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Non-aspirin non-steroidal anti-inflammatory drugs in prevention of colorectal cancer in people aged 40 or older: A systematic review and meta-analysis

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ABSTRACT

There is still insufficient data about the risk-benefit profile about recommending non-aspirin, non-steroidal anti-inflammatory drugs (NA-NSAIDs) for colorectal cancer (CRC) prevention, especially in people aged 40 years or older. This study specifically addressed the association between regular NA-NSAIDs use and CRC risk in the population aged 40 years or older, performing a comprehensive systematic review and meta-analysis of all published studies on this topic until April 2018, by a search of PubMed, Scopus and Web of science databases and clinical trial registries. Two reviewers independently selected studies based on predefined inclusion criteria and assessed study quality using the Newcastle-Otawa scale. The data was combined with the random effects model. Potential heterogeneity was calculated as Q statistic and I^2 value. A total of 23 studies involving more than 1 million subjects contributed to the analysis. Pooled odds ratio (OR) of NA-NSAIDs effects on CRC risk was 0.74 (0.67-0.81), $I^2 = 75.9\%$, $p < 0.001$. Heterogeneity was explained by a number of variables including the quality of the studies. Significant protective effects of NA-NSAIDs use were found for women (risk reduction of 19%), higher doses (risk reduction of 18%), distal colon cancer (risk reduction of 22%) and white people (risk reduction from 31% to 41%). From the results NA-NSAIDs use appears to be CRC chemopreventive for a specific subgroup of the population.

1. Introduction

Colorectal cancer (CRC) represents an important public health problem. It remains the third most common cancer in men (10.0% of all cancers in men worldwide) and the second most common in women (9.2% of all cancers in women worldwide) [1]. It is one of the leading causes of cancer-related deaths, mainly in industrialized countries, providing an important proportion of cancer deaths in the Western world and the prediction is that over the next 15 years the number of CRC cases is expected to rise by 60 per cent to more than 2.2 million [2].

The presence of precancerous lesions as adenomas is associated with an increased risk of CRC [3]. The improvement in the strategies of secondary prevention with techniques of early diagnosis has dramatically increased the life expectancy of patients with CRC [4]. Nevertheless, it would be even more interesting to focus on reducing the incidence of CRC through primary prevention interventions taking into account that one of the most obvious limitations is the relative infrequency of transformation of small adenomas to cancer [5]; more than 90% of adenomas do not progress to cancer [6]. Achieving this goal, chemoprevention could be a good strategy aimed at preventing the initiation of CRC [7]. The term chemoprevention was created by Michael B. Sporn in 1976, in order to describe the use of pharmacologic or natural agents for the purpose of "prevention of the initiation, promotion and progression of carcinogenesis" [8].

There are numerous experimental, epidemiologic, and clinical studies that have been investigating the chemoprevention of CRC [9–11]. However, a scarce number of these studies are referred to the primary prevention of CRC, and their results are not absolutely consistent. The non-steroidal anti-inflammatory drugs (NSAIDs) have been highlighted as one of the most promising agents for the prevention of CRC [12]. Thus, the relation between NSAIDs and CRC has been the focus of a

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growing body of basic and preclinical studies, indicating NSAIDs preventive effects [9,12–22]. Also, a number of clinical studies have examined the effects of NSAIDs on CRC risk. However its results are controversial ranging from significant protective results (80% risk reduction 95% confidence interval, CI, between 0.08 and 0.50) [23] to no significant protective results (6% risk reduction 95% CI: 0.87–1.02) [24]. These differences might be attributed to the variability of the age in the population studied [25–34]. Although the best age to start NSAIDs for cancer prevention is still unknown, it is suggested that the optimum treatment might start at age 40–50 years, taking into account the apparent delay in the NSAIDs chemopreventive effect (about 10 years) [35].

A number of reviews and meta-analyses have been previously published examining the association between NSAIDs use and CRC [12,36–40]. These studies have been done in specific subpopulations at risk (familial adenomatous polyposis, inflammatory bowel disease or advanced metachronous neoplasia) [37,39,40] or taking into account the aspirin intake in the analysis [38], and its results are very diverse ranging from 0.37 (95% CI: 0.24-0.53) [40] to 0.80 (95% CI 0.73–0.87) [38]. On the other hand, many questions remain unanswered, including identification of the most effective type, dose or duration of an NSAID intervention in adults with age for the optimum treatment.

Therefore, our main objective was to conduct a systematic review to explore the association between non-aspirin non-steroidal anti-inflammatory drugs (NA-NSAIDs) use and risk of CRC, focusing on the specific age group, adults aged 40 years, or older. Moreover, we aimed to update previous meta-analyses by including data from all studies published on this topic until April 2018 and by exploring several sources of heterogeneity that have not yet been analysed.

2. Material and methods

2.1. Design and eligibility criteria

We conducted a systematic review and meta-analysis of epidemiological data on the association between NA-NSAIDs use and CRC risk in the population aged 40 years or older. The PRISMA-P 2015 statements along with Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were followed to report the present study [41]. Predefined eligibility criteria were: (1) original clinical studies; (2) studies that included participants aged 40 years or older, male and/or female; (3) exposure- NA-NSAIDs; (4) case-control, cohort or randomized control trials studies providing information about association measures- odds ratios (OR), relative risks (RR)- and their CI analysing the effects of NA-NSAIDs on CRC risk or providing sufficient data from which it could be calculated; and finally (7) studies written in English, French, Spanish, German or Italian. We have searched for articles published from 1985 until April 2018.

Exclusion criteria were (1) preclinical studies; (2) studies that included participants of all ages; (3) exposure- Aspirin included; (4) studies based solely on mortality/survival rates; (5) secondary prevention studies, where the main aim has not been the investigation of the NA-NSAIDs effect on CRC prevention; and finally (6) reviews, previous meta-analysis, editorials or letters.

2.2. Search strategy and selection of articles

The initial strategy included searching multiple electronic databases including PubMed MEDLINE database (US National Library of Medicine, Bethesda, Maryland, USA), Web of Science (Thomson Reuters), and Scopus (Elsevier).In addition, we searched clinical trial registries (www.clinicaltrials.gov) for additional studies.

The medical subject heading terms and free text keywords search terms included the following: "colorectal cancer", "bowel cancer", "colorectal neoplasms", "colon cancer", "rectal cancer", CRC, "non-steroidal anti-inflammatory drugs", "nonsteroidal anti-inflammatory drugs", "nonsteroidal anti-inflammatory agents", "nonsteroidal anti-inflammatory medicines", NSAIDs, "non-aspirin non-steroidal anti-inflammatory drugs", "non-aspirin nonsteroidal anti-inflammatory drugs", NA-NSAIDs, "anti-inflammatory agents, non-steroidal", chemoprevention, prevention, use, "primary prevention", "clinical trials", "clinical studies", "case-control study", "cohort study", "epidemiological study".

The second stage was a manual search of reference lists from all the relevant original articles, to make sure that eligible articles are not missed out. Finally, in the case of the lack of information concerning our systematic review, we contacted the authors for extra data necessary for our analysis and were provided with answers [24,42–45].

Titles and abstracts of the identified articles were assessed independently by two researchers (TT and SLD-L). Those articles not considered relevant for further checking of the full text were excluded and the reasons were listed. Relevant articles were further read and analysed independently by two researchers, which was followed by data extraction and tabulating a number of variables of interest following a standardized procedure that is going to be explained later in the article.

2.3. Data extraction and quality assessment

The following information was collected from each study: (1) citation data, first author's last name, year of publication, and country of the population studied; (2) study design; (3) range of age of the participants; (4) sample size; (5) the information about the method of collection of the participants' data; (6) methodology adopted for NA-NSAIDs use assessment (7) magnitude of the association: odds ratio (OR) or relative risk (RR) estimators and 95% CI according to exposure level. Where both crude and adjusted ORs were presented, we used the latter; (8) confounding factors: we also extracted and tabulated information about all confounding variables that were adjusted for in each study; (9) the NA-NSAID drug type, where the information is provided; (10) treatment duration, where the information is provided. NA-NSAIDs considered in our analysis were all the agents that were included in our elected studies and that were grouped under NA-NSAIDs type of NSAIDs, excluding aspirin. As reported in the included articles, those agents are: ibuprofen, indomethacin, sulindac, naproxen, diclofenac, piroxicam, flurbiprofen, or other NA-NSAIDs. If results in the studies were given individually for acetaminophen only, it was not included in our analysis, because it does not have the anti-inflammatory or cyclooxygenase (COX)-2 inhibitory effects linked to NSAIDs, and it has not been consistently associated with a decreased CRC risk [23]. Primarily, the results about the use of non-selective NA-NSAIDs have been included. Therefore, where the results in the studies were given individually for COX-2 selective inhibitors, it was not included in our analysis.

To systematically assess the quality of the included articles, we applied the Newcastle Ottawa Scale (NOS) [46]. The NOS contains eight items, categorized into three dimensions including selection, comparability and-depending on the type of study-outcome (cohort studies) or exposure (case-control studies). Each satisfactory answer scores one point. A 'star system' is used for assessment, thus the overall range of points is 0-9. Taking into account that there is no specific reference for categorization, we regarded scores of 0–3 as low, 4–6 as medium and 7–9 as high methodological quality. Finally, after the comparison of the data extraction, the differences and disagreements were resolved by consensus after the discussion.

2.4. Data synthesis and analysis

Studies were grouped on the basis of study design, first a combined analyses was conducted and then two separated meta-analyses: one for cohort studies and one for case-control studies, in order to examine consistency of results across varying study designs with different potential biases. Moreover, the subgroup analyses have been done: pooled

CRC risk estimates considering: overall quality of the studies, methodology adopted for NA-NSAIDs assessment, geographical location of the studies, tumour location, publication years, gender, race, dose and duration of NA-NSAIDs use.

We explored heterogeneity by stratifying studies based on several potential variables that we assumed might have produced the detected heterogeneity (subset analyses). These defined variables included overall quality of the studies, methodology adopted for NA-NSAIDs assessment, geographical location of the studies, tumour location, publication years, gender, race, dose and duration of NA-NSAIDs use. In order to describe the degree of between-study comparability in a group of studies, we have defined the homogeneity among the included studies in each model by examining the percentage of inter-study variation by using the Cochran Q test and I^2 test [47,48]. According to Higgins, we have considered low heterogeneity for I^2 between 25% and 50%, moderate for 50–75% and high for more than 75%. Due to the expected heterogeneity among the included studies, we applied a random-effects model (Der Simonian and Laird) [49] in order to pool the ORs for each analysis. We calculated the natural log and its standard error (SE) for the effect estimates from the CI presented in the articles. Statistical analyses were performed using Stata version 14 statistical software (Stata Corp, College Station, TX, USA).

2.5. Sensitivity analysis and publication bias

Sensitivity analysis was performed to investigate the influences of individual studies on the pooled effect size estimate by omitting one or two studies at a time and recalculating the pooled estimate. Publication bias was assessed using a test for asymmetry of the funnel plot proposed by Egger et al [50] and a p value less than 0.05 was considered statistically significant.

3. Results

3.1. Selection of primary studies

As seen in Fig. 1 (flow chart summing up the selection process of the articles), our search strategy yielded 941 articles after eliminating the duplicates. Based on the abstracts and titles, 873 of them have been excluded, and the reasons have been listed. After reviewing the full text of the 68 potentially eligible articles, 47 have been omitted for various reasons, as presented in the flow chart. Finally, two articles were included for references of hand searched references. In total, twenty three articles have been included in the systematic review and meta-analysis. These include thirteen case-control studies [10,23,24,51–60] and ten cohort studies [42–45,61–66], and no clinical trial study.

3.2. Study characteristics

The main characteristics of the included studies are summarized in Table 1 for cohort studies and Table 2 for case-control studies. The information provided was: the first author, year of publication and study location, study design, sample size, NOS score, main results for regular users and conclusion for each study. Moreover, in the online supplementary Tables S1 and S2 further study information has been provided for cohort and case-control study, respectively, that included: the first author, year of publication, study population, age of the participants, the methodology used for NA-NSAIDs intake assessment, NA-NSAIDs type, control for potential confounding factors and results depending on dose and duration for each study. As regards the NA-NSAIDs type, in eight studies it has not been specified which exact agents the authors considered under this type of drug for their analysis [10,23,44,45,53,54,56,57].

Considering the location and period of the studies, they have come from seven different countries that included USA or Canada (n = 14), Europe (n = 7), Australia (n = 1) and Israel (n = 1), and their publication dates ranged from 1988 to 2017.

Regarding the characteristics of the study population, there have been eight studies that investigated women only [10,42,52,54,56,59,62,64], five studies where the participants were men only [10,42,45,54]. Two articles provided the results separately for women and men, however, after contacting the authors, the results for total NA-NSAIDs use in men and women combined have also been given (with adjustment for sex) [42,43]. In the other two articles there

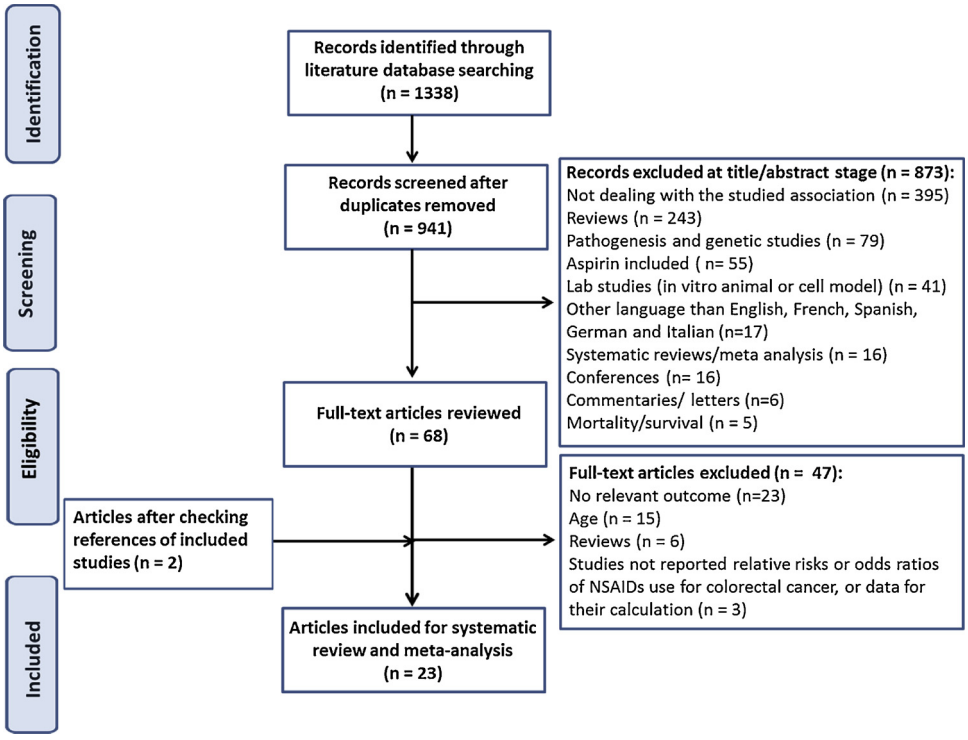

Fig. 1. Flow chart for the selection process of the included articles.

Table 1
Characteristics of cohort studies that assessed the NA-NSAIDs effects on CRC risk (abbreviations not defined in Table are defined below).

First Author/ (Publication Year)/ Study location	Study design/ follow-up median	Sample size	NOS Criteria #			OR (95% CI)/ Conclusion
			S	C	O	
Smalley et al, [61]/ (1999)/ United States	Population-based retrospective cohort study /5 years	104217	+ + +	+ +	+	0.59 (0.45-0.77)/ The duration of use but not daily dose of NA-NSAIDs is an important factor for chemoprevention.
Stürmer et al, [45]/ (2006)/ United States	Prospective cohort study/ 19 years	22071	+ + +	+ +	+ + +	● ○ (0.8- 1.5)/ No association after controlling for time-varying predictors of both NA-NSAID use and CRC.
Mahipal et al, [62]/ (2006)/ United States	Prospective cohort study/ 11 years	27160	+ + +	+ +	+ +	0.63 (0.41-0.96)/ Stronger associations between NA-NSAID use and proximal versus distal CRC.
Friis et al, [44]/ (2009)/ Denmark	Prospective cohort study/ 5 years	51053	+ + +	+ +	+ +	1.44 (0.96-2.16)/ For the NA-NSAIDs use (1–6 pills per week) has not been observed the CRC protective effect.
Ruder et al, [63]/ (2011)/ United States	Prospective cohort study/ 10 years	301240	+ + + +	+ +	+ +	0.82 (0.77-0.87)/ NA-NSAID use was associated with a reduced CRC risk.
Brasky et al, [43]/ (2012)/ United States	Prospective cohort study/ 7 years	64847	+ + +	+ +	+ +	0.71 (0.53-0.95)/ Long-term NA-NSAIDs use was associated with a reduced CRC risk among both sexes.
Brasky et al, [64]/ (2014)/ United States	Prospective cohort study/ 9.7 years	129013	+ + +	+ +	+ +	0.79 (0.53-1.19)/ It has not been confirmed a NA-NSAIDs chemopreventive benefit for CRC.
Shebl et al, [65]/ (2014)/ United States	Prospective cohort study/ 10.1 years	314522	+	+	+ + +	0.68 (0.60-0.76)/ 12 months NA-NSAIDs use had a significantly lower risk of CRC.
Wang et al, [66]/ (2015)/ United States	Prospective cohort study/ 10 years	73458	+	+	+ + +	0.79 (0.63-0.98)/ NA NSAIDs had a generally beneficial role, largely unmodified by other exposures
Yi Park et al, [42]/ (2017)/ United States	Prospective multi-ethnic cohort Study/ 16.1 years	165793	+ + + +	+ +	+ +	0.86 (0.80-0.93)/ the benefit may be strongest for white men and African American, Japanese, and Latino, but not to Native Hawaiian men.

[a]Abbreviations: NA-NSAIDs = non-aspirin non-steroidal anti-inflammatory drugs, CRC = colorectal cancer, OR = odds ratio, CI = confidence interval, S = selection, C = comparability, O = outcome. # NOS appraises quality according to assessing 4 sources of selection bias, 3 sources of information bias as well as adjustment for confounders (comparability between exposed and unexposed cohort). "+" refers to stars given for fulfilling the criteria, more pluses indicate higher quality of the study and less sources of information or selection bias.

were already results for combined genders [10,54]. Additionally, there have been six studies that specifiy their research by race, including African Americans, Whites, Jews, Native Hawaiian, Japanese Americans and Latinos [23,42,54,55,57,63].

Seven articles reported data on ORs for the association between the NA-NSAIDs use and CRC, by tumour location [42,54,55,61–63,66].

The data in the studies was mainly collected by using questionnaires, administered either by personal or telephone interviews [10,23,42,44,45,51,54–57,59,62,63], and the other method of collecting data was by different types of mainly large structured institutional databases and/or medical and pharmacy records [24,52,53,58,60,61].

In view of the comprehension of NA-NSAIDs exposure, frequency and duration, and its evaluation by the authors, quite a difference between the studies has been noted. In the online supplementary table S1 those particularities have been displayed for each study in detail with given ORs. We pooled CRC risk estimates for regular NA-NSAIDs users for our combined analysis. In this regards, as for the regular NA-NSAID users, its definition varies from study to study. Regular NA-NSAID use was defined as taking at least one tablet, twice weekly or more for a month or longer [59], or as using any NA-NSAIDs in the past 5 years for greater than or equal to three days per week, and for greater than or equal to three months [23,54], or as use on more than 60 days per year [45]. Moreover, in several studies (words removed) the information of calculated ORs has been given depending of the level of NA-NSAIDs, therefore, we pooled CRC risk estimates presented for high and low NA-NSAIDs categories. As the definition of low dose and high dose varied from study to study, we used "lower dose" and "higher dose" and they were defined as followed: the minimum and maximum starting doses recommended for treatment of arthritis [61]; as one to nine dispensing prescriptions per year and more than thirty dispensing prescriptions per year [52]; as ≤ 1 pills per week during a period of ten years and more than six pills per week during a period of ten years [62]; as < 2 g and ≥ 2 g [60]; or as two to twelve dispensing prescriptions and twenty five and thirty six prescribing prescriptions, during a period of between one and eight years [24]; as fewer than 2 pills per month and ≥ 1 pill per day [44], and finally, as < 4 days/week or < 4 years and ≥ 4 days/week and ≥ 4 years [43,66].

3.3. Quality assessment of studies

Tables 1 and 2 provide the scores given for each study according to NOS. Regarding to the quality of the studies included in our meta-analysis, in total there were 13 studies of high quality, 70% of cohort studies (n = 7) and 46% of case-control studies (n = 6). Therefore, according to NOS, thirteen studies received from seven to nine points, while five studies received six and the other five received five points.

For case-control studies, a potential source of selection bias was observed in one study where hospital controls were used that were regularly followed in hospital for the same duration as the cases, but for other reasons than CRC [58]. On the other hand, the potential source of information bias in the case-control studies observed was, as in the majority of studies, that the NA-NSAIDs assessment was mainly self-reported (possible memory bias) [10,23,51,54–57,59] or the information was taken just from patient records, medical or pharmacy record databases (possible incomplete information) [24,52,53,58,60]. A similar methodological deficiency was also observed in the included cohort studies: potential sources of selection bias was noticed also regarding the NA-NSAIDs assessment, since it was self-reported [42,43,45,62,63,65,66] or patient records, medical or pharmacy record databases were used [61]. Moreover, the outcome assessment varied significantly (for example, colonoscopy, patient records and databases).

Table 2
Characteristics of case-control studies that assessed the NA-NSAIDs effects on CRC risk (abbreviations not defined in Table are defined below).

First Author/ (Publication Year)/ Study location	Study design	Cases/ Controls	NOS Criteria #			OR (95% CI)/ Conclusion
			S	C	E	
Kune et al, [10]/ (1988)/ Australia	Population based case-control study	713/ 727	+ + +	+ +	+	0.77 (0.6-1.01)/ For the NA-NSAIDs use was observed mild CRC protective effect.
Peleg et al, [58]/ (1994)/ United Kingdom	Hospital based case-control study	97/ 388	+ + +	+	+ +	0.34 (0.15-0.77)/ It was observed a causal relationship between NA-NSAIDs use and CRC prevention.
Reeves et al, [59]/ (1996)/ United Kingdom	Population based case-control study	184/ 293	+ + +	+	+	0.43 (0.2-0.89)/ Regular NA-NSAIDs use was associated with lower CRC risk in women and the type of NA-NSAID used may be important.
Rodríguez et al, [60]/ (2001)/ United Kingdom	Secondary nested case-control analysis from a population-based cohort study	2002/ 477	+ + + +	+ +	+	0.4 (0.2-0.7)/ One-year treatment with NA-NSAIDs would prevent one case of CRC in a population of 1000 persons 70–79 years of age.
Juarranz et al, [51]/ (2002)/ Spain	Population paired case-control study	196/ 228	+ + +	+ +	+	0.30 (0.08-0.98)/ It has been observed the CRC protective effect of NA-NSAIDs.
Meier et al, [52]/ (2002)/ United Kingdom	Population based case-control study	635/ 2434	+ + +	+ +	+	0.8 (0.6-1.2)/ CRC risk was not decreased in subjects with regular exposure to NA-NSAIDs.
Rahme et al, [53]/ (2003)/ Canada	Nested case-control study	179/ 2568	+ +	+ +	+	0.67 (0.24-1.92)/ NA-NSAIDs seemed not to have a protective effect against the development of CRC.
Sansbury et al, [54]/ (2005)/ United States	Population based case-control study	638/ 1048	+ + + +	+ +	+	0.46 (0.29-0.74)/ Inverse associations between regular NA-NSAID use and CRC were stronger for women than menand slightly weaker for occasional versus regular NA-NSAID use.
Sansbury et al, [23]/ (2006)/ United States	Population based case-control study	240/ 326	+ + + +	+ +	+	0.2 (0.08-0.5)/ There has been observed the NA-NSAIDs protective effect on CRC risk.
Vinogradova et al, [24]/ (2007)/ United Kingdom	Nested case-control study	2425/ 9706	+ + + +	+ +	+	0.94 (0.88-1.00)/ Prolonged use of NA-NSAIDs was not associated with a reduced CRC risk.
Kim et al, [55]/ (2008)/ United States	Population based case-control study	1057/ 1057	+ + +	+ +	+ +	0.72 (0.51-1.02)/ It was observed the weak inverse association between NA-NSAIDs and CRC risk. The chemopreventive potential of NA- NSAIDs might differ by population and by tumor characteristics.
Shadman et al, [56]/ (2009)/ United States	Population based case-control study	657/ 1342	+ +	+ +	+	0.70 (0.52-0.94)/ It was confirmed the inverse association between NA-NSAIDs and CRC risk.
Samadder et al, [57]/ (2010)/ Israel	Population based case-control study	1882/ 1900	+ + + +	+ +	+	0.62 (0.53-0.73)/ The use of NA- NSAID was associated with a reduced risk of CRC.

[a]Abbreviations: NA-NSAIDs = non-aspirin non-steroidal anti-inflammatory drugs, CRC = colorectal cancer, OR = odds ratio, CI = confidence interval, S = selection, C = comparability, E = exposure. # NOS appraises quality according to assessing 4 sources of selection bias, 3 sources of information bias as well as adjustment for confounders (comparability between cases and controls). "+" refers to stars given for fulfilling the criteria, more pluses indicate higher quality of the study and less sources of information or selection bias.

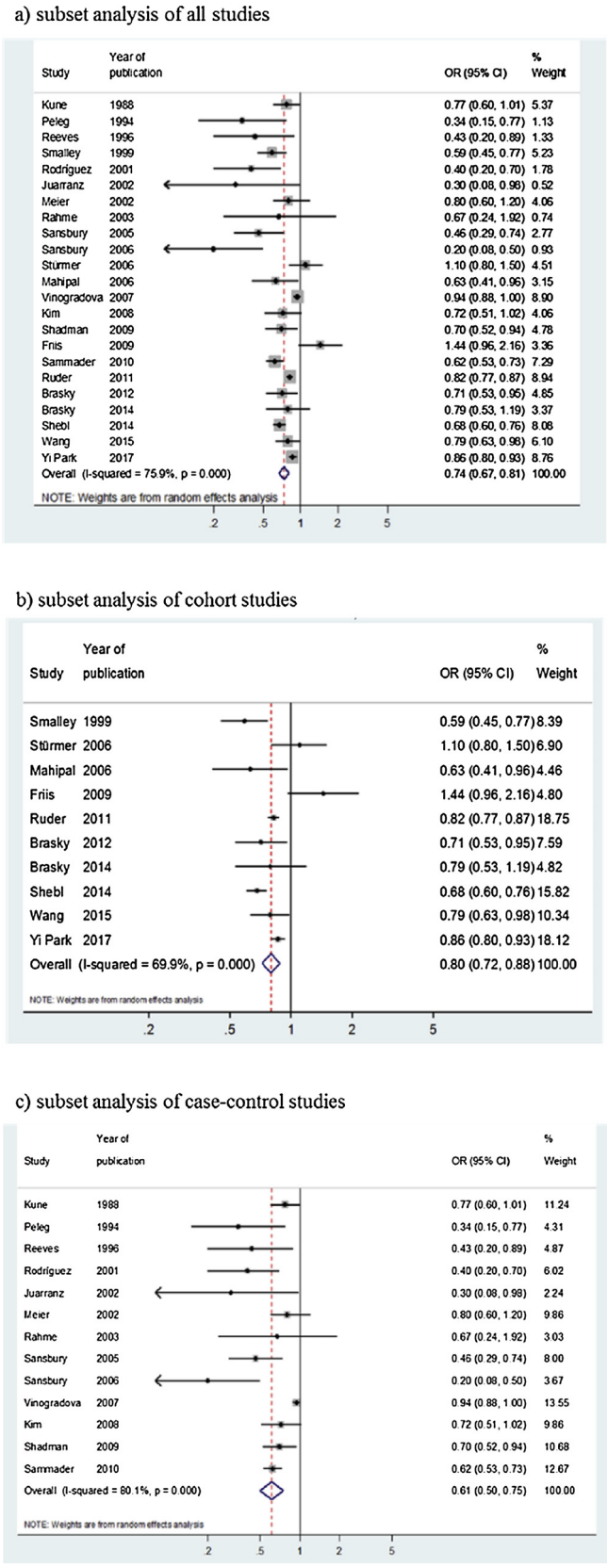

Fig. 2. Forest plot displaying random-effects model of the association between NA-NSAIDs effect and CRC risk among the general population: (a) subset analysis of all studies (b) subset analysis of cohort studies (c) subset analysis of case-control studies.
*Study specific ORs are shown as circles. Sizes of the squares represent the weight given to each study from random-effects meta-analysis.

It was noticed the existence of the inconsistency across studies due to the definitions of NA-NSAIDs dose. For instance, some studies provided specific dose levels. On the other hand, in other studies, the dose effect was reported in terms of frequency of use, like number of pills per day or week or month or prescription refills in a certain time period, thereby combining the effects of dose and duration, the details have been given in the online supplementary Tables S1 and S2. Regarding comparability, between cases and controls, ages were adjusted in almost all studies, except in four studies where they have been considered in the study design (age-matched) [24,51,52,58]. Similar for cohort studies, where either exposed or non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis, in our selection there were age-adjustments in all studies.

3.4. Summary of the results reported by studies included in the meta-analysis

3.4.1. Combined analysis

Fig. 2, which presents a pooled analysis of 23 studies, indicated that compared to non-use, regular use of NA-NSAIDs in the general population aged 40 or older was statistically significantly associated with a reduction in the risk of CRC of 26% (random-effects models: pooled OR = 0.74, 95% CI 0.67-0.81). However, a high degree of heterogeneity was observed among all the studies, $I^2 = 75.9\%$, $p < 0.001$.

3.4.2. Meta-analysis of cohort studies

Ten cohort studies evaluating exposure to NA-NSAIDs and CRC risk were included in the meta-analysis Approximately 1,253,374 patients participated in these studies, with the occurrence of more than 12,000 CRC cases. The regular use of NA-NSAIDs in the general population aged 40 or older was associated with a statistically significant decrease in the CRC risk: OR = 0.80, 95%CI: 0.72-0.88 (Fig. 2). However, I^2 statistic was 69.9%, $p < 0.001$, indicating the existence of heterogeneity between the studies.

3.4.3. Meta-analysis of case-control studies

Thirteen case-control studies evaluating exposure to NA-NSAIDs and CRC risk were included in the meta-analysis. 993,640 patients participated in these studies, with the occurrence of 1095 CRC cases. NA-NSAIDs use was associated with a statistically important reduction in the risk of CRC: OR = 0.61, 95%CI: 0.50-0.75 (Fig. 2). There was substantial heterogeneity between the studies, with I^2 statistic of 80.1%, $p < 0.001$.

3.5. Exploring heterogeneity and sensitivity analysis

Tables 3–5 represent the results of sub stratifying studies by different variables of interest for all studies, for cohort studies and for case-control studies, respectively. Homogeneity was revealed in medium quality studies demonstrating significant CRC risk reduction of approximately 30% in any of the three subgroup analyses. After stratifying by gender no significant result was obtained for protective effect of NA-NSAIDs for men in subset analysis for all studies and for case-control studies (pooled OR was 0.86, 95% CI: 0.70–1.06 and 0.80, 95% CI: 0.58–1.12 respectively). Conversely, this effect was significant for women in subset analysis of cohort studies: pooled OR 0.81, 95% CI: 0.67-0.98. The stratification for dose of NA-NSAIDs also presented homogeneity: protective action of NA-NSAIDs was only statistically significant in the group “higher doses” (pooled OR of the five cohort studies was 0.82, 95% CI: 0.69-0.99) becoming not statistically significant in the group “lower doses” (pooled OR of the three case-control studies was 0.92, 95% CI: 0.83–1.01). Other homogeneity strata were observed for tumour location where significant risk reduction was 22% for distal colon cancer in subset analysis of all studies and for white samples with significant risk reduction from 31% in all studies to 41% in case-control studies. Treatment duration of NA-NSAIDs use for ≥5

Table 3
Pooled estimates, 95% CI, and I^2 and p values for homogeneity between all studies presenting CRC risk estimates for NA-NSAIDs use by various grouping of studies (subset analyses for all studies).

Grouping	Studies included in the analyses	Number of studies	Pooled OR	CI (95%)	Heterogeneity	
					I^2 (%)	*p* value
Overall quality of the studies according to NOS	High quality	13	0.78	0.69- 0.87	80.3	0.001
	Medium quality	10	**0.69**	**0.62-0.76**	**12.8**	0.326
Methodology adopted for assessment of NA-NSAIDs use	Questionnaire (self-assessment)	17	0.74	0.67-0.82	71.0	0.001
	Medical or pharmacy record	6	0.65	0.47-0.89	79.1	0.001
Geographical location of the study *	European countries	7	0.68	0.49-0.96	76.3	0.001
	USA or Canada	14	0.74	0.67-0.81	65.4	0.001
Tumour location**	Proximal colon cancer	5	0.73	0.60-0.87	63.8	0.017
	Distal colon cancer	5	**0.78**	**0.69-0.88**	**0.0**	0.880
	Rectal cancer	6	0.82	0.67-1.01	51.0	0.057
Publication years	1988-2005	9	0.58	0.48-0.72	36.6	0.126
	2006-2017	14	0.79	0.72-0.87	79.5	0.001
Gender	Women	8	0.67	0.53-0.85	54.5	0.031
	Men	4	**0.86**	**0.70-1.06**	**15.9**	0.312
Race**	African Americans	4	0.66	0.36-1.20	80.9	0.001
	Whites	3	**0.69**	**0.55-0.87**	**13.0**	0.328
Dose of NA-NSAIDs	Higher	8	0.70	0.57-0.87	49.8	0.052
	Lower	8	0.90	0.78-1.04	60.8	0.013
Duration- of NA-NSAIDs use**	≥5 years	5	**0.80**	**0.68-0.94**	**0.0**	0.465

Bold figures indicate homogeneity.
NOS, Newcastle-Ottawa Scale; NA-NSAIDs, Non-aspirin non-steroidal anti-inflammatory drugs; CRC, colorectal cancer.
* Two missing studies, Australia and Israel [7,54].
** One study reported ORs for women and men separately [40].

years had a significant risk reduction in subset analysis for all studies with pooled OR 0.80, 95% CI: 0.68-0.94, $I^2 = 0.0\%$, $p < 0.465$ but the significance was lost in the pooled OR of subset for cohort studies (OR 0.83, 95% CI: 0.70–1.00, $I^2 = 0.0\%$, $p < 0.431$).

The online supplementary Table S3 displays results of sensitivity analyses. After deleting studies reporting extreme ORs, a slightly decreased heterogeneity can be observed, but with no important significant change in the pooled estimates. Worth mentioning is a much higher decrease in the heterogeneity, from 80.1% to 43.6%, after deleting one study [24] in the case-control group of studies, but no change in pooled estimates. However, the high degree of heterogeneity noticed between the cohort studies could not be resolved.

3.6. Detection of publication bias

Fig. 3 displays a contour-enhanced funnel plot with corresponding random-effects pooled estimates across all studies and separately for case-control and cohort studies for regular NA-NSAIDs use in the general population aged 40 or older. Asymmetry could be observed indicating the existence of publication bias in all of the studies (Egger's test: bias coefficient = 1.58, SE = 0.516, p = 0.006), in case-control studies (Egger's test: bias coefficient = 2.38, SE = 0.48, p = 0.001) and in cohort studies (Egger's test: bias coefficient = 0.25, SE = 0.98, p = 0.809).

4. Discussion

To our knowledge, we present the first systematic review and meta-analysis focusing on the effects of NA-NSAIDs for CRC chemoprevention in the specific age- population, aged 40 or older. The results of our meta-analysis showed consistent statistically significant risk reduction in CRC when using NA-NSAIDs in medium quality studies. It is also suggested that the protective effects of NA-NSAIDs are only produced for women, using higher doses of NA-NSAIDs, for distal colon cancer and for white people.

In contrast to this study, a previous meta-analysis did not find evidence for the role of NA-NSAIDs or aspirin as chemopreventive for CRC [37]. The differences in the results could be due to the inclusion of

Table 4
Pooled estimates, 95% CI, and I^2 and p values for homogeneity between cohort studies presenting CRC risk estimates for NA-NSAIDs use by various grouping of studies (subset analyses).

Grouping	Studies included in the analyses	Number of studies	Pooled OR	CI (95%)	Heterogeneity	
					I^2 (%)	*p* value
Overall quality of the studies according to NOS	High quality	7	0.86	0.77-0.95	56.2	0.033
	Medium quality	3	**0.69**	**0.61-0.78**	**28.5**	0.247
Methodology adopted for assessment of NA-NSAIDs use	Questionnaire (self-assessment)	9	0.82	0.74-0.90	67.3	0.002
Geographical location of the study	USA or Canada	9	0.78	0.71-0.85	63.8	0.005
Tumour location*	Rectal cancer	5	0.83	0.66-1.05	58.6	0.034
Publication years	2006-2017	9	0.82	0.74-0.90	67.3	0.002
Gender	Women	3	**0.81**	**0.67-0.98**	**0.1**	0.368
	Men	2	0.90	0.60-1.34	69.6	0.070
Dose of NA-NSAIDs	Higher	5	**0.82**	**0.69-0.99**	**0.0**	0.594
	Lower	5	0.90	0.70-1.16	74.6	0.003
Duration- of NA-NSAIDs use*	≥5 years (cohort studies)	4	**0.83**	**0.70-1.00**	**0.0**	0.431

Bold figures indicate homogeneity.
NOS, Newcastle-Ottawa Scale; NA-NSAIDs, Non-aspirin non-steroidal anti-inflammatory drugs; CRC, colorectal cancer.
* One study reported ORs for women and men separately [40].

Table 5
Pooled estimates, 95% CI, and I^2 and p values for homogeneity between case-control studies presenting CRC risk estimates for NA-NSAIDs use by various grouping of studies (subset analyses).

Grouping	Studies included in the analyses	Number of studies	Pooled OR	CI (95%)	Heterogeneity	
					I^2 (%)	p Value
Overall quality of the studies according to NOS	High quality	6	0.58	0.42-0.80	89.3	0.001
	Medium quality	7	**0.68**	**0.58-0.83**	**19.8**	0.279
Methodology adopted for assessment of NA-NSAIDs use	Questionnaire (self-assessment)	8	0.61	0.50-0.73	48	0.062
	Medical or pharmacy record	5	0.66	0.46-0.96	71.2	0.008
Geographical location of the study	European countries	6	0.57	0.39-0.85	75.7	0.001
	USA or Canada	5	0.56	0.41-0.79	54.5	0.066
Publication years	1988-2005	8	0.56	0.43-0.73	43.5	0.088
	2006-2017	5	0.67	0.50-0.90	88.9	0.001
Gender	Women	5	0.57	0.38-0.85	63.7	0.026
	Men	2	**0.80**	**0.58-1.12**	**0.0**	0.936
Race**	African Americans	3	0.48	0.13-1.84	86.8	0.001
	Whites	2	**0.59**	**0.42-0.82**	**0.0**	0.748
Dose of NA-NSAIDs	Higher	3	0.54	0.36-0.80	60.3	0.081
	Lower	3	**0.92**	**0.83-1.01**	**0.9**	0.365

Bold figures indicate homogeneity.
NOS, Newcastle-Ottawa Scale; NA-NSAIDs, Non-aspirin non-steroidal anti-inflammatory drugs; CRC, colorectal cancer.
** One study reported ORs for women and men separately [40].

aspirin and of all age groups of people in the analysis of the compared study what, on the other hand, could be sources of the heterogeneity described by authors. Taking into account the greatest effectiveness presented for NA-NSAIDs compared to aspirin [40] and its apparent delay effect [35], we focused the meta-analysis on the protective effect of NA-NSAIDs at age 40 years or older. This difference between NA-NSAIDs and aspirin with regard to CRC chemoprevention may be explained through their different mechanisms of action. The irreversible inhibition of COX is a unique property of aspirin, while NA-NSAIDs inhibit COX reversibly and may also involve COX-independent mechanisms [67]. This dissimilarity may be consistent with the observations of this study that greater protection is associated with higher NA-NSAIDs dosages. Accumulating evidence for COX-independent molecular targets effects describing, above all, how NSAIDs inhibit tumour growth has recently been reviewed [68].

Exploring sources of heterogeneity, only medium quality studies presented homogeneity with significant protective effects independently of the subgroup analysis. It could be a problem for the possible implication of the results but comparing to pooled OR of high-quality studies, they are along the same line and not with a clear tendency to overestimate risk reduction. Continuing with the analysis of the homogeneous strata, our results suggest that NA-NSAIDs could therefore potentially be considered as chemopreventive agents only in women, reducing the risk in 19%, not presenting significant protection in men. This is an important finding as there are gender disparities in CRC with women obtaining worse outcomes [69]. However, gender-specific pharmacologic responses to NSAIDs have been poorly explored. There are findings suggesting ibuprofen as a compound more active in men than in women, although this does not represent a general assumption for the majority of NSAIDs [70]. Tumour location and race also have an implication on the homogeneity of the results. A significant protective role of the NA-NSAIDs was presented for distal colon cancer and for the white population. Both findings could be explained for the possible underlying interaction of the NA-NSAIDs treatment with genetic causes associated with different risks depending on ethnicity and location [71–73]. However, more research regarding the biological aspects of why NA-NSAIDs might be gender or race specific is needed.

In order to see how much the potential contribution of the NA-NSAIDs is in relation to the other potential chemoprotectives in regards to CRC prevention we searched for the reviews investigating the association between statin use and CRC risk. Regarding this, one recent meta-analysis showed a modest reduction in CRC risk in the general population of all ages, RR = 0.92, 95%CI: 0.87-0.96, with high heterogeneity, I^2 = 75% [74]. Compared to our findings, NA-NSAIDs appeared to have higher CRC chemoprevention than statins. Nevertheless, it is very important to contemplate the adverse effects possible from prescribing these drugs when our data indicated that only higher doses would be effective (18% risk reduction) and they also suggested treatment duration of ≥5 years. Long term NA-NSAIDs use has been hampered due to fatal toxicities, mainly by the increased risk of cardiovascular and gastrointestinal side effects, linked with their mechanism of action involving COX inhibition [75]. The most important negative effects include dyspepsia, peptic ulcer, and bleeding [76] but the risk varies depending upon the clinical context, age, type of medication, and dose. Elderly patients are especially at higher risk of NSAID-related adverse events [77]. Moreover, all NA-NSAIDs (including celecoxib and topical NSAIDs) currently on the market in the United States have ''black box" warnings outlining the risk of cardiovascular and gastrointestinal events [78]. Despite this fact, just two articles (cohort studies) included in our meta-analysis considered the appearance of adverse effects of NA-NSAIDs in their analysis [45,61], from which just one provided that data in the article [45]. Regarding this, the first step would be to unify what is considered high/low doses since, as it has been described in the results, the definition of doses varied significantly between studies. Consequently, the long-term side effects of the minimum effective dose of different NSAIDs in possible population targets need to be considered. On the other hand, combinational intervention may be another option, allowing a decreased NA-NSAIDs dose that could lower the incidence of the adverse effects while preserving the desired effect. Therefore, it is necessary that clinical recommendations balance the risks and benefits of NA-NSAIDs use for CRC prevention.

There have been a few limitations in this study that should be noted while interpreting our results. First, only the observational studies have been included in this analysis since we have not found any randomized controlled trials matching our search criteria. The observational studies included are mainly large, representative, multi ethnic, but are subject to biases and confounding. Publication bias is another possible limitation since the studies that are published are more likely to report statistically significant findings. Moreover, asymmetry of the funnel plot, either visually interpreted or statistically tested, does not accurately predict publication bias [79]. Nevertheless, an effort to reduce the possibility of publication bias has been attempted by conducting a comprehensive search of the literature. The next barrier for our study would be our depending on a relatively small number of studies and

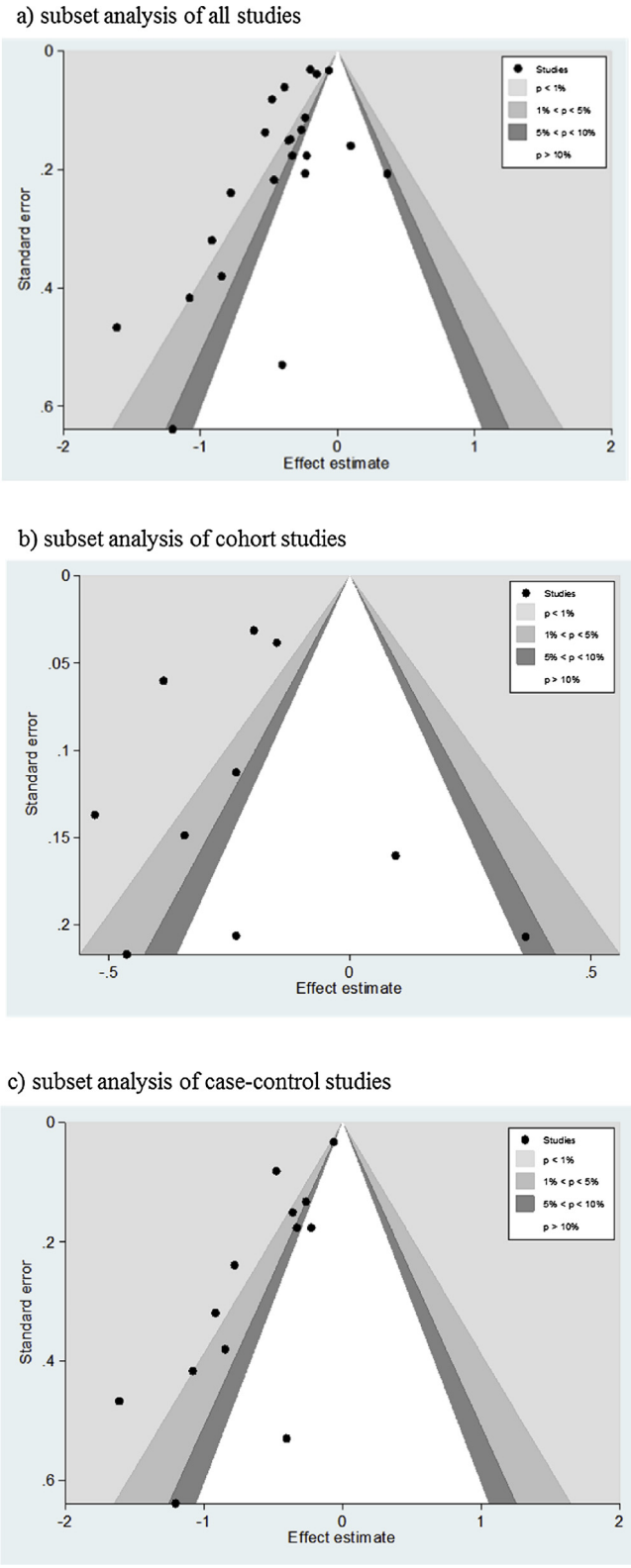

Fig. 3. Contour enhanced funnel plot for the natural logarithm of CRC risk estimates for regular NA-NSAIDs use in the general population versus their standard errors: (a) subset analysis of all studies (b) subset analysis of cohort studies (c) subset analysis of case-control studies.

therefore the difficulty to compare our results with other meta-analyses as specific as ours, due to our specific inclusion criteria. Fourth, the studies differed in terms of definitions of drug exposure and used NA-NSAIDs type, as well as CRC subtypes which could explain the persistence of heterogeneity of some data. As for drug exposure, the dose categorizations used in each study, if provided, was very varied. In order to homogenize this data as much as possible, we made two groups: patient group with "higher doses" and patient group with "lower doses". Considering the frequency of NA-NSAIDs use, we have considered mainly cases that lasted about one year, and regular use, since the majority of studies have provided us with this data. However, our definition of "regular use" is based on availability of data and it varied a lot among studies, which could have led to non-significant results.

The strength of the present systematic review and meta-analysis is in the inclusion of 23 studies, involving more than 1 million subjects, and more than 13,000 CRC cases. It also included more recent studies than previous meta-analyses and explored different sources of heterogeneity. Moreover, our focus was on the specific age group, adults aged 40 years, or older. Considering NSAIDs, there is an important difference between NA-NSAIDs and aspirin due to their different mechanisms of action [80] taking this into account in order to specify our research on one subgroup of drugs, our focus therefore has been based on the NA-NSAIDs.

5. Conclusion

The available data suggests the use of higher doses of NA-NSAIDs in the general population aged 40 or older reduces CRC risk, specifically for women, for distal colon cancer and for the white population. The lowest effective NA-NSAID dose, treatment duration, and effects on survival have not yet been defined. It is clear that we need more clinical studies about this topic dealing with specific population ages, with uniformed pattern considering the type, dose and treatment duration, and not forgetting their potential known adverse effects. The use of these drugs would not replace primary prevention measures for CRC such as healthy lifestyles but the analysis of different sources of heterogeneity with this meta-analysis goes towards a possible chemoprevention inclusion in the approach of specific population types.

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Conflict of interest

The authors declare no conflicts of interest.

Author Contributions

Tanja Tomić: study design, statistical analysis, data interpretation, manuscript preparation, manuscript edition, manuscript review.

Santiago Domínguez-López: study design, data collection, data interpretation, manuscript edition, manuscript review.

Rocío Barrios-Rodríguez: study design, statistical analysis, data interpretation, manuscript preparation, manuscript edition, manuscript review.

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Appendix A. Supplementary data

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