–5,29] which could further increase the prevalence of low-dose aspirin use in the future. For the primary prevention of atherosclerotic cardiovascular disease, the American Heart Association and the American College of Cardiology recommend the use of aspirin at 75–100 mg orally daily among adults 40–70 years of age who are at higher atherosclerotic cardiovascular disease risk, but not at increased bleeding risk. For secondary prevention of atherosclerotic cardiovascular disease in patients with coronary heart disease, 75–162 mg of aspirin daily is recommended in all patients unless contraindicated.[1,30] For weighing the potential risks against the potential benefits in the decision about low-dose aspirin treatment initiation, the free, evidence-based Aspirin-Guide mobile app can be recommended.[31]

With respect to other peptic ulcer risk factors, the UK Biobank analysis showed that age 65–69 years versus younger age, male sex, low education, current smoking, being alcohol abstainer, hypertension, diabetes mellitus, regular use of pain medication (either with NSAIDs or non-NSAIDs) and use of proton pump inhibitor or

H_2-antagonists were associated with the development of both gastric and duodenal ulcers. These risk factors shall be discussed in the following paragraphs.

NSAIDs use has been identified as one of the main risk factors for gastric and duodenal ulcers, in both complicated and uncomplicated forms.[12,14,32] The hazard ratio observed in the UK Biobank for gastric ulcers (1.35 [95% CI: 1.22–1.49]) was close to the odds ratio for uncomplicated ulcers (1.40 [95% CI: 1.28–1.54]) reported by Lassen et al.,[11] but no significant association with duodenal ulcer was found. The use of non-NSAIDs pain medication, presumably mainly paracetamol, was also found to be associated with increased risk for both gastric and duodenal ulcers in the UK Biobank. Though being biologically plausible at high doses and also observed in other studies,[12,33] this association might be spurious and needs cautious interpretation.

Although proton pump inhibitors and H_2-antagonists are known to actually decrease peptic ulcer risk by reducing intragastric acidity, the opposite direction was observed in our study. This might be explained by unconsidered confounders or reverse causality. Reverse causality means in this case that proton pump inhibitors and H_2-antagonists might be used against symptoms of undiagnosed peptic ulcer disease.

Among comorbidities investigated in the UK Biobank, diabetes and hypertension were associated with both gastric and duodenal ulcer risk. Furthermore, obesity (body mass index >30 kg/m^2), coronary heart disease and dyslipidemia (as measured by the use of lipid-lowering drugs) were associated with gastric but not duodenal ulcer risk. These conditions are often related to each other and are sometimes summarised in the cardiometabolic syndrome, which is mainly characterised by insulin resistance.[34] It has been known that patients with diabetes mellitus have higher peptic ulcer disease incidence than the non-diabetic population.[35] Diabetes was also observed to independently increase the risk of peptic ulcers by 40% in a large study from Taiwan.[36] The mechanisms could be an aggravating of gastric mucosal susceptibility to stress and ulcerogenic drugs, and the impairing of ulcer healing.[37,38]

The level of education is a possible proxy for family living standards and economic possibilities, and the increased peptic ulcer risk associated with lower education and low socio-economic status was also observed formerly.[39,40]

The role of smoking as a risk factor for peptic ulcer disease is inconclusive in the literature.[41,42] Support for a pathogenic role of smoking comes from the finding that smoking may decrease pancreatic bicarbonate production and accelerate gastric emptying, leading to a high acid load delivered to the first part of the duodenum, where 95% of all duodenal ulcers are located. *Helicobacter pylori* infiltration was also found to be denser in the gastric atrium of smokers, suggesting that smoking is harmful to the gastroduodenal mucosa.[43] Our findings, showing that current smokers, were at higher risk for both gastric and duodenal ulcers, one more time emphasises the importance of smoking prevention and cessation for peptic ulcer disease prevention.

Previous prospective studies had conflicting results regarding older age, male sex and alcohol abstinence as risk factors for peptic ulcer disease and also the results of the ESTHER study did not back up those of the UK Biobank.[32] These might either be weak risk factors for which the large sample size of the UK Biobank was needed to detect them with statistical significance or the results are specific for the population included in this British study.

This research with two cohort studies needs to be evaluated while keeping in mind its limitations. The ESTHER study participants were recruited during a voluntary health check-up in the Saarland region and the UK Biobank invited only people living near the study centres and had a low response rate leading to a "healthy volunteer" selection bias. Thus, both studies are not truly representative samples of Germany's and the UK's population. However, the overall incidence of peptic ulcer disease for ESTHER and the UK Biobank in the prevalent-user design of 1.42 and 1.51 per 1000 person-year, respectively, were comparable to those reported in previous population-based studies from Europe[11,44] and the limitations of the representativeness should not hinder a valid assessment of relative risk estimates for exposure–disease relationships in these cohorts.[45]

Furthermore, gastroscopy in non-cases was not undertaken to exclude asymptomatic peptic ulcer disease in both cohorts. Gastroscopy is invasive, and therefore not feasible in large cohorts of healthy study participants due to the risks involved (eg bleeding, infection). In addition, *H. pylori* measurements and information on the family history of peptic ulcer disease were not available for the UK Biobank. However, the ESTHER analyses suggested that family history of peptic ulcer disease and *H. pylori* infection are not confounders for the association of low-dose aspirin with peptic ulcer disease and thus, the results for the UK Biobank seem unlikely to be biased by lack of adjustment for these risk factors. Furthermore, low-dose aspirin can be purchased over-the-counter and this was captured in the ESTHER study analysis, which is a strength of this study underlying its real-world nature. In the UK Biobank, however, low-dose aspirin use, which includes over-the-counter purchases, was not used in this analysis because it was only assessed once at baseline and the prevalence was only slightly higher (14.4%) than in the primary care data set (11.5% received at least one prescription of low-dose aspirin prior to the baseline assessment date).[5] As the difference in prevalence was not very large and the agreement between the two assessment methods was close to the threshold between moderate and substantial agreement (Cohen's Kappa coefficient: 0.59), we do not think that the non-consideration of over-the-counter low-dose aspirin use had a strong influence on the results from the UK Biobank. Finally, as with any observational study, residual confounding remains possible, and causation could not be tested, although we controlled for a high number of potentially important confounders.

The strengths of this study include the prospective cohort design and the large sample size ($n = 7737$ for ESTHER, and $n = 213{,}598$ for the UK Biobank). In addition, the use of the new-user design was possible by utilising the follow-up questionnaires in ESTHER, and the primary care data in the UK Biobank, which provide detailed information regarding new initiations of low-dose aspirin therapy.

In conclusion, both analysed cohort studies showed that low-dose aspirin is a strong and independent risk factor for both gastric and duodenal ulcers among new low-dose aspirin users. Individuals

already using low-dose aspirin for years, who do not experience unusual gastrointestinal symptoms, may tolerate the drug well. In the UK Biobank, only slightly increased gastric ulcer and duodenal ulcer risks of about 10% and 27%, respectively, were observed among prevalent users (the former narrowly missed statistical significance). Thus, primarily when low-dose aspirin therapy shall be initiated, a careful weighing of risks and benefits is recommended and tools such as the Aspirin-Guide mobile app are available for this purpose in clinical routine. Furthermore, once low-dose aspirin therapy is started, adverse events monitoring is recommended to ensure its safe long-term use.

AUTHOR CONTRIBUTIONS

Thi Ngoc Mai Nguyen: Conceptualization (supporting); formal analysis (lead); investigation (lead); methodology (supporting); visualization (lead); writing – original draft (lead). **Sha Sha:** Writing – review and editing (equal). **Li-Ju Chen:** Writing – review and editing (supporting). **Bernd Holleczek:** Data curation (equal); writing – review and editing (supporting). **Hermann Brenner:** Data curation (equal); resources (lead); writing – review and editing (supporting). **Ben Schöttker:** Conceptualization (lead); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (equal); project administration (lead); supervision (lead); writing – review and editing (lead).

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AUTHORSHIP

Guarantor of the article: Ben Schöttker.

DATA AVAILABILITY STATEMENT

Data from the ESTHER study is available upon reasonable request that is compatible with participants' informed consent. Data from the UK Biobank is available to bona fide researchers upon a data access application.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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