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The effect of low-dose aspirin on colorectal cancer prevention and gastrointestinal bleeding according to bodyweight and body mass index: Analysis of UK primary care data

Lucía Cea Soriano [a,b,*,1], Pareen Vora [c,2], Montse Soriano-Gabarró [c,3], Luis A. García Rodríguez [a,4]

[a] Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain
[b] Department of Public Health and Maternal and Child Health, Faculty of Medicine, Complutense University of Madrid, Spain
[c] Epidemiology, Bayer AG, Berlin, Germany

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ABSTRACT

Background: Meta-analysis of trial data suggests that in primary cardiovascular disease (CVD) prevention bodyweight modifies low-dose aspirin's effects on colorectal cancer (CRC) and major bleeding risk. We sought to investigate whether these effects are seen in patients with or without CVD in routine clinical practice by undertaking sub-analyses of data from two cohort studies with nested-case-control analyses.

Methods: We followed ~200,000 new users of low-dose aspirin (75–300 mg/day) and a matched cohort of non-users to identify incident cases of CRC/upper gastrointestinal bleeding (UGIB). Adjusted relative risks (RRs) with 95% confidence intervals (CIs) were calculated for current vs. non-use of low-dose aspirin using logistic regression stratified by bodyweight/body mass index (BMI) strata.

Results: RRs (95% CIs) for CRC by bodyweight were: 0.60 (0.50–0.72) for ≤70 kg, 0.68 (0.60–0.76) for >70 kg; and by BMI were 0.60 (0.52–0.68) for ≤28 kg/m^2, 0.76 (0.64–0.89) for >28 kg/m^2. For UGIB, estimates were: 1.49 (1.28–1.74) for ≤90 kg, 1.78 (1.29–2.45) for >90 kg/m^2, 1.44 (1.21–1.72) for ≤28 kg/m^2, 1.72 (1.38–2.16) for >28 kg/m^2. Results were similar in the primary CVD prevention population.

Conclusion: Our findings suggest that the effects of low-dose aspirin in reducing CRC risk and increasing UGIB risk are not modified by bodyweight/BMI.

1. Introduction

Low-dose aspirin is well-established in reducing the risk of ischaemic vascular events [1,2] – an effect mediated through its irreversible inhibition of cyclooxygenase I (COX-1) in platelets leading to suppression of thromboxane A_2 [3]. There is mounting evidence from both randomized controlled trials (RCTs) and observational studies that low-dose aspirin protects against colorectal cancer (CRC) [4–6] – an effect possibly also mediated by platelet inhibition, [7,8] and a factor to be considered when evaluating whether the benefits of low-dose aspirin outweigh the risk of major bleeding in specific patient populations.

There is some evidence to suggest that obesity is associated with impaired antiplatelet pharmacodynamics of low-dose aspirin [9,10]. In an analysis of data from five trials of aspirin in the primary prevention of cardiovascular events, with 20-years' post-trial follow-up and available data on weight, Rothwell and colleagues [11] found that low-dose aspirin (75–100 mg) only reduced the risk of cardiovascular events and CRC in participants weighing <70 kg, and only increased the risk of major bleeding among those weighing <90 kg. In these trials of selected participants, low-dose aspirin and weight were analyzed according to randomized treatment; however, aspirin exposure may have changed over the long post-trial follow-up period.

We have previously published findings from two large population-based studies evaluating the association between low-dose aspirin (75–300 mg/day) and risk of CRC/upper gastrointestinal bleeding (UGIB) [5,12]. These studies used a matched cohort study design to minimize bias from differences at the start of follow-up between low-dose aspirin users and non-users that are difficult to control for, and a nested

* Corresponding author at: Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Almirante 28, 28004 Madrid, Spain.
E-mail address: luciaceife@gmail.com (L. Cea Soriano).

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[3] Montse Soriano-Gabarró contributed to the study concept, the interpretation of the data, the revision of manuscript drafts and the decision to submit the final approved manuscript for publication.

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case–control analysis to accurately analyze recent low-dose aspirin exposure. Here, we present results of a sub-analysis of data from these two previous studies investigating whether the effect of low-dose aspirin on risks of CRC and upper GI bleeding (UGIB) is modified by bodyweight or BMI.

2. Methods

2.1. Data source and study design

We used The Health Improvement Network, a database of primary care electronic health records in the UK, covering, as of January 2018, 3.1 million patients [13]. The database is representative of the UK demographic [14] and validated for pharmacoepidemiological research [15]. Data held includes clinical information entered as part of routine patient care, including prescriptions issued and information communicated from secondary care. Full details of our two original studies, including approval of the study protocols, have been published previously [5,12].

In both studies, outcomes (3303 incident CRC cases and 1843 incident UGIB cases) were validated through manual review of patient records including free text comments and linked hospitalization data [16]. The index date for cases was the date of CRC/UGIB, and for the controls (10,000 for CRC and 5000 for UGIB; frequency matched by age, sex and calendar year of the index date) it was a random date within their observation period. Low-dose aspirin exposure was determined using prescription records. Current use was defined as when the most recent prescription lasted until (or over) the index date or ended within 90 days before the index date in the CRC analysis, or ended within 30 days before the index date in the UGIB analysis (current users could have had any previous duration of use). Non-use was defined as never having a prescription for low-dose aspirin before the index date for CRC, and no prescription in the year before the index date for UGIB. Potential misclassification of low-dose aspirin exposure due to its availability over-the-counter in the UK was deemed negligible based on findings from our previous validation study [17].

2.2. Bodyweight and body mass index

In the UGIB analysis, we used the nearest weight and height measurements recorded before the index date. For the CRC analysis, we used the same approach but disregarded weight measurements in the year before the index date because weight changes in that period could have been a reflection of prodromal symptoms for CRC. Body mass index was calculated as weight in kg divided by height in metres squared. To be able to compare our results with findings from Rothwell et al, bodyweight was dichotomized using a 70 kg cut-off (≤70 kg and >70 kg) for the CRC analysis and 90 kg (≤90 kg and >90 kg) for the UGIB analysis. For both the CRC and UGIB analyses, BMI was dichotomized as 28 kg/m^2 or >28 kg/m^2.

2.3. Statistical analysis

Using unconditional logistic regression, we calculated incidence rate ratios (RRs) with 95% confidence intervals (CIs) adjusted for confounders (see Table 1) to quantify the association between low-dose aspirin (current use vs. non-use) and risk of CRC and UGIB stratified by bodyweight and BMI. We also performed a stratified analysis by primary/secondary CVD prevention population, and sensitivity analyses changing the bodyweight cut-off to 80 kg (≤80 kg and >80 kg) and BMI cut-off to 24 kg/m^2 in both the CRC and UGIB analyses.

3. Results

Measures of association between low-dose aspirin and CRC/UGIB, stratified by bodyweight and by BMI, are shown in Fig. 1 and Table 1.

3.1. Colorectal cancer

Current use of low-dose aspirin (vs. non-use) was associated with a reduced risk of CRC irrespective of bodyweight or BMI strata: for bodyweight, effect sizes were 40% for ≤70 kg and 32% for >70 kg, and for BMI, effect sizes were 40% for ≤28 kg/m^2 and 24% for >28 kg/m^2. Findings were similar in analyses restricted to the primary CVD prevention sub-population (Table 2). Among the secondary CVD prevention sub-population, strong evidence of a protective effect of low-dose aspirin on CRC risk was seen among individuals with lower bodyweight (RR 0.59, 95% CI: 0.39–0.89 for ≤70 kg), but among those with higher bodyweight the confidence intervals overlapped 1.0 (RR 0.88, 95% CI: 0.63–1.23 for >70 kg). RRs by BMI strata in the secondary CVD prevention population also showed CIs overlapping 1.0: 0.71 (95% CI: 0.51–1.00) for ≤28 kg/m^2 and 0.81 (95% CI: 0.53–1.24) for >28 kg/m^2. Sensitivity analysis, changing the bodyweight and BMI cut-offs, showed no material differences in the results from the main analysis.

3.2. Upper gastrointestinal bleeding

Low-dose aspirin was associated with an increased risk of UGIB across weight/BMI strata, with a similar magnitude of effect seen in the overall study population (Table 1 and Fig. 1) and in the primary CVD prevention sub-population (Table 2). In the secondary CVD prevention population (Table 3), there was no evidence of an increase in UGIB risk in any bodyweight or BMI strata: RRs (95% CI) for bodyweight were 1.25 (0.92–1.68) for ≤90 kg and 0.90 (0.47–1.74) for >90 kg/m^2, and for BMI were 1.20 (0.85–1.70) for ≤28 kg/m^2 and 1.05 (0.65–1.69) for >28 kg/m^2. No appreciable differences in the results for UGIB were seen in the sensitivity analyses.

4. Discussion

In our study set in UK primary care, we found no evidence that the effect of low-dose aspirin in reducing CRC risk and increasing UGIB risk was modified by bodyweight or BMI, either in our overall study population or in our primary CVD prevention sub-population. Evidence for a protective effect of low-dose aspirin against CRC in secondary CVD prevention was weaker, yet the smaller sample size for analysis had limited statistical power to detect significant differences between exposure groups.

Our results for CRC contrast with those reported by Rothwell et al [11] in their meta-analysis of RCT data, which suggested that the protective effect of low-dose aspirin against CRC is lost among people with a bodyweight of ≥70 kg. To the best of our knowledge, there have been no other published analyses of the effects of low-dose aspirin on CRC risk by bodyweight or BMI strata. Our findings for UGIB also do not support those reported by Rothwell et al for major bleeding, but are in line with those from the ASCEND (A Study of Cardiovascular Events in Diabetes) [18] RCT of aspirin in primary CVD prevention and the ATT Collaboration's meta-analysis of data from primary CVD prevention trials, both reporting that the effects of low-dose aspirin in increasing major bleeding risk are not modified by BMI. Similarly, despite differences in the definition of the bleeding outcome investigated, the ASPREE (Aspirin in Reducing events in the Elderly) primary prevention trial [19] also found no interaction between BMI and low-dose aspirin on the risk of major haemorrhage, which is more in line with our findings. It is noteworthy that, in contrast to Rothwell et al, the ATT Collaboration's meta-analysis did not find BMI to modify the risk of major cardiovascular outcomes, while in ASCEND, low-dose aspirin only reduced the risk of vascular events/revascularization in diabetic participants who were obese.

Strengths of our study include the large population-based sample and inclusion of patients with gastrointestinal and other comorbidities, thereby reflecting the range of patients receiving and not receiving low-dose aspirin in routine clinical practice, and meaning our results are

Table 1
RRs (95% CI) for the association between low-dose aspirin (current use vs. non-use) and CRC/UGIB, stratified by bodyweight/BMI.

	Colorectal cancer			Upper gastrointestinal bleeding		
	Cases	Controls	Adjusted RR[a] (95% CI)	Cases	Controls	Adjusted RR[b] (95% CI)
Overall	$N = 3033$	$N = 10{,}000$		$N = 1843$	$N = 5000$	1.0 (reference)
Non-use	1247 (41.1)[c]	3557 (35.6)[d]	1.0 (reference)	672 (36.5)[e]	2412 (48.2)[f]	
Current low-dose aspirin use	1255 (41.4)[c]	4562 (45.6)[d]	0.66 (0.60–0.73)	987 (53.6)[e]	2160 (43.2)[f]	1.53 (1.34–1.75)
Bodyweight (kg)						
≤70 for CRC; ≤90 for UGIB	$N = 854$	$N = 3188$		$N = 1366$	$N = 3730$	
Non-use	373 (43.7)	1183 (37.1)	1.0 (reference)	517 (37.8)	1821 (48.8)	1.0 (reference)
Current low-dose aspirin use	322 (37.7)	1383 (43.4)	0.60 (0.50–0.72)	715 (52.3)	1572 (42.1)	1.49 (1.28–1.74)
>70 for CRC; >90 for UGIB	$N = 1952$	$N = 6088$		$N = 356$	$N = 885$	
Non-use	741 (38.0)	1972 (32.4)	1.0 (reference)	108 (30.3)	368 (41.6)	1.0 (reference)
Current low-dose aspirin use	857 (43.9)	2953 (48.5)	0.68 (0.60–0.76)	205 (57.6)	457 (51.6)	1.78 (1.29–2.45)
BMI (kg/m^2)						
≤28	$N = 1544$	$N = 5417$		$N = 1018$	$N = 2772$	
Non-use	680 (44.0)	1984 (36.6)	1.0 (reference)	401 (39.4)	1403 (50.6)	1.0 (reference)
Current low-dose aspirin use	581 (37.6)	2405 (44.4)	0.60 (0.52–0.68)	512 (50.3)	1122 (40.5)	1.44 (1.21–1.72)
>28	$N = 1151$	$N = 3553$		$N = 664$	$N = 1774$	
Non-use	376 (32.7)	1053 (29.6)	1.0 (reference)	209 (31.5)	749 (42.2)	1.0 (reference)
Current low-dose aspirin use	557 (48.4)	1788 (50.3)	0.76 (0.64–0.89)	387 (58.3)	882 (49.7)	1.72 (1.38–2.16)

Data are n (%) unless otherwise specified.
Note: Non-use was defined as having no prescription for low-dose aspirin ever before the index date for CRC, and no prescription for low-dose aspirin in the year before the index date for UGIB. Current use was defined as when supply of the most recent prescription lasted until (or over) the index date or ended within 90 days before the index date in the CRC analysis, or ended within 30 days before the index date in the UGIB analysis.
BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; GI, gastrointestinal; RR, rate ratio; UGIB, upper gastrointestinal bleeding.
[a] Adjusted by age, sex, calendar year, number of primary care practitioner visits in the previous year, smoking, insulin, non-steroidal anti-inflammatory drugs, body mass index and oral steroids.
[b] Adjusted by age, sex, calendar year, number of primary care visits in the year before the index date, smoking, alcohol consumption, prior UGIB, prior lower GI bleeding, prior GI bleeding unspecified, pancreatic disease, uncomplicated peptic ulcer, polypharmacy, use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, clopidogrel and warfarin.
[c] Numbers do not add up to N because 531 cases were classed as recent/past users of low-dose aspirin, which was use ≥91 days before the index date.
[d] Numbers do not add up to N because 1881 controls were either classed as recent/past users of low-dose aspirin recent/past use, which was use ≥91 days before the index date.
[e] Numbers do not add up to N because 184 cases were classed as recent/past users of low-dose aspirin, which was use 31–365 days before the index date.
[f] Numbers do not add up to N because 428 controls were classed as recent/past users of low-dose aspirin, which was use 31–365 days before the index date.

generalizable to the UK general population. The matched cohort design helped to minimize bias from differences between low-dose aspirin users and non-users that could potentially confound observed associations if not controlled for, although residual confounding cannot be excluded. The nested case–control analysis enabled us to accurately ascertain both exposure to low-dose aspirin and weight measurements around the time of the index date, reducing bias from misclassification of low-dose aspirin use and weight that is more likely to occur in analyses based on information collected at the start of follow-up. Moreover, this may account for the difference in between our findings and those in the study by Rothwell and colleagues, in which analysis of these two variables was based on exposure at the start of a 20-year follow-up period. Other limitations include the inability to make direct comparisons with risks of major bleeding outcomes reported in RCTs because we did not include other major bleeding events – intracranial or lower gastrointestinal bleeding – in our sub-analyses, and potential misclassification of bodyweight/BMI from measurement/recording inaccuracies, which would likely be non-differential biasing risk estimates towards the null.

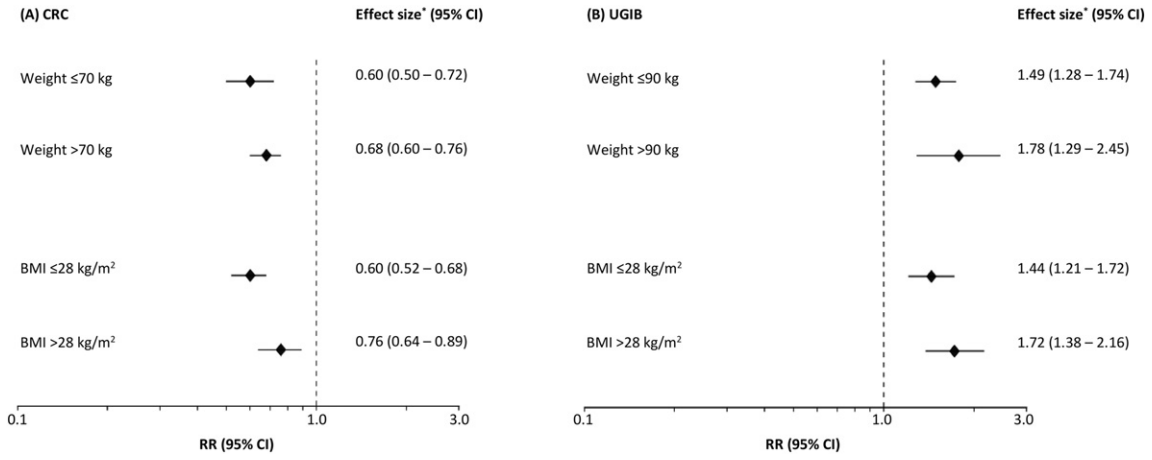

Fig. 1. Rate ratios (95% CIs) for the association between low-dose aspirin (current vs. non-use) and (A) colorectal cancer, (B) upper gastrointestinal bleeding, by bodyweight and BMI. *In the CRC analysis, adjustment was made for age, sex, calendar year, number of primary care practitioner visits in the previous year, insulin, non-steroidal anti-inflammatory drugs, body mass index and oral steroids. †In the UGIB analysis, adjustment was made for age, sex, calendar year, number of primary care visits in the year before the index date, smoking, alcohol consumption, prevoius UGIB, previous lower GI bleeding, previous GI bleeding unspecified, pancreatic disease, uncomplicated peptic ulcer, polypharmacy, use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, clopidogrel and warfarin. BMI, body mass index; CRC, colorectal cancer; GI, gastrointestinal; UGIB, upper gastrointestinal bleeding. Note: Current use was defined as when supply of the most recent prescription lasted until (or over) the index date or ended within 90 days before the index date in the CRC analysis, or ended within 30 days before the index date in the UGIB analysis. Non-use was defined as having no prescription for low-dose aspirin ever before the index date for CRC, and no prescription for low-dose aspirin in the year before the index date for UGIB.

Table 2
RRs (95% CI) for the association between low-dose aspirin (current use vs. non-use) and CRC/UGIB among the **primary** CVD prevention population, stratified by bodyweight/BMI.

	Colorectal cancer			Upper gastrointestinal bleeding		
	Cases	Controls	Adjusted RR[a] (95% CI)	Cases	Controls	Adjusted RR[b] (95% CI)
Overall	*N* = 2330	*N* = 7441		*N* = 1200	*N* = 3663	1.0 (reference)
Non-use	1139 (48.9)[c]	3218 (43.2)[d]	1.0 (reference)	512 (42.7)[e]	2096 (57.2)[f]	1.0 (reference)
Current low-dose aspirin use	810 (34.8)[c]	2825 (38.0)[d]	0.68 (0.61–0.76)	572 (47.7)[e]	1262 (34.5)[f]	1.62 (1.38–1.90)
Bodyweight (kg)						
≤70 for CRC; ≤90 for UGIB	*N* = 639	*N* = 2348		*N* = 873	*N* = 2742	
Non-use	329 (51.5)	1057 (45.0)	1.0 (reference)	394 (45.1)	1575 (57.4)	1.0 (reference)
Current low-dose aspirin use	201 (31.5)	824 (35.1)	0.64 (0.52–0.79)	395 (45.3)	928 (33.8)	1.50 (1.25–1.81)
>70 for CRC; >90 for UGIB	*N* = 1495	*N* = 4496		*N* = 246	*N* = 643	
Non-use	685 (45.8)	1785 (39.7)	1.0 (reference)	79 (32.1)	321 (49.9)	1.0 (reference)
Current low-dose aspirin use	554 (37.1)	1858 (41.3)	0.68 (0.59–0.78)	137 (55.7)	277 (43.1)	2.13 (1.45–3.13)
BMI (kg/m^2)						
≤28	*N* = 1185	*N* = 3986		*N* = 644	*N* = 2026	
Non-use	621 (52.4)	1783 (44.7)	1.0 (reference)	307 (47.7)	1209 (59.7)	1.0 (reference)
Current low-dose aspirin use	368 (31.1)	1445 (36.3)	0.63 (0.54–0.73)	273 (42.4)	644 (31.8)	1.43 (1.15–1.78)
>28	*N* = 859	*N* = 2632		*N* = 450	*N* = 1307	
Non-use	340 (39.6)	957 (36.4)	1.0 (reference)	155 (34.4)	656 (50.2)	1.0 (reference)
Current low-dose aspirin use	358 (41.7)	1149 (43.7)	0.75 (0.62–0.90)	246 (54.7)	544 (41.6)	1.99 (1.52–2.60)

Data are n (%) unless otherwise specified.
Note: Non-use was defined as having no prescription for low-dose aspirin ever before the index date for CRC, and no prescription for low-dose aspirin in the year before the index date for UGIB. Current use was defined as when supply of the most recent prescription lasted until the index date or ended within 90 days before the index date in the CRC analysis, or ended within 30 days before the index date in the UGIB analysis.
BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; CVD, cardiovascular disease; GI, gastrointestinal; RR, rate ratio; UGIB, upper gastrointestinal bleeding.
[a] Adjusted by age, sex, calendar year, number of primary care practitioner visits in the previous year, smoking, insulin, non-steroidal anti-inflammatory drugs, body mass index and oral steroids.
[b] Adjusted by age, sex, calendar year, number of primary care visits in the year before the index date, smoking, alcohol consumption, previous UGIB, previous lower GI bleeding, previous GI bleeding unspecified, pancreatic disease, uncomplicated peptic ulcer, polypharmacy, use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, clopidogrel and warfarin.
[c] Numbers do not add up to N because 381 cases were classed as recent/past users of low-dose aspirin, which was use ≥91 days before the index date.
[d] Numbers do not add up to N because 1398 controls were either classed as recent/past users of low-dose aspirin recent/past use, which was use ≥91 days before the index date.
[e] Numbers do not add up to N because 116 cases were classed as recent/past users of low-dose aspirin, which was use 31–365 days before the index date.
[f] Numbers do not add up to N because 305 controls were classed as recent/past users of low-dose aspirin, which was use 31–365 days before the index date.

Mechanisms by which low-dose aspirin reduces the risk of CRC are still under debate, and future clinical studies should be performed incorporating biomarker assessments of its action. These should include evaluation of serum thromboxane A_2 to measure the extent of inhibition of COX-I in platelets, as well as the extent of acetylation of COX-isozymes in platelets and tissue biopsies. It is these types of studies

Table 3
RRs (95% CI) for the association between low-dose aspirin (current use vs. non-use) and CRC/UGIB among the **secondary** CVD prevention population, stratified by bodyweight/BMI.

	Colorectal cancer			Upper gastrointestinal bleeding		
	Cases	Controls	Adjusted RR[a] (95% CI)	Cases	Controls	Adjusted RR[b] (95% CI)
Overall	*N* = 703	*N* = 2559		N = 643	*N* = 1337	
Non-use	108 (15.4)[c]	339 (13.2)[d]	1.0 (reference)	160 (24.9)[e]	316 (23.6)[f]	1.0 (reference)
Current low-dose aspirin use	445 (63.3)[c]	1737 (67.9)[d]	0.76 (0.60–0.98)	415 (64.5)[e]	898 (67.2)[f]	1.16 (0.89–1.50)
Bodyweight (kg)						
≤70 for CRC; ≤90 for UGIB	*N* = 215	*N* = 840		*N* = 493	*N* = 988	
Non-use	44 (20.5)	126 (15.0)	1.0 (reference)	123 (25.0)	246 (24.9)	1.0 (reference)
Current low-dose aspirin use	121 (56.3)	559 (66.5)	0.59 (0.39–0.89)	320 (64.9)	644 (65.2)	1.25 (0.92–1.68)
>70 for CRC; >90 for UGIB	*N* = 457	*N* = 1592		*N* = 110	*N* = 242	
Non-use	56 (12.3)	187 (11.7)	1.0 (reference)	29 (26.4)	47 (19.4)	1.0 (reference)
Current low-dose aspirin use	303 (66.3)	1095 (68.8)	0.88 (0.63–1.23)	68 (61.8)	180 (74.4)	0.90 (0.47–1.74)
BMI (kg/m^2)						
≤28	*N* = 359	*N* = 1431		*N* = 374	*N* = 746	
Non-use	59 (16.4)	201 (14.0)	1.0 (reference)	94 (25.1)	194 (26.0)	1.0 (reference)
Current low-dose aspirin use	213 (59.3)	960 (67.1)	0.71 (0.51–1.00)	239 (63.9)	478 (64.1)	1.20 (0.85–1.70)
>28	*N* = 292	*N* = 921		*N* = 214	*N* = 467	
Non-use	36 (12.3)	96 (10.4)	1.0 (reference)	54 (25.2)	93 (19.9)	1.0 (reference)
Current low-dose aspirin use	199 (68.2)	639 (69.4)	0.81 (0.53–1.24)	141 (65.9)	338 (72.4)	1.05 (0.65–1.69)

Data are n (%) unless otherwise specified.
Note: Non-use was defined as having no prescription for low-dose aspirin ever before the index date for CRC, and no prescription for low-dose aspirin in the year before the index date for UGIB. Current use defined as when supply of the most recent prescription lasted until (or over) the index date or ended within 90 days before the index date in the CRC analysis, or ended within 30 days before the index date in the UGIB analysis.
BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; CVD, cardiovascular disease; GI, gastrointestinal; RR, rate ratio; UGIB, upper gastrointestinal bleeding.
[a] Adjusted by age, sex, calendar year, number of primary care practitioner visits in the previous year, smoking, insulin, non-steroidal anti-inflammatory drugs, body mass index and oral steroids.
[b] Adjusted by age, sex, calendar year, number of primary care visits in the year before the index date, smoking, alcohol consumption, previous UGIB, previous lower GI bleeding, previous GI bleeding unspecified, pancreatic disease, uncomplicated peptic ulcer, polypharmacy, use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, clopidogrel and warfarin.
[c] Numbers do not add up to N because 150 cases were classed as recent/past users of low-dose aspirin, which was use ≥91 days before the index date.
[d] Numbers do not add up to N because 483 controls were either classed as recent/past users of low-dose aspirin recent/past use, which was use ≥91 days before the index date.
[e] Numbers do not add up to N because 68 cases were classed as recent/past users of low-dose aspirin, which was use 31–365 days before the index date.
[f] Numbers do not add up to N because 123 controls were classed as recent/past users of low-dose aspirin, which was use 31–365 days before the index date.

that will help shed light into mechanisms of low-dose aspirin's anti-cancer effects. Also, use of novel marker tools, such as those used to investigate the proteomics and genomics of platelets, have the potential to help identify individuals most likely to respond to low-dose aspirin's beneficial effects in reducing CRC risk and its negative effects on bleeding risk. Ultimately though, further investigation from robustly designed studies in non-trial settings are needed to corroborate/refute our findings, and help guide benefit–risk decisions regarding the use of low-dose aspirin in patients of differing bodyweight.

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Declaration of competing interest

LAGR and LCS work for CEIFE, which has received research funding from Bayer AG for other studies. LAGR has previously received honoraria for serving on advisory boards for Bayer AG. PV and MS-G are employees of Bayer AG.

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