



Review

Association between Dietary Fibre Intake and Colorectal Adenoma: A Systematic Review and Meta-Analysis

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Abstract: PubMed/Medline, Excerpta Medica dataBASE (EMBASE) and Scopus were searched in January 2021 in order to retrieve evidence assessing the association between dietary fibre intake and the risk of colorectal adenoma in adults. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for the reporting of results. Only primary observational studies were included. Publication bias was estimated through the Egger's test and the visual inspection of the funnel plot. Heterogeneity between studies was calculated with I^2 statistics. The search strategy identified 683 papers, 21 of which were included in our meta-analysis. Having evaluated a total of 157,725 subjects, the results suggest a protective effect of dietary fibre intake against colorectal adenoma. Effect Size (ES) was [0.71 (95% CI = 0.68–0.75), $p = 0.000$]. Moderate statistical heterogeneity ($\text{Chi}^2 = 61.68$, $\text{df} = 23$, $I^2 = 62.71\%$, $p = 0.000$) was found. Findings show a statistically significant ($p = 0.000$) and robust association between a higher intake of dietary fibre and a lower risk of colorectal adenoma, considering both the prevalent and incident risk. Moreover, the meta-regression analysis showed a borderline significant negative linear correlation between the amount of dietary fibre intake and colorectal adenoma. Lastly, we performed a subgroup analysis by sex, showing a higher protective effect for men.

Keywords: diet; fibre; colorectal; adenoma; systematic review



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1. Introduction

Colorectal cancer is the third most common cancer among men (after lung and prostate cancer) and the second among women (after breast cancer) worldwide, with approximately 2 new million cases (among both men and women) in 2020 [1]. Colorectal cancer is one of the few cancers for which a population screening program is in place practically all over the world [2]. There are several important reasons why colorectal cancer is suitable for population screening, including cancer progression from a preneoplastic (and subclinical) lesion (adenoma), the long lag time before invasive and malignant transformation, an easily detectable and treatable preneoplastic lesion, and the direct association between the stage of the disease and mortality [3]. It should be noted that colorectal adenoma is a proliferative dysplastic epithelial lesion that is harmful in most cases. It can have a malignant evolution based on the size, number, histology (grade of dysplasia) and duration in time [4]. Moreover, some other unmodifiable and modifiable factors might play an important role, such as age, ethnicity and genetics. Smoking, body mass index and diet seem to be the most important modifiable risk factors [5]. A high-fibre diet provide several

plausible biological mechanisms that potentially provide a beneficial effect. Fibre might play a protective role through several mechanisms, including physical mechanisms, anti-inflammatory properties and prebiotic effects. Results from two extensive and recent meta-analyses confirm the protective role of fibre on colon [6] and rectal cancer risk [7]. However, despite the fact that adenoma as a preneoplastic lesion is recognized as a precursor of colorectal cancer, previous studies failed to univocally assess the role of dietary fibre intake and the risk of colorectal adenoma. These inconclusive results are probably due to a small population size, differences in the population's characteristics, the adenoma site, the follow-up duration or the dose of fibre intake.

In this perspective, we performed the current systematic review with meta-analysis in order to collect and retrieve all relevant studies assessing the association between dietary fibre intake and the risk of colorectal adenoma. Moreover, we aimed to identify the amount of dietary fibre useful to prevent colorectal adenoma and also to estimate the risk among women and men and to evaluate the different risks of incident and prevalent colorectal adenoma.

2. Materials and Methods

The current systematic review with meta-analysis was accomplished following the methods recommended by the Cochrane Collaboration [8] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [9]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] guidelines [11] to report the process and results. The review protocol was registered, in advance, on the International Prospective Register of Systematic Reviews (PROSPERO) (ID number: CRD42021230276), funded by the National Institute of Health Research (<https://www.crd.york.ac.uk/prospero/>, accessed on 8 January 2021). This systematic review was developed to answer the following research question: "Is dietary fibre intake associated with a lower (or higher) risk of colorectal adenoma?"

2.1. Search Strategy and Data Sources

Searches were independently carried out on the PubMed/Medline, Excerpta Medica dataBASE (EMBASE) and Scopus databases by two of the authors (VG and DN) in order to identify eligible studies. The structured computer literature search was built on a pre-determined combination of keywords, according to the type of database consulted. The search strategy was developed based on three domains: dietary fibre intake, colorectal adenoma and study design. Selected keywords were opportunely combined using Boolean operators. Moreover, we also built our search strategy using Medical Subject Headings (MeSH), text and title/abstract words. The strategy was first developed in PubMed/MEDLINE and then adapted for use in the other databases. The full search strategy is reported in Supplementary Table S1. The literature search on all the databases was carried out on the same day (10 January 2021) and included articles from inception (no time filter was used). Reference lists were also screened in order to identify additional relevant articles and experts in the field were consulted. The corresponding authors of included articles were contacted in case of missing data.

2.2. Inclusion/Exclusion Criteria

As recommended by the Cochrane Collaboration [12], a detailed description of inclusion/exclusion criteria, based on a Population, Exposure, Comparison, Outcomes and Study (PECOS) design [13], is reported in Supplementary Table S2. In brief, only those articles assessing the association between dietary fibre intake in healthy adults (both men and women) and the risk of colorectal adenoma were considered eligible. On the contrary, those studies that were conducted to assess the different outcomes or different fibre intake (for instance, supplementation) among subjects with comorbidities were excluded. With reference to the study design, only observational studies (cohort, case-control, cross-sectional or ecological studies) were considered for eligibility. Outcomes should be reported as risks

[e.g., Odds Ratio (OR), Risk Ratio (RR) or Hazard Ratio (HR)], with their 95% Confidence Interval (CI 95%), or as a mean. Lastly, only articles published in English and with full-text available were considered.

2.3. Data Extraction

As had been done in previous studies [14,15], a two-step double-blind selection process was adopted by two researchers (DN and VG) to identify relevant articles. The selection process was firstly based on title and abstract screening; therefore the full-text was only obtained for potentially relevant studies. Data screening and data extraction was independently performed by two researchers (DN and CF) using a spreadsheet created in Microsoft Excel[®] for Windows. The spreadsheet was pre-piloted on 5 randomly selected papers. This allowed us to increase methodological concordance. Selected articles and extracted data were compared, with any discrepancies being resolved through discussion between the two researchers (DN and CF). If the disagreement persisted, a third researcher was consulted (VG). Both qualitative and quantitative data were extracted. Recorded quantitative data included sample size, study duration (expressed in years), amount of fibre intake and outcome (expressed as risk). Any adjusted estimated risks available in primary studies, were used preferentially. Qualitative data included: name of the first author, year of publication, country where the study was conducted, subjects' characteristics, outcome measured, and tools used to assess dietary information and outcome diagnosis. Moreover, the presence of funding supporting the original research studies and information on conflict of interests (CoI) were also recorded.

2.4. Critical Appraisal

Two researchers (CF and DN) independently performed the critical appraisal, using the Newcastle-Ottawa Scale (NOS) [16] for observational studies. However, since the NOS did not provide a checklist for cross-sectional studies, we used a modified version [17] adapted to perform a quality assessment of cross-sectional studies. Using these criteria and based on a standard cut-off, we identified high-quality studies by means of the NOS if this was equal to or higher than 7 points.

2.5. Statistical Analysis

The effect size (ES) was calculated based on the odds ratio (OR), risk ratio (RR) and mean and sample size provided per study. It was estimated by OR and reported with its 95% CI. If papers presented a number of events (cases) among those exposed and not exposed and the mean value for dietary fibre intake for each group, the OR and CIs were computed from these data and included in the meta-analysis. The comparison was performed between subjects exposed to the highest intake of dietary fibre and subjects exposed to the lowest (or none) intake of dietary fibre consumption. Since the dietary fibre intake collected in each study was homogeneously reported, it allowed us to perform a meta-regression analysis. We applied a fixed and random model. A fixed model is used when the universe of studies is judged a priori to be sufficiently similar to those in the study sample, or when the number of included studies is small. The assumption behind the random effect model is that inferences are not limited to studies represented in the sample. In other words, it is presumed that the universe of studies contains studies with differences in their characteristics, and generalizations are based on studies that differ from those in the study sample. In this perspective, the random effect model is recommended if heterogeneity estimated values are considered high. Heterogeneity among included studies was evaluated through Chi^2 and I^2 tests. Heterogeneity was considered to be high when I^2 values $> 75\%$, moderate for I^2 values ranging between 50% and 75% , low for values ranging between 25% and 50% , and no heterogeneity for values below 25% . The graphical evaluation of the Funnel plot and the Egger's regression asymmetry test were used to estimate potential publication bias; statistical significance was set at $p < 0.10$ [18]. If any publication bias was detected, a trim and fill method, to search for missing studies to the

right of overall, was used in order to adjust for publication bias [19]. The meta-analysis was performed using the Prometa3[®] (Internovi, Cesena, Italy) software.

2.6. Sub-Group and Sensitivity Analysis

In order to exclude a potential overlapping effect due to the inclusion of studies referring to the same cohort of patients, a sensitivity analysis was run which only considered the study with the highest quality score (QS) or with the larger sample size in case of equal QS. We also performed the meta-analysis by excluding studies with computed OR. Furthermore, sensitivity analyses were conducted which only included studies with a follow-up (FU) equal to or higher than 9 years, with validated tools to assess dietary fibre intake, the type of diagnosis and a QS higher than 7. In addition, in order to corroborate the obtained results, sub-group analyses were performed based on the adenoma site, study design (case-control and cross-sectional vs. cohort studies) and sex.

2.7. Cumulative Analysis

A cumulative analysis is a sequential meta-analysis, intended to evaluate how adding one study at a time modifies the ES. We performed three cumulative analyses: the first one adding studies chronologically (starting from the first published analysis to the most recent publication), the second one based on the growing sample size (from the smallest to the biggest), and the third based on the ascending dose of dietary fibre intake (from the lowest to the highest). These types of analyses improve the potential consistency of results [20].

3. Results

3.1. Literature Search

We identified a total of 683 articles as follows: 424 in PubMed/Medline, 204 in the Scopus and 55 in EMBASE. After the removal of duplicates, a total of 569 original articles were preliminarily screened by title and abstract. From these, 549 were excluded because they were unrelated topics ($n = 443$), reviews ($n = 55$), not original studies (erratum, conference paper, commentary, letter and book chapters $n = 21$), in a different language ($n = 19$), in vitro studies ($n = 8$) and in vivo studies ($n = 4$). Overall, 29 studies were eligible, but 8 studies were excluded because of the reasons reported in Supplementary Table S2 [21–28]. Figure 1 depicts the flow diagram reporting the selection process. At the end of the screening process, 21 articles were included in the quantitative analysis [29–49]; however, because four papers reported separate data based on the adenoma site (colorectal, colon and rectal) [29,37,44,45], one paper reported the results for both incident and recurrent adenoma [37], another used a different control group (general population and hospital-based patients) [29], and two papers reported data stratified by sex [36,46], these were considered to be independent studies. Lastly, five studies [30,35,36,45,49] did not report the association between dietary fibre intake and colorectal adenoma as a risk, but as a number of events among those with higher and lower intake. Thus, ORs were computed for this reason. We considered them in the overall pooled estimate, but removed them in the sensitivity analysis.

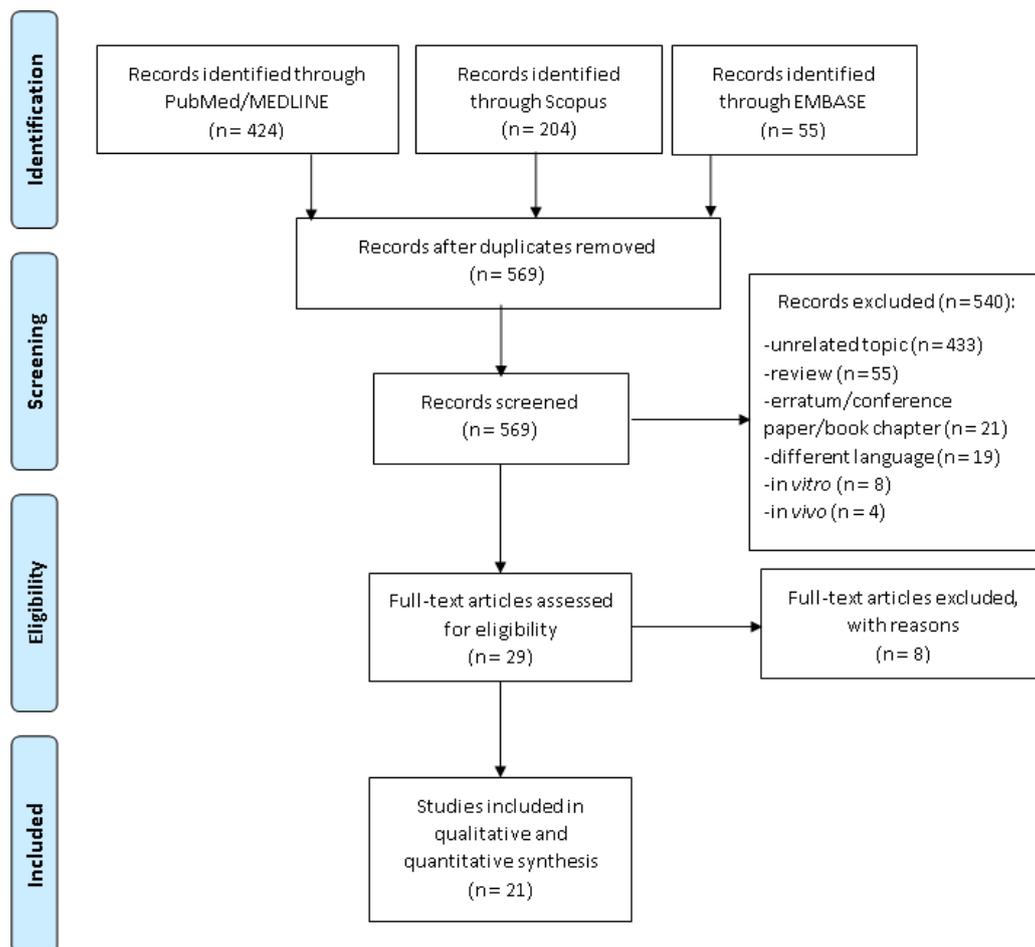


Figure 1. Flow diagram of the studies' selection process.

3.2. Characteristics of Included Studies

Tables 1 and 2 show the characteristics of the studies included in the meta-analysis in alphabetical order. Supplementary Table S3 shows the quality evaluation. The first included study was published in 1986 [36], whereas the most recent was published in 2020 [30], however, the period with the highest number of publications on the topic were the decades 1990–2000 and 2010–2020. Almost all the included studies were conducted in the United States of America (USA), but one was conducted in Israel [39] and two in Europe (Germany [29] and Norway [36], respectively). As regards the study design, 13 studies were case-control [29–31,34,36,38–42,44,46,49], seven were cohort studies [32,33,35,37,43,45,48], and one was a cross-sectional study [47]. Only considering cohort studies, the follow-up (FU) period ranged between 2 years to 26 years [43]. The sample size ranged between 100 [36] and 37,562 participants [44], with a population age ranging from 18 to 79 years. More than half of the included studies ($n = 13$) used a validated self-administered Food Frequency Questionnaire (FFQ) to assess dietary fibre intake [30–35,37,41–45,49], one study used a diet history questionnaire [47], and another used the food diary [36]. Furthermore, five studies performed an interview [29,38–40,46], however three studies did not provide information on validation [40,44,48]. When pooling data in meta-analysis, higher dietary fibre intake was associated with a lower risk of colorectal adenoma [in the fixed effect model, pooled ES = 0.71 (95% CI = 0.68–0.75), $p = 0.000$; in the random effect model, pooled ES = 0.73 (95% CI = 0.66–0.81), $p = 0.000$; based on 157,725 participants, with moderate statistical heterogeneity ($\text{Chi}^2 = 61.68$, $\text{df} = 23$, $I^2 = 62.71\%$, $p = 0.000$)] (Figure 2a) and potential publication bias (Figure 2b), at which trim and fill method was applied (Table 3).

Table 1. Qualitative characteristics of included studies, reported in alphabetical order.

| Author, Year [Ref] | Country | Study Period | Study Design | Population Characteristics | Tool | Diagnostic Assessment | Funds | Conflicts of Interest |
|-----------------------------------|---------|-------------------------------------|---------------|---|---|-----------------------------|-------|-----------------------|
| Breuer-Katschinski, 2001 [29] | Germany | 2 years | Case-controls | Patients from five major hospitals in Essen; controls were selected from among hospital patients and stratified by sex | Personal interview not validated | Endoscopy and histology | yes | n.a. |
| Breuer-Katschinski, 2001 (a) [29] | Germany | 2 years | Case-controls | Patients from five major hospitals in Essen; controls were selected from among the general population and stratified by sex | Personal interview not validated | Endoscopy and histology | yes | n.a. |
| Byrd, 2020 [30] | USA | 1991–1994 1994–1997 1997–2002 | Case-controls | MAP I and MAP II | Validated self-administered 61-FFQs and 98-FFQ | Colonoscopy and histology | yes | yes |
| Fu, 2014 [31] | USA | 7 years | Case-controls | TCPs | Validated self-administered 108-FFQ | Colonoscopy and histology | yes | no |
| Fuchs, 1999 [32] | USA | 16 years | Cohort | Without history of cancer, IBD, or familial polyposis | Validated self-administered 136-FFQ | Medical records | n.a. | n.a. |
| Giovannucci, 1992 [33] | USA | 2 years | Cohort | HPF | Validated self-administered 131-FFQ | Endoscopy and histology | n.a. | n.a. |
| Haile, 1997 [34] | USA | 2 years | Case-controls | Screening sigmoidoscopy subjects from 2 Southern California Kaiser Permanente Medical Centers | Validated 126-item semi-quantitative FFQ | Sigmoidoscopy and histology | yes | n.a. |
| Haslam, 2017 [35] | USA | 7 years | Cohort | PLCO | Validated questionnaire 137-FFQ | Sigmoidoscopy and histology | no | yes |
| Hoff, 1986 [36] | Norway | | Case-controls | Endoscopic population screening study | Food diary for 5 consecutive days | Rectosigmoidoscopy | n.a. | n.a. |
| Kunzmann, 2015 [37] | USA | 13 years | Cohort | PLCO outcome stratified by adenoma site (incident) | Validated self-administered 137-FFQ | Sigmoidoscopy and histology | n.a. | no |
| Kunzmann, 2015 (a) [37] | USA | 13 years | Cohort | PLCO outcome stratified by adenoma site (recurrent) | Validated self-administered 137-FFQ | Sigmoidoscopy and histology | n.a. | no |
| Little, 1993 [38] | UK | 7 years | Case-controls | Subjects recruited in a colorectal cancer screening trial in Nottingham | Interview conducted at the subject's home by specially trained interviewers | Colonoscopy and histology | yes | n.a. |

Table 1. Cont.

| Author, Year [Ref] | Country | Study Period | Study Design | Population Characteristics | Tool | Diagnostic Assessment | Funds | Conflicts of Interest |
|-----------------------|---------|-------------------------------------|----------------------|--|--|--|-------|-----------------------|
| Lubin, 1997 [39] | Israel | 3 years | Paired Case-controls | Subjects identified in the SPGD at the Tel Aviv Medical Center | 180-item questionnaire (interview) | Endoscopy and histology | n.a. | n.a. |
| Martinez, 1996 [40] | USA | 2 years | Case-controls | Population without history of colorectal polyps and familial polyposis | 138-FFQ (interview) validation n.a. | Sigmoidoscopy or colonoscopy and histology | n.a. | n.a. |
| Mathew, 2004 [41] | USA | 2 years | Case-controls | Subjects with new or recurrent adenomas in a study conducted at the NNMC | Validated self-administered 100-item | Sigmoidoscopy or colonoscopy and histology | n.a. | n.a. |
| Mujtaba, 2018 [42] | USA | 1991–1994 1994–1997 1997–2002 | Case-controls | CPRU MAP I MAP II | Validated self-administered 61-FFQs | Colonoscopy and histology | n.a. | no |
| Nimptsch, 2014 [43] | USA | 9 years | Cohort | NHS II | Validated self-administered 131-FFQ | Medical record | yes | n.a. |
| Peters, 2003 [44] | USA | 7 years | Case-controls | PLCO | Self-administered 137-FFQ (adaptation from previous validated FFQ) | Endoscopy and histology | n.a. | n.a. |
| Platz, 1997 [45] | USA | 8 years | Cohort | HPF | Validated self-administered 131-FFQ | Sigmoidoscopy or colonoscopy and histology | yes | n.a. |
| Sandler, 1993 [46] | USA | 2 years | Case-controls | Subjects who underwent colonoscopy at the University of North Carolina Hospitals | Validated quantitative food frequency questionnaire (interview) | Sigmoidoscopy or colonoscopy and histology | n.a. | n.a. |
| Shaw, 2017 [47] | USA | 7 years | Cross-sectional | FMCCSC | DHQ I or II | Colonoscopy and histology | yes | no |
| Tantamango, 2011 [48] | USA | 26 years | Cohort | AHS-1 and AHS-2 | Self-administered 55-FFQ validation n.a. | Self-reported | yes | no |
| Witte, 1996 [49] | USA | 2 years | Paired Case-controls | Subjects free of invasive cancer, IBD and familial polyposis | Validated self-administered 126-FFQ | Sigmoidoscopy and histology | n.a. | n.a. |

n.a.: not available; no: declared, but conflicts of interest absent; yes: declared and present. AHS: Adventist Health Study; CPRU: Cancer Prevention Research Unit Study; DHQ: Diet History Questionnaire; FFQ: food frequency questionnaire; FMCCSC: Forzani & MacPhail Colon Cancer Screening Centre; IBD: Inflammatory bowel disease; HPF: Health Professionals Follow-up Study; MAP: Markers of Adenomatous Polyps; NHS: Nurses' Health Study; NNMC: National Navy Medical Center; NSAID: Nonsteroidal anti-inflammatory drug; PA: Physical Activity; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SAF: Saturated fatty acids; SPGD: Screening Program of the Gastroenterology Department; TCP: Tennessee Colorectal Polyp Study; TEn: Total Energy intake; UK: United Kingdom; USA: United States of America.

Table 2. Quantitative characteristics of included studies, reported in alphabetical order.

| Author, Year [Ref] (Number of Stratified Analysis) | Total Sample ^ | Sex | Age (In Years) Mean ± SD | Dietary Fibre Intake Mean ± SD | Outcome | n. Subjects at the Highest Fibre Intake | Highest Dietary Fibre Intake | Effect Size (95% CI) <i>p</i> | Adjustment |
|--|-----------------------|-----------------------------|-------------------------------------|--|-----------------------|---|---------------------------------|--|--|
| Breuer-Katschinski, 2001 [29] (1) | Ca: 182 Co I: 178 | Ca: M = 94 Co I: M = 88 | Ca: 63.8 ± 9.9 Co I: 63.4 ± 9.8 | Ca: 23.01 ± 7.68 g/d Co: 24.27 ± 8.09 g/d | | | | RR 0.47 (0.23–0.99) <i>p</i> < 0.05 | |
| Breuer-Katschinski, 2001 [29] (2) | Ca: 94 Co I: 88 | Ca: M = 94 Co I: M = 88 | Ca: 63.8 ± 9.9 Co I: 63.4 ± 9.8 | n.a. | colorectal adenoma | n.a. | n.a. | RR 0.16 (0.05–0.57) <i>p</i> < 0.05 | TEn, BMI, and social class |
| Breuer-Katschinski, 2001 [29] (3) | Ca: 88 Co I: 90 | Ca: F = 88 Co I: F = 90 | Ca: 63.8 ± 9.9 Co I: 63.4 ± 9.8 | n.a. | | | | RR 0.66 (0.23–1.86) <i>p</i> = n.s. | |
| Breuer-Katschinski, 2001 (a) [29] (4) | Ca: 182 Co II: 182 | Ca: M = 94 Co II: M = 92 | Ca: 63.8 ± 9.9 Co II: 64.2 ± 9.9 | Ca: 23.01 ± 7.68 g/d Co: 23.60 ± 6.75 g/d | | | | RR 0.87 (0.33–2.33) <i>p</i> = n.s. | |
| Breuer-Katschinski, 2001 (a) [29] (5) | Ca: 94 Co II: 92 | Ca: M = 94 Co II: M = 92 | Ca: 63.8 ± 9.9 Co II: 64.2 ± 9.9 | n.a. | colorectal adenoma | n.a. | n.a. | RR 0.38 (0.14–1.05) <i>p</i> = n.s. | TEn, BMI, and social class |
| Breuer-Katschinski, 2001 (a) [29] (6) | Ca: 88 Co II: 90 | Ca: F = 88 Co II: F = 90 | Ca: 63.8 ± 9.9 Co II: 64.2 ± 9.9 | n.a. | | | | RR 0.86 (0.29–2.29) <i>p</i> = n.s. | |
| Byrd, 2020 [30] | Ca: 765 Co: 1986 | Ca: M = 462 Co: M = 846 | Ca: 58.2 ± 9.2 Co: 54.5 ± 10.9 | Ca: 10.9 ± 3.7 g/1000 kcal/d Co: 11.3 ± 3.9 g/1000 kcal/d | colorectal adenoma | n.a. | n.a. | OR 0.82 (0.70–0.95) <i>p</i> = 0.01 | none |
| Fu, 2014 [31] | Ca: 1315 Co: 3184 | Ca: M = 913 Co: M = 1732 | Ca: 59.2 Co: 57.5 | Ca: 17.0 ± 1.0 g/d Co: 17.3 ± 1.0 g/d | colorectal adenoma | Ca: 278 | 24.8 g/d | OR 0.85 (0.68–1.06) <i>p</i> = 0.06 | Age, sex, sites, education, smoking, PA, food supplement, dietary calcium and folate intake, and TEn |
| Fuchs, 1999 [32] | 27,530 Ca: 787 | only F | 49 | n.a. | colorectal adenoma | Ca: 212 | 24.9 ± 5.5 g/d | RR: 0.91 (0.71–1.16) <i>p</i> = 0.36 | Age, smoking, BMI, PA, aspirin use, family history of CRC, history of colorectal adenoma, red meat intake, alcohol, TEn, folate, methionine, calcium, vitamin D intake |
| Giovannucci, 1992 [33] | 7284 Ca: 170 | only M | 40–75 (range) | n.a. | colorectal adenoma | n.a. | ≥28.3 g/d | RR: 0.36 (0.22–0.60) <i>p</i> < 0.0001 | Age, TEn, and family history of CRC |
| Haile, 1997 [34] | Ca: 488 Co: 488 | Ca: M = 325 Co: M = 325 | Ca: 61.9 ± 6.7 Co: 61.8 ± 6.8 | Ca: 19.1 g/d Co: 20.1 g/d | colorectal adenoma | n.a. | 27.6 g/d | OR: 0.52 (0.33–0.80) <i>p</i> < 0.01 | BMI, TEn, PA, smoking and ethnicity |
| Haslam, 2017 [35] | 24,251 Ca: 4063 | Ca: M = 1418 | 55–74 (range) | n.a. | colorectal adenoma | Ca: 796 | 26.8 ± 10.8 g/d | OR 0.57 (0.52–0.63) <i>p</i> < 0.0001 | none |

Table 2. Cont.

| Author, Year [Ref] (Number of Stratified Analysis) | Total Sample ^ | Sex | Age (In Years) Mean ± SD | Dietary Fibre Intake Mean ± SD | Outcome | n. Subjects at the Highest Fibre Intake | Highest Dietary Fibre Intake | Effect Size (95% CI) <i>p</i> | Adjustment |
|--|---------------------|-----------------------------|-----------------------------------|--|------------------------------------|---|---|---|--|
| Hoff, 1986 [36] (1) | Ca: 23 Co: 77 | Ca: M: 16 Co: M = 40 | 50–59 (range) | Ca: 18.3 ± 1.2 M Co: 21.2 ± 0.9 M | rectal adenoma | n.a. | n.a. | OR: 0.36 (0.12–1.04) <i>p</i> = 0.06 | none |
| Hoff, 1986 [36] (2) | | Ca: F: 7 Co: F = 37 | | Ca: 18.9 ± 2.0 F Co: 21.9 ± 0.9 F | | | | OR: 0.34 (0.08–1.51) <i>p</i> = 0.16 | |
| Kunzmann, 2015 [37] (1) | 19,258 Ca: 1004 | | | | colorectal adenoma | Ca: 270 | | OR: 0.76 (0.63–0.91) <i>p</i> < 0.003 | Age, sex, study center, ethnicity, TEn, smoking status, alcohol intake, total folate intake from diet |
| Kunzmann, 2015 [37] (2) | Ca: 770 | Ca: M = 665 Co: M = 8756 | Ca: 66.6 ± 5.0 Co: 66.7 ± 4.9 | Ca: 11.2 ± 3.5 g/1000 kcal Co: 12.0 ± 3.6 g/1000 kcal | colon adenoma | Ca: 206 | ≥12.8 g/1000 kcal | OR: 0.75 (0.61–0.92) <i>p</i> < 0.006 | |
| Kunzmann, 2015 [37] (3) | Ca: 262 | | | | rectal adenoma | Ca: 69 | | OR 0.68 (0.48–0.96) <i>p</i> = 0.03 | |
| Kunzmann, 2015 (a) [37] (4) | Ca: 738 Co: 929 | | | | recurrent colorectal adenoma | Ca: 203 | | OR: 1.08 (0.75–1.55) <i>p</i> = 0.67 | |
| Kunzmann, 2015 (a) [37] (5) | Ca: 257 | Ca: M = 535 Co: M = 570 | Ca: 66.9 ± 5.3 Co: 68.2 ± 5.4 | Ca: 11.1 ± 3.4 g/1000 kcal Co: 11.2 ± 3.5 g/1000 kcal | recurrent colon adenoma | Ca: 70 | ≥12.8 g/1000 kcal | OR: 0.99 (0.59–1.66) <i>p</i> = 0.96 | |
| Kunzmann, 2015 (a) [37] (6) | Ca: 78 | | | | recurrent rectal adenoma | Ca: 26 | | OR: 0.88 (0.39–1.99) <i>p</i> = 0.86 | |
| Little, 1993 [38] | Ca: 147 Co: 153 | Ca: M = 65 Co: M = 65 | Ca: 66.0 ± 7.0 Co: 66.0 ± 7.0 | Ca: 25.5 g/d Co: 25 g/d | colorectal adenoma | Ca: 26 | 38 g/d | RR: 0.81 (0.37–1.78) <i>p</i> = n.a. | Age, sex, social class and total energy intake |
| Lubin, 1997 [39] | Ca: 196 Co: 196 | Ca: M = 111 Co: M = 111 | 21–75 (range) | n.a. | colorectal adenoma | n.a. | >34 g/d | OR 0.6 (0.3–1.2) <i>p</i> = 0.14 | TEn, PA, weight smoking |
| Martinez, 1996 [40] | Ca: 157 Co: 480 | Ca: M = 98 Co: M = 229 | Ca: 57.7 Co: 54.7 | n.a. | colorectal adenoma | Ca: 29 Co: 120 | 28.0–86.8 g/d | OR 0.5 (0.3–0.9) <i>p</i> = 0.01 | Age, sex, race, BMI, smoking status, family history of CRC, NSAID and aspirin, calcium and fat intake |
| Mathew, 2004 [41] | Ca: 239 Co: 228 | Ca: M = Co: M = | 18–74 (range) | n.a. | colorectal adenoma | n.a. | Median (10th–90th percentiles) 6 (4, 11) of energy from various fibres | OR 0.67 (0.45–0.99) <i>p</i> = n.a. | Age, sex and TEn |
| Mujtaba, 2018 [42] | Ca: 789 Co: 2035 | Ca: M = 482 Co: M = 871 | Ca: 58.1 ± 9.2 Co: 54.5 ± 10.9 | Ca: 21.7 ± 9.4 g/d Co: 22.0 ± 10.1 g/d | colorectal adenoma | Ca: 187 | n.a. | OR 1.25 (0.89–1.75) <i>p</i> = 0.28 | Age, sex, family history of CRC, smoking, alcohol, BMI, height, PA, hormone therapy, aspirin use, NSAID calcium, folate, TEn, total fat, SFA, red and processed meat intake |

Table 2. Cont.

| Author, Year [Ref] (Number of Stratified Analysis) | Total Sample ^ | Sex | Age (In Years) Mean ± SD | Dietary Fibre Intake Mean ± SD | Outcome | n. Subjects at the Highest Fibre Intake | Highest Dietary Fibre Intake | Effect Size (95% CI) <i>p</i> | Adjustment |
|--|------------------------|--------------------------------|----------------------------------|--|-----------------------|---|---------------------------------|---|---|
| Nimptsch, 2014 [43] | 17,221 Ca: 1299 | only F | 34–51 (range) | E: 22.0 ± 5.5 g/d nE: 16.7 ± 4.8 g/d | colorectal adenoma | Ca E: 231 Ca nE: 293 | n.a. | OR 0.77 (0.65–0.92) <i>p</i> = n.a. | TEn |
| Peters, 2003 [44] (1) | Ca: 3591 Co: 33,971 | | | | colorectal adenoma | Ca: 637 | | OR 0.73 (0.62–0.86) <i>p</i> < 0.002 | |
| Peters, 2003 [44] (2) | Ca: 2378 Co: 33,971 | Ca: M = n.a. Co: M = 17,435 | 55–74 (range) | 21.9 g/d | colon adenoma | Ca: 412 | 30.6 g/d | OR 0.70 (0.58–0.85) <i>p</i> < 0.0006 | Age, sex, study center, TEn |
| Peters, 2003 [44] (3) | Ca: 659 Co: 33,971 | | | | rectal adenoma | Ca: 123 | | OR 0.93 (0.65–1.33) <i>p</i> = 0.97 | |
| Platz, 1997 [45] (1) | 16,448 Ca: 690 | | | | colorectal adenoma | Ca: 120 Co: 3171 | | RR = 0.88 (0.72–1.08) <i>p</i> = 0.218 | |
| Platz, 1997 [45] (2) | Ca: 531 | only M | 59.5 ± 9.4 | n.a. | colon adenoma | Ca: 91 | 32.3 g/d | RR: 0.88 (0.59–1.31) <i>p</i> = 0.10 | Age, endoscopy prior 1986, family history of CRC, BMI, smoking, multivitamin use, PA, aspirin use, alcohol, red meat, folate and methionine |
| Platz, 1997 [45] (3) | Ca: 159 | | | | rectal adenoma | Ca: 29 | | RR: 1.12 (0.54–2.35) <i>p</i> = 0.78 | |
| Sandler, 1993 [46] (1) | Ca: 105 Co: 165 | only M | Ca:63.5 ± 12.2 Co:58.7 ± 12.1 | n.a. | colorectal adenoma | Ca: n.a. | ≥18.6 g/d | OR 0.74 (0.32–1.74) <i>p</i> = 0.873 | Age, alcohol intake, BMI, and TEn |
| Sandler, 1993 [46] (2) | Ca: 131 Co: 244 | only F | Ca:62.2 ± 11.6 Co:58.7 ± 12.5 | | | Ca: n.a. | ≥15.6 g/d | OR 0.71 (0.35–1.43) <i>p</i> = 0.120 | |
| Shaw, 2017 [47] | Ca:1098 no Ca: 1450 | Ca: M = 710 no Ca: 675 | 50–75 (range) | Ca: 10.5–33.59 g/d no Ca: 11.01–33.88 g/d | colorectal adenoma | Ca:205 no Ca: 347 | >25.52 g/d | OR 0.77 (0.56–1.07) <i>p</i> = 0.14 | Age, sex, BMI, smoking, reason for colonoscopy, family history of polyps, TEn |
| Tantamango, 2011 [48] | 2818 Ca: 441 | Ca: M = 211 Ca: M = 922 | Ca: 73.4 ± 9.2 Co: 71.2 ± 9.7 | Ca: 11.2 ± 4.3 g/d Co: 11.7 ± 4.8 g/d | colon adenoma | Ca: 93 | 16.9 g/d | OR 0.71 (0.51–0.99) <i>p</i> = 0.04 | Age, sex, BMI, education, PA, alcohol and meat intake |
| Witte, 1996 [49] | Ca: 488 Co: 488 | Ca: M = 334 Co: M = 334 | Ca: 61.9 ± 6.7 Co: 61.8 ± 6.8 | Ca: 18.9 ± 9.6 g/d Co: 20.0 ± 9.7 g/d | colorectal adenoma | n.a. | n.a. | OR 0.82 (0.65–1.03) <i>p</i> = 0.09 | None |

n.a.: not available; F: Female; M: male; ^ The total sample and number of cases are reported for the cohort study, both the number of Cases (Ca) and Controls (Co) are reported for the case-control study, while the number of Ca and non-cases (no Ca) are reported for the cross-sectional study. BMI: Body Mass Index; Ca/Co: case/control; CRC: Colorectal cancer; IBD: Inflammatory bowel disease; NSAID: Nonsteroidal anti-inflammatory drug; PA: Physical Activity; SAF: Saturated fatty acids; TEn: Total Energy intake.

Table 3. Results of the sensitivity and subgroup analyses.

| Analysis | Model | n. Studies Included | ES | 95% CI | p | Sample Size | I ² | p | Intercept | Tau (t) | p |
|---|----------|---------------------|------|-----------|-------|-------------|----------------|-------|-----------|---------|-------|
| Trim and Fill colorectal | Fixed * | 24 | 0.71 | 0.68–0.75 | 0.000 | 157,725 | 62.71 | 0.000 | 0.12 | 0.21 | 0.838 |
| | Random ^ | | 0.74 | 0.67–0.82 | 0.000 | | | | | | |
| Excluding potential overlapping cohort | Fixed | 19 | 0.79 | 0.74–0.85 | 0.000 | 87,629 | 13.00 | 0.295 | −0.89 | −1.93 | 0.070 |
| | Random | | 0.79 | 0.73–0.86 | 0.000 | | | | | | |
| Excluding studies with estimated OR | Fixed | 18 | 0.76 | 0.71–0.82 | 0.000 | 115,311 | 39.33 | 0.045 | −0.84 | −1.41 | 0.179 |
| | Random | | 0.74 | 0.67–0.83 | 0.000 | | | | | | |
| 9y FU | Fixed | 4 | 0.79 | 0.71–0.88 | 0.000 | 56,453 | 0.00 | 0.595 | 0.15 | 0.07 | 0.950 |
| | Random | | 0.79 | 0.71–0.88 | 0.000 | | | | | | |
| Validated FFQ | Fixed | 15 | 0.71 | 0.68–0.75 | 0.000 | 115,192 | 74.88 | 0.000 | 1.16 | 1.14 | 0.276 |
| | Random | | 0.75 | 0.66–0.86 | 0.000 | | | | | | |
| Diagnosis | Fixed | 21 | 0.70 | 0.66–0.73 | 0.000 | 120,530 | 64.52 | 0.000 | 0.09 | 0.14 | 0.891 |
| | Random | | 0.71 | 0.63–0.80 | 0.000 | | | | | | |
| Quality score ≥ 7 | Fixed | 20 | 0.78 | 0.73–0.83 | 0.000 | 125,561 | 38.10 | 0.044 | −0.99 | −1.96 | 0.065 |
| | Random | | 0.77 | 0.70–0.84 | 0.000 | | | | | | |
| Colon adenoma | Fixed | 4 | 0.73 | 0.65–0.83 | 0.000 | 74,714 | 0.00 | 0.774 | 1.20 | 1.20 | 0.352 |
| | Random | | 0.73 | 0.65–0.83 | 0.000 | | | | | | |
| Rectal adenoma | Fixed | 5 | 0.77 | 0.62–0.96 | 0.019 | 69,905 | 30.54 | 0.218 | −0.98 | −0.86 | 0.455 |
| | Random | | 0.76 | 0.56–1.03 | 0.074 | | | | | | |
| Cohort studies (incidence) | Fixed | 10 | 0.67 | 0.63–0.71 | 0.000 | 135,506 | 75.38 | 0.000 | 1.32 | 1.12 | 0.297 |
| | Random | | 0.72 | 0.61–0.84 | 0.000 | | | | | | |
| Case-Control/Cross-sectional (prevalence) | Fixed | 17 | 0.78 | 0.72–0.84 | 0.000 | 55,401 | 25.13 | 0.165 | −0.86 | −1.89 | 0.079 |
| | Random | | 0.76 | 0.69–0.85 | 0.000 | | | | | | |
| Women | Fixed | 6 | 0.81 | 0.70–0.92 | 0.002 | 35,152 | 0.00 | 0.745 | −0.50 | −1.06 | 0.349 |
| | Random | | 0.81 | 0.70–0.92 | 0.002 | | | | | | |
| Men | Fixed | 6 | 0.69 | 0.58–0.82 | 0.000 | 24,426 | 72.73 | 0.003 | −2.24 | −2.72 | 0.053 |
| | Random | | 0.46 | 0.27–0.78 | 0.004 | | | | | | |

* Trimmed studies: 0; ^ Trimmed studies: 2.

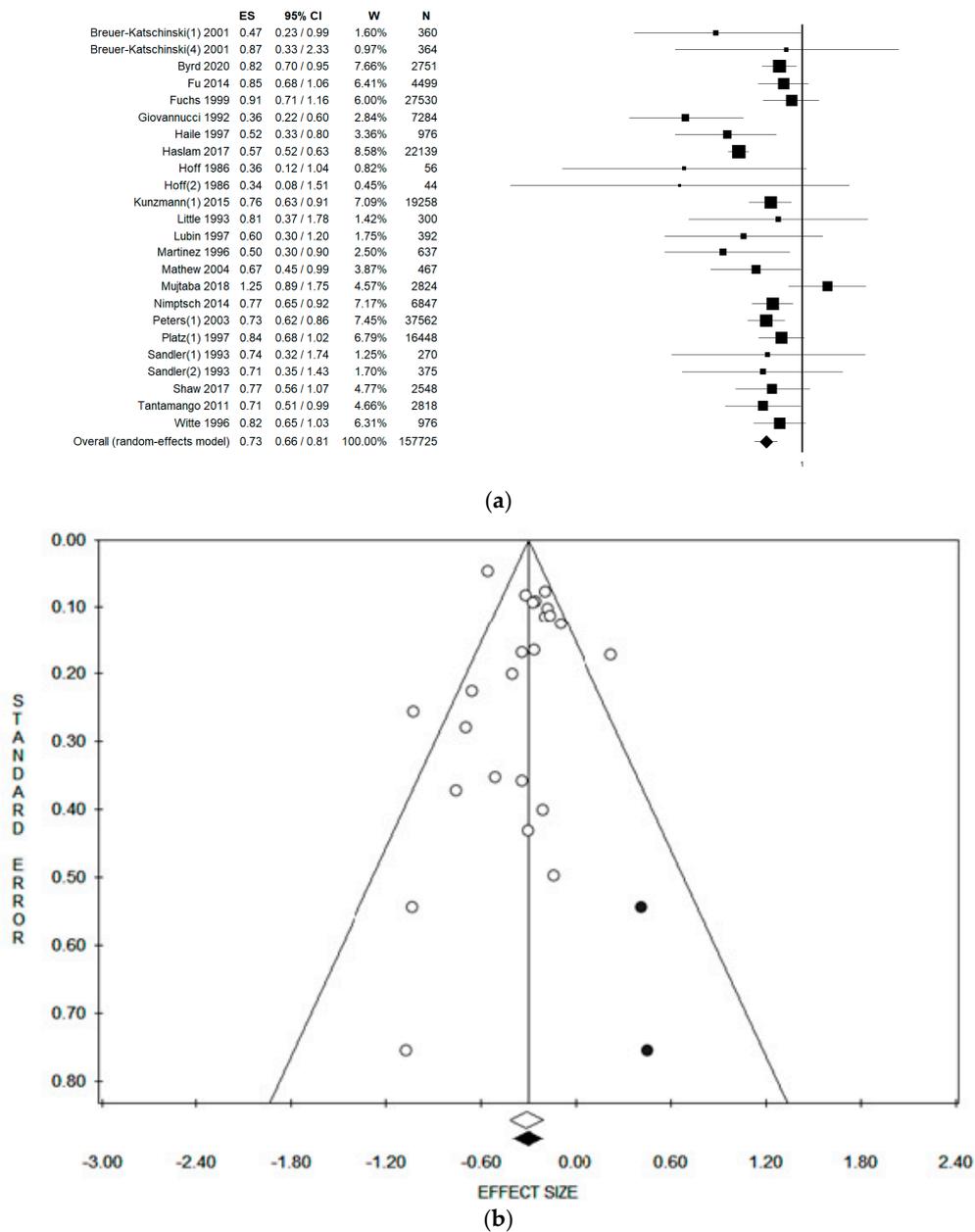


Figure 2. (a) Forest plot and (b) Funnel plot (after trim and fill method) of the meta-analysis comparing dietary fibre intake (lower vs higher intake) and risk of colorectal adenoma (random effect model). In (a) squares represent the effect size values of the individual studies. In (b) white dots represent single studies included. The black dots represent estimated studies after the trim and fill method. The white diamond represents the overall effect size of the included studies. The black diamond represents the estimated overall effect size after the trim and fill method.

No publication bias was found when considering the fixed effect model, as demonstrated by the symmetry of the Funnel plot and confirmed by Egger’s linear regression Test (Intercept 0.12, $t = 0.21$, $p = 0.838$) (Figure 2b). However, a potential publication bias was found when the random effect model was considered. In this case, we applied the trim and fill method and, after trimming 2 studies, we obtained an estimated pooled ES = 0.71 (95% CI = 0.68–0.75), $p = 0.000$ in the fixed effect model and an estimated pooled ES = 0.74 (95% CI = 0.67–0.82), $p = 0.000$ in the random effect model (Table 3). With regard to the dose-response meta-regression analysis, all studies reported dietary fibre as grams per day

(g/d), but two studies reported dietary fibre as g/1000 kcal/d [30,37]. In view of this, we assumed a standard daily energy intake of 2000 kcal and, for this reason we multiplied the reported intake by two. Figure 3 shows the meta-regression plot of the log OR (colorectal adenoma) on the dose of dietary fibre intake, using the fixed effect (Figure 3a) and the random effect models (Figure 3b). The size of the circles (identifying the included studies) denotes the study's weight which is represented by the inverse of the within-study variance in the fixed model, and the total variance for each study in the random effect model. The line shows the predicted values where, in the fixed effect model, the intake of dietary fibre showed negative weak-border line significant correlation with colorectal adenoma ($Y = -0.06$, $z = -0.02$, $p = 0.056$), whilst in the random effect model, the linear correlation was not significant ($Y = -0.01$, $z = -0.01$, $p = 0.095$).

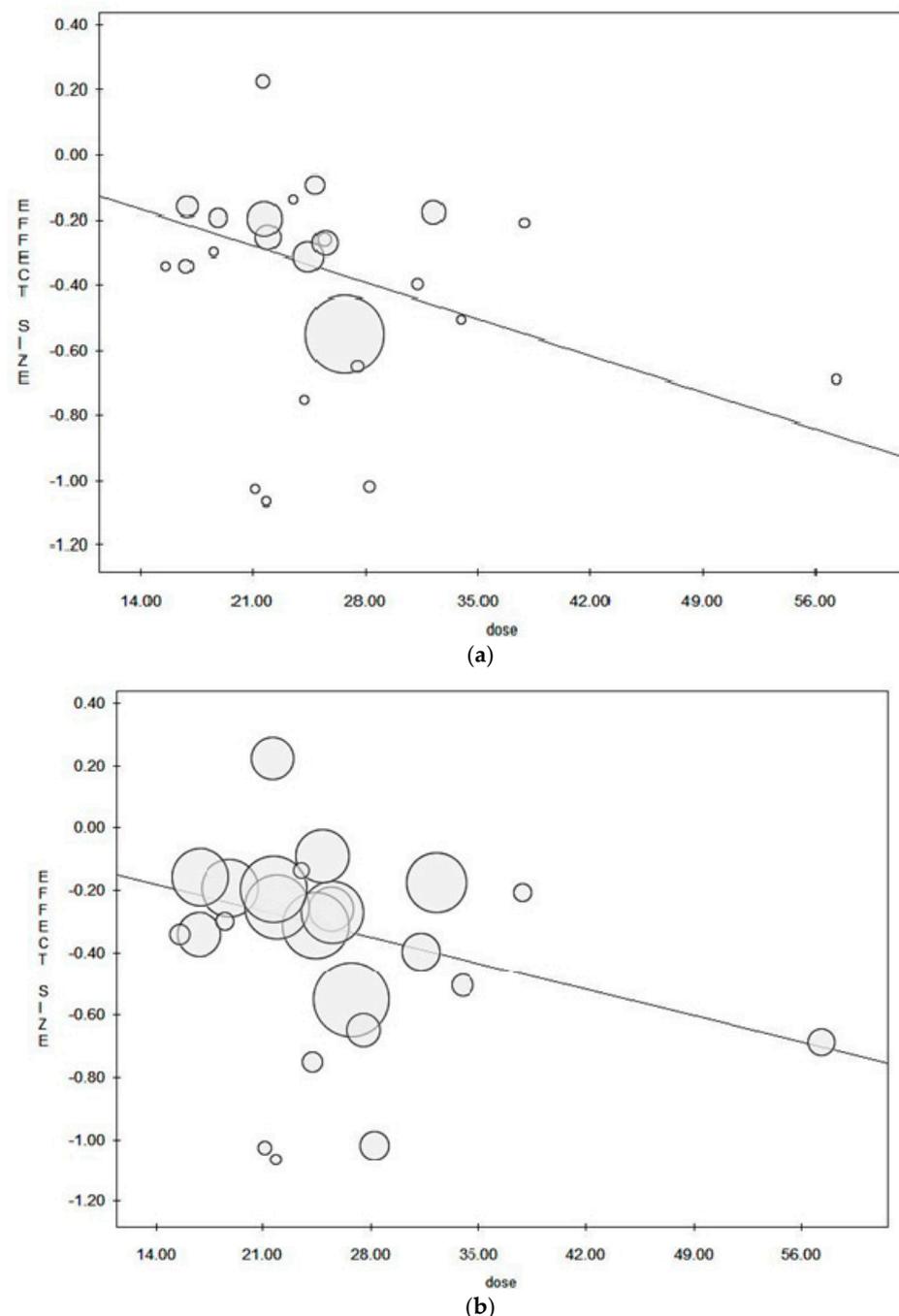


Figure 3. Meta-regression plot for (a) fixed effect model and (b) random effect model.

3.3. Sub-Group and Sensitivity Analysis

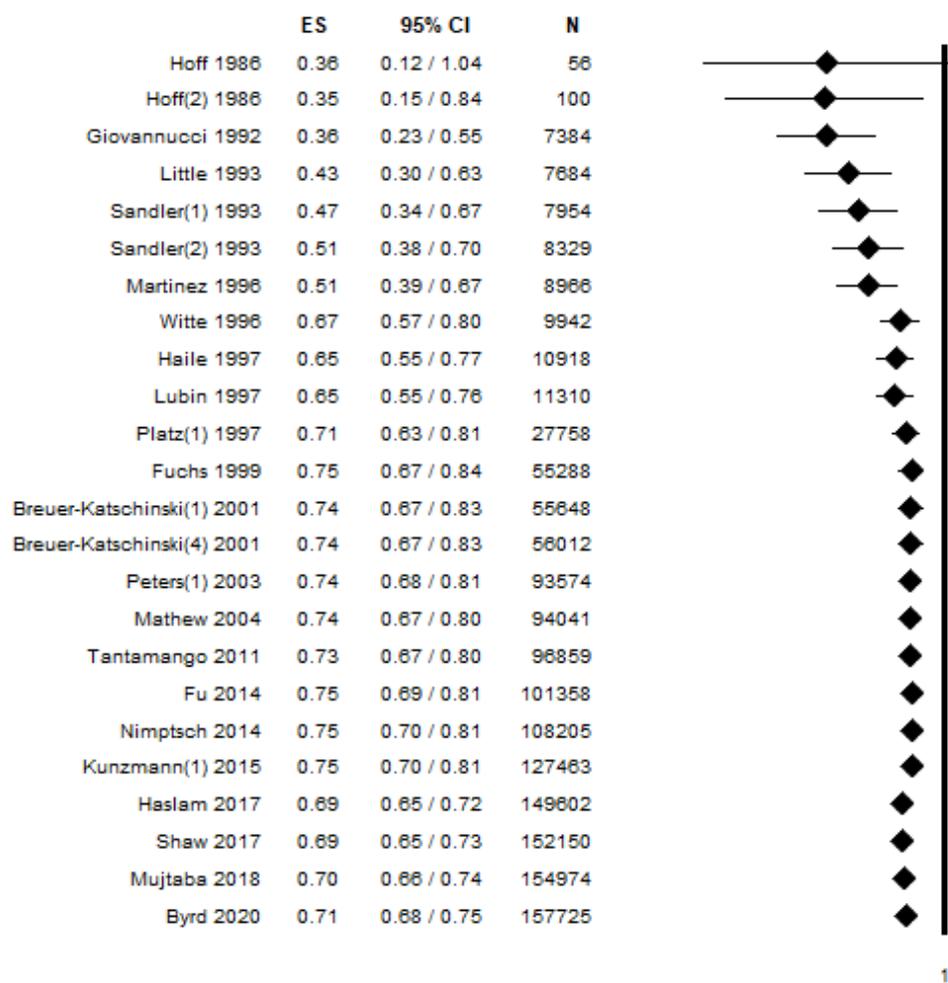
A series of sensitivity analyses were conducted in order to confirm the robustness of our results. Firstly, we removed those studies that used the same cohort in order to reduce ES overestimation due to the potential overlapping effect. In particular, four studies were excluded from the analysis [30,33,35,44], thus obtaining similar results compared to the main analysis but with no statistical heterogeneity ($I^2 = 13.00\%$, $p = 0.295$) (Table 3). Potential publication bias was found, as confirmed by Egger's Linear Regression Test (Intercept -0.89 , $t = -1.93$, $p = 0.070$). Also, in this case, a trim and fill method was applied by trimming six studies on the right and the results did not change [fixed effect estimated ES = 0.79 (95% CI = $0.74 - 0.85$), $p = 0.000$; the random effect model estimated ES = 0.82 (95% CI = $0.77 - 0.91$), $p = 0.000$].

Secondly, we removed studies for which OR was computed based on data reported in the original studies [30,35,36,45,49], obtaining similar results with no heterogeneity and an absence of potential publication bias as confirmed by Egger's Linear Regression Test (Table 3). Thirdly, only those studies with an FU equal to or higher than 9 years were included; the results based on 53,827 participants did not materially change and no statistical heterogeneity ($I^2 = 0.00\%$, $p = 0.018$) was found (Table 3). No publication bias was found as confirmed by Egger's Linear Regression Test (Intercept 0.15 , $t = 0.07$, $p = 0.950$). Fourthly, results were not affected by limiting the analysis to only include studies that used validated tools to assess dietary fibre intake; however, a high statistical heterogeneity was found (Table 3) but with no publication bias.

Stronger results were obtained when limiting the pooling of studies by only using colonoscopy and histopathological confirmation for the diagnosis of adenoma and for studies with a quality score higher than 7 [low statistical heterogeneity ($I^2 = 38.10\%$, $p = 0.007$) but with potential publication bias (Egger's Linear Regression Test Intercept -0.99 , $t = -1.96$, $p = 0.065$); however, the trim and fill method, by trimming 6 studies on the right, did not change results: in the fixed effect model, the pooled ES was 0.81 (95% CI = $0.76-0.86$), $p = 0.000$; in the random effect model ES was 0.82 (95% CI = $0.73-0.91$) $p = 0.000$]. In order to corroborate the results obtained, sub-group analyses were additionally performed, based on the adenoma site (colon and rectal separately), study design (case-control/cross-sectional and cohort studies) and sex. Results also remained similar in these cases. We detected a potential publication bias in the subgroup analyses by study design and sex when only including case control/cross-sectional studies and men, respectively. However, ES estimated after the trim and fill method did not change. Data are shown in Table 3. Results should be interpreted with caution for adenoma site and sex since a few studies for each analysis were pooled and also due to the low number of stratified analyses conducted in the original studies retrieved.

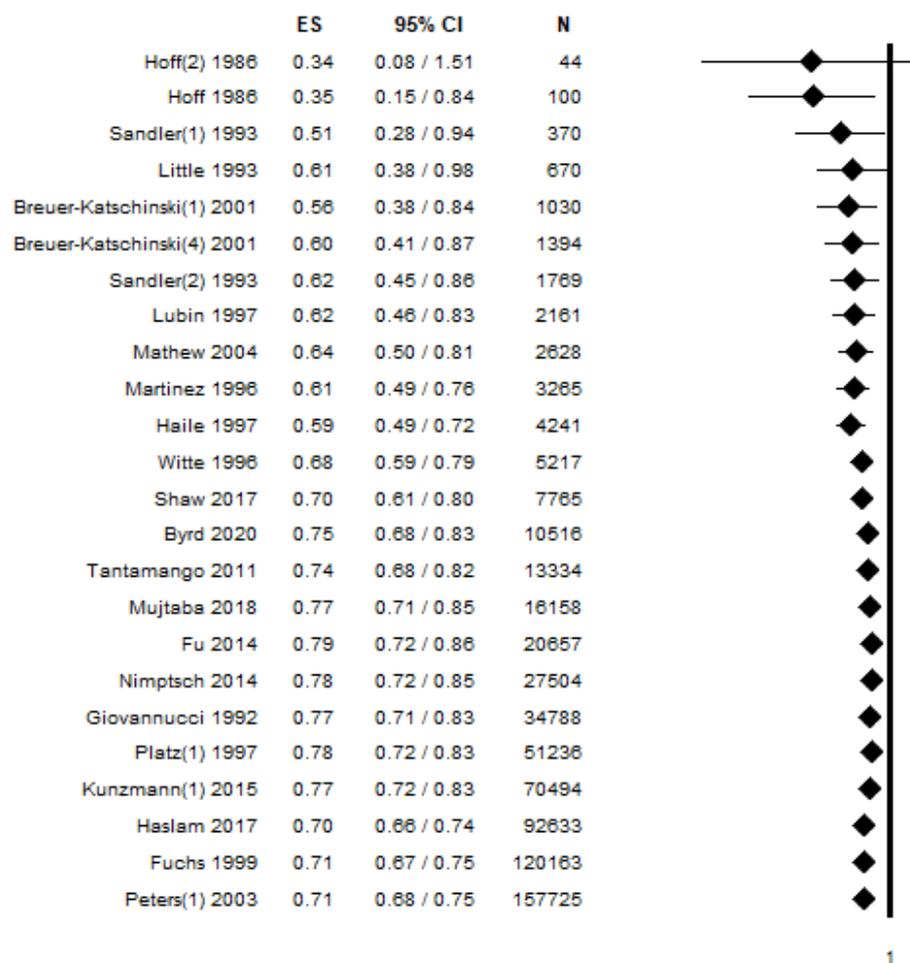
3.4. Cumulative Analysis

The cumulative analysis in Figure 4a reveals that early studies, even if suggesting an inverse association between fibre intake and risk of colorectal adenoma, had a wide 95% CI which decreased in the late 1990s and relatively stabilized during the first decade of 2000. However, a really narrow 95% CI and a consistent ES was obtained during the second decade of 2000. With reference to the cumulative analysis by sample size (Figure 4b), studies with a sample size smaller than 1000 subjects, even if establishing an inverse statistically-significant association, had a wide 95% CI. As expected, a larger sample size contributed to stabilizing the results both by reducing the 95% CI and by corroborating the ES value. Considering the cumulative analysis by dietary fibre dose, ES was higher when studies examined a dietary dose lower than 26 g/d. Conversely, ES was lower and stable and with a narrow 95% CI, when higher dietary fibre intake was considered (Figure 4c).



(a)

Figure 4. Cont.



(b)

Figure 4. Cont.

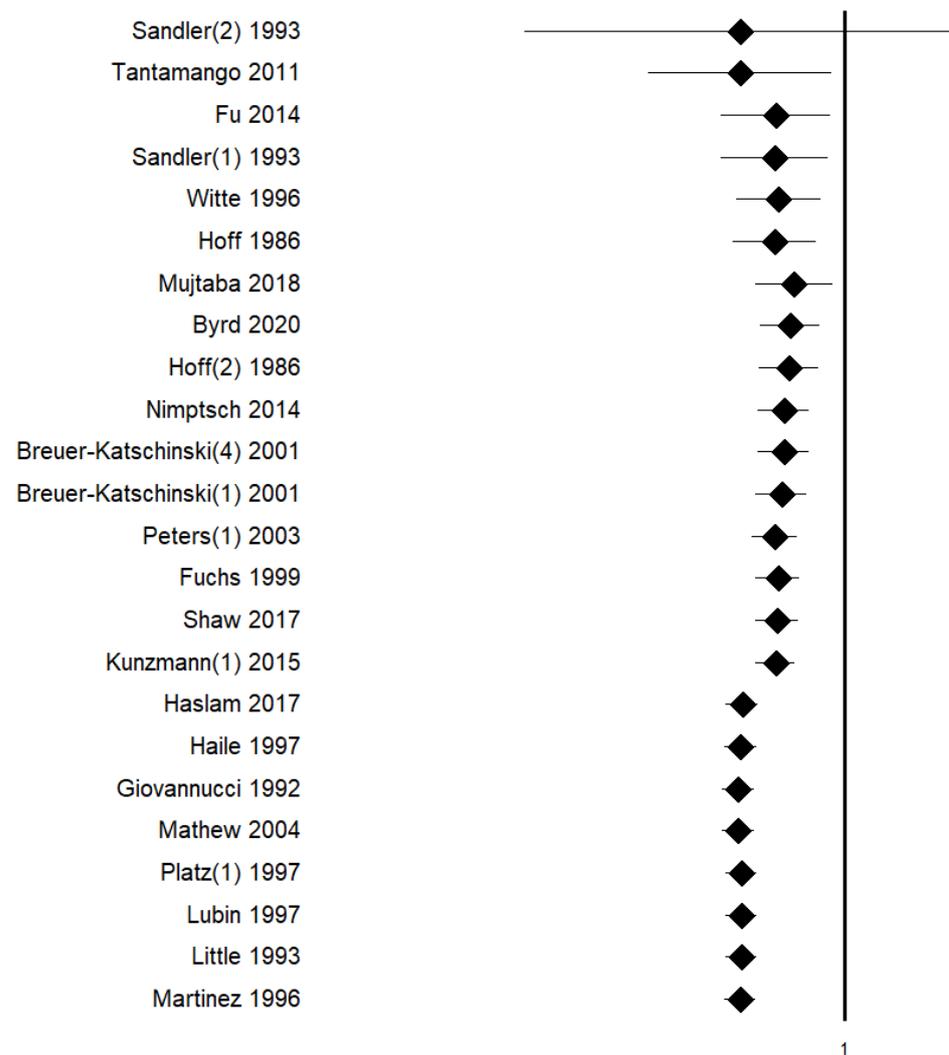


Figure 4. Forest plot of the cumulative analysis by (a) year of publication (from the first to the most recent published study), (b) by sample size (from the smallest to the largest), (c) dietary fibre dose (from the lowest to the highest intake) between dietary fibre intake and risk of colorectal adenoma. Diamonds represent the effect size estimated using the cumulative analysis calculated adding one study at a time.

4. Discussion

This is an extensive systematic review and meta-analysis of observational studies conducted by searching three different databases (PubMed/Medline, Scopus and EMBASE) and assessing the association between dietary fibre intake and the risk of colorectal adenoma. Our meta-analysis of 21 studies in total found an approximate 30% risk reduction of adenoma associated with a higher intake of dietary fibre. This result was confirmed in both the fixed and random effect models. Moreover, meta-regression analysis was performed since the original studies reported dietary fibre intake homogeneously. Meta-regression analysis predicts the changes of the outcome (colorectal adenoma) for a unit increase in dietary fibre intake. Our results showed a border-line significant negative linear correlation between the amount of dietary fibre intake and colorectal adenoma (the higher the intake of dietary fibre, the lower the risk of colorectal adenoma). This observation is in line with the cumulative analysis by dietary fibre dose, according to which the lowest risk of adenoma was associated with a dietary fibre intake equal to or higher than 26 g/d. However, it

should be noted that the ES from the pooling of the 21 studies was associated with moderate heterogeneity and a potential publication bias. For these reasons, we performed several sensitivity analyses and the trim and fill method was applied. With regard to the potential publication bias, the trim and fill methods trimmed two possible studies on the right, however, the result did not change. Looking at the subgroup analysis by sex, a higher protective effect for men was found when compared to women, yet there was higher heterogeneity in men than in women. Furthermore, the highest strength of the association between dietary fibre intake and colorectal adenoma was found when focusing on cohort studies wherein higher heterogeneity was found when compared to case-control/cross-sectional studies. This is probably because a different duration of FU was considered among the original pooled cohort studies, and this hypothesis can be confirmed when considering a sensitivity analysis limited to 9 years (or more) of FU, where heterogeneity dramatically dropped. Moreover, the natural history of colorectal adenoma should be considered when interpreting these results. On the one hand, colorectal adenoma is characterized by a long latency period, which might not be better appraised in short cohort studies, nor in long cohort studies, where maintaining an FU might be difficult while increasing the risk of selection bias. On the other hand, case-control studies are more prone to potential recall bias. However, the high number of retrieved studies and consequently, the large sample size, might mitigate the risk. An important aspect that should be considered is that the vast majority of included studies were conducted in the USA, a population that largely did not meet healthy dietary guidelines, and where the eating pattern of approximately three-fourths of the population is low in vegetables, fruits, dairy, and oils and rich in refined grain, proteins, saturated fats, sodium and total calories [50]. This dietary pattern is frequently associated with several preventable, diet-related chronic diseases, including cancers. Based on this, we can speculate that the healthy beneficial effects of dietary fibre intake might be higher with respect to what we found in this meta-analysis if assessed in a population with a more Mediterranean—or, generally speaking, healthier—dietary pattern. It should be considered that the most relevant source of dietary fibre derives from vegetables, legumes and fruits which have been shown to prevent colorectal cancer [51] and which are heterogeneous in respect to their composition; therefore, it can be assumed that they have various anticarcinogenic properties. They are rich in bioactive compounds such as vitamins, anti-oxidants and polyphenols. Previous *in vitro* studies showed that some of these polyphenols, such as sulforaphane and epigallocatechin, are able to reprogram gene expression through epigenetic modification, thus reverting cancer progression [52,53]. Moreover, it should be considered that almost all the included studies used FFQs to assess dietary fibre intake, and even if they were frequently validated, it is difficult to precisely estimate the intake, often resulting in underestimation. Furthermore, our results suggest that there might be differences in the responses to fibre by sex.

4.1. Potential Biological Mechanisms

Since colorectal adenomas are considered to be potential precancerous lesions, they are likely to share a common etiopathogenesis with colorectal cancer.

According to the European Food Safety Authority (EFSA) dietary fibre is “non-digestible carbohydrates plus lignin, including non-starch polysaccharides, fructo-oligosaccharides, galactooligosaccharides, other resistant oligosaccharides and resistant” [54]. Major food sources for dietary fibre are cereals/grains, vegetables, fruits and legumes. Based on its components, previous studies suggested to differentiate dietary fibre into “soluble” and “insoluble”. Such distinction was used to differentiate between viscous, soluble types of fibre (e.g., pectins) and insoluble components such as cellulose. Even if the distinction was mainly proposed to identify different patterns of beneficial effects, it should be noticed that both soluble and insoluble components have different and synergic advantages. The insoluble fibre is mainly responsible for the increase in stool bulk, important for reducing transit time and diluting carcinogens in the lumen by means of both reducing exposure to carcinogens and lowering secondary bile acid production [5]. The soluble fibre, instead,

seems to be implicated in the wellbeing of microbiota through fibre fermentation which, in turn, is able to promote the production of short-chain fatty acids (SCFA) and which, by lowering the colonic pH, might inhibit pathogenic microorganisms and increase the absorption of some nutrients [55]. In addition, experimental studies have shown that butyrate, SCFA, has anti-proliferative effects, promotes colon motility and induces apoptosis [56]. The consequent reduction in cholesterol, and insulin resistance, seem to inherently reduce the risk of colorectal cancer. Furthermore, dietary fibre intake seems to also promote the eubiosis of the gut microbiota ecosystem [57]. On the contrary, dysbiosis (increased number of harmful bacteria in the gut) seems to be associated with an increased release of enterotoxins that alter the immune system, inducing the production of pro-inflammatory cytokines responsible for the disease status [58], including colorectal cancer [59].

Considering the beneficial effects of both dietary fibre components, and based on the suggestion provided by Food and Agriculture Organization (FAO) and World Health Organization (WHO) stating that the above mentioned distinction should be overcome as solubility does not always predict physiological effects [60], we did not perform a separate analysis among soluble and insoluble fibre. Indeed, the potential role of fibre in preventing colorectal adenoma and then cancer could be attributed to all of the mentioned mechanisms, mainly on account of the dietary fibre heterogeneity in chemical composition, physicochemical properties, and solubility. On the other hand, selectively focusing on one of the two components and consequently on a particular food source might lead to a reduction in diet variety. In light of this, international healthy dietary guidelines consider dietary fibre as a single entity [61] and recommend satisfying the daily dietary fibre intake of at least 30 g, derived from a varied and balanced diet, rich in plant-based foods, such as wholegrains, legumes, non-starchy vegetables and fruit [62], as the Mediterranean diet advocates [63]. Nevertheless, in our society, the increased rate of colorectal adenoma (and cancer) can be attributed, among the others, to unhealthy lifestyles, including the so-called Western diet. This dietary pattern is characterized on one hand by a high intake of refined grains, sugars, salt, saturated and trans-fatty acids mainly due to a high consumption of ultra-processed food [64,65], and on the other hand by a low intake of dietary fibre. In this respect, previous studies showed that a low intake of fibre along with a high consumption of typical western diet food increase the risk of dysbiosis, which in turn can be responsible for a lower production in SCFA [66,67].

4.2. Strengths and Limitations

This meta-analysis is affected by some limitations directly stemming from the included studies. First of all, dietary fibre intake was self-reported, most of the time using FFQ which, even if validated, cannot prevent recall bias or social desirability bias, thus both resulting in mis-reporting. Secondly, information on cooking methods were not assessed and reported in the original studies, and recent evidence showed a modification in the fibre structure and biological effect based on the processing method used [68,69]. Thirdly, in the main analysis, the funnel plot confirmed by the Egger's test showed a potential publication bias. However, when applying the trim and fill methods the estimated ES did not change when compared to the observed ES. Another possible limitation is the language used (only articles published in English), which can lead to a bias in the selection of studies. Since English is the commonly-used scientific language, we believe that this did not affect our results as the most relevant and high-quality articles are published in English. Despite the above-mentioned limitations, our review with meta-analysis has important strengths. Worth highlighting is that this is a systematic and extensive review of available evidence, conducted according to the main guidelines. Furthermore, we conducted several sensitivity and sub-group analyses that make our results stronger and consistent. All the sub-group analyses performed offer a deep understanding of the association, useful for public health experts, dietitians and clinicians—the former involved in issuing health-related policies and campaigns and the latter in educating and assisting patients. Moreover, we were able to perform a meta-regression analysis as well as a cumulative analysis, confirming the

association between a higher intake of dietary fibre and a lower risk of colorectal adenoma. Lastly, in our meta-analysis we pooled ES with a higher level of adjustment than was reported in each original study.

5. Conclusions

To conclude, the results of our systematic review with meta-analysis show a statistically significant and robust association between a higher intake of dietary fibre and a lower risk of colorectal adenoma, both considering a prevalent and incident risk of adenoma (as confirmed by the subgroup analysis by study design). These results are extremely important because we were able to estimate the reduction in the risk of the development of a preneoplastic lesion as a result of a higher dietary fibre intake, which can be considered as a valid healthy dietary recommendation. Given the relatively simple implementation of this dietary behaviour, our findings confirm the importance of reinforcing this knowledge and awareness among both health care professionals (including, but not limited to those involved in nutritional educational programmes) and the general population.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/ijerph18084168/s1>, Table S1: Full search strategy; Table S2: Studies excluded with reasons after full-text assessment; Table S3: Quality assessment of the included studies.

Author Contributions: V.G. and D.N., contributed to the conception and design of the study and search. D.N. and C.F., extracted meta-data from the included manuscripts and performed the quality assessment. V.G. performed the analyses. V.G. and D.N. drafted the manuscript and performed the analysis. D.N. contributed to the assembly of the paper and data interpretation. V.G., T.S., M.N. and S.R. helped in the literature review and provided a critical revision of drafts. All authors have read and agreed to the published version of the manuscript.

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