Supplementary materials

Online Supplement: 1-12

Efficacy and safety of chemopreventive agents on colorectal cancer incidence and mortality: systematic review and network meta-analysis

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Version 28-06-2018

Number of pages: 101

This supplementary material has been provided by the authors to give readers additional information about their work.

Online Supplementary Content

Supplement 1: Search strategies

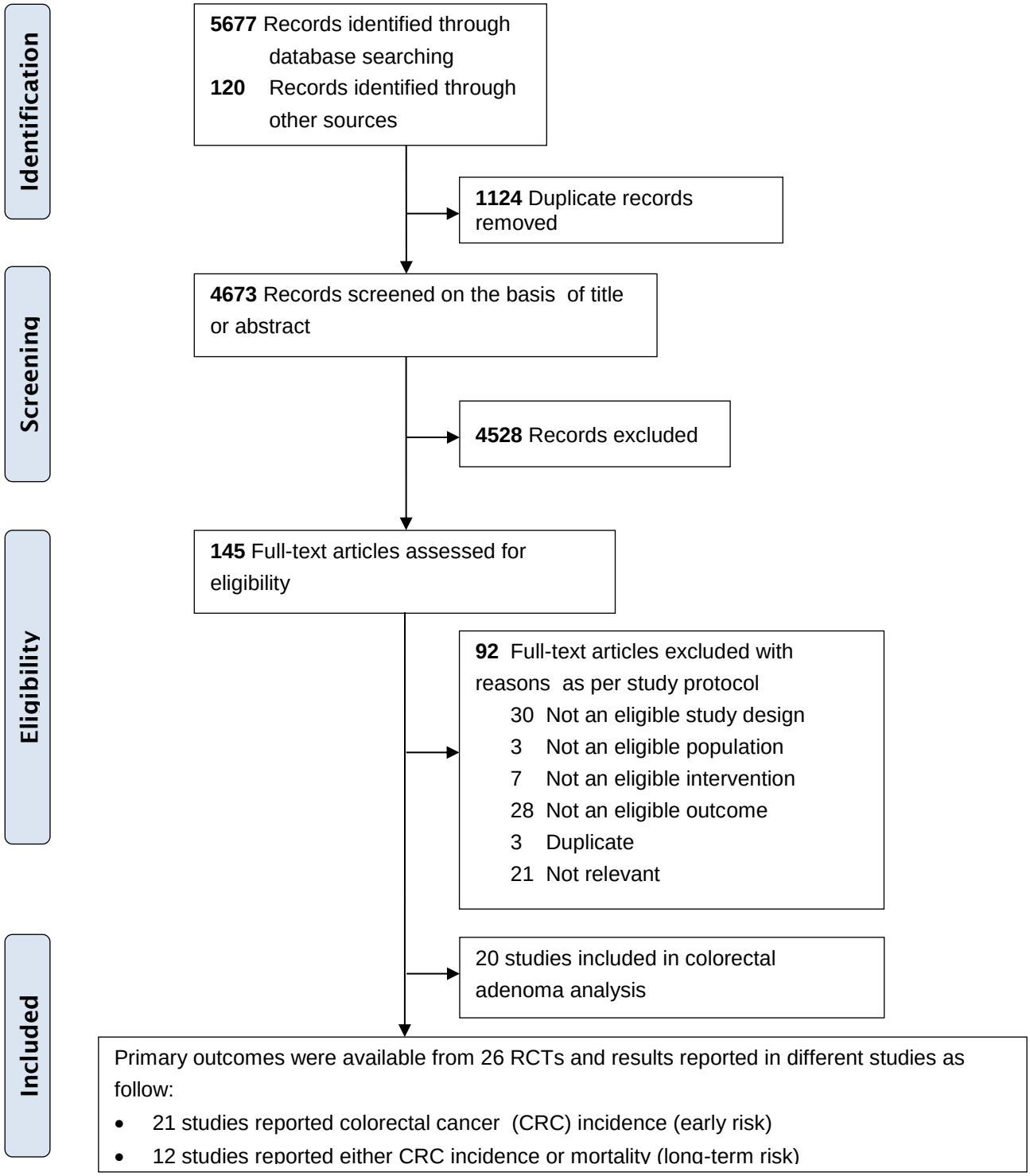
Table S1.1- Search algorithms for primary outcomes

Search algorithms as per the parent study design (Medline)	
#1	Adenoma
#2	Adenoma$
#3	Adenocarcinoma
#4	Adenomatous$
#5	Adenomatous polyps
#6	Colon cancer$
#7	Colon neoplas$
#8	Colon tumo$
#9	Colonic cancer$
#10	Colonic neoplas$
#11	Colonic neoplasms
#12	Colonic polyps
#13	Colonic tumo$
#14	Colorectal cancer$
#15	Colorectal neoplas$
#16	Colorectal neoplasms
#17	Colorectal tumo$
#18	Intestinal polyps
#19	Polyp$
#20	Rectal cancer$
#21	Rectal neoplas$
#22	Rectal neoplasms
#23	Rectal tumo$
#24	Rectum cancer$
#25	Rectum neoplas$
#26	Rectum tumo$
#27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28	Aspirin
#29	Acetylsalicylic acid
#30	COX-1 inhibitor$
#31	COX-2 inhibitor$
#32	COX-2 selective inhibitor$
#33	Coxib$
#34	Cyclooxygenase 1 inhibitor$
#35	Cyclooxygenase 2 inhibitor$
#36	Cyclooxygenase 2 inhibitors

#37	Cyclooxygenase inhibitor$
#38	Cyclo-oxygenase inhibitor$
#39	Cyclooxygenase inhibitors
#40	Nonsteroidal antiinflammatory$
#41	Non-steroidal antiinflammatory$
#42	Nonsteroidal anti-inflammatory$
#43	Non-steroidal anti-inflammatory$
#44	Anti-inflammatory agents, non-steroidal
#45	NSAID$
#46	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45
#47	Folate$
#48	Folic$
#49	Folic acid
#50	#47 OR #48 OR #49
#51	Calcium
#52	Calcium$
#53	Calcium, dietary
#54	#51 OR #52 OR #53
#55	Cholecalciferol
#56	Cholecalciferol$
#57	Ergocalciferol$
#58	Ergocalciferols
#59	Vitamin D
#60	#55 OR #56 OR #57 OR #58 OR #59
#61	Antioxidant$
#62	Anti-oxidant$
#63	Antioxidants
#64	Ascorbic acid
#65	Vitamin C
#66	Vitamin A
#67	Beta-carotene
#68	Carotenoid$
#69	Carotenoids
#70	Selenium
#71	Tocopherol$
#72	Tocopherols
#73	Tocotrienol$
#74	Tocotrienols
#75	Alpha-tocopherol$
#76	Vitamin E
#77	#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76

#78	Clinical trial
#79	Controlled clinical trial
#80	Single blind method
#81	Double blind method
#82	Placebo
#83	Placebo$
#84	Random$
#85	Random allocation
#86	Randomized controlled trial
#87	Randomized controlled trials
#88	#78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87
#89	#46 OR #50 OR #54 OR #60 OR #77
#90	#27 AND #88 AND #89
This search strategy (include search terms for both adenomas and colorectal cancer (CRC)) was developed for parent study[1]: a systematic review and network meta-analysis of CPAs (chemopreventive agents) for CRC, which has been registered (registration number: CRD42015025849) with PROSPERO, previously.	

Figure S1.1- PRISMA flow diagram for primary outcomes



Safety outcomes were available from additional 18 RCTs from US preventive task force review (total 25 RCTs reported safety outcomes): for more details refer Appendix 3 (eTable 3.9 and 3.10)

*This flow diagram represents the results based on search strategy given in Table A.1 (parent study). 20 RCTs reported the incidence of adenoma recurrence and analysed separately [2].

Supplement 2: Additional description of methods

Primary outcomes

Early risk of colorectal cancer

Identified 21 RCTs reported early risk of CRC incidence (follow-up ≤ 10 years). ***(refer eTable 3.1-3.3 in Appendix 3)***.

Long-term risk of incidence and mortality due to colorectal cancer

12 RCTs reported either CRC incidence or mortality were included. Nine RCTs reported long-term risk of CRC incidence and 7 RCTs reported long-term risk of CRC mortality ***(refer eTable 3.5-3.7 in Appendix 3)***. Data on long-term risk of CRC incidence or mortality from these 12 RCTs were identified from 6 post-trial observational studies [3–8] and 2 IPD meta-analyses [9,10].

Reasons for exclusion of identified studies

One RCT[11] (Gaziano 2012- Physicians' Health Study II (PHS-II)), excluded because of following reasons: In Physicians' Health Study II, participants were randomized to one of 16 possible combinations of vitamin C (500 mg synthetic ascorbic acid), vitamin E (400 IU of synthetic alpha-tocopherol), beta-carotene (50 mg Lurotin), a multivitamin (Centrum Silver), or their placebos (2x2X2X2 factorial design). There are two reports of the same study available. The first published one was Gaziano 2009 ***(Refer eTable 3.1 Appendix 3)***, which reported 8-year follow-up results of PHS-II [12]. However, no data available for individual arms for network meta-analysis. When requested for data, authors provided data for two arms (any antioxidants including multivitamins versus placebo). The second report of PHS-II was Gaziano 2012, which is around 11.2 year (10-13 years) follow-up of the same study looking efficacy of only multivitamin versus placebo. Furthermore, no data available for individual arms in Gaziano 2012 report. Since the data from Gaziano 2009 was available from authors, we used 8-year follow-up results of PHS-II in our analysis and excluded Gaziano 2012 study.

Table S2.1 Data available on request

Early risk of colorectal cancer	
Women Health Study (WHS) [13]	No published data available for individual arms. Authors provided data (incidence of CRC) on request for 4 arms [aspirin; vitamin E; aspirin with vitamin E; placebo]. (Refer eTable 3.1 Appendix 3)
WACS (The Women's Antioxidant Cardiovascular Study) [14,15]	No published data available for individual arms. Authors provided data (incidence of CRC) on request for 2 arms after intention to treat (ITT) analyses on request [any antioxidants *(vitamin C+ vitamin E+ beta-carotene)*; placebo]. (Refer eTable 3.1 Appendix 3)
WAFACS (Women's Antioxidant and Folic Acid Cardiovascular Study) [16]	No published data available for individual arms. Authors provided data (incidence of CRC) on request for 3 arms after ITT analyses *[folic acid arm; any antioxidants arm; placebo].* (Refer eTable 3.1 Appendix 3) WACS and WAFACS assumed as different trials. Refer *section 1f. Description of data collection from some studies (for more details)*
Physicians' Health Study II [12]	No published data available for individual arms. Authors provided data (incidence of CRC/deaths due to CRC) on request for 2 arms *[any antioxidants; placebo].* ((Refer eTable 3.1 Appendix 3)

Methods S2.1 Strategies of data synthesis and statistical analysis

Definition of primary outcomes:
Primary efficacy outcomes of interest were incidence and mortality due to CRC. We present primary efficacy outcomes stratified by follow-up period after initiation of CPA as early risk (0-10 years) and long-term risk (0 to ≥20 years)

Definition of safety outcomes:
Safety outcomes of interest were major gastrointestinal (GI) bleeding events, defined as events requiring hospitalization, transfusion, leading to death, or defined as fatal or major by the study investigators and cardiovascular (CV) mortality, defined as deaths due to any CV complications including myocardial infarction (MI), stroke (ischemic and haemorrhagic) or defined as CV deaths (excluding deaths due to GI events) by the study investigators.
Description of search strategy and data synthesis for safety outcomes is provided in eTables 3.9-3.10 and eFigure 3.1 in Supplement 3.

1	Early risk: incidence from intervention phase with a follow-up of 0 to 10 years Long-term risk: incidence from both intervention and post-trial phase with a follow-up of 0 to ≥20 years
2	The development of CRC takes place slowly and the full effect of any preventive measure will only be seen in the longer terms (especially CRC mortality).[17] Hence, for long-term risk of CRC incidence and mortality, we stratified studies by follow-up period after initiation of CPA. For primary analysis, we focused studies with follow-up ≥10 years to capture precise long-term effect. In sensitivity analysis, we included all studies with follow-up 0 to ≥ 20 years.
3	We followed the intention to treat principle by using the initial number of randomized participants to each trial arm and performed the analyses irrespective of how the authors of the original trials had analysed the data. Participants who were lost to follow-up were considered survivors, free of CRC or adverse events.
4	We excluded randomized groups that included other interventions (those not defined as CPA/intervention as per our protocol)
5	If there is no separate/complete report of results (events) from each arm of a factorial trial, our results were based on 'at-margins' analysis, comparing all groups that received intervention with groups that did not receive intervention [18].
6	If multiple publications or data of the same trial were retrieved, only the most recent, informative or relevant data were included from these publications.
7	If the same trial (e.g. 2 X 2 factorial with 4 arms (A, B, A+B, Placebo)) reporting the effect of interventions in different publications (e.g. Article-1 reports: A and A+B versus B and Placebo; Article-2 reports: B and A+B versus A and Placebo), we used the results from one publication at a time in our network meta-analysis (because both publications reported results of same population). We used the report of the most relevant

	intervention in the first place (main analysis) and later replaced with the report of the other intervention in the sensitivity analysis.
8	We classified aspirin into three groups for the analysis of long-term risk of CRC incidence and mortality as described by the latest review for the United States Preventive Services Task Force (USPSTF) [19]: high-dose, HDASA (>325 mg/day), low-dose, LDASA (≤325 mg/day) and very-low-dose, VLDASA (≤100 mg/day) aspirin.
9	We defined alternate-day dose of aspirin as follows: we followed the method used by the recent systematic review by USPTF [19,20]; 100 mg every other day is defined as ASA-VLD; and 325 mg every other day defined as ASA-LD.
10	Strategy of data extraction/synthesis for safety outcomes is provided in eTable 3.9
11	**Statistical analysis:** The outcome measure was the risk ratio (RR), which is the ratio between the incidence of CRC (or CRC mortality or adverse events) in the intervention arm and that in the placebo or control arm along with a 95% confidence interval (CI). A RR below 1 indicated that the treatment was associated with a lower risk of the outcome (CRC incidence and mortality and adverse effects) than the comparator while a RR above 1 indicated that the treatment was associated with a greater risks of the outcome than the comparator. For direct comparisons, a standard pairwise meta-analysis was performed by using a random-effects model. If a direct comparison was based on two or more studies, heterogeneity between trials was assessed by considering the I^2 statistics; an I^2 estimate ≥50% was interpreted as evidence of substantial levels of heterogeneity. A random-effects network meta-analysis using either a consistency or an inconsistency model was applied to synthesize the available evidence by combining direct and indirect evidence from different studies. Network inconsistency assumption, which refers to a disagreement between the direct and indirect estimates, was evaluated using a global inconsistency test by fitting design-by-treatment in the inconsistency model. In addition to the indirect comparisons, we also estimated the probability of each treatment being the best (lowest rate of CRC, mortality due to CRC or cardiovascular (CV) mortality) and safest (lowest rate of major gastrointestinal (GI) bleeding events) and constructed rankograms (relative ranking of CPAs) and their surface area under the cumulative ranking (SUCRA). Higher SUCRA scores (ranging from 0 to 1) correspond to higher ranking for prevention of CRC incidence and mortality and lower SUCRA scores correspond to higher ranking for safety in terms of CV mortality and GI bleeding events, compared with other CPAs. Publication bias was examined with a comparison-adjusted funnel plot. The systematic review was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement incorporating network meta-analyses of health care Interventions.
12	**Differences between protocol and final review:** The following changes to the review were made before data analyses were done: • Search was extended to September 2015 to March 2017 • We stratified studies by follow-up period after initiation of CPA • We classified aspirin into three groups for the analysis of long-term risk of CRC as described by the latest review for the USPSTF: high-dose or HDASA (>325 mg/day), low-dose or LDASA (>100 and ≤325 mg/day) and very-low-dose or VLDASA (≤100 mg/day) aspirin. The following changes to the review were made after data analyses were done: • We decided to abstract data on safety outcomes (such as CV mortality and major GI bleeding events) for those interventions with evidence of efficacy (that is, aspirin) • Additional sensitivity analyses were conducted as described in eTable 2.4 • We also performed net clinical benefit analysis of aspirin at different doses
13	**Description of GRADE** The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach adapted to network meta-analysis was used to rate the quality of evidence into four levels [21]: high, moderate, low and very low quality. In this approach, direct estimates from RCTs rated at high quality and can be graded down to moderate, low and very-low quality based on risk of bias, indirectness, imprecision, inconsistency and publication bias. The rating of the quality of the indirect estimates starts at the lowest rating of the two direct estimates that contribute to the indirect estimate of the comparison of interest as first order loops. In the presence of intransitivity, indirect estimate can be further rate down from the lower of the confidence ratings of the contributing direct comparisons. Finally, if both direct and indirect evidence are available then the higher of the two quality ratings can be assigned to the quality rating for NMA estimates.

Table S2.2 Description of data collection and analysis for studies comes under sections 6 and 7 of Table 2.2

Early risk of colorectal cancer	
1	***Physicians' Health Study (PHS)-I:*** This landmark study was begun in the fall of 1982 to test the benefits and risks of aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer. It employed 2X2 factorial design and assigned participants to get one of four possible combinations: active aspirin and active beta-carotene, active aspirin and beta-carotene placebo, aspirin placebo and active beta-carotene, or aspirin placebo and beta-carotene placebo. Aspirin component terminated early after 5 years (participants could then take open label aspirin) and beta-carotene component continued up to 12 years. There were two publications reported based on PHS-I on cancer outcomes (Gann 1993 [22] and Hennekens 1996 [23]). Gann 1993 [22] reported 5-year results of aspirin and Hennekens 1996 [23] reported results of beta-carotene. However, no data/results available for individual arms in this factorial trial. We did not use the data from these two papers together in our analysis. We used aspirin data (5 years) (will be considered as study with high risk of bias-see eTable 3.4) for our main analysis. Beta-carotene data tested in sensitivity analysis (trials with low risk of bias) by excluding aspirin data. We communicated with the PHS study group for getting individual arms data; however, data were not available on request. ***Author's reply:*** Author's not recommended utilizing the Gann paper (report of aspirin arm) as the sole data source for PHS I – it was not analysed as a RCT in the way other main PHS analyses were typically conducted. Hence we considered data from Gann's paper as study with high risk of bias.
2	***Heart Outcomes Prevention Evaluation trial (HOPE):*** HOPE study [24] was designed (2X2 factorial design) to test the hypotheses that two preventive intervention strategies, namely angiotensin-converting enzyme (ACE) inhibition or vitamin E, would improve morbidity and mortality in patients at high risk of cardiovascular events compared with placebo [24]. HOPE also reported whether long-term supplementation with vitamin E or folic acid (later added into trial) decreases the risk of cancer, cancer death. There were 2 publications related to HOPE based on cancer with intervention vitamin E and folic acid: • Lonn 2005 (HOPE/HOPE-TOO) [25] reported effect of vitamin E using all HOPE participants (Primary analysis; N = 9541; follow-up 4.5 years) and results of extension trial (N=7030; follow-up 7 years). In our analysis we used results from all HOPE participants (primary analysis; follow-up 4.5 years). • Lonn 2006 (HOPE 2) [26]: HOPE-2 is a subset of HOPE/HOPE-TOO trial (n=5522). Folic acid component added during the follow-up (5 years) as a part of HOPE-2 investigation (looking the effect on cardio vascular events and cancer). Lonn 2005 [25] and Lonn 2006 [26] reported the results of vitamin E and folic acid components, respectively. No data for separate arms reported. For our primary network meta-analysis analysis, we used data from Lonn 2006 (the latest report of HOPE study). In sensitivity analysis, we replaced HOPE-2 participants with HOPE/HOPE-TOO (Lonn 2005).
3	***Women's Health Study (WHS)*** [13,27]***:*** WHS was designed as a randomized trial (2X2 factorial design) of low-dose aspirin (ASA) and vitamin E (VE) supplementation for the primary prevention of cardiovascular disease and cancer in healthy women with a follow-up around 10 years. No data/results available for individual arms in this factorial trial (ASA; VE; ASA+VE; Placebo). However, we were able to successfully obtained unpublished data for factorial arms from study authors. We used this data for network meta-analysis. But, long-term data of WHS[6] for individual arms were not available. Hence we used the principle of 'at-margins' analysis, i.e. aspirin versus no-aspirin for the analysis of long-term risk of CRC incidence.
4	***The Women's Antioxidant Cardiovascular Study (WACS)/ Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS):*** WACS [14,15] is a randomized, double-blind, placebo-controlled trial (Cook 2007/Lin 2009). It employed 2X2X2 factorial design and participants were assigned to several antioxidants—vitamin E, vitamin C, beta-carotene. Approximately 2 to 3 years following randomization to the antioxidant arms, a folic acid–vitamin B6/B12 component was added to the trial called WAFAC study [16]; a subset of WACS. For our analysis of WACS, we categorized interventions into (provided by author): any antioxidants (vitamin C 500 mg/day + vitamin E 600 IU EOD + beta-carotene 50 mg EOD) (n=7149) and placebo (n= 1022) [WACS period prior to WAFACS, randomized only to antioxidants (June 1995- October 1996 through April 15, 1998)]. WAFACS (Zhang 2008 [16]) is considered as 4-arm factorial design trial. The WAFACS population was first only in WACS and then randomized to folic acid and vitamins B on April 16, 1998. For our analysis of WAFACS, we

	categorized interventions into (provided by author): Folic acid with vitamins B alone (Folic acid 2.5 mg/day + vitamin B12 1 mg/day + vitamin B6 50 mg/day) (n=342); antioxidants alone (vitamin C 500 mg/day + vitamin E 600 IU EOD + beta-carotene 50 mg EOD) (n= 2376); folic acid with vitamins B + antioxidants (n = 2379) and placebo alone (n= 345) [Follow-up: April 16, 1998 - July 31, 2005]. Authors provided data of WACS period (randomized only to antioxidants) prior to WAFACS (June 1995-October 1996 through April 15, 1998 – mean duration 2.2 years). Among 8171 participants of WACS, 2729 participants were not agreed to participate in WAFACS (April 1998). Follow-up data of these participants were also provided (duration ≈ 8 years) by authors. We used the follow-up data from these 2729 participants (considered as WACS participants) not participated in WAFACS for our NMA. Due to the high attrition rate, analysis considered with caveats. Remaining 5442 participants from WACS additionally willing to forgo the use of folic acid with vitamins B (randomization starts from April 1998-WAFACS). We consider it as a different trial (WAFACS) starting from April 1998. We used 4-arm data of WAFACS provided by author (status till July 31, 2005) for analysis (mean follow-up was ≈ 7.3 years for all interventions). For both studies, authors provided data after ITT analyses on request.
5	**Physicians' Health Study II** [12] : Participants were assigned to one of 16 possible combinations of vitamin C (500 mg/day), vitamin E (400 IU EOD), beta-carotene (terminated early), a multivitamin, or their placebos. For our analysis, we categorized interventions into (provided by author): Any anti-oxidants (including multivitamins) (n=13619); Placebo alone (n=901). Participants with prior cancer event at baseline were excluded.
Long-term risk of colorectal cancer	
1	***Norwegian Vitamin Trial (NORVIT) and Western Norway B Vitamin Intervention Trial (WENBIT) follow-up:*** Ebbing 2009 [5] reported combined analysis of extended follow-up of participants from 2 RCTs (randomized double-blind): NORVIT [28] and WENBIT [29] trials, which evaluated the effects of folic acid treatment with B vitamins on cancer outcomes for a duration of 3.2 years. Ebbing reported extended observational follow-up of these 2 trials (combined analysis) for duration of 6.4 years. Since this study considered outcomes from both intervention and post-trial phase as seen in other studies included in long-term evaluation (not "early risk" which considered outcomes from only intervention phase), we included this study in the analysis of long-term incidence of CRC (follow-up period after initiation of CPA 0 to ≥20 years). We did not include the data from these two trials in our primary analysis for long-term CRC incidence, which considered a follow-up period after initiation of CPA with ≥ 10 years.
2	***Physician health study (PHS) follow-up:*** Participants were assigned to aspirin 325 mg EOD and beta-carotene 50 mg EOD in 2X2 factorial design. The aspirin arm of the study was terminated early (after 5 years). Sturmer 1998 [8] reported long-term follow-up results of aspirin arm (12 years); we used this report for long-term analysis.

Table S2.3 Assumptions of sensitivity analyses for network meta-analyses

Early risk of colorectal cancer	
1	Exclusion of studies with high risk of bias
2	Consider folic acid (FA) ± other CPAs as single intervention called Folic acid (instead of considering FA alone, FA+B12, FA+B6+B12 etc.) – in order to confirm the effect of folic acid
3	PHS aspirin data replaced with PHS antioxidants data as discussed above (because of high ROB)
4	Modifying HOPE study data from HOPE-2 (Lonn 2006) participants (Folic acid + vitamin B6 + vitamin B12 vs. placebo) with data from HOPE/HOPE-TOO (Lonn 2005) participants (vitamin E vs. placebo) as discussed above.
Long-term risk of colorectal cancer- Primary analysis: RCTs with follow-up more than 10 years	
Long-term incidence	
1	All RCTs (follow-up 0-20 years or more)
Long-term mortality	
1	All RCTs (follow-up 0-20 years or more)

Methods S2.2 Description of Net clinical benefit analysis

The evidence base on aspirin suggests that it can reduce the risk of cardiovascular disease (CVD) events and colorectal cancer mortality over the long term[19,30]. On the other hand, aspirin increase the risk of major gastrointestinal (GI) bleeding and haemorrhagic stroke or other intracranial bleeding events [19,20,31]. To appreciate the balance of benefits from colorectal cancer mortality prevention and CV benefits with other risks, we performed net clinical benefit analysis (NBA).

In this approach, we review the estimated absolute effect of aspirin on following outcomes:

1) Long-term CRC mortality (as shown in our network meta-analysis) –See Supplement 7 for NMA results

2) CV mortality (defined as mortality due to cardiovascular (CV) events and bleeding events (haemorrhagic stroke or intracranial or other bleeding events), excluding GI bleeding events) - See Appendix 8 for NMA results

CV mortality here may indirectly represent the overall benefits from CV outcomes (Overall CV benefits = Benefits (CV events such as MI, ischemic stroke etc.) - harms (haemorrhagic stroke or intracranial or other bleeding events except GI bleeding events) of aspirin therapy.

3) Major GI bleeding events - See Supplement 8 for NMA results

[Item 1 and 2 represents the benefits and item 3 represents harms from aspirin therapy]

Net clinical benefit analysis (NBA) analysis was based on the approach used in a previous meta-analyses [32,33] and was calculated according to the formula,

We calculated net survival gain (a way to represent the results of NCB) by reviewed reviewing the estimated absolute effect of aspirin on long-term CRC mortality and CV mortality, and other CV events apart from GI bleeding events) and subtracted the risk of mortality due to major GI bleeding events.

Net survival gain (%)= Difference in pooled risk estimates of CRC mortality between reference and intervention + Difference in pooled risk estimates of CV mortality between reference and intervention - Weight x difference in pooled risk estimates of major GI bleeding events between reference and intervention.

The weighting factor was determined from the proportion of death among patients with GI bleeding. Based on several previous publications [31,34–38], fatal GI bleeding event had 6% of the effect of a single mortality, therefore a weighting factor of 0.06 was used. Additional sensitivity analyses of net clinical benefit were conducted by varying weighting factors from 0.01 to 0.16. (See below)

Description of derivation of weighting factor

According to the NCB calculation method from Chatterjee et al [32], the weighting factor was derived from the previous publication [39], which is basically based on the likelihood of death and serious disability due to ICH.

- Quote “At hospital discharge, 76% of patients with intracranial haemorrhage had severe disability or died.”

Similarly, weighting factor to indicate the relative effect of gastro intestinal bleed to death associated with aspirin therapy can be derived based on:
1) the previous observational study to investigate the estimate of mortality associated with major GI events with NSAIDs use was conducted in Spain by using the Spanish National Health System [36]. The prevalence of NSAID/aspirin use (including OTC use) in the study population was estimated to be approximately 19% (17.7% to 19.8%). The estimated rate of GI complications in patients not previously exposed to NSAIDs/aspirin was over 120 per 100,000 patients/year, while in patients previously exposed to NSAIDs/aspirin rates were substantially higher at 480/100,000 patients/year. Therefore, the proportion of complications and deaths attributed to NSAID/aspirin use was 36.3%.

- Using the data given above, the estimated number of GI complication events and deaths attributed to NSAID/aspirin use for the entire country was 15,031 and 860 (5.72%), respectively, for study 1, and 18,191 and 1,022 (5.62%), respectively, for study 2.
- When the number of complications and deaths were calculated by the type of NSAID used, low-dose aspirin was responsible for no less than 8.2% and no more than 12.2% of all complications and deaths; therefore, between 4,109 and 6,113 complications, and 231 (5.62%) and 343 (5.61%) deaths, approximately, were due to low-dose aspirin use.

2) Elwood et al.[40] conducted a systematic review and meta-analysis of randomised trials to estimate the frequency of fatal GI bleeds from aspirin. 11 RCT were included in the review with 9 trials were assessed as having low risk of bias. Aspirin was used at dose ranging from 100 mg alternate days to 1900 mg daily. The risk of a bleed attributable to aspirin being fatal was 0.45 (95% CI 0.25, 0.80).

- From table 1, estimated number of fatal GI bleeding that attributed to aspirin use from each of included trials was ranging from 0-14%, with an average about 7.5%.

- From table 2, the number of bleeds during on aspirin was 468 patients. Of these, 24 patients were death (5.1%).

Therefore, if we assume that the incidence of GI bleeding is constant persists throughout the duration of aspirin use, **weighting factor to demonstrate death contributed by aspirin should be 0.06.**

Variation of weighting factor for sensitivity analysis to demonstrate the different in risk of deaths attributed to aspirin can be derived based on the studies below.
- Rockall et al [37] demonstrated the incidence of and mortality from acute upper GI bleeding in United Kingdom. The overall incidence of acute upper gastrointestinal haemorrhage in the United Kingdom is 103/100,000 adults per year. **Overall mortality was 14%** (11% in emergency admissions and 33% in haemorrhage in inpatients).
- Straube et al [38] published a systematic review on mortality with UGIB attributed from NSAIDs or aspirin.4 77 data sets during 1997-2008 with variation of method from case report to RCTs were included in their analysis. **The study demonstrated the overall mortality rate of UGIB or perforation among case using NSAIDs for 16.4% (15.4 to 17.3).**
    - The major limitation of this study is included studies rarely stratified mortality according to a specific diagnosis, and it was not possible to perform analyses based on diagnosis. Mortality was reported in different ways; as a simple report of death, 30-day mortality, death in hospital or at home, upper-gastrointestinal-related death, and others.
- Whitlock et al [31] performed systematic review on bleeding risks with aspirin use for primary prevention in adults. Using available trial and cohort data, the study found that the risk for bleeding associated with low-dose aspirin use probably persists throughout use but declines with discontinuation.
    - In the Women's Health Study, the cumulative incidence of GI bleeding did not plateau in very-low-dose aspirin users compared with placebo recipients throughout 10 years of follow-up.
    - In contrast, a time point–stratified IPD meta-analysis suggested that the risk for major extracranial bleeding seen in early years decreased after 3 years. Because bleeding risks with placebo also declined with time, however, another mechanism for reduced bleeding events (such as unequal observation time) could have driven this observation.
    - Two cohort studies found that bleeding risk in regular aspirin users did not vary by duration of use (<5 years or ≥5 years).
    - Weak evidence from the Women's Health Study suggested that excess GI bleeding risk rapidly attenuates after stopping aspirin.
- The U.S. Preventive Services Task Force (USPSTF) [34,35] initiated the decision analysis to assess the net balance of benefits and harms from routine aspirin use. Case-fatality rates for GI bleeding, based on patients without complicating comorbidities, were derived from a prospective study conducted in the United Kingdom. **The probability of dying from GI bleeding was increase from 1% for age 40-59 years to 19% for age more than 80 years.**

Based on above data, if we assume that the incidence of GI bleeding is constant persists throughout the duration of aspirin use, weighting factor to demonstrate death contributed by aspirin should be 0.06 (vary from 0.01-0.16).

Statistical analysis: Pooled risk estimate of the treatment with reference was calculated by using meta-analyses of proportions (calculated by using meta-analyses of proportions in Stata with metaprop command) [41]. To obtain the 95% confidence intervals of NBA, we performed 1000 bootstrap samples of risk estimates for each intervention to calculate the risk differences among group receiving placebo and various doses of aspirin [42,43].

Supplement 3: Characteristics and risk of bias assessment of included studies

Table S3.1 - Characteristics of RCTs reported early risk of CRC incidence

Author year, (reference)	Study name	Location	Design	Interventions (n=number of subjects randomized)	Primary outcome	Secondary outcomes	Treatment duration (mean/median)	Adherence – strategies and study compliance
Gann 1993/ Hennekens 1996 [22,23]	Physicians' Health Study (PHS)	USA	Randomized, double-blind, placebo-controlled trial; 2x2 factorial design	Aspirin 325 mg EOD and beta-carotene 50 mg EOD (n=5,517); Aspirin 325 mg EOD (n=5,520); Beta-carotene 50 mg EOD (n=5,519); Placebo (n=5,515)	MI and other CV events (aspirin component); cancer (beta-carotene component)	Mortality due to cancer and/or CV events; adverse effects	5 years for aspirin; 12 years for beta-carotene (aspirin component terminated early; after 5 years participants could then take open label aspirin)	≈ 4 mo. run-in; questionnaire; blood samples; >80% adherence reported
Peto 1988 [9,10,44]	British doctor aspirin trial (BDA) follow-up	UK	Open control; ; parallel	Aspirin 300 or 500 mg/day (not analysed separately) (*n* = 3429); Open control (n = 1710)	CV events	Mortality from CV causes	6 years [at least 5 years for all patients] (follow-up to 9)	Questionnaire; 81% were compliant after 1 year but that a further 5% discontinued study aspirin during each of the next 5 years, mainly as a result of gastrointestinal symptoms
Farrell 1991 [9,10,45]	United Kingdom transient ischaemic attack (UK-TIA) aspirin	UK and Ireland	Randomized, double-blind, placebo-controlled trial; 2x2 factorial design	Aspirin 300 or 1200 mg/ day (not analysed separately) (*n* = 1632); Placebo (*n* = 817)	CV events	Mortality from vascular and non-vascular causes	4.4 years [1-7 years] (Follow-up up to 9)	By interview and urine sample; about 12% of patients stopped trial medication before the 4-month

Author year, (reference)	Study name	Location	Design	Interventions (n=number of subjects randomized)	Primary outcome	Secondary outcomes	Treatment duration (mean/median)	Adherence – strategies and study compliance
	trial follow-up							follow-up (although some restarted later), and 12% of patients randomised to placebo started taking non-trial aspirin at some stage during the trial
Omenn 1996 [46,47]	Carotene and Retinol Efficacy Trial (CARET)	USA	Randomized, double-blind, placebo-controlled trial; parallel	Vitamin A 25,000 IU/day + beta-carotene 30 mg/day (n = 9420); Placebo (n = 8894)	Lung cancer	Other cancers; CV events; overall mortality	4 years	No run-in period; Questionnaire; pills count; 88% of the participants took over 90% of the prescribed capsules
HPS group 2002 [48]	Heart Protection Study (HPS)	UK	Randomized, double-blind, placebo-controlled trial; 2x2 factorial design	Vitamin C 250 mg/day + vitamin E 600 mg/day + beta-carotene 20 mg/day (n = 10,269); Placebo (n= 10, 267) [approximately 50% of participants in both intervention and placebo groups also received simvastatin, 40 mg/day]	Major coronary events and fatal or non-fatal vascular events	Cancers and of other major morbidity	5 years	≈ 1-2 mo. run-in; pills count; blood assays; >80% adherence reported
Duffield-Lillico 2002 [49,50]	Nutritional Prevention of Cancer trial (NPCT)	USA	Randomized, double-blind, placebo-controlled trial; parallel	Selenium 200 microgram/day (n=653); Placebo (n=659)	Recurrence of non-melanoma skin cancer	Other cancers, and overall mortality	4.5 years (treatment duration); 7.4 years (follow-up).	No run-in period; follow-up visit and enquiry; selenium assay; 79.3% of participants missed taking a pill less than twice a month
Albanes 2000/ Virtamo	Alpha-Tocopherol, Beta-	Finland	Randomized, double-blind, placebo-controlled trial; 2x2	Vitamin E 50 mg/day (n=7286); Beta-carotene 20 mg/day (n=7282); Vitamin E 50 mg/day + Beta-	Lung cancer	Other cancers, and overall mortality	6.1 years	No run-in period; pills count; blood assays; participants

Author year, (reference)	Study name	Location	Design	Interventions (n=number of subjects randomized)	Primary outcome	Secondary outcomes	Treatment duration (mean/median)	Adherence – strategies and study compliance
2003 [3,51,52]	Carotene Cancer Prevention (ATBC) Study		factorial design	carotene 20 mg/day (n=7278); Placebo (n= 7287)				took over 95% of their capsules
Trivedi 2003 [53]	NA	UK	Randomized, double-blind, placebo-controlled trial; parallel	Vitamin D3 100 000 IU every four months (n= 1345); Placebo (n= 1341)	Fracture incidence	Cancers, CV events and total mortality by cause	5 years	No run-in period; send form by freepost (intake of capsule); 76% of participants had at least 80% compliance
Zhu 2003 [54]	NA	China	Randomized, double-blind, placebo-controlled trial; 4 arms trial	Folic acid, 20 mg/day + vitamin-B12 1 mg, intramuscularly, per month for one year, then 20 mg two times a week plus 1 mg per three months for the next year (n=44); Beta-carotene (natural), 30 mg/day for 1 year then 30 mg twice/week for 1 year) (n = 61); Beta-carotene (synthetic), administered as in natural beta-carotene (n = 57); Placebo (n=54)	Stomach cancer	Other gastro-intestinal cancer	2 years (treatment duration); 6 years (follow-up)	No run-in period; pills count; blood assays; adherence ≥ 90% reported
Hercberg 2004 [55,56]	Supple´mentationen Vitamines et Minéraux Antioxydants study (SU.VI.MAX)	France	Randomized, double-blind, placebo-controlled trial; parallel	Vitamin C 120 mg/day + vitamin E 30 mg/day + beta-carotene 96 mg/day + selenium 100 microgram/day + zinc 20 mg/day (n = 6481); Placebo (n=6536)	CV events and cancer	All-cause mortality	7.5 years	No run-in period; monthly questionnaire; blood assays; 74% of the participants reported having taken at least two thirds of the capsules
Lonn 2005 [25,57]	Heart Outcomes	Canada, USA,	Randomized, double-blind, placebo-	Vitamin E 400 IU/day (n = 4761); Placebo (n=4780)	Cancer incidence,	Heart failure, unstable angina,	4.5 years (primary	No run-in period; pills count; blood

Author year, (reference)	Study name	Location	Design	Interventions (n=number of subjects randomized)	Primary outcome	Secondary outcomes	Treatment duration (mean/median)	Adherence – strategies and study compliance
Lonn 2006 [24,26]	Prevention Evaluation trial (HOPE)/ Heart Outcomes Prevention Evaluation-2 (HOPE-2)	Brazil, Slovakia and Western Europe	controlled trial; 2x2 factorial design; We used results from all HOPE participants, not HOPE–The Ongoing Outcomes [HOPE-TOO] results.	[factorial trial; approximately 50% of participants in both vitamin E and placebo groups also received ramipril, 10 mg/day; later added folic acid component as a part of HOPE-2]	cancer deaths, and major CV events	and revascularizatio ns	analysis duration); 7 years (extension phase)- HOPE/HOPE TOO	assay; compliance around 90% reported
				Folic acid 2.5 mg/day + vitamin B6 50 mg/day + vitamin B12 1 mg/day (n=2758); placebo (n= 2764) [some participants also received vitamin E; subset of HOPE/HOPE-TOO trial]	Composite of death from cardiovascular causes, myocardial infarction, and stroke	Ischemic events, death from any cause, the incidence of cancer, and death from cancer	5 years - HOPE-2	No run-in period; by interview and pill count; plasma levels of folate; compliance around 90% reported
Cook 2005/Lee 2005 [13,27]	Women's Health Study (WHS)	USA	Randomized, double-blind, placebo-controlled trial; 2x2 factorial design	Vitamin E 600 IU EOD and aspirin 100 mg EOD (n=9,966); Vitamin E 600 IU EOD (n=9,971); Aspirin 100 mg EOD (n=9,968); Placebo (n=9,971) [The trial initially contained a beta-carotene component (50mg EOD for 2 years); stopped early due to lack of effectiveness]	Cancer or CV events	Breast, colorectal, and lung cancer	10.1 years	≈ 4 mo. run-in; annual questionnaire; taking at least two thirds of the study aspirin or aspirin placebo, was 76% at 5 years and 67% at 10 years, with an average of 73% throughout the trial
Wactawski-Wende 2006 [58]	Women's Health Initiative study (WHI)	USA	Randomized, double-blind, placebo-controlled trial; parallel	Calcium carbonate 1000 mg/day (elemental calcium) + vitamin D3 400 IU/ day (taken in two divided doses daily) (n= 18,176); Placebo (n= 18,106)	Hip fractures	Other fractures, colorectal cancer	7 years	No run-in period; weighing returned pill bottles; 70 % took >50% of their study medication through year 6
Lappe 2007 [59]	NA	USA	Randomized, double-blind, placebo-	Calcium (calcium citrate 1400 mg/day OR calcium carbonate	Fracture	Cancer	4 years	No run-in period; weighing returned

Author year, (reference)	Study name	Location	Design	Interventions (n=number of subjects randomized)	Primary outcome	Secondary outcomes	Treatment duration (mean/median)	Adherence – strategies and study compliance
			controlled trial; 3 arms	1500 mg/day) (n= 445); Calcium + vitamin D 1000 -1100 IU/day (n=446); Placebo (n = 288) (article reports two different doses of vitamin D in abstract and methods)				pill bottles in 6-mo interval; mean adherence (74-86%) reported
Cook 2007/Lin 2009 [14,15]	The Women's Antioxidant Cardiovascular Study (WACS)	USA	Randomized, double-blind, placebo-controlled trial; 2X2X2 factorial design; participants were assigned to several antioxidants—vitamin E, vitamin C, beta-carotene: approximately 2 to 3 years following randomization to the antioxidant arms, a folic acid–vitamin B6/B12 component was added to the trial (called WAFAC study; subset of WACS)	For our analysis, we categorized interventions into (provided by author): any antioxidants (vitamin C 500 mg/day + vitamin E 600 IU EOD + beta-carotene 50 mg EOD) (n=7149); Placebo (n= 1022) [WACS period prior to WAFACS, randomized only to antioxidants (June 1995- October 1996 through April 15, 1998)]	CV events	Cancer , overall mortality	≈ 8 years (for those participants not agreed to be a part of WAFACS; provided by author)	No run-in period; self-report; mean adherence 76% reported
Zhang 2008 [16]	Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS)	USA	Randomized, double-blind, placebo-controlled trial (WACS is the parent trial of WAFACS– 4-arm factorial design; The WAFACS population was first	For our analysis, we categorized interventions into (provided by author): folic acid with vitamins B alone (Folic acid 2.5 mg/day + vitamin B12 1 mg/day + vitamin B6 50 mg/day) (n=342); Antioxidants alone (vitamin C 500	CV events	Cancer , overall mortality	6.8 years (provided by author) Reported 7.3 years	No run-in period; self-report; mean adherence 83% reported

Author year, (reference)	Study name	Location	Design	Interventions (n=number of subjects randomized)	Primary outcome	Secondary outcomes	Treatment duration (mean/median)	Adherence – strategies and study compliance
			only in WACS and then randomized to folic acid and vitamins B on April 16, 1998)	mg/day + vitamin E 600 IU EOD + beta-carotene 50 mg EOD) (n= 2376); Folic acid with vitamins B + antioxidants (n = 2379); Placebo alone (n= 345) [April 16, 1998 - July 31, 2005]				

Lippman 2009 [60]	Selenium and Vitamin E Cancer Prevention Trial (SELECT)	USA, Canada, and Puerto Rico	Randomized, double blind, placebo-controlled trial; 2x2 factorial design	Selenium 200 microgram/day (n = 8910);
				vitamin E 400 IU/day (n = 8904);
				selenium + vitamin E (n = 8863);
				placebo (n = 8856)
					Prostate cancer	Other cancers	5.5 years	No run-in period; follow-up every 6 mo.; blood assay; pill count; adherence 83% at year 1 and 65% at year 5

Gaziano 2009 [12]	The Physicians' Health Study II (PHS II)	USA	Randomized, double blind, placebo-controlled trial; 2x2X2X2 factorial design	Participants were assigned to one of 16 possible combinations of vitamin C (500 mg/day), vitamin E (400 IU EOD), beta-carotene (terminated early), a multivitamin, or their placebos. For our analysis, we categorized interventions into (provided by author): Any anti-oxidants (including multivitamins) (n=13619): Placebo alone (n=901) Participants with prior cancer event at baseline were excluded.	CV disease, Prostate and total cancer	Other cancers	8 years	3 mo. run-in; annual questionnaire; adherence 78% reported.
Armitage 2010 [61,62]	Study of the Effectiveness of Additional Reductions	UK	Randomized, double blind, placebo-controlled trial; 2x2 factorial design	Folic acid 2 mg/day + vitamin B12 1 mg/day (n= 6033); Placebo (n= 6031) [factorial trial; approximately 50% of participants in both vitamin E and	CV events	Cancer	6.7 years	run-in period (duration not mentioned); pill count; blood assay; adherence around

Author year, (reference)	Study name	Location	Design	Interventions (n=number of subjects randomized)	Primary outcome	Secondary outcomes	Treatment duration (mean/median)	Adherence – strategies and study compliance
	in Cholesterol and Homocysteine (SEARCH)			placebo groups also received simvastatin, 20-80 mg/day]				90% after 1 year and 84% after 6 years
Hankey 2012 [63,64]	Vitamins to Prevent Stroke (VITATOPS) trial	20 countries	Randomized, double blind, placebo-controlled trial; parallel	Folic acid 2 mg/day + vitamin B6 25 mg/day + vitamin B12 0·5 mg/day (n= 4089); Placebo (n= 4075)	CV events	Cancer , overall mortality	3.4 years	No run-in period; follow-up every 6 mo.; blood assay; adherence-unclear
Gao 2013 [65]	NA	China	Open-control; parallel	Folic acid 1 mg/ day (n=430); Control (without folic acid or multivitamins) (n=430)	Colorectal adenomas	Number, size, location and sub-type of adenomas	3 years	2 weeks run-in period; follow-up visit and enquiry (for control group: telephone enquiry or self-report); adherence-not reported

EOD: every other day; NA: not available or not applicable; CV: cardiovascular; MI: myocardial infarction; IU: international unit

Table S3.2- Population characteristics of RCTs reported early risk of CRC incidence

Author, year	Study name	Population	No. of participants randomized	Age	Sex (% males)	Smokers (% current)	Baseline comparability between groups	Number of randomized participants excluded from main analysis
Gann 1993/ Hennekens 1996 [22,23]	PHS	Male physician	22,071	Mean, 53	100	11	Yes	0 of 22,071 (0%) excluded from main analysis
Peto 1988 [9,10,44]	BMD	Male physicians	5139	Mean, 61.6	100	18	Yes	0 of 5139 (0%) excluded from analysis
Farrell 1991 [9,10,45]	UK-TIA	History of TIA or stroke	2449	Mean, 60.3	73%	52	Yes	0 of 2435 (0%) excluded from analysis
Omenn 1996 [46,47]	CARET	Smokers, former smokers and workers exposed to asbestos at high risk of developing lung cancer	18,314	Mean, 57	66	60	Yes	0 of 18,314 (0%) excluded from main analysis
HPS group 2002 [48]	HPS	History of coronary and other occlusive arterial disease or diabetes	20, 536	Range, 40–80	75	NA	Yes	67 of 20,536 (0.3%) participants without information to end of the scheduled treatment period for mortality and morbidity were excluded.
Duffield-Lillico 2002 [49,50]	NPCT	History of non-melanoma skin cancer	1312	Mean, 63	75	28.5	Yes	62 of 1312 (5%) participants excluded as no valid baseline selenium values
Albanes 2000/Virtamo 2003 [3,51,52,66,67]	ATBC	Male cigarette smokers	29,133	Mean, 57	100	100	Yes	9061 of 29,133 (31%) participants left the study for any reason, including death. All participants were included for main analysis.
Trivedi 2003 [53]	NA	Doctors and the general practice population	2686	Mean, 75	76	56	Yes	0 of 2686 (0%) excluded from analysis
Zhu 2003 [54]	NA	Patients with atrophic gastritis	216	Mean, 56	63	NA	Unclear	0 of 216 (0%) excluded from analysis

Author, year	Study name	Population	No. of participants randomized	Age	Sex (% males)	Smokers (% current)	Baseline comparability between groups	Number of randomized participants excluded from main analysis
Hercberg 2004 [55,56]	SU.VI.MAX	General population	13,017	Mean, 49	39	16	Yes	1567 of 13,017 (12%) lost to follow-up. All participants were included for main analysis.
Lonn 2005/ [25,57] Lonn 2006 [24,26]	HOPE/ HOPE-2	History of CV disease or diabetes	9541	Mean, 66	73	14	Yes	0 of 9541 (0%) excluded from main analysis
			5504	Mean, 69	72	11.5	Yes	37 of 5522 (0.7%) participants did not complete the study (declined to continue or lost to follow-up). All participants were included for main analysis.
Cook 2005/Lee 2005 [13,27]	WHS	Female health professionals	39, 876	Mean, 55	0	13	Yes	1596 of 39, 876 (4%) with unknown vital status or dead. All participants were included for main analysis.
Wactawski-Wende 2006 [58,68]	WHI	Postmenopausal women	36,282	Mean, 59	0	0.12 (annualized %)	Yes	2531 of 36,282 (7%) participants died, withdrawn or lost to follow-up. All participants were included for main analysis.
Lappe 2007 [59]	NA	Postmenopausal women	1179	Mean, 67	0	NA	NA	92 of 1179 (8%) lost to follow-up. All participants were included for 1-4 year analysis.
Cook 2007/Lin 2009 [14,15]	WACS	Female health professionals at high risk of CV disease	8171 (only to WACS-2729)	Mean, 60	0	15	Yes	544 of 8171 (7%) excluded; with prior history of cancer before enrolment. All participants were included for main analysis (follow-up 2.2 years). 5442 WACS participants agreed to continue WAFACS. Hence, we used only data from 2729 participants those who not agreed to participate in WAFACS (67% excluded)
Zhang 2008 [16]	WAFACS	Female health professionals at high risk of CV disease	5442	Mean, 63	0	11.8	Yes	418 of 5442 (7.6%) excluded; with prior history of cancer before enrolment. All participants were included for main analysis
Lippman	SELECT	General population	35,533	Median,	100	8	Yes	645 of 35,533 (2%) excluded from primary

Author, year	Study name	Population	No. of participants randomized	Age	Sex (% males)	Smokers (% current)	Baseline comparability between groups	Number of randomized participants excluded from main analysis
2009 [60]		(men only)		62-63				analysis as ineligible, insufficient data or lost to follow-up.
Gaziano 2009 [12]	PHS II	Male physicians	14,641	Mean, 64	100	3.5	Yes	121 of 14,641 (1%) not analysed for colorectal cancer; prior history of colorectal cancer at baseline
Armitage 2010 [61,62]	SEARCH	History of MI	12,064	Mean, 64	83	12	Yes	119 of 12,064 (6%) not completed follow-up. All participants were included for main analysis.
Hankey 2012 [63,64]	VITATOPS	History of recent stroke or transient ischaemic attack	8164	Mean, 62	64	50 (ever smoked)	Yes	702 of 8164 (8.6%) lost to follow-up. All participants were included for main analysis.
Gao 2013 [65]	NA	General population	860	Mean, 61	50%	17.3	Yes	69 of 860 (8%) participants not completed follow-up colonoscopy. All participants were included for main analysis.

NA: not available/not applicable; CV: cardiovascular; MI: myocardial infarction

Table S3.3- Efficacy outcomes of RCTs reported early risk of CRC incidence

Author, year (reference)	Study name	Study group	Efficacy outcome	Remarks
			Incidence of CRC (n/N)	
Gann 1993/ Hennekens 1996 [22,23,69,70]	PHS-I	Aspirin 325 mg EOD (5 years)	63/11 037	Description provided in Appendix 2 (Table 2.4).
		No aspirin (5 years)	55/11034	
		Beta-carotene 50 mg EOD (12 years)	167/11036	
		Aspirin 325 mg EOD (5 years)	174/11035	
Peto 1988 [9,10,44]	BMD	Aspirin 500 mg (or 300 mg if requested) daily	28/3429	Long-term follow-up results also reported.
		No aspirin	17/1710	Considered as ASA-HD (no data for individual dose available). Long-term follow-up results also reported.
Farrell 1991 [9,10,45]	UK-TIA	Aspirin 300 mg daily or 600 mg twice daily (1200 mg total per day)	18/1632	
		Placebo	8/817	
Omenn 1996 [46,47,71]	CARET	Vitamin A 25,000 IU + beta-carotene 30 mg/day	56/9420	Post-trial follow-up data of CARET also reported and analysed separately.
		Placebo	36/8894	
HPS group 2002 [48,70,71]	HPS	Vitamin C 250 mg/day + vitamin E 600 mg/day + beta-carotene 20 mg/day	117/10269	We used the initial number of randomized participants for analysis
		Placebo	140/10267	
Duffield-Lillico 2002 [49,50,71]	NPCT	Selenium 200 microgram/day	9/653	We used the initial number of randomized participants for analysis.
		Placebo	19/659	
Albanes 2000/Virtamo 2003 [3,51,52,66]	ATBC	Vitamin E 50 mg/day	29/7286	Post-trial follow-up data of ATBC also reported and analysed separately. We used the initial number of randomized participants for analysis as reported.
		Beta-carotene 20 mg/day	39/7282	
		Vitamin E 50 mg/day + Beta-carotene 20 mg/day	30/7278	
		Placebo	37/7287	
Trivedi 2003 [53]	NA	Vitamin D3 100 000 IU every four months	28/1345	Reported as colon cancer.
		Placebo	27/1341	
Zhu 2003 [54]	NA	Folic acid + vitamin B12	0/44	Data on beta-carotene natural and synthetic analysed together
		Beta-carotene (natural and synthetic)	0/118	

Author, year (reference)	Study name	Study group	Efficacy outcome Incidence of CRC (n/N)	Remarks
		Placebo	1/54	
Hercberg 2004 [55,56]	SU.VI.MAX	Vitamin C + vitamin E + beta-carotene + selenium + zinc	21/6481	We used the initial number of randomized participants for analysis as reported.
		Placebo	24/6536	
Lonn 2005 [25,70]	HOPE/ HOPE TOO	Vitamin E 400 IU/day	69/4761	Used all HOPE Study participants. Description provided in Appendix 2 (Table 2.4).
		Placebo	57/4780	
Lonn 2006 [24,26,70]	HOPE-2	Folic acid 2.5 mg/day + vitamin B6 50 mg/day + vitamin B12 1 mg/day	50/2758	HOPE-2 (Lonn 2006) is a subset of HOPE/HOPE-TOO trial. Description provided in Appendix 2 (Table 2.4).
		Placebo	37/2764	
Cook 2005/Lee 2005 [13,27,72]	WHS	Aspirin 100 mg EOD + vitamin E 600 IU EOD	75/9,966	Authors provided data for factorial arms on request. Description provided in Appendix 2 (Table 2.4).
		Aspirin 100 mg EOD	69/9,968	
		Vitamin E 600 IU EOD	68/9,971	
		Placebo	82/9,971	
Wactawski-Wende 2006 [58,70]	WHI	Calcium 1000 mg/day (elemental calcium) + vitamin D3 400 IU/day	168/18,176	A total of 339 colorectal cancers were reported. Analyses limited to the 322 invasive colorectal cancers.
		Placebo	154/18,106	
Lappe 2007 [59]	NA	Calcium (as Ca. citrate 1400 mg/day or Ca. carbonate 1500 mg/day)	0/445	Reported as colon cancer.
		Calcium 1400-1500 mg/day + vitamin D 1000-1100 IU/day	1/446	
		Placebo	2/288	
Cook 2007/Lin 2009 [14,15]	WACS	Any antioxidants	3/7149 (2.2 yrs) 5/2394 (8 yrs)	Description provided in Appendix 2 (Table 2.4).
		Placebo	2/1022(2.2 yrs) 2/335 (8 yrs)	
Zhang 2008 [16]	WAFACS	Folic acid with vitamins B (B12 and B6)	2/342	Description provided in Appendix 2 (Table 2.4).
		Antioxidants	20/2376	
		Folic acid with vitamins B +	16/2379	

Author, year (reference)	Study name	Study group	Efficacy outcome Incidence of CRC (n/N)	Remarks
		antioxidants		
		Placebo	2/345	
Lippman 2009 [60]	SELECT	Selenium 200 microgram/day	63/8910	We used the initial number of randomized participants to each trial arm.
		Vitamin E 400 IU/day	66/8904	
		Selenium + vitamin E	77/8863	
		Placebo	60/8856	
Gaziano 2009 [12]	PHS II	Any antioxidants	152/13619	Authors provided data for two arms on request. 121 of 14,641 participants not analysed for colorectal cancer because of prior history of colorectal cancer at baseline.
		Placebo	43/13619	
Armitage 2010 [61,62]	SEARCH	Folic acid 2 mg/day + vitamin B12 1 mg/day	86/6033	Nil
		Placebo	91/6031	
Hankey 2012 [63,64]	VITATOPS	Folic acid 2 mg/day + vitamin B6 25 mg/day + vitamin B12 0·5 mg/day	21/4089	Nil
		Placebo	21/4075	
Gao 2013 [65]	NA	Folic acid 1 mg/day	2/430	Nil
		Control	2/430	

All our analyses followed the intention-to-treat principle. We used the initial number of randomized participants to each trial arm and performed the analyses irrespective of how the authors of the original trials had analysed the data. Participants who were lost to follow-up were considered survivors, free of colorectal cancers/adverse events.

n: number of events; N: number of randomized participants; EOD: every other day; NA: not available or not applicable; CV: cardiovascular; MI: myocardial infarction; IU: international unit; ADR: adverse events; CRC: colorectal cancer; GIB: gastrointestinal bleeding; PU: peptic ulcer

Table S3.4- Risk of bias assessment (Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) of RCTs reported early risk of CRC incidence

We used unpublished data and assumptions for several studies in our analysis (appendix 2), which is provided by authors and we followed direction from authors of these studies for data extraction for our analysis. Hence, we followed ROB assessment by considering the provided data and comments from authors, not solely based on the original papers published.

Author, year	Study	A	B	C	D	E	F
Gann 1993 [22,23]	PHS (ASA)	+	+	+	+	-	-
Hennekens 1996 [22,23]	PHS (AO)	+	+	+	+	+	+
Peto 1988 [9,10,44]	BDAT	+	?	+	+	+	+
Farrell 1991 [9,10,45]	UK-TIA	+	+	+	+	+	+
Omenn 1996 [46,47]	CARET	+	+	+	+	?	+
HPS group 2002 [48]	HPS	+	+	+	+	+	+
Duffield-Lillico 2002 [49,50]	NPCT	+	+	+	+	+	+
Albanes 2000/Virtamo 2003 [3,51]	ATBC	+	+	?	+	+	+
Trivedi 2003 [53]	NA	+	+	+	+	+	?
Zhu 2003 [54]	NA	-	?	+	?	?	-
Hercberg 2004 [55,56]	SU.VI.MAX	+	+	+	+	+	+
Lonn 2006 [24,26]	HOPE-2	+	+	+	+	+	+
Cook 2005/Lee 2005 [13,27]	WHS	+	+	+	+	+	+
Wactawski-Wende 2006 [58,68]	WHI	+	+	+	+	+	+
Lappe 2007 [59]	NA	-	+	?	+	+	+
Cook 2007/Lin 2009 [14,15]	WACS	+	+	-	+	?	-
Zhang 2008 [16]	WAFACS	+	+	+	+	+	+
Lippman 2009 [60]	SELECT	+	+	+	+	+	+
Gaziano 2009 [12]	PHS II	+	+	+	+	+	+
Armitage 2010 [61,62]	SEARCH	+	+	+	+	+	+
Hankey 2012 [63,64]	VITATOPS	+	+	+	+	+	+
Gao 2013 [65]	NA	?	+	+	+	+	+

A-Bias arising from the randomization process; B- Bias due to deviations from intended interventions; C- Bias due to missing outcome data; D- Bias in measurement of the outcome; E-Bias in selection of the reported result; F-Overall bias.

+symbol/green colour means 'low risk of bias'; symbol/yellow colour means 'some concerns'; - symbol/red colour means 'high risk of bias'

Gann 1993 (PHS): primary outcome was CV events. Aspirin component terminated early (after 5 years). *Author's comment-"No data available for separate arms; not recommend utilizing the Gann paper as the sole data source for PHS I (original data not published)– it was not analysed as a RCT in the way our other main PHS analyses were typically conducted; analysis needs to be considered with caveats."* But not applicable for anti-oxidants arms. **Judgment: plausible bias that seriously weakens confidence in the results for aspirin report (Gann 1993).**

Peto 1988 (**BDAT):** low risk **(**Randomization-yes; allocation concealment: no information; baseline comparability: similar); some concerns (participants aware about blinding (open label) and there is no information on whether there were deviations from usual practice that were likely to impact on the outcome. **Judgment: no plausible bias may seriously weakens confidence in the results (low risk).**

Omenn 1996 (CARET): interim analysis of CARET study (1995- mean of 4.0 years of follow-up after randomization); promptly after 1996, announced that active intervention has stopped because of no evidence of benefit. **Judgment: no plausible bias that seriously weakens confidence in the results (low risk).**

ATBC: 9061 of 29,133 (31%) participants left the study for any reason, including death; the groups differed in the number of such dropouts by less than 37 (unclear) **Judgment: plausible bias that seriously weakens confidence in the results.**

Trivedi 2003: Used questionnaire-"incidences of cancer by using events identified from questionnaires or death certification by cause". **Judgment: no plausible bias that seriously weakens confidence in the results (low risk).**

Zhu 2003: Allocation probably not concealed; baseline comparability unclear; participants were consecutive out-patients (inadequate random sequence); blinding unclear for participants, personals and outcome assessors. **Judgment: plausible bias that seriously weakens confidence in the results.**

Lappe 2007: Allocation concealment-unclear; baseline comparability no reported; 92 of 1179 (8%) lost to follow-up; proportion and reasons for missing among groups not given. **Judgment: plausible bias that seriously weakens confidence in the results.**

WACS: In our analysis, we used data from 2729 participants (provided by author) not participated in WAFACS (refer: Table A.6). Due to the high attrition rate in the available data, analysis needs to be considered with caveats. **Judgment: plausible bias (due to the data provided by authors-high attrition rate) that seriously weakens confidence in the results (not the original paper).**

Gao 2013: Allocation concealment –probably not done; no differences in baseline characteristics

Table S3.5-Characteristics of RCTs reported either long-term risk of CRC incidence or mortality

Author, year (reference)	Study name	Location	Follow-up of placebo controlled and double-blind trial	Number of participants randomized	Interventions	Treatment duration (follow-up) in years	Method of post-trial follow-up	Trial Primary Outcomes	Number of randomized participants excluded from post-trial analysis
Peto 1988 [9,10,44]	British doctor aspirin trial (BDA) follow-up	UK	Open control	5139	Aspirin 500 mg/day (or 300 if requested)-classified as ASA-HD (n= 3429); Control (n= 1710)	Mean 6 [at least 5 years for all patients] (up to 23)	Death certification, cancer registration	CV events; mortality from CV causes	0 of 18,314 (0%) participants excluded from main analysis
Farrell 1991 [9,10,45]	United Kingdom transient ischaemic attack (UK-TIA) aspirin trial follow-up	UK and Ireland	Yes	2449	Aspirin 300 mg/day (n=811); Aspirin 1200 mg/day (n=821); Placebo (n=817)	Median 4.4 [1-7 years] (up to 21-27)	Death certification, cancer registration	CV events; mortality from vascular and non-vascular causes	0 of 2449 (0%) participants excluded from post-trial analysis. 14 of 2449 (0.6%) participants' data were not available for trial analysis (for safety outcomes).
Sturmer 1998 [8,22,69]	Physicians' Health Study (PHS) follow-up	USA	Yes	22,071	Participants were assigned to aspirin 325 mg EOD and beta-carotene 50 mg EOD in 2X2 factorial design. The aspirin arm of the study was terminated early (after 5 years); Aspirin 325 mg EOD (n=11,037); Placebo (n= 11,034) [half of participants also received beta-carotene component]	Mean 5 (mean 12)	Annual questionnaires; medical records	MI and other CV events; cancer	0 of 22,071 (0%) excluded from main analysis

Author, year (reference)	Study name	Location	Follow-up of placebo controlled and double-blind trial	Number of participants randomized	Interventions	Treatment duration (follow-up) in years	Method of post-trial follow-up	Trial Primary Outcomes	Number of randomized participants excluded from post-trial analysis
Virtamo 2003 [3,51]	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study follow-up	Finland	Yes	29,133	Vitamin E 50 mg/day (n=7286); Beta-carotene 20 mg/day (n=7282); Vitamin E 50 mg/day + Beta-carotene 20 mg/day (n=7278); Placebo (n= 7287)	Mean 6.1 (mean 12)	National registry	Cancer incidence and mortality	0 of 29,133 (0%) excluded from CRC analysis
Goodman 2004 [4,46]	Carotene and Retinol Efficacy Trial (CARET) follow-up	USA	Yes	18,314	Vitamin A 25,000 IU/day + beta-carotene 30 mg/day (n = 9420); Placebo (n = 8894)	mean ≈4 (mean 10)	Medical records and death certificates	Lung cancer; other cancers	1174 of 18,314 (6.4%) excluded from analysis. [1092 participants died; 82 participants lost to follow-up]
Ebbing 2009 [5,28,29]	Norwegian Vitamin Trial (NORVIT) and Western Norway B Vitamin Intervention Trial (WENBIT) follow-up	Norway	Combined analysis and extended follow-up of participants from 2 RCTs (randomized double-blind)	6837 (from both trials)	Folic acid 0.8 mg/day + vitamins B12 0.4 mg/day+ vitamin B6 40 mg/day (n=1708); Folic acid 0.8 mg/day + vitamin B12 0.4 mg/day (n=1703); Vitamin B6 40 mg/day (n=1705); Placebo (n=1721)	Median 3.2 (median 6.4)	Cancer registry of Norway; Cause of death registry at statistics Norway	CV outcomes	6261 (91.6%) participants participated in post-trial follow-up; 549 of 6261 participants died and emigrated during post-trial follow-up. 0 of 6837 (0%) excluded from main analysis.

Author, year (reference)	Study name	Location	Follow-up of placebo controlled and double-blind trial	Number of participants randomized	Interventions	Treatment duration (follow-up) in years	Method of post-trial follow-up	Trial Primary Outcomes	Number of randomized participants excluded from post-trial analysis
Cook 2013 [6,13]	Women Health Study (WHS) follow-up	USA	Yes	39, 876	Vitamin E 600 IU EOD and aspirin 100 mg EOD (n=9,966); Vitamin E 600 IU EOD (n=9,971); Aspirin 100 mg EOD (n=9,968); Placebo (n=9,971) [The trial initially contained a beta-carotene component (50mg EOD for 2 years); stopped early due to lack of effectiveness]	Mean10.1 (mean 18)	Questionnaires ; medical records National Death Index	Any invasive cancer	0 of 39, 876 (0%) excluded from main analysis.
Cauley 2013 [7,58]	Women's Health Initiative study (WHI) follow-up	USA	Yes	36,282	Calcium carbonate 1000 mg/day (elemental calcium) + vitamin D3 400 IU/ day (taken in two divided doses daily) (n= 18,176); Placebo (n= 18,106)	Mean 7 (mean 11)	Medical records	Fractures; colorectal cancer	6420 of 36,282 (18%) not participated in the extension phase. 0 of 36,282 (0%) excluded from main analysis.
Rothwell 2010 [10,73–75]	Thrombosis Prevention Trial (TPT) follow-up [74]	UK	Analysis of individual patient data from randomized trials (All	5085	Aspirin 75 mg/day (n=2545); Placebo (n=2540) [half of the participants also received warfarin; 2X2 factorial]	Median 7 [at least 5 years] (range 17–20)	Death certification, cancer registration	Ischaemic heart disease	0 of 5085 (0%) excluded from main analysis.

Author, year (reference)	Study name	Location	Follow-up of placebo controlled and double-blind trial	Number of participants randomized	Interventions	Treatment duration (follow-up) in years	Method of post-trial follow-up	Trial Primary Outcomes	Number of randomized participants excluded from post-trial analysis
	Swedish Aspirin Low Dose Trial (SALT) follow-up [73]	Sweden	RCTs were randomized double-blind)	1360	Aspirin 75 mg/day (n=676); Placebo (n=684)	Mean 2.7 [1-5 years] (range 18-23)	Death certification	Composite outcome of stroke or death from any causes	0 of 1360 (0%) excluded from main analysis.
	Dutch TIA trial (DTIA) follow-up [75]	Netherlands		3131	Aspirin 30 mg/day (n=1555)); Aspirin 283 mg/day (n=1576) [some participants also received atenolol]	Mean 2.6 [1-4 years] (up to 17)	Death certification, record review, patient contact	Death from CV causes	684 of 3131 (22%) participants with unknown vital status; excluded from analysis

EOD: every other day; NA: not available or not applicable; CV: cardiovascular; MI: myocardial infarction; IU: international unit; ADR: adverse events; CRC: colorectal cancer

Table S3.6-Population characteristics of RCTs reported either long-term risk of CRC incidence or mortality

Author, year	Study name	**Population**	**Age at randomisation (mean/ median)**	**Sex (% males)**	**Smokers (% current) at randomisation**	**Baseline comparability between groups**	**Adherence to medications during trial period**
Peto 1988 [9,10,44,70]	BDAT	Male physicians	62	100	31	Yes	During the first year after randomisation 19% of the doctors allocated to take aspirin stopped doing so, and during the subsequent five years a further 5% of those originally allocated to aspirin stopped each year
Fareell 1991 [9,45]	UK-TIA	History of TIA or minor ischaemic stroke	60	73	53	Yes	About 12% of patients stopped trial medication before the 4-month follow-up (although some restarted later), and 12% of patients randomised to placebo started taking non-trial aspirin at some stage during the trial
Sturmer 1998 [8,22,69,70]	PHS	Male physician	53	100	11	Yes	More than 80% were adherent to intervention
Virtamo 2003 [3,51]	ATBC	Male cigarette smokers	57.2	100	100	Yes	Participants took over 95% of their capsules; similar in all arms
Goodman 2004 [4,46]	CARET	Smokers, former smokers and workers exposed to asbestos at high risk of developing lung cancer	57	66	60	Yes	88% of the participants took over 90% of the prescribed capsules
Ebbing 2009 [5,28,29]	NORVIT/ WENBIT	History of ischemic heart disease	62	76	40	Yes	84.7% of participants took at least80% of the study capsules
Cook 2013[6,13]	WHS	Postmenopausal women	55	0	13	Yes	64% of participants in the aspirin group and 65% in the placebo group had used at least two thirds of the study medication
Cauley 2013 [7,58]	WHI	Postmenopausal women	59	0	7 (extension phase)	Yes	70 % took >50% of their study medication during intervention phase
Rothwell 2010 [10,73–75]	TPT	High risk for IHD	57.5	100	41.2	Yes	only about 2% of tablets (warfarin or aspirin) being missed according to tablet counts at follow-up visits
	SALT	History of TIA or stroke	70	66	27	Yes	99 % of the patients had a mean compliance rate of more than 90% over the study period as a whole.

Author, year	Study name	**Population**	**Age at randomisation (mean/ median)**	**Sex (% males)**	**Smokers (% current) at randomisation**	**Baseline comparability between groups**	**Adherence to medications during trial period**
	DTIA	History of TIA or stroke	65.3	65	45	Yes	82% of the participants using trial intervention at the end of the trial

Table S3.7- Efficacy outcomes of RCTs reported either long-term risk of CRC incidence or mortality

Author, year (reference)	Study name	Study group	Efficacy outcomes		Remarks
			CRC incidence (n/N)	CRC mortality (n/N)	
Peto 1988 [9,10,44,70]	BDAT	Aspirin 300 or 500 mg/day (classified as ASA-HD)	92/3429 (all, including 20 years or more); *78/3429 (up to 19 years)*	59/3429	**Follow-up for CRC mortality: 22-23 years.** Used 20 years or more follow-up data for NMA.
		Control	64/1710 (all, including 20 years or more); *55/1710 (up to 19 years)*	40/1710	
Farrell 1991 [9,10,45,70]	UK-TIA	Aspirin 300 mg/day	37/1632 (all, including 20 years or more); *33/1632 (up to 19 years) Considered as ASAHD*	8/811	**CRC incidence:** not analysed separately for aspirin 300 mg and 1200 mg **Follow-up for CRC mortality:** 21-27 years. Used 20 years or more follow-up data for NMA.
		Aspirin 1200 mg/day		11/821	
		Placebo	23/817 (all, including 20 years or more); *23/817 (up to 19 years)*	16/817	
Sturmer 1998 [8,22,69]	PHS	Aspirin 325 mg EOD	173/11037	NA	Description provided in Appendix 2 (Table 2.4).
		Placebo	168/11034	NA	
Virtamo 2003 [3,51,71]	ATBC	Vitamin E 50 mg/day	76/7286	NA	Nil
		Beta-carotene 20 mg/day	99/7282	NA	
		Vitamin E 50 mg/day + Beta-carotene 20 mg/day	90/7278	NA	
		Placebo	75/7287	NA	
Goodman 2004 [4,46,70,71]	CARET	Vitamin A 25,000 IU/day + beta-carotene 30 mg/day	127/9420	NA	We used the initial number of randomized participants to each trial arm.
		Placebo	123/8894	NA	
Ebbing 2009 [5,28,29]	NORVIT and	Folic acid 0.8 mg/day + vitamins B12 0.4	25/1708	3/1708	Combined analysis of 2 trials; follow-up is comparatively small (only 6.4 years) compared to other studies; analysis needs to be considered with caveats.

Author, year (reference)	Study name	Study group	Efficacy outcomes		Remarks
			CRC incidence (n/N)	CRC mortality (n/N)	
	WENBIT	mg/day+ vitamin B6 40 mg/day			Description provided in Appendix 2 (Table 2.4).
		Folic acid 0.8 mg/day + vitamin B12 0.4 mg/day	22/1703	9/1703	
		Vitamin B6 40 mg/day	26/1705	5/1705	
		Placebo	22/1721	7/1721	
Cook 2013 [6,13]	WHS	Aspirin 100 mg EOD	202/19934	NA	Factorial arm data was not available
		No aspirin (Vitamin E 600 IU EOD + Placebo)	249/19942	NA	
Cauley 2013 [7,58]	WHI	Calcium 1000 mg/day (elemental calcium) + vitamin D3 400 IU/day	256/18,176	NA	
		Placebo	267/18,106	NA	
Rothwell 2010 [10,73–75]	TPT	Aspirin 75 mg/day	NA	34/2545	Data included based on 'at-margins' analysis.
		Placebo	NA	55/2540	
	SALT	Aspirin 75 mg/day	NA	7/676	Nil
		Placebo	NA	10/684	
	DTIA	Aspirin 30 mg/day	NA	12/1555	We used the initial number of randomized participants for analysis.
		Aspirin 283 mg/day	NA	6/1576	

All our analyses followed the intention-to-treat principle. We used the initial number of randomized participants to each trial arm and performed the analyses irrespective of how the authors of the original trials had analysed the data. Participants who were lost to follow-up were considered survivors, free of colorectal cancers.
n/N: number of events/ number of randomized participants; EOD: every other day; NA: not available or not applicable; CV: cardiovascular; MI: myocardial infarction; IU: international unit; ADR: adverse events; CRC: colorectal cancer; GIB: gastro-intestinal bleeding; PU: peptic ulcer; BARC: Bleeding Academic Research Consortium

Table S3.8- Risk of bias assessment (Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) of RCTs reported either long-term risk of CRC incidence or mortality

Elven studies (long-term observational follow-up of 12 RCTs) reported either CRC incidence or mortality during both trial and post-trial phase (defined as long-term risk) were included in our analysis. One report from Ebbing and colleagues [5] was a combined analysis and extended follow-up of participants from 2 RCTs (NORVIT [28] and WENBIT[29]). We followed Cochrane risk of bias tool to assess the risk of bias among these studies. Since our research objective is to look the long-term effect of chemopreventive agents (CPAs) on CRC after treatment period, we assessed the quality of all studies till trial phase for the following criteria: randomization; deviations from the intended intervention, con-interventions; adherence. However, other criteria such as missing outcome data, bias in measurement of the outcome and bias in selection of the reported result considered for the quality assessment of the whole study (including trial and post-trial phase).

Author, year	Study	A	B	C	D	E	F
Peto 1988 [9,10,44]	**BDAT**	+	?	+	+	+	+
Fareell 1991 [9,45]	**UK-TIA**	+	+	+	+	+	+
Sturmer 1998 [8,22,69]	**PHS**	+	+	+	+	+	+
Virtamo 2003 [3,51,71]	**ATBC**	+	+	+	+	+	+
Goodman 2004 [4,46]	**CARET**	+	+	+	+	+	+
Ebbing 2009 [5,28,29]	**NORVIT/ WENBIT**	+	+	+	+	+	+
Cook 2013 [6,13]	**WHS**	+	+	+	+	+	+
Cauley 2013 [7,58]	**WHI**	+	+	+	+	+	+
Rothwell 2010 [10,73–75]	**TPT**	+	+	+	+	+	+
	SALT	+	+	+	+	+	+
	DTIA	+	+	?	+	+	+
A-Bias arising from the randomization process; B- Bias due to deviations from intended interventions; C- Bias due to missing outcome data; D- Bias in measurement of the outcome; E-Bias in selection of the reported result; F-Overall bias.							
+symbol/green colour means 'low risk of bias'; symbol/yellow colour means 'some concerns'; - symbol/red colour means 'high risk of bias'							

BDAT: A: low risk **(**Randomization-yes; allocation concealment: no information; baseline comparability: similar); B: some concerns (participants aware about blinding (open label) and there is no information on whether there were deviations from usual practice that were likely to impact on the outcome; no deviations from the intended intervention beyond what would be expected in usual practice (withdrawal of aspirin due to side effect); co-intervention: unclear; adherence (halfway through the study roughly 70% of doctors who had been allocated aspirin were still taking it on most days)); C: low risk; D: low risk; E: low risk; F:low risk.

UK-TIA: A: low risk **(**Randomization-yes, method not clear; allocation concealment: yes; baseline comparability: similar); B: low risk (participants were blinded; no deviations from the intended intervention beyond what would be expected in usual practice; co-intervention: unclear; adherence reported); C: low risk; D: low risk; E: low risk; F: low risk. .

PHS: A: low risk **(**Randomization-yes, computer generated; allocation concealment: yes; baseline comparability: similar); B: low risk (participants were blinded; no deviations from the intended intervention beyond what would be expected in usual practice; half of the participants received beta-carotene (no results available for separate factorial arms (refer appendix 2), however, beta-carotene use were balanced; adherence reported); C: low risk; D: low risk; E: low risk; F: low risk.

ATBC: A: low risk **(**Block randomization, allocation concealment: unclear; baseline comparability: similar); B: low risk (participants were blinded; no deviations from the intended intervention beyond what would be expected in usual practice; co-interventions: not reported, adherence reported); C: low risk (all included in the analysis); D: low risk; E: low risk; F: low risk.

CARET: A: low risk **(**Permuted block randomization design, allocation concealment: yes; baseline comparability: similar); B: low risk (participants were blinded; no deviations from the intended

intervention beyond what would be expected in usual practice; co-interventions: not reported, adherence: reported); C: low risk; D: low risk; E: low risk; F: low risk.

NORVIT/WENBIT: Both trials were used same design (PICO-similar); A: low risk **(**block randomization design, allocation concealment: yes; baseline comparability: similar for the combined analysis); B: low risk (participants were blinded; no deviations from the intended intervention beyond what would be expected in usual practice; co-interventions: yes, adherence: reported); C: low risk; D: low risk; E: low risk; F: low risk.

WHS: A: low risk **(**block randomization design, allocation concealment: yes; baseline comparability: similar); B: low risk (participants were blinded; no deviations from the intended intervention beyond what would be expected in usual practice; co-interventions: 50% received vitamin E for 10 years and 50% received beta-carotene for 2 years, but balanced between groups, adherence: reported); C: low risk; D: low risk; E: low risk; F: low risk.

WHI: A: low risk **(**randomization computer generated, allocation concealment: yes; baseline comparability: similar); B: low risk (participants were blinded; no deviations from the intended intervention beyond what would be expected in usual practice; co-interventions: not reported, adherence: reported); C: low risk; D: low risk; E: low risk; F: low risk.

TPT: A: low risk **(**randomization computer generated, allocation concealment: yes; baseline comparability: similar); B: low risk (participants were blinded; no deviations from the intended intervention beyond what would be expected in usual practice; co-interventions: not reported, 50% received warfarin-balanced between groups, adherence: reported); C: low risk (all included in the analysis); D: low risk; E: low risk; F: low risk.

SALT: A: low risk **(**block randomization, randomisation code, allocation concealment: yes; baseline comparability: similar); B: low risk (participants were blinded; no deviations from the intended intervention beyond what would be expected in usual practice; co-interventions: similar, adherence: reported); C: low risk (all included in the analysis); D: low risk; E: low risk; F: low risk.

DTIA: A: low risk **(**permuted block randomization/randomization code by telephone, allocation concealment: unclear; baseline comparability: similar); B: low risk (participants were blinded; no deviations from the intended intervention beyond what would be expected in usual practice; co-interventions: similar, adherence: reported); C: some concerns (684 of 3131 (22%) participants with unknown vital status; excluded from post-trial analysis; reasons for missing data among both groups not reported); D: low risk; E: low risk; F: low risk.

Table S3.9 Search strategy for safety outcomes

Objective of our network meta-analysis is to compare the relative efficacy and safety of competing CPAs (chemopreventive agents with evidence of efficacy, i.e. aspirin at different doses) on colorectal cancer incidence and mortality in persons at average risk. To appreciate the balance of benefits from CRC mortality prevention and CV benefits with other risks of aspirin at different doses (interventions with evidence of efficacy), we performed net clinical benefit analysis. Net clinical benefit analysis (NBA) is to demonstrate the benefit of aspirin therapy in reducing long-term CRC mortality and CV benefits (i.e. CV mortality) when subtracted by the additional risk of adverse outcomes, such as major GI bleeding events. However, there are an insufficient number of safety outcomes reported from the 5 RCTs of aspirin on long-term CRC mortality in average risk individuals; hence, disallowing us to test the comparative evaluation of requisite safety outcomes among aspirin at different doses.
To tackle this, we identified all RCTs (based on below mentioned criteria) on aspirin in average risk individuals for CRC reported in a recent systematic review by USPTF [20] and extracted the requisite safety data.

Definition: Safety outcomes of interest were major gastrointestinal (GI) bleeding events, defined as events requiring hospitalization, transfusion, leading to death, or defined as fatal or major by the study investigators and cardiovascular (CV) mortality, defined as deaths due to any CV complications including myocardial infarction (MI), stroke (ischemic and haemorrhagic) or defined as CV deaths (excluding deaths due to GI events) by the study investigators.

Data source for safety outcomes:

We identified following recent high-quality systematic reviews on aspirin to support the U.S. Preventive Services Task Force (USPSTF) in making evidence-based recommendations about the use of aspirin for primary prevention in adults and to understand the risks of regular aspirin use. Both reviews used an extensive search strategy to identify all RCTs on aspirin till 2014 June.

1) Aspirin Use in Adults: Cancer, All-Cause Mortality, and Harms: A Systematic Evidence Review for the U.S. Preventive Services Task Force, 205. [20]

2) Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force, 2016. [30]

Data sources of the systematic reviews: PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials (Search till 2014 June).

Selection criteria used in the systematic review
Inclusion criteria:
- Included only fair- and good-quality RCTs using criteria defined by the USPSTF[76].
- Included all primary and secondary CVD prevention trials conducted in individuals at average risk for colorectal cancer

Exclusion criteria:
- Poor quality
- Population at increased risk for colorectal cancer
- Non-English
- Primary or secondary prevention of CVD with no relevant outcomes
- Exposure to aspirin < 1 year
- 20% adults aged < 40 years at BL or mean age < 40 years

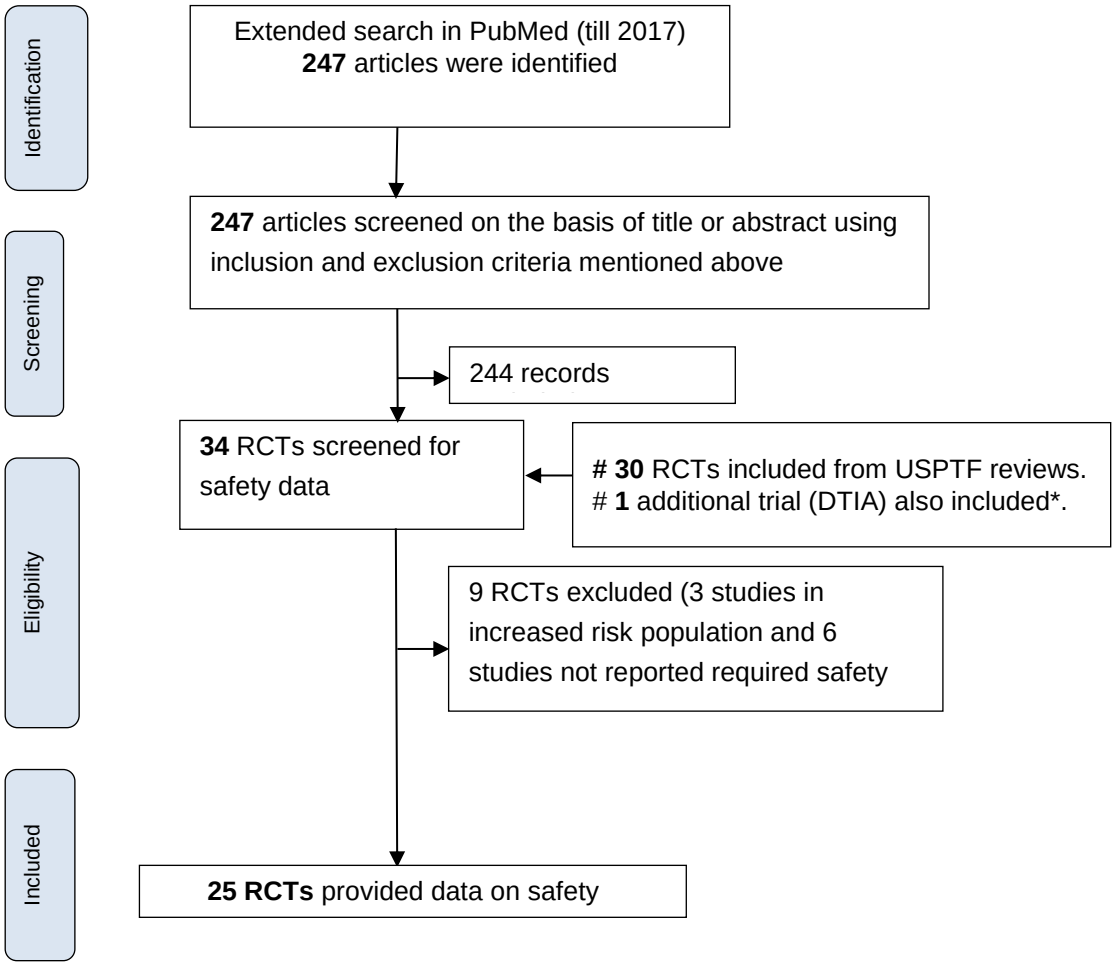
- Wrong ASA dosage

[These criteria are taken from the latest systematic review by Whitlock et al. for USPTF [20]]
Search results of systematic review by Whitlock et al.**:** After screening 4,393 abstracts and 336 full-text articles, 30 RCTs were included as per the inclusion criteria [20].

Additional search: We also conducted an additional search in PubMed till 2017 using following search terms "Aspirin"[Mesh] AND "Cardiovascular Diseases"[Mesh] AND (Randomized Controlled Trial[ptyp] AND ("2014/07/01"[PDAT] : "2017/12/31"[PDAT])).

Search strategy for updated search in PubMed		Items
1	Aspirin [Mesh]	41693
2	Cardiovascular Diseases [Mesh]	2143866
3	1 AND 2	16674
4	Limit 3 to (Randomized Controlled Trial[ptyp], humans and "2014/07/01"[PDAT] : "2017/12/31"[PDAT]))	247

Figure S3.1- Literature search diagram for safety outcomes (CV mortality and major GI bleeding events)



*Data from an additional trial (DTIA) [57] (a trial testing different doses of aspirin without control), which reported long-term CRC mortality, was also included. Which is not previously reported in USPTF review.

Table S3.10 Characteristics of RCTs on aspirin reported safety outcomes

Author, study (reference)	Population (Mean age in years); current smokers in %	Mean follow-up in years	Interventions	Safety outcomes			Dose of aspirin	Co-interventions
				1. CV mortality (excludes deaths due to GI bleeding)	**2. GI bleeding events** (required transfusion, hospitalization, leading to death, or defined as major by the study investigators)	**Definitions of 1) CV mortality and 2) GI bleeding events**		
CVD primary prevention trials								
Belch, 2008 (POPADAD) [77]	Male and female with DM and ABI ≤ 0.99 (60.3) Smoking 31.1%	6.7	ASA-VLD Placebo	43/638 35/638	NA	1. Death from coronary heart disease or stroke 2. GI bleeding events reported, but not defined	100 mg qd	Antioxidants (factorial)
Cook, 2005 (WHS) [13,78]	Postmenopausal women (55) Smoking 13.1%	10.1	ASA-VLD Placebo	120/19934 126/19942	129/19934 94/19942	1. Death from CV causes 2. GI bleeding events required transfusion	100 mg qod	Vitamin E or beta-carotene (factorial)
de Gaetano, 2001 (PPP) [79]	Males and females with ≥ 1 CVD risk factor (64.4) Smoking 14.8%	3.6	ASA-VLD Placebo	17/2226 31/2269	NA	1. Death from CV causes 2. GI bleeding events reported, but not defined	100 mg qd	Vitamin E (factorial)
ETDRS, 1992 [80]	Males and females with diabetes and diabetic retinopathy (range 18-70) Smoking: NA	5	ASA-HD Placebo	244/1856 275/1855	NA	1. Death from CV causes 2. NA	650 mg qd	Nil
Fowkes, 2010 (AAA) [81]	Males and females with low ankle brachial index ≤ 0.95 (62) Smoking 32.4%	8.2	ASA-VLD Placebo	NA NA	9/1675 8/1675	1. NA 2. Required admission to hospital to control bleeding.	100 mg qd	Nil

Author, study (reference)	Population (Mean age in years); current smokers in %	Mean follow-up in years	Interventions	Safety outcomes			Dose of aspirin	Co-interventions
				1. CV mortality (excludes deaths due to GI bleeding)	**2. GI bleeding events** (required transfusion, hospitalization, leading to death, or defined as major by the study investigators)	**Definitions of 1) CV mortality and 2) GI bleeding events**		
Hansson, 1998 (HOT)[82]	Males and females with hypertension (61.5) Smoking 15.9%	3.8	ASA-VLD Placebo	133/9399 140/9391	5/9399 3/9391	1. CV mortality 2. Fatal GI bleeding (excluded non-fatal major bleeding events)	75 mg qd	Nil
MRC, 1998 (TPT)[74]	Males at high-risk for IHD (57.5) Smoking 14.3%	Median 6.8	ASA-VLD Placebo	101/2545 81/2540	14/2545 10/2540	1. Deaths due to IHD, stroke and other cardiovascular disease 2. Major GI bleeding (excluded cases due to gastric cancer)	75 mg qd	Warfarin (factorial)
Ogawa, 2008 (JPAD)[83]	Males and females with diabetes (64.5) Smoking 21.2%	Median 4.37	ASA-VLD Placebo	1/1262 10/1277	4/1263 0/1278	1. Coronary and cerebrovascular mortality 2. Severe gastrointestinal bleeding required transfusion (Data from U.S. Preventive Services Task Force review)	81 or 100 mg qd	Nil
Peto, 1988 (BMD) [44]	Male physicians (62) Smoking 12.9%	6	ASA-HD Placebo	143/3429 75/1710	NA	1. MI, stroke and other vascular and related causes (excluding deaths associated with gastric haemorrhage and peptic ulcers). 2. Data taken from U.S. Preventive Services Task Force review.	500 mg, or 300 mg if requested qd	Nil
PHS, 1989 [69]	Male physicians (53.2) Smoking 11%	5	ASA-LD Placebo Placebo	258/11037 337/11034	49/11037 28/11034	1. CV causes, which include IHD, MI and stroke 2. Data from U.S. Preventive	325 mg qod	Beta-carotene (factorial)

Author, study (reference)	Population (Mean age in years); current smokers in %	Mean follow-up in years	Interventions	Safety outcomes			Dose of aspirin	Co-interventions
				1. CV mortality (excludes deaths due to GI bleeding)	**2. GI bleeding events** (required transfusion, hospitalization, leading to death, or defined as major by the study investigators)	**Definitions of 1) CV mortality and 2) GI bleeding events**		
						Services Task Force review.		
Silagy, 1993 [84]	Males and females aged ≥ 70 years)73) Smoking: 5.8%	1	ASA-VLD Placebo	NA	1/201 0/201	1. NA 2. Bleeding required hospital admission, for surgery and transfusion (Data from U.S. Preventive Services Task Force review)	100 mg qd	Nil
CVD secondary prevention trials								
AMIS, 1980 [85]	Males and females with prior MI (54.8) Smoking: 27.3%	3.2	ASA-HD Placebo Placebo	211/2267 196/2257	1/2268 0/2258	1. Coronary deaths and deaths due to Non-atherosclerotic cardiovascular disease 2. Blood transfusion required during hospitalization (Data from U.S. Preventive Services Task Force review)	0.5 g (1.0 g total per day) bid	Nil
Brighton, 2012 (ASPIRE)[86]	Males and females with prior DVT or PE (54.5) Smoking: NA	Median 3.1	ASA-VLD Placebo	4/411 8/411	NA	1. deaths from pulmonary embolism, MI and other CV causes 2. GI bleeding not reported	100 mg qd	Nil
CDPRG, 1980 (CDPA) [87]	Males with prior MI (≥55; mean age not reported) Smoking: NA	1.83	ASA-HD Placebo	41/758 60/771	NA	1. deaths from all CV causes 2. NA	324 mg (972 mg total per day) tid	Nil
Cote, 1995 (ACBS) [88]	Males and females with an audible cervical bruit (66.7)	2.4	ASA-LD Placebo	10/188 7/184	1/188 1/184	1. Death from vascular causes (stroke, MI etc.) 2. GI bleeding required	325 mg qd	Nil

Author, study (reference)	Population (Mean age in years); current smokers in %	Mean follow-up in years	Interventions	Safety outcomes			Dose of aspirin	Co-interventions
				1. CV mortality (excludes deaths due to GI bleeding)	**2. GI bleeding events** (required transfusion, hospitalization, leading to death, or defined as major by the study investigators)	**Definitions of 1) CV mortality and 2) GI bleeding events**		
	Smoking: 36.8%					hospitalization/transfusion		
Diener, 1997 (ESPS-2) [89]	Males and females w/ prior TIA or stroke (66.7) Smoking: 23.5%	2	ASA-VLD Placebo	162/3299 180/3303	NA	1. Deaths from CVA, MI, cardiac failure, vascular events(excluded bleeding) 2. NA	25 mg (50 mg total per day) bid	Dipyridamole (factorial)
EAFT, 1993 [90]	Males and females w/ prior TIA or stroke (73) Smoking: 19.1%	2.3	ASA-LD Placebo	77/404 77/378	2/404 1/378	1. Vascular deaths due to cerebral, cardiac and other causes (embolism, peripheral vascular disease and other undefined causes). Excluded deaths due to non-cerebral bleeding. 2. GI bleeding events requiring hospital admission with blood transfusion and/or surgery	300 mg qd	Nil
Farrell, 1991 (UK-TIA) [45]	Males and females with prior TIA or stroke (60) Smoking: 53.1%	4	ASA-HD ASA-LD Placebo	82/821 80/811 76/817	19/821 10/811 2/817	1. Vascular deaths due to cerebrovascular, cardiovascular, other vascular and unknown causes. Excluded deaths due to GI bleeding. 2. GI bleeding events requiring hospital admission,	150 mg (2 tablets; 300 mg total per day) bid or 300 mg (2 tablets; 1200 mg	Nil

Author, study (reference)	Population (Mean age in years); current smokers in %	Mean follow-up in years	Interventions	Safety outcomes			Dose of aspirin	Co-interventions
				1. CV mortality (excludes deaths due to GI bleeding)	**2. GI bleeding events** (required transfusion, hospitalization, leading to death, or defined as major by the study investigators)	**Definitions of 1) CV mortality and 2) GI bleeding events**		
						transfusion and surgery and defined as fatal.	total per day) bid	
Juul-Moller, 1992 (SAPAT) [91]	Males and females with stable angina (67) Smoking: 16%	4.2	ASA-VLD Placebo	49/1009 69/1026	11/1009 6/1026	1. Vascular deaths as fatal vascular events (since the trail reported 2 fatal GI bleeding events in aspirin group and 1 in placebo group, we excluded these events from CV mortality) 2. Major GI bleeding required transfusion or caused death	75 mg qd	Sotalol
PARIS, 1980 [92]	Males and females with prior MI (56.3) Smoking: 26.8%	3.4	ASA-HD Placebo	74/810 45/406	NA	1. All CV deaths (CV events defined as recurrent MI, angina pectoris (AP), congestive heart failure (CHF), stroke, pulmonary embolism and cardiovascular surgery) 2. NA	324 mg (972 mg total per day) tid	Nil
Petersen, 1989 (Copenhagen AFASAK) [93]	Males and females with chronic AF (74.9) Smoking: 35.9%	2	ASA-VLD Placebo	12/336 15/336	1/337 0/337	1. Vascular deaths (both cerebrovascular and cardiovascular) 2. GI bleeding event required transfusion. There were no bleeding episodes in the	75 mg qd	Nil

Author, study (reference)	Population (Mean age in years); current smokers in %	Mean follow-up in years	Interventions	Safety outcomes			Dose of aspirin	Co-interventions
				1. CV mortality (excludes deaths due to GI bleeding)	**2. GI bleeding events** (required transfusion, hospitalization, leading to death, or defined as major by the study investigators)	**Definitions of 1) CV mortality and 2) GI bleeding events**		
						placebo group. Hence, we used the same method presented by U.S. Preventive Services Task Force review to handle zero event.		
SALT, 1991 [73]	Males and females with prior TIA or stroke (67) Smoking: 25.4%	2.7	ASA-VLD Placebo	NA	9/676 4/684	1. only non-stroke deaths were reported 2. Data from U.S. Preventive Services Task Force review	75 mg qd	Nil
Sato, 2006 (JAST) [94]	Males and females with AF (65.1) Smoking: 30.4%	2.1	ASA-LD Placebo	3/426 3/445	NA	1. CV deaths 2. NA	150-200 mg qd (or qod if 330 mg preferred)	Nil
SPAF, 1991 [95]	Males and females with AF (67) Smoking: 16%	1.3	ASA-LD Placebo	18/552 19/568	NA	1. Vascular deaths due to myocardial infarction, congestive heart failure, arrhythmia, stroke, pulmonary embolism) 2. NA	325 mg qd	Nil
Additional trial included								
DTIA [75]	History of TIA or stroke (65.3) Smoking: 44.5%	2.6	ASA-VLD ASA-LD	105/1555 107/1576	2/1555 2/1576	1. Deaths from vascular causes 2. Fatal gastrointestinal bleeding	30 mg qd and 283 mg qd	Nil

Table S3.11 RCTs reported efficacy and safety outcomes of any anti-oxidants

Author, year	Study name	Population	N randomized	Mean age (years)	Male %	Interventions	Antioxidants used with dose and frequency (n= randomized participants)	Mean intended treatment duration (years)	Mean follow-up (years)	Efficacy outcomes (n/N)	Safety outcomes with definition (n/N)
											As per protocol safety outcomes are bleeding or CV events. If not available, we presented reported safety outcomes in the study
Early risk of colorectal cancer incidence											
Gann 1993/ Hennekens 1996	PHS[a]	Male physicians	22071	53	0	AOs; PLB	Beta-carotene 50 mg EOD (n=11036)	12	12	AO:167/11036 PLB: 174/11035	Death from any cause: AO: 979/11036 PLB: 968/11035
Omenn 1996	CARET	Cigarette smokers, former smokers, and workers exposed to asbestos	18314	57	66	AOs; PLB	Vitamin A 25,000 IU/day + beta-carotene 30 mg/day (n = 9420)	4	4	AO: 56/9420 PLB: 36/8894	NA
HPS group 2002	HPS	History of coronary and other occlusive arterial disease or diabetes	20536	40-80[b]	75	AOs; PLB	Vitamin C 250 mg/day + vitamin E 600 mg/day + beta-carotene 20 mg/day (n = 10269)	5	5	AO: 117/10269 PLB: 140/10267	Vascular death: AO: 878/10269 PLB: 840/10267 Death from any cause: AO: 1446/10269 PLB: 1389/10267
Duffield-Lillico 2002	NPCT	History of non-melanoma skin cancer	1312	63	75	AOs; PLB	Selenium 200 microgram/day (n=653)	4.5	7.4	AO: 9/653 PLB: 19/659	Death from any cause: AO: 108/653 PLB: 129/659
Virtamo 2003	ATBC	Male cigarette smokers	29133	57	100	AOs; PLB	Vitamin E 50 mg/day (n=7286); Beta-carotene 20 mg/day	6.1	6.1	VE: 29/7286 BC: 39/7282	NA

							(n=7282); Vitamin E 50 mg/day + Beta-carotene 20 mg/day (n=7278)			VE+BC: 30/7278 PLB: 37/7287	
Zhu 2003	NA	History of atrophic gastritis	216	56	63	FA+B12; AOs; PLB	Beta-carotene (natural), 30 mg/day for 1 year then 30 mg twice/week for 1 year) (n = 61); Beta-carotene (synthetic), administered as in natural beta-carotene (n = 57)	2	6	BC (natural and synthetic): 0/118 PLB: 1/54	NA
Hercberg 2004	SU.VI. MAX	General population	13017	49	39	AOs; PLB	Vitamin C 120 mg/day + vitamin E 30 mg/day + beta-carotene 96 mg/day + selenium 100 microgram/day + zinc 20 mg/day (n = 6481)	7.5	7.5	AO: 21/6481 PLB: 24/6536	Death from any cause: AO: 76/6481 PLB: 98/6536
Lonn 2005/ Lonn 2006	HOPE [a]	History of CV diseases or diabetes	9541	66	73	AOs; PLB	Vitamin E 400 IU/day (n = 4761)	4.5	4.5	AO: 69/4761 PLB: 57/4780	Death from any cause: AO: 799/4761 PLB: 801/4780
Cook 2005	WHS[a]	Female health professionals	39 876	55	0	ASA-VLD; AOs; ASA-VLD+AOs; PLB	Vitamin E 600 IU EOD (n=9,971); Vitamin E 600 IU EOD and aspirin 100 mg EOD (n=9966)	10.1	10.1	AO: 69/9968 AO+ASA: 75/9966 PLB: 82/9,71	Any GI bleeding events (not defined) AO: 662/9971 AO+ASA: 754/9966 PLB: 638/9971 Peptic ulcer: AO: 462/9966 AO+ASA: 553/9966 PLB: 469/9971
Lin 2009	WACS [a]	Female health professionals at high risk of CV disease	8171 (2729)[d]	60	0	AOs; PLB	Vitamin C 500 mg/day + vitamin E 600 IU EOD + beta-carotene 50 mg EOD (n=7149)	8[d]	8[d]	AO: 5/2394 PLB: 2/335 (ITT data provided by authors)	Death from any cause: (follow-up 2years only) AO: 871/7149 PLB: 124/1022
Zhang 2008	WAFACS[a]	Female health professionals at	5442[d]	63	0	AOs; FAVB; FAVB+ AOs;	Vitamin C 500 mg/day + vitamin E 600 IU EOD + beta-carotene	6.8[d]	6.8[d]	AO: 20/2376 FA+AO:	NA

		high risk of CV disease				PLB	50 mg EOD) (n= 2376)			16/2379 PLB: 2/345 (ITT data provided by authors)	
Lippman 2009	SELECT	General population (men only)	35533	62-6[c]	100	AOs; PLB	Selenium 200 microgram/day (n = 8910); vitamin E 400 IU/day (n = 8904); selenium + vitamin E (n = 8863)	5.5	5.5	Seli.: 63/8910 VE: 63/8910 Seli+VE: 77/8863 PLB: 60/8856	Death from any cause: Seli.: 378/8910 VE: 358 /8904 Seli+VE: 359 /8863 PLB: 382/8856
Gaziano 2009	PHS II	Male physicians	14641	64	100	AOs; PLB	Vitamin C 500 mg/day, vitamin E 400 IU EOD, beta-carotene (terminated early) with multivitamins (n=13619)	8	8	AO: 152/13619 PLB: 43/13619	NA
Long-term risk of colorectal cancer incidence											
Virtamo 2003	ATBC	Male cigarette smokers	29133	57.2	100	AOs; PLB	Vitamin E 50 mg/day (n=7286); Beta-carotene 20 mg/day (n=7282); Vitamin E 50 mg/day + Beta-carotene 20 mg/day (n=7278)	6.1	12	VE: 76/7286 BC: 99/7282 VE+BC: 90/7278	Death from any cause: VE: 2671/7286 BC: 2793/7282 VE+BC: 2762/7278
Goodman 2004	CARET	Cigarette smokers, former smokers, and workers exposed to asbestos	18314	57	66	AOs; PLB	Vitamin A 25,000 IU/day + beta-carotene 30 mg/day (n= 9420)	4	10	AO: 127/9420 PLB: 123/8894	Death from any cause: AO: 1855/9420 PLB: 1509/8894

NA = not available; CV = cardiovascular; GI = gastrointestinal; ASA-LD = low-dose aspirin; ASA-VLD = very-low-dose aspirin; ASA-HD = high-dose aspirin; AOs = antioxidants; PLB = placebo; BC = Beta-carotene; Sele. = Selenium; IHD = ischaemic heart disease; TIA = transient ischaemic attack; PHS = Physicians' Health Study; CARET = Carotene and Retinol Efficacy Trial; HPS = Heart Protection Study; NPCT = Nutritional Prevention of Cancer trial; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention study; SU.VI.MAX = Supple´mentation en Vitamines et Minéraux Antioxydants study; HOPE = Heart Outcomes Prevention Evaluation trial; WHS = Women's Health Study; WACS= The Women's Antioxidant Cardiovascular Study; WAFACS = Women's Antioxidant and Folic Acid Cardiovascular Study; SELECT = Selenium and Vitamin E Cancer Prevention Trial; adetailed description of studies provided in eTable 2.4 in Appendix-2; brange; c median; dbased on data provided by author (refer Appendix-2).

Table S3.12 RCTs reported efficacy and safety outcomes of folic acid

Author, year (reference)	Study name	Population	N randomized	Mean age (years)	Male %	Interventions	Antioxidants used with dose and frequency (n= randomized participants)	Mean intended treatment duration (years)	Mean follow-up (years)	Efficacy outcomes (n/N)	Safety outcomes with definition (n/N) As per protocol safety outcomes are bleeding or CV events. If not available, we presented other safety outcomes reported in the study
Early risk of colorectal cancer incidence											
Zhu 2003	NA	History of atrophic gastritis	216	56	63	FA+B12; AOs; PLB	Folic acid, 20 mg/day + vitamin-B12 1 mg, intramuscularly, per month for one year, then 20 mg two times a week plus 1 mg per three months for the next year (n=44)	2	6	FA: 0/44 PLB: 1/54	NA
Lonn 2005/ Lonn 2006	HOPE[a]	History of CV diseases or diabetes	9541	66	73	AOs; FA+B6+B12; PLB	Folic acid 2.5 mg/day + vitamin B6 50 mg/day + vitamin B12 1 mg/day (n=2758) [some participants also received vitamin E; subset of HOPE/HOPE-TOO trial]	4.5	4.5	FA: 50/2758 PLB: 37/2764	Death from any cause: FA: 470/2758 PLB: 475/2764
Zhang 2008	WAFACS[a]	Female health professionals at high risk of CV disease	5442[d]	63	0	AOs; FAVB; FAVB+ AOs; PLB	Folic acid with vitamins B alone (Folic acid 2.5 mg/day + vitamin B12 1 mg/day + vitamin B6 50 mg/day) (n=342); Folic acid with vitamins B + antioxidants (n = 2379) [provided by author from the data April 16, 1998 - July 31, 2005]	6.8[d]	6.8[d]	FA: 2/342 FA+AO: 16/2379 AO: 20/2376 PLB: 2/345	Death from any cause: FA gp: 147/2721 Control: 152/2721
Gaziano 2009	PHS II	History of MI	12064	64	83	FA+B12; PLB	Folic acid 2 mg/day + vitamin B12	6.7	6.7	FA: 86/6033 PLB:	Death from any cause:

							1 mg/day (n= 6033)			91/6031	FA: 983/6033 PLB: 951/6031
Hankey 2012	VITATOPS	History of recent stroke or transient ischaemic attack	8164	62	64	FAVB; PLB	Folic acid 2 mg/day + vitamin B6 25 mg/day + vitamin B12 0·5 mg/day (n= 4089)	3.4	3.4	FA: 21/4089 PLB: 21/4075	Death from any cause: FA: 614/4089 PLB: 633/4075
Gao 2013	NA	General population	860	61	50	FA;CTL	Folic acid 1 mg/ day (n=430)	3	3	FA: 2/430 CLT: 2/430	NA
Long-term risk of colorectal cancer incidence or mortality											
Ebbing 2009 (combined analysis of 2 trials)	NORVIT/ WENBIT[a]	History of ischemic heart disease	6837 (both trials)	62	76	FAVB; FA+B12; PLB	Folic acid 0.8 mg/day + vitamins B12 0.4 mg/day + vitamin B6 40 mg/day (n=1708); Folic acid 0.8 mg/day + vitamin B12 0.4 mg/day (n=1703)	3.2	6.4	CRC incidence FAVB: 25/1708 FA+B12: 22/1703 PLB: 22/1721 CRC incidence FAVB: 9/1703 FA+B12: 5/1705 PLB: 7/1721	Death from any cause: FAVB: 281/1708 FA+B12: 267/1703 PLB: 232/1721

NA = not available; CV = cardiovascular; GI = gastrointestinal; AOs = antioxidants; PLB = placebo; FA=folic acid; FAVB= folic acid with vitamin B6 and B12; B6= vitamin B6; B12=vitamin B12; HOPE = Heart Outcomes Prevention Evaluation trial; WHS = Women's Health Study; WACS= The Women's Antioxidant Cardiovascular Study; WAFACS = Women's Antioxidant and Folic Acid Cardiovascular Study; SELECT = Selenium and Vitamin E Cancer Prevention Trial; SEARCH= Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; PHS = Physicians' Health Study; NORVIT = Norwegian Vitamin Trial; WENBIT = Western Norway B Vitamin Intervention Trial; WAFACS = Women's Antioxidant and Folic Acid Cardiovascular Study.

[a]detailed description of studies provided in eTable 2.4 in Appendix-2; [b]range; [c] median; [d]based on data provided by author (refer Appendix-2)

Early risk of CRC incidence

Comparisons	Main analysis-All RCTs	Sensitivity analysis	
		RCTs with low ROB (with HOPE study data for folic acid)	RCTs with low ROB (FA: folic acid ± other co-interventions as single CPA)
FA vs PLB	1.00 [0.14, 7.14]	1.00 [0.14, 7.10]	1.02 [0.82, 1.26]
Folic+B12 vs PLB	0.94 [0.66, 1.35]	0.94 [0.68, 1.31]	NA
Folic+B12+B6 vs PLB	1.17 [0.81, 1.70]	0.94 [0.53, 1.67]	NA
Folic+B12+B6+Antiox Vs PLB	0.83 [0.42, 1.62]	0.83 [0.43, 1.60]	NA

Long-term risk of CRC incidence (0-20 years or more)
Combined analysis and extended follow-up of 2 RCTs (NORVIT/ WENBIT)
Folic+B12 vs PLB: 1.01 [0.56, 1.82]
Folic+B12+B6 vs PLB: 1.15 [0.65, 2.02]

Supplement 4: Pairwise meta-analysis of chemopreventive agents (CPAs)

Table S4.1 Pairwise meta-analyses: early risk of CRC incidence

Comparisons		Main analysis		
		No. of studies (all RCTs)	Pairwise meta-analysis risk ratio [95% CI]	Heterogeneity, I^2
ASA-HD	PCB	2	0.92 [0.56, 1.49]	0%
ASA-LD	PCB	1	1.15 [0.80, 1.64]	NA
ASA-VLD	PCB	1	0.84 [0.61, 1.16]	NA
Antiox	PCB	11	0.94 [0.79, 1.11]	26.6%
VitD	PCB	1	1.03 [0.61, 1.74]	NA
Folic+B12	PCB	2	0.94 [0.70, 1.26]	0.0%
Folic+B12	Antiox	1	2.64 [0.05, 131.28]	NA
Folic+B12+B6	PCB	3	1.22 [0.87, 1.71]	0.0%
ASA-VLD+Antiox	PCB	1	0.92 [0.67, 1.25]	NA
ASA-VLD+Antiox	ASA-VLD	1	1.09 [0.78, 1.51]	NA
Antiox	ASA-VLD	1	0.98 [0.71, 1.38]	NA
Antiox	ASA-VLD+Antiox	1	0.99 [0.65, 1.25]	NA
Calcium+VitD	PCB	2	1.07 [0.86, 1.33]	0.0%
Calcium	PCB	1	0.13 [0.01, 2.69]	NA
Calcium+VitD	Calcium	1	2.99 [0.12, 73.28]	NA
Folic+B12+B6+Antiox	PCB	1	1.16 [0.27, 5.02]	NA
Folic+B12+B6	Antiox	1	0.69 [0.16, 2.96]	NA
Folic+B12+B6+Antiox	Antiox	1	0.80 [0.41, 1.54]	NA
Folic+B12+B6+Antiox	Folic+B12+B6	1	1.15 [0.27, 4.98]	NA
Folic	PCB	1	1.00 [0.14, 7.07]	NA

Inference: No interventions demonstrated statistically significant reduction in early risk of CRC incidence.
Abbreviations: Antiox, antioxidants; ASA-VLD, very-low-dose-aspirin; ASA-LD, low-dose-aspirin; ASA-HD, high-dose-aspirin; B12, vitamin B12; B6, vitamin B6; Calcium, calcium supplements; Folic, folic acid; PCB, placebo; VitD, vitamin D; NA: not available.

Table S4.2 Pairwise meta-analyses: long-term risk of CRC incidence and mortality

Comparisons		No. of studies (RCTs follow-up more than 10 years) Scenario 1- Primary analysis	Pairwise meta-analysis risk ratio [95% CI]	Heterogeneity, I^2	No. of studies (all RCTs: follow-up 0 to 20 years or more) Scenario 2	Pairwise meta-analysis risk ratio [95% CI]	Heterogeneity, I^2
Incidence of colorectal cancer-long-term follow-up							
ASA-HD	PCB	2	**0.74 [0.57, 0.97]**	0.0%	2	**0.74 [0.57, 0.97]**	0.0%
ASA-LD	PCB	1	1.03 [0.83, 1.28]	NA	1	1.03 [0.83, 1.28]	NA
Antiox	PCB	2	1.06 [0.89, 1.30]	9.2%	3	1.06 [0.89, 1.30]	0.0%
B6	PCB	-	-	-	1	1.19 [0.68, 2.10]	NA
Folic+B12	PCB	-	-	-	1	1.01 [0.56, 1.82]	NA
Folic+B12+B6	PCB	-	-	-	1	1.15 [0.65, 2.02]	NA
Folic+B12	B6	-	-	-	1	0.85 [0.48, 1.49]	NA
Folic+B12+B6	B6	-	-	-	1	0.96 [0.56, 1.66]	NA
Folic+B12+B6	Folic+B12	-	-	-	1	1.13 [0.64, 2.00]	NA
ASA-VLD	PCB	1	**0.81 [0.67, 0.98]**	NA	1	**0.81 [0.67, 0.98]**	NA
Calcium+VitD	PCB	1	0.96 [0.81, 1.14]	NA	1	0.96 [0.81, 1.14]	NA
Mortality due to colorectal cancer							
ASA-HD	PCB	2	0.72 [0.51, 1.03]	0.0%	2	0.72 [0.51 1.03]	0.0%
ASA-LD	ASA-HD	1	0.74 [0.30, 1.82]	NA	1	0.74 [0.30, 1.82]	NA

Comparisons		No. of studies (RCTs follow-up more than 10 years) Scenario 1- Primary analysis	Pairwise meta-analysis risk ratio [95% CI]	Heterogeneity, I^2	No. of studies (all RCTs: follow-up 0 to 20 years or more) Scenario 2	Pairwise meta-analysis risk ratio [95% CI]	Heterogeneity, I^2
ASA-LD	PCB	1	0.50 [0.22, 1.17]	NA	1	0.50 [0.22, 1.17]	NA
ASA-VLD	ASA-LD	1	2.03 [0.76, 5.39]	NA	1	2.03 [0.76, 5.39]	NA
ASA-VLD	PCB	2	**0.63 [0.43, 0.93]**	0.0	2	**0.63 [0.43, 0.93]**	0.0%
B6	PCB	-	-	-	1	0.72 [0.23, 2.27]	NA
Folic+B12	B6	-	-	-	1	1.80 [0.61, 5.37]	NA
Folic+B12	PCB	-	-	-	1	1.30 [0.48, 3.48]	NA
Folic+B12+B6	B6	-	-	-	1	0.60 [0.14, 2.50]	NA
Folic+B12+B6	Folic+B12+B6+Antiox	-	-	-	1	0.33 [0.09, 1.23]	NA
Folic+B12+B6	PCB	-	-	-	1	0.43 [0.11, 1.67]	NA

Abbreviations: Antiox, any antioxidants; ASA-VLD, very-low-dose-aspirin; ASA-LD, low-dose-aspirin; ASA-HD, high-dose-aspirin; PCB, placebo; Folic, folic acid; B12, vitamin B12; B6, vitamin B6; Calcium, calcium supplements; PCB, VitD, vitamin D.

Table S4.3 Pairwise meta-analyses: Safety outcomes

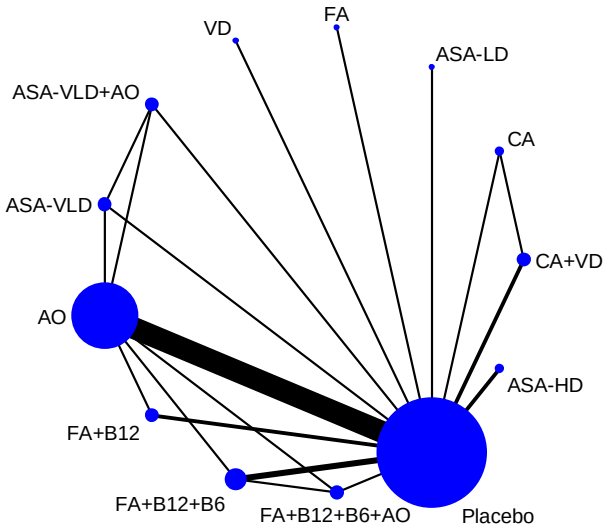
Comparisons		No. of studies (all RCTs)	Pairwise meta-analysis risk ratio [95% CI]	Heterogeneity, I^2
Incidence of major gastrointestinal bleeding				
ASA-HD	PCB	2	**7.76 [2.07, 29.16]**	0.0%
ASA-HD	ASA-LD	1	1.88 [0.88, 4.01]	NA
ASA-LD	PCB	4	**1.88 [1.22, 2.90]**	0.0%
ASA-LD	ASA-VLD	1	0.99 [0.14, 7.00]	NA
ASA-VLD	PCB	8	**1.44 [1.14, 1.80]**	0.0%
CV Deaths				
ASA-HD	PCB	6	0.94 [0.84, 1.05]	18.3%
ASA-LD	PCB	6	0.87 [0.76, 1.01]	9.0%
ASA-VLD	PCB	10	0.91 [0.77, 1.07]	44.4%

Safety outcomes: data from intervention phase (trial phase) of all RCTs of aspirin reported by the latest systematic review by USPTF; our analyses followed the intention-to-treat principle; data were based on 'at-margins' analysis (comparing all groups that received intervention with groups that did not receive intervention). For more details see eTable 3.8.
Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; B12, vitamin B12; B6, vitamin B6; Calcium, calcium supplements; Folic, folic acid; PCB, placebo; VitD, vitamin D.

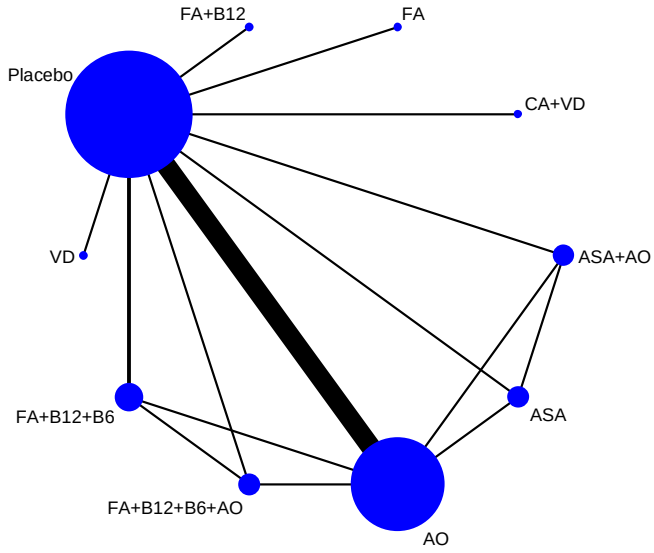
Supplement 5: Network meta-analyses of CPAs: early risk of CRC incidence

Figure S5.1 Network plot of CPAs: Early risk of CRC incidence

i. All RCTs



ii. RCTs with low risk of bias



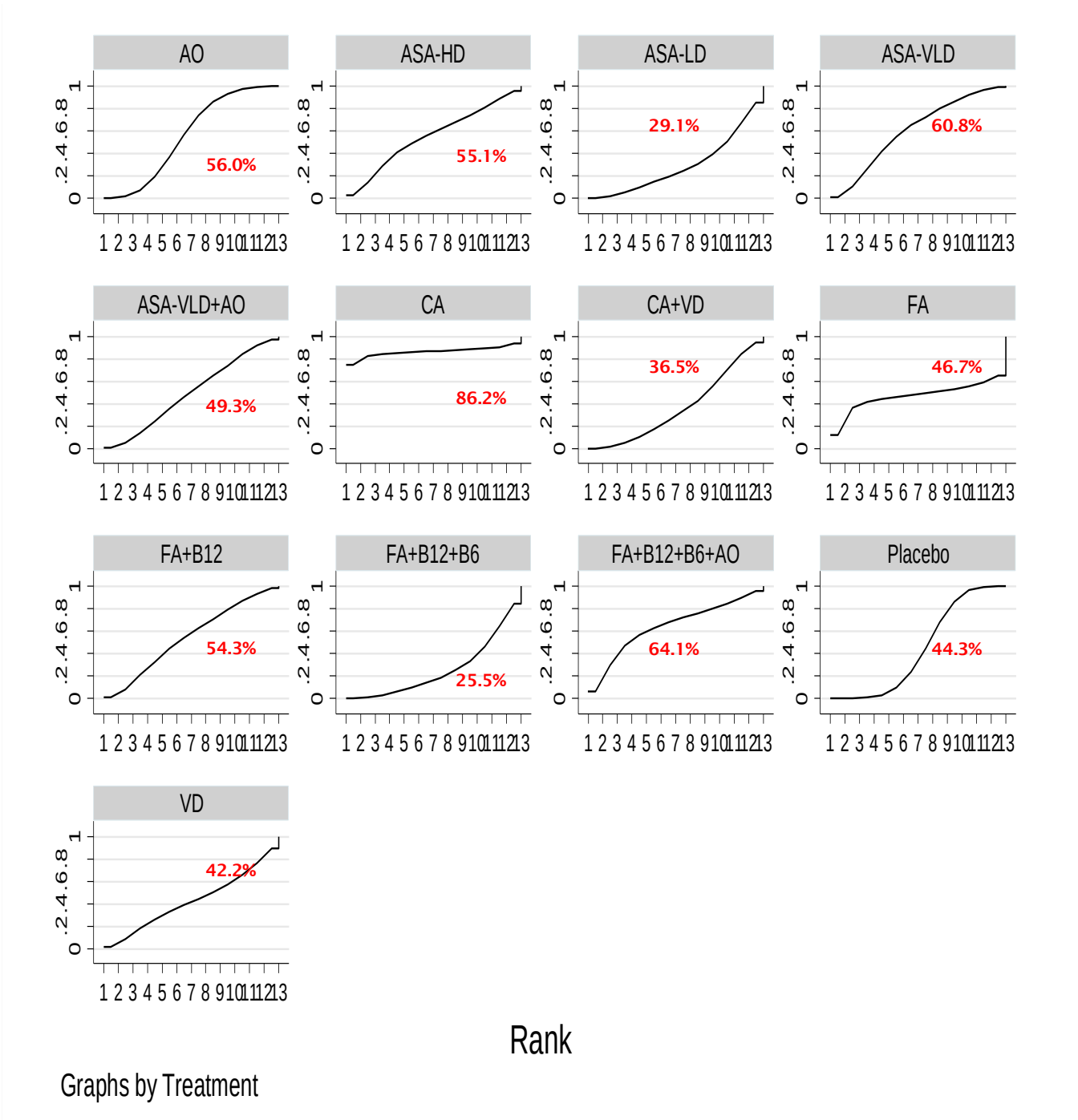
Abbreviations: AO, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; B12, vitamin B12; B6, vitamin B6; CA, calcium supplements; FA, folic acid; VD, vitamin D.

Table S5.1: Results of network meta-analysis: Early risk of CRC incidence (primary analysis: all RCTs)

Intervention	All RCTs	
	RR [95% CI]	**SUCRA rank**
Calcium	0.19 [0.01, 3.60]	1
Folic+B12+B6+Antiox	0.83 [0.42, 1.62]	2
ASA-VLD	0.89 [0.63, 1.26]	3
Antiox	0.94 [0.81, 1.10]	4
ASA-HD	0.91 [0.55, 1.53]	5
Folic+B12	0.94 [0.66, 1.35]	6
ASA-VLD+Antiox	0.97 [0.69, 1.37]	7
Folic	1.00 [0.14, 7.14]	8
PCB	Reference	9
VitD	1.03 [0.59, 1.82]	10
Calcium+VitD	1.06 [0.78, 1.44]	11
ASA-LD	1.15 [0.75, 1.74]	12
Folic+B12+B6	1.17 [0.81, 1.70]	13
Overall inconsistency Chi-square (p value)	3.53 (0.740)	
Number of studies	**21**	

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; B12, vitamin B12; B6, vitamin B6; Calcium, calcium supplements; Folic, folic acid; PCB, placebo; VitD, vitamin D.

Figure S5.2 SUCRA ranking curve for early risk of CRC incidence



Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; B12, vitamin B12; B6, vitamin B6; Calcium, calcium supplements; Folic, folic acid; PCB, placebo; VitD, vitamin D.

Higher SUCRA scores (ranging from 0 to 1) correspond to higher ranking for prevention of CRC incidence and mortality and lower SUCRA scores correspond to higher ranking for safety in terms of CV mortality and GI bleeding events, compared with other CPAs.

Figure S5.3 Pairwise (upper right portion) and network (lower left portion) meta-analytic results for early risk of CRC incidence – (all RCTs)

AO	**NA**	**NA**	**0.98 (0.71, 1.38)**	**0.99 (0.65, 1.25)**	**NA**	**NA**	**1.00 (0.14, 7.07)**	**0.39 [0.008, 20]**	**1.45 (0.34, 6.25)**	**1.25 (0.65, 2.43)**	**NA**	**0.94 (0.79, 1.11)**
1.03 (0.60,1.75)	**ASA-HD**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**0.92 [0.56, 1.49]**
0.82 (0.53,1.29)	**0.80 (0.41,1.55)**	**ASA-LD**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**1.15 [0.80, 1.64]**
1.05 (0.74,1.50)	**1.03 (0.55,1.91)**	**1.28 (0.74,2.21)**	**ASA-VLD**	**0.92 [0.66, 1.28]**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**0.84 [0.61, 1.16]**
0.97 (0.69,1.37)	**0.95 (0.51,1.75)**	**1.18 (0.69,2.02)**	**0.92 (0.62,1.36)**	**ASA-VLD+AO**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**0.92 [0.67, 1.25]**
4.98 (0.26,95.18)	**4.86 (0.24,96.62)**	**6.06 (0.31,118.65)**	**4.73 (0.24,91.73)**	**5.14 (0.26,99.65)**	**CA**	**0.33 [0.01,0.33]**	**NA**	**NA**	**NA**	**NA**	**NA**	**0.13 [0.01, 2.69]**
0.89 (0.63,1.25)	**0.87 (0.48,1.57)**	**1.08 (0.64,1.81)**	**0.84 (0.53,1.34)**	**0.91 (0.58,1.44)**	**0.18 (0.01,3.40)**	**CA+VD**	**NA**	**NA**	**NA**	**NA**	**NA**	**1.07 [0.86, 1.33]**
1.00 (0.68,1.48)	**0.98 (0.52,1.83)**	**1.22 (0.70,2.12)**	**0.95 (0.58,1.57)**	**1.03 (0.63,1.70)**	**0.20 (0.01,3.91)**	**1.13 (0.71,1.81)**	**FA**	**FA+B12**	**NA**	**NA**	**NA**	**0.94 [0.70, 1.26]**
0.80 (0.54,1.20)	**0.78 (0.42,1.48)**	**0.98 (0.56,1.71)**	**0.76 (0.46,1.27)**	**0.83 (0.50,1.37)**	**0.16 (0.01,3.14)**	**0.91 (0.56,1.46)**	**1.06 (0.14,7.86)**	**0.80 (0.48,1.34)**	**FA+B12+B6**	**0.87 [0.20, 3.70]**		**1.22 [0.87, 1.71]**
1.14 (0.59,2.21)	**1.11 (0.48,2.59)**	**1.39 (0.63,3.07)**	**1.08 (0.51,2.28)**	**1.18 (0.56,2.47)**	**0.23 (0.01,4.70)**	**1.29 (0.61,2.70)**	**0.85 (0.12,6.32)**	**1.14 (0.53,2.44)**	**1.42 (0.67,3.01)**	**FA+B12+B6 + AO**		**1.16 [0.27, 5.02]**
0.91 (0.51,1.64)	**0.89 (0.41,1.90)**	**1.11 (0.55,2.24)**	**0.86 (0.45,1.68)**	**0.94 (0.49,1.82)**	**0.18 (0.01,3.67)**	**1.03 (0.54,1.95)**	**1.21 (0.15,9.69)**	**0.91 (0.47,1.78)**	**1.13 (0.58,2.23)**	**0.80 (0.33,1.92)**	**VD**	**1.03 [0.61, 1.74]**
0.94 (0.81,1.10)	**0.92 (0.55,1.53)**	**1.15 (0.75,1.74)**	**0.89 (0.63,1.26)**	**0.97 (0.69,1.37)**	**0.19 (0.01,3.60)**	**1.06 (0.78,1.44)**	**0.97 (0.12,7.49)**	**0.94 (0.66,1.35)**	**1.17 (0.81,1.70)**	**0.83 (0.42,1.62)**	**1.03 (0.59,1.82)**	**Placebo**

Outcomes are expressed as risk ratios (95% confidence intervals). For the pairwise meta-analyses, risk ratio less than 1 indicate that the treatment specified in the column is more efficacious. For the network meta-analysis, risk ratio less than 1 indicate that the treatment specified in the row is more efficacious. Bold results indicate statistical significance. Abbreviations: AO, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; B12, vitamin B12; B6, vitamin B6; CA, calcium supplements; FA, folic acid; VD, vitamin D; NA, not available.

Table S5.2 Results of sensitivity analyses of network meta-analysis: Early risk of CRC incidence

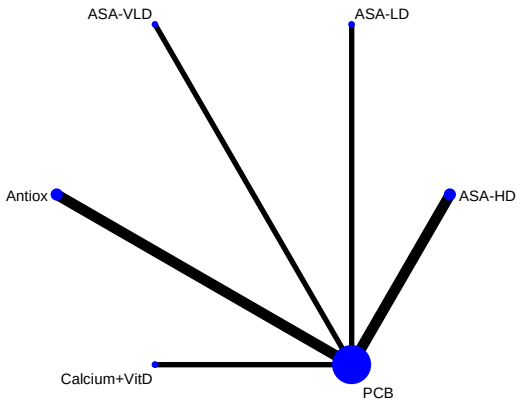
Strategies of sensitivity analyses described in Appendix 2 (eTable 2.3)								
Intervention	**Main analysis-All RCTs**		**RCTs with low ROB [and PHS-1 anti-oxidant data]**		**RCTs with low ROB (FA: folic acid ± other co-interventions as single CPA)**		**RCTs with low ROB and Modifying HOPE study data**	
	RR [95% CI]	**SUCRA rank**	**RR [95% CI]**	**SUCRA rank**	**RR [95% CI]**	**SUCRA rank**	**RR [95% CI]**	**SUCRA rank**
Calcium	0.19 [0.01, 3.60]	1	NA	-	NA	-	NA	-
ASA-VLD	0.89 [0.63, 1.26]	2	0.90 [0.67, 1.21]	2	0.90 [0.67, 1.21]	1	0.91 [0.66, 1.24]	2
Folic+B12+B6+Antiox	0.83 [0.42, 1.62]	3	0.82 [0.44, 1.58]	1	NA	-	0.83 [0.43, 1.60]	1
Antiox	0.94 [0.81, 1.10]	4	0.95 [0.85, 1.07]	4	0.96 [0.84, 1.10]	3	0.98 [0.87, 1.10]	6
ASA-HD	0.91 [0.55, 1.53]	5	0.92 [0.56, 1.50]	3	0.92 [0.56, 1.50]	2	0.92 [0.56, 1.51]	3
Folic+B12	0.94 [0.66, 1.35]	6	0.94 [0.69, 1.30]	5	NA	-	0.94 [0.68, 1.31]	4
ASA-VLD+Antiox	0.97 [0.69, 1.37]	7	0.92 [0.65, 1.28]	6	0.98 [0.73, 1.31]	4	0.99 [0.73, 1.34]	8
Folic	1.00 [0.14, 7.14]	8	1.00 [0.14, 7.09]	7	1.02 [0.82, 1.26]	7	1.00 [0.14, 7.10]	7
PCB	Reference	9	Reference	8	Reference	5	Reference	9
VitD	1.03 [0.59, 1.82]	10	1.03 [0.61, 1.76]	9	1.03 [0.61, 1.76]	6	1.03 [0.60, 1.78]	11
Calcium+VitD	1.06 [0.78, 1.44]	11	1.09 [0.84, 1.40]	10	1.09 [0.86, 1.38]	8	1.09 [0.84, 1.41]	10
ASA-LD	1.15 [0.75, 1.74]	12	NA	-	NA	-	NA	-
Folic+B12+B6	1.17 [0.81, 1.70]	13	1.18 [0.84, 1.67]	11	NA	-	0.94 [0.53, 1.67]	5
Overall inconsistency Chi-square (p value)	**3.53 (0.740)**		**1.56 (0.669)**		**1.73 (0.629)**		**1.32 (0.724)**	
Number of studies	**21**		**18**		**18**		**18**	

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; B12, vitamin B12; B6, vitamin B6; Calcium, calcium supplements; Folic, folic acid; PCB, placebo; VitD, vitamin D; NA, not available.

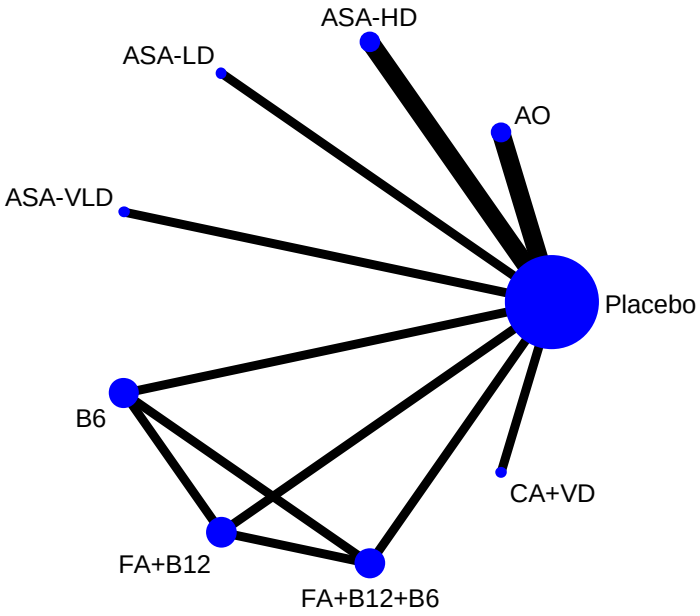
Supplement 6: Network meta-analyses of CPAs: Long-term risk of CRC incidence

Figure S6.1 Network plot of CPAs: long-term risk of CRC incidence

i. RCTs reported long-term CRC incidence with follow-up more than 10 years (primary analysis)



ii. All RCTs reported long-term CRC incidence with follow-up 0-20 years or more



Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; B12, vitamin B12; B6, vitamin B6; Calcium, calcium supplements; Folic, folic acid; PCB, placebo; VitD, vitamin D.

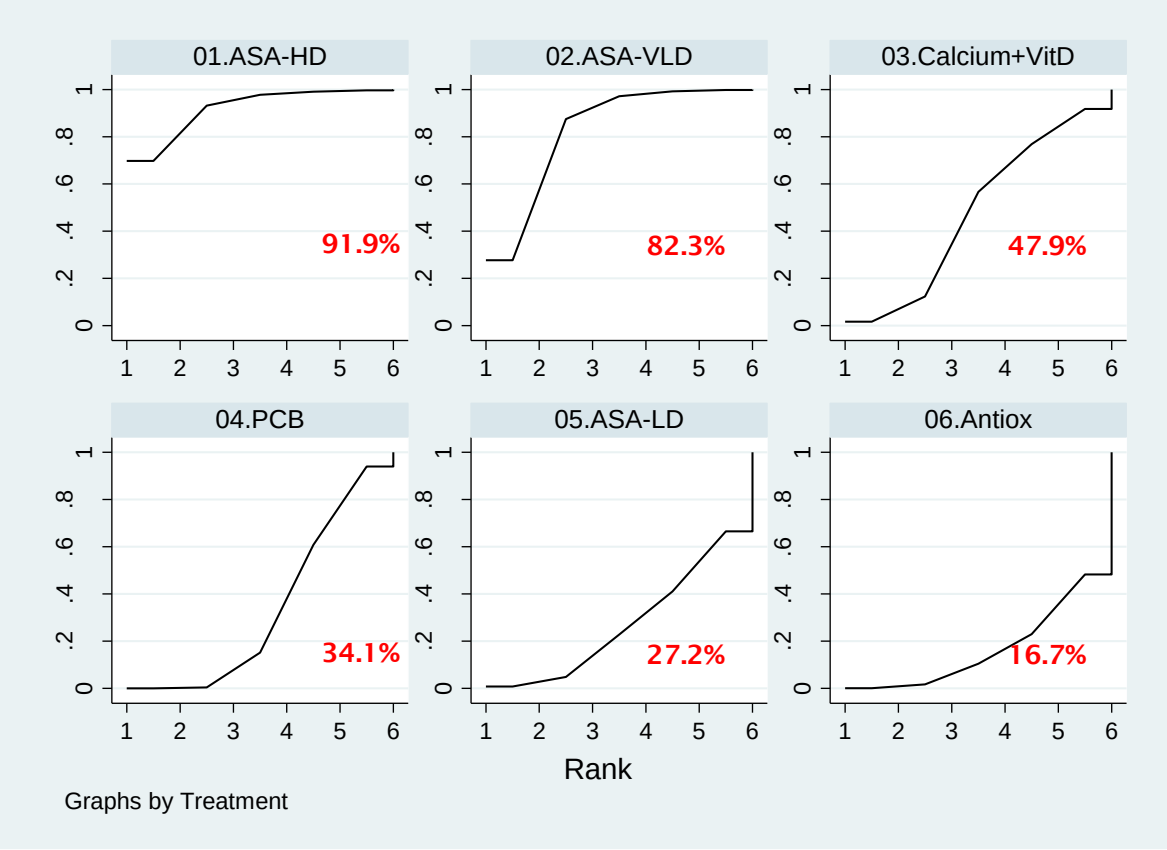
Table S6.1 Results of network meta-analysis: Long-term risk of CRC incidence (studies with follow-up more than 10 years-primary analysis)

Intervention	RCTs follow-up more than 10 years	
	RR [95% CI]	**SUCRA rank**
ASA-HD	**0.74 [0.57, 0.97]**	1
ASA-VLD	**0.81 [0.67, 0.98]**	2
Calcium+VitD	0.96 [0.81, 1.13]	3
PCB	reference	4
ASA-LD	***1.03 [0.83, 1.27]***	5
Antiox	1.07 [0.89,1.28]	6
Overall inconsistency Chi-square (p value)	0.28 (0.597)	
Number of studies	**7**	

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; Calcium, calcium supplements; PCB, placebo; VitD, vitamin D.

Note: We could not demonstrate the protective effect of low-dose-aspirin on CRC incidence from the available single study (long-term follow-up of PHS-1 trial [8,22,69]). An obvious reason for this discrepancy could be the short duration of follow-up in this study, which was extended to only 12 years and therefore could not really contribute to the analyses of long-term effects on CRC incidence. Whereas duration of follow-up was 18 years or more in the studies tested high-dose-aspirin and very-low-dose aspirin.

Figure S6.2 SUCRA ranking curve for long-term risk of CRC incidence (Studies with follow-up more than 10 years)



Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; Calcium, calcium supplements; PCB, placebo; VitD, vitamin D.

Higher SUCRA scores (ranging from 0 to 1) correspond to higher ranking for prevention of CRC incidence and mortality and lower SUCRA scores correspond to higher ranking for safety in terms of CV mortality and GI bleeding events, compared with other CPAs.

Figure S6.3 Pairwise (upper right portion) and network (lower left portion) meta-analytic results for long-term risk of CRC incidence (Studies with follow-up more than 10 years)

ASA-HD	NA	NA	NA	NA	**0.74 (0.57,0.97)**
0.72 (0.51,1.01)	**ASA-LD**	NA	NA	NA	1.03 (0.83,1.28)
0.91 (0.66,1.26)	1.27 (0.96,1.68)	**ASA-VLD**	NA	NA	**0.81 (0.67,0.98)**
0.69 (0.50,0.95)	0.96 (0.73,1.27)	**0.76 (0.59,0.98)**	**Antiox**	NA	1.06 (0.89,1.30)
0.77 (0.56,1.06)	1.08 (0.82,1.41)	0.85 (0.66,1.09)	1.12 (0.87,1.43)	**Calcium+ VitD**	0.96 (0.81,1.14)
0.74 (0.57,0.97)	1.03 (0.83,1.27)	**0.81 (0.67,0.98)**	1.07 (0.89,1.28)	0.96 (0.81,1.13)	**PCB**

Outcomes are expressed as risk ratio (95% confidence intervals). For the pairwise meta-analyses, relative risk less than 1 indicate that the treatment specified in the row is more efficacious. For the network meta-analysis, relative risk less than 1 indicate that the treatment specified in the column is more efficacious. Bold results indicate statistical significance.

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; Calcium, calcium supplements; PCB, placebo; VitD, vitamin D; NA, not available.

Table S6.2 Results of sensitivity analyses of network meta-analysis: Long-term risk of CRC incidence

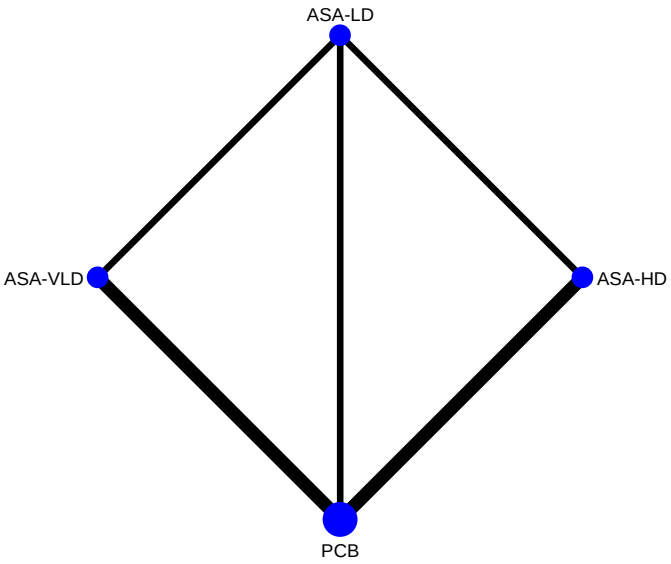
Intervention	RCTs follow-up more than 10 years (main analysis)		All RCTs (0-20 years or more)-	
	RR [95% CI]	**SUCRA rank**	**RR [95% CI]**	**SUCRA rank**
ASA-HD	**0.74 [0.57, 0.97]**	1	**0.74 [0.57, 0.97]**	1
ASA-VLD	**0.81 [0.67, 0.98]**	2	**0.81 [0.67, 0.98]**	2
Calcium+VitD	0.96 [0.81, 1.13]	3	0.96 [0.81, 1.13]	3
PCB	reference	4	reference	5
ASA-LD	1.03 [0.83, 1.27]	5	1.03 [0.83, 1.27]	6
Antiox	1.07 [0.89, 1.28]	6	1.07 [0.89, 1.28]	7
ASA-VLD+Antiox	-	-	**-**	-
Folic+B12	-	-	1.01 [0.56, 1.82]	4
Folic+B12+B6	-	-	1.15 [0.65, 2.02]	8
B6	-	-	1.19 [0.68, 2.10]	9
Overall inconsistency Chi-square (p value)	0.28 (0.59)		0.62 (0.43)	
Number of studies	**7**		**8**	

Strategies of sensitivity analyses: refer Appendix 2 eTable 2.3
Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; Calcium, calcium supplements; PCB, placebo; VitD, vitamin D; NA, not available.

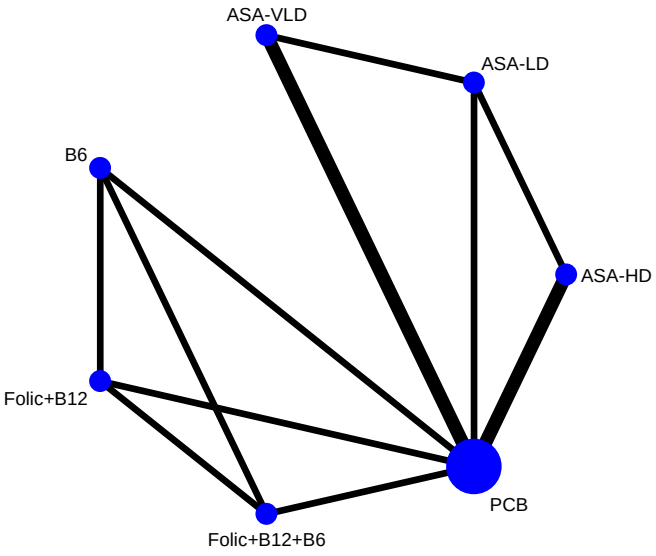
Supplement 7: Network meta-analyses of CPAs: Long-term risk of CRC mortality

Figure S7.1 Network plot of CPAs: long-term risk of CRC mortality

i. RCTs reported long-term risk of CRC mortality with follow-up more than 10 years (primary analysis)



ii. All RCTs reported long-term risk of CRC mortality with follow-up 0-20 years or more



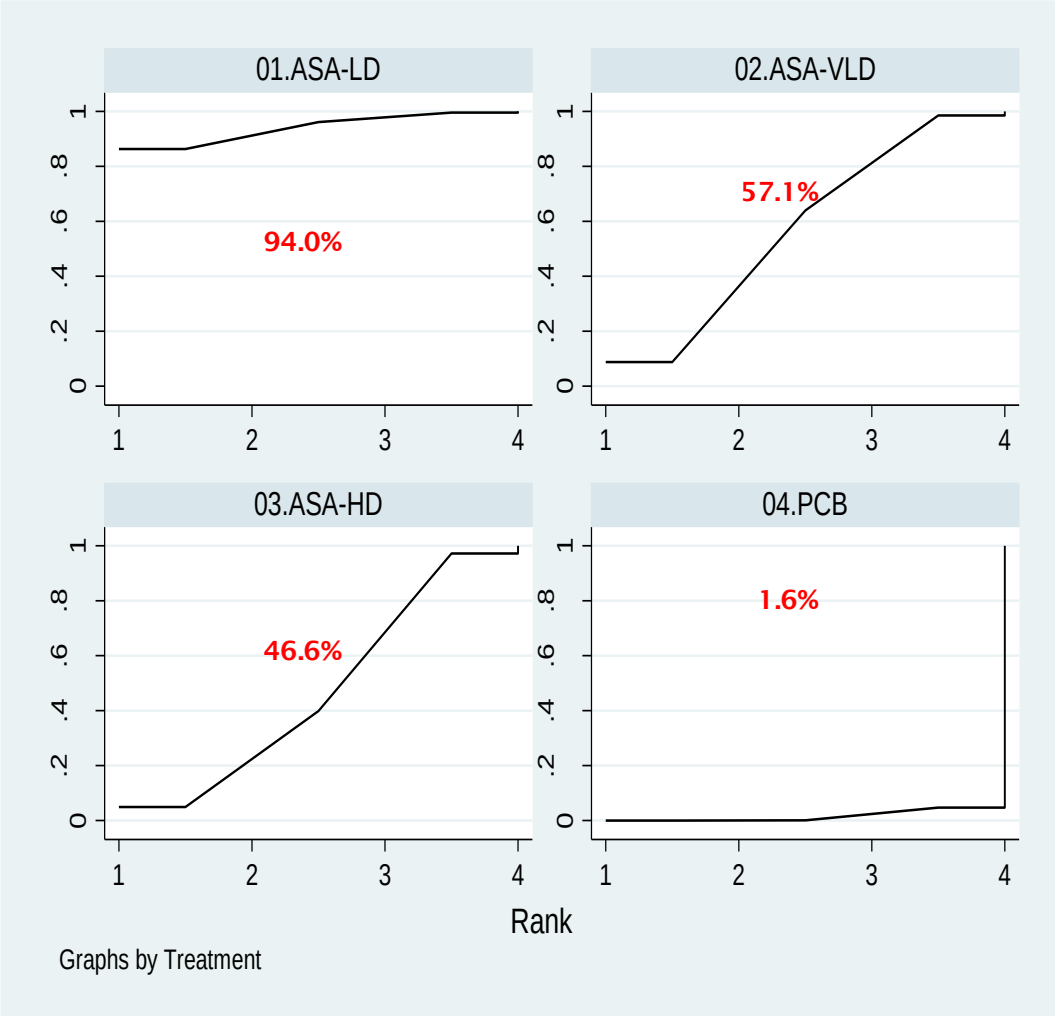
Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; B12, vitamin B12; B6, vitamin B6; Folic, folic acid; PCB, placebo.

Table S7.1 Results of network meta-analysis: Long-term risk of CRC mortality (RCTs with follow-up more than 10 years: primary analysis)

Intervention	RCTs follow-up more than 10 years	
	RR [95% CI]	**SUCRA rank**
ASA-LD	**0.43 [0.23, 0.81]**	1
ASA-VLD	**0.66 [0.45, 0.95]**	2
ASA-HD	0.71 [0.50, 1.01]	3
PCB	reference	4
Overall inconsistency Chi-square (p value)	0.59 (0.745)	
Number of studies	**5**	

Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin

Figure S7.2 SUCRA ranking curve: long-term risk of CRC mortality (RCTs with follow-up more than 10 years)



Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; PCB, placebo.

Higher SUCRA scores (ranging from 0 to 1) correspond to higher ranking for prevention of CRC incidence and mortality and lower SUCRA scores correspond to higher ranking for safety in terms of CV mortality and GI bleeding events, compared with other CPAs.

Figure S7.3 Pairwise (upper right portion) and network (lower left portion) meta-analytic results for long-term colorectal cancer mortality

ASA-HD	1.35 (0.55,3.33)	NA	0.72 (0.51,1.03)
1.66 (0.84,3.29)	**ASA-LD**	0.49 (0.19,1.32)	0.50 (0.22,1.17)
1.08 (0.66,1.79)	0.65 (0.34,1.25)	**ASA-VLD**	**0.63 (0.43,0.93)**
0.71 (0.50,1.01)	**0.43 (0.23,0.81)**	**0.66 (0.45,0.95)**	**PCB**

Outcomes are expressed as risk ratio (95% confidence intervals). For the pairwise meta-analyses, relative risk less than 1 indicate that the treatment specified in the row is more efficacious. For the network meta-analysis, relative risk less than 1 indicate that the treatment specified in the column is more efficacious. Bold results indicate statistical significance.

Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; PCB, placebo; NA, not available.

Note: NMA results of ASA-LD is not consistent with pairwise meta-analysis results. Pairwise meta-analysis estimate of ASA-LD is from only 1 trial (UK-TIA).[45] However, in our NMA, we were able to incorporate data of the DTIA trial (a trial testing different doses of aspirin (ASA-LD and ASA-VLD) without control)[75] which was not included in the pairwise meta-analysis of earlier studies reporting the long-term risk of CRC mortality.

Table S7.2 Results of sensitivity analyses of network meta-analysis: Long-term risk of CRC mortality

Strategies of sensitivity analyses described in Appendix 2 (section 2e.)

- Follow-up period after initiation of any CPAs: for primary analysis we used RCTs with follow-up >10 years. In sensitivity analysis we included all studies identified reported post-trial data (follow-up 0 to ≥ 20 years).

Intervention	RCTs follow-up more than 10 years		All RCTs (0-20 years or more)	
	RR [95% CI]	SUCRA rank	RR [95% CI]	SUCRA rank
ASA-LD	**0.43 [0.23, 0.81]**	1	**0.43 [0.23, 0.81]**	1
ASA-VLD	**0.66 [0.45, 0.95]**	2	**0.66 [0.45, 0.95]**	3
ASA-HD	0.71 [0.50, 1.01]	3	0.71 [0.50, 1.01]	4
PCB	reference	4	reference	6
Folic+B12+B6	-	-	0.43 [0.11, 1.67]	2
B6	-	-	0.72 [0.23, 2.27]	5
Folic+B12	-	-	1.30 [0.48, 3.48]	7
Overall inconsistency Chi-square (p value)	0.59 (0.75)		1.35 (0.51)	
Number of studies	**5**		**6**	

Strategies of sensitivity analyses: Refer Appendix 2 eTable 2.3

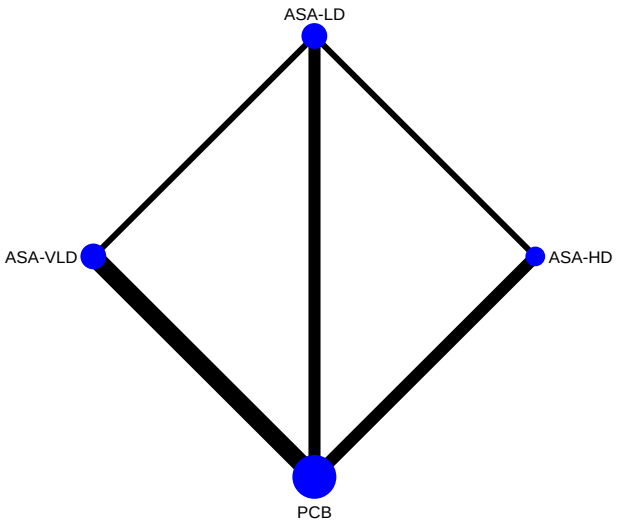
Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; B12, vitamin B12; B6, vitamin B6; Folic, folic acid; PCB, placebo.

Supplement 8: Network meta-analysis of safety outcomes

We limited this analysis to the three CPAs (high-dose-aspirin, low-dose-aspirin and very-low-dose-aspirin) with evidence of efficacy in reducing long-term CRC incidence or mortality based on the analysis mentioned in the Appendix 6 and 7. Data of safety outcomes provided in **Appendix 3 eTable 3.10.**

NMA of major GI bleeding events

Figure S8.1 Network plot of CPAs: Major GI bleeding events

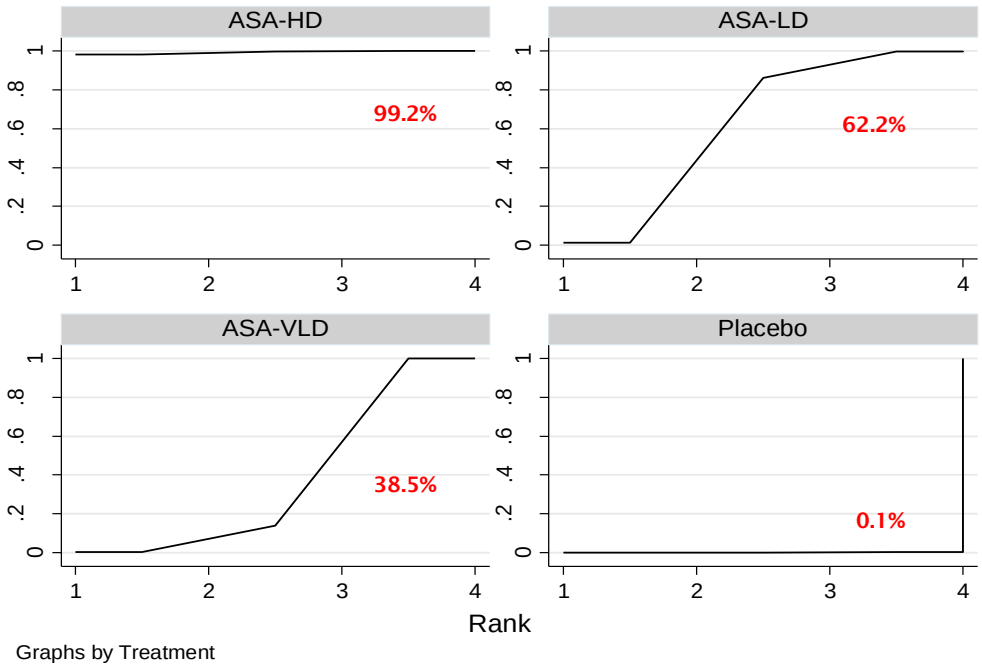


Connecting lines represent head-to-head comparisons, indicated by the connected nodes (size proportional to number of studies). Numbers above and below the lines indicate studies and patient-days respectively. Line thickness is proportional to the number of trials comparing the two strategies. Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; PCB, placebo.

Table S8.1 Results of network meta-analysis: major GI bleeding events

Intervention	RCTs follow-up more than 10 years	
	RR [95% CI]	SUCRA rank for safety
PCB	reference	1
ASA-VLD	**1.44 [1.15, 1.81]**	2
ASA-LD	**1.85 [1.22, 2.81]**	3
ASA-HD	**4.04 [1.86, 8.76]**	4
Overall inconsistency Chi-square (p value)	1.87 (0.60)	
Number of studies	**14**	

Figure S8.2 SUCRA ranking curve: major GI bleeding events



Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; PCB, placebo.

Higher SUCRA scores (ranging from 0 to 1) correspond to higher ranking for prevention of CRC incidence and mortality and lower SUCRA scores correspond to higher ranking for safety in terms of CV mortality and GI bleeding events, compared with other CPAs.

Figure S8.3 Pairwise (upper right portion) and network (lower left portion) meta-analytic results for major GI bleeding events

ASA-HD	1.88 (0.88,4.01)	NA	7.76 (2.07,29.16)
2.18 (1.08,4.41)	**ASA-LD**	NA	1.88 (1.22,2.90)
2.80 (1.25,6.26)	1.28 (0.80,2.05)	**ASA-VLD**	1.44 (1.14,1.80)
4.04 (1.86,8.76)	1.85 (1.22,2.81)	1.44 (1.15,1.81)	**PCB**

Outcomes are expressed as risk ratio (95% confidence intervals). For the pairwise meta-analyses, relative risk less than 1 indicate that the treatment specified in the row is more efficacious. For the network meta-analysis, relative risk less than 1 indicate that the treatment specified in the column is more efficacious. Bold and shaded results indicate statistical significance.

Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; PCB, placebo; NA, not available.

NMA of cardiovascular (CV) mortality

Figure S8.4 Network plot of CPAs: CV mortality

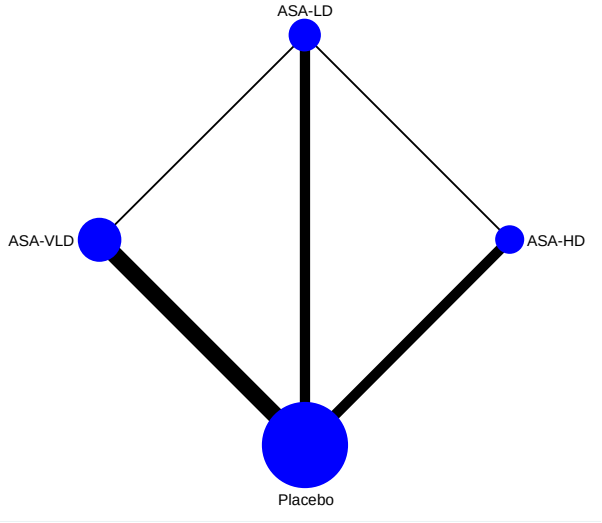
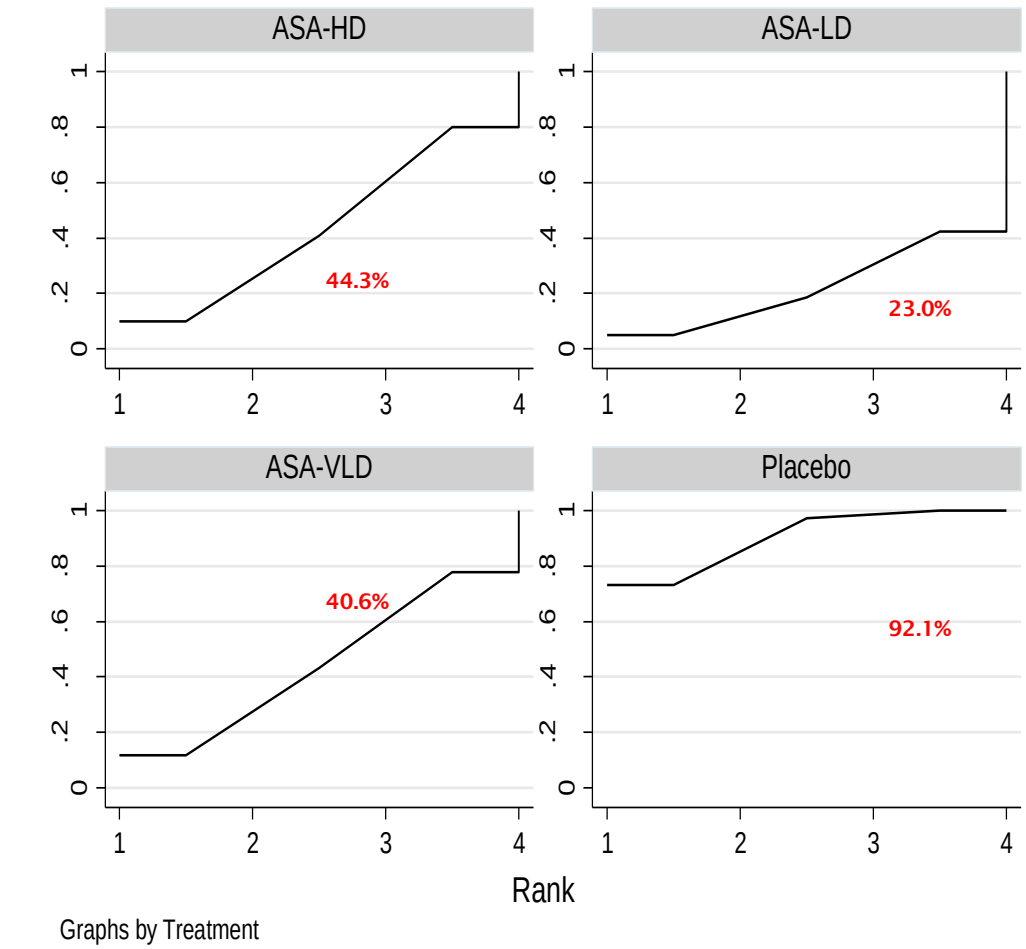


Table S8.2 Results of network meta-analysis: CV mortality

Intervention	RCTs follow-up more than 10 years	
	RR [95% CI]	SUCRA rank for safety
ASA-LD	0.89 [0.77, 1.02]	1
ASA-VLD	0.92 [0.82, 1.03]	2
ASA-HD	0.93 [0.83, 1.04]	3
PCB	reference	4
Overall inconsistency Chi-square (p value)	1.61 (0.657)	
Number of studies	**22**	

Figure S8.5 SUCRA ranking curve: CV mortality



Higher SUCRA scores (ranging from 0 to 1) correspond to higher ranking for prevention of CRC incidence and mortality and lower SUCRA scores correspond to higher ranking for safety in terms of CV mortality and GI bleeding events, compared with other CPAs.

Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; PCB, placebo

Figure S8.6 Pairwise (upper right portion) and network (lower left portion) meta-analytic results for CV mortality

ASA-HD	1.01 (0.76,1.35)	NA	0.94 (0.84,1.05)
1.05 (0.88,1.25)	**ASA-LD**	1.04 (0.88,1.23)	0.87 (0.76,1.01)
1.01 (0.86,1.18)	0.96 (0.81,1.14)	**ASA-VLD**	0.91 (0.77,1.07)
0.93 (0.83,1.04)	0.89 (0.77,1.02)	0.92 (0.82,1.03)	**PCB**

Outcomes are expressed as risk ratio (95% confidence intervals). For the pairwise meta-analyses, relative risk less than 1 indicate that the treatment specified in the row is more efficacious. For the network meta-analysis, relative risk less than 1 indicate that the treatment specified in the column is more efficacious. Bold and shaded results indicate statistical significance.
Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; PCB, placebo; NA, not available.

Supplement 9: Assessment of inconsistency for each outcome network

Table S9.1 Assessment of inconsistency: early risk of CRC incidence

Assessment of global inconsistency in networks using the 'design-by-treatment' interaction model

Network outcome	Chi-square	P value for test of global inconsistency
Early risk of CRC incidence (all RCTs)	3.53	0.74
Early risk of CRC incidence (RCTs with low risk of bias)	1.56	0.67

Table S9.2 Assessment of inconsistency: long-term risk of CRC incidence or mortality

Assessment of global inconsistency in networks using the 'design-by-treatment' interaction model

Network outcome	Chi-square	P value for test of global inconsistency
Long-term risk of CRC incidence (RCTs with follow-up more than 10 years)	0.28	0.597
Long-term risk of CRC incidence (RCTs with follow-up 0-20 years)	0.62	0.43
Long-term risk of CRC mortality (RCTs with follow-up more than 10 years)	0.59	0.75
Long-term risk of CRC mortality (RCTs with follow-up 0-20 years)	1.35	0.51

Table S9.3 Assessment of inconsistency: safety outcomes

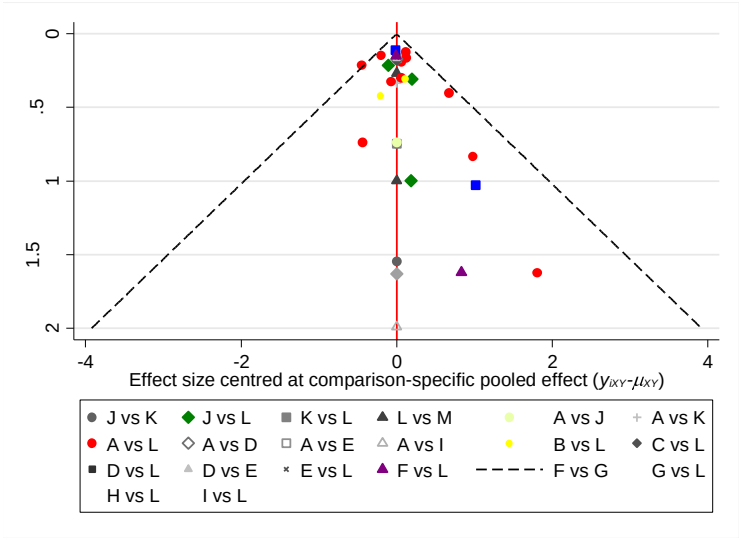
i. Assessment of global inconsistency in networks using the 'design-by-treatment' interaction model

Network outcome	Chi-square	P value for test of global inconsistency
Incidence of major gastrointestinal bleeding	1.87	0.60
Incidence of CV mortality	1.61	0.66

Supplement 10: Comparison-adjusted funnel plot for each outcome form the network meta-analyses

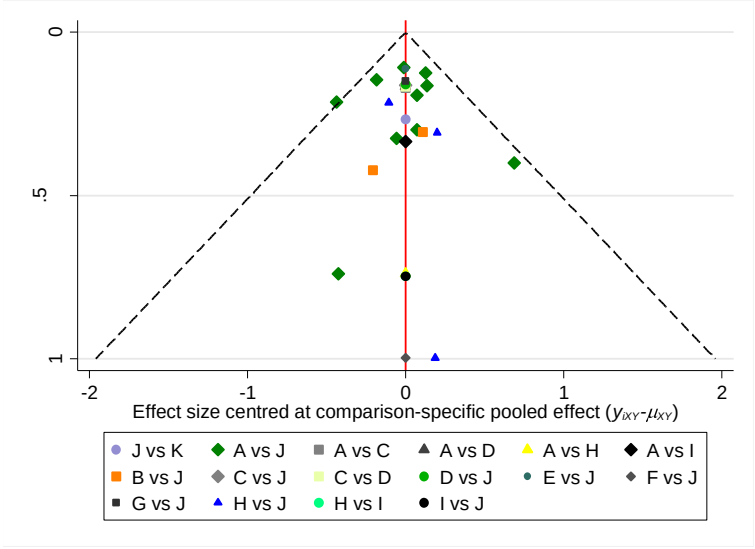
Figure S10.1 Comparison-adjusted funnel plots from the network meta-analyses: Early risk of CRC incidence

i. All RCTs



A, Antioxidant; B, ASA-HD; C, ASA-LD; D, ASA-VLD; E, ASA-VLD+AO; F, Calcium; G, calcium+vitaminD; H, Folic acid; I, Folic+B12; J, Folic+B12+B6; K, Folic+ B12+B6+antioxidant; KL Placebo; M, vitamin D

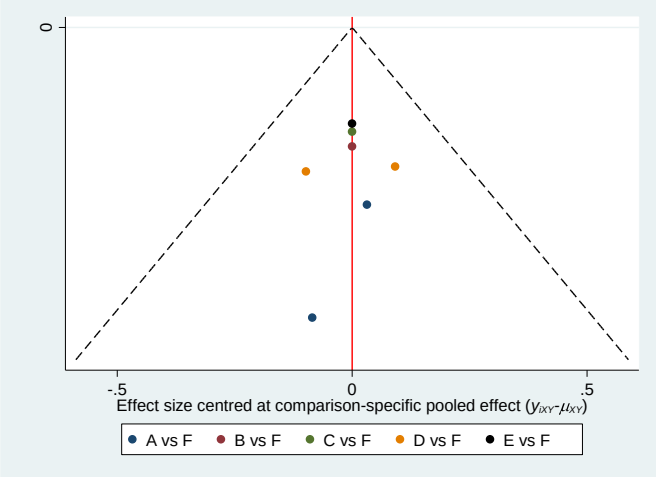
ii. RCTs with low ROB



A, Antioxidant; B, ASA-HD; C, ASA-LD; D, ASA-VLD; E, ASA-VLD+AO; F, Calcium; G, calcium+vitaminD; H, Folic acid; I, Folic+B12; J, Folic+B12+B6; K, Folic+ B12+B6+antioxidant; KL Placebo; M, vitamin D

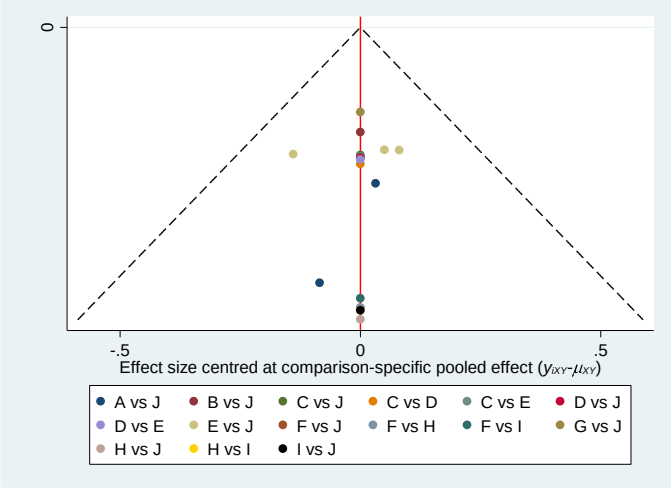
Figure S10.2 Comparison-adjusted funnel plots from the network meta-analyses: long-term risk of CRC incidence

i. RCTs reported long-term CRC incidence with follow-up more than 10 years



A, ASA-HD; B, ASA-LD; C, ASA-VLD; D, Antiox; E, Calcium+VitD; F, PCB.

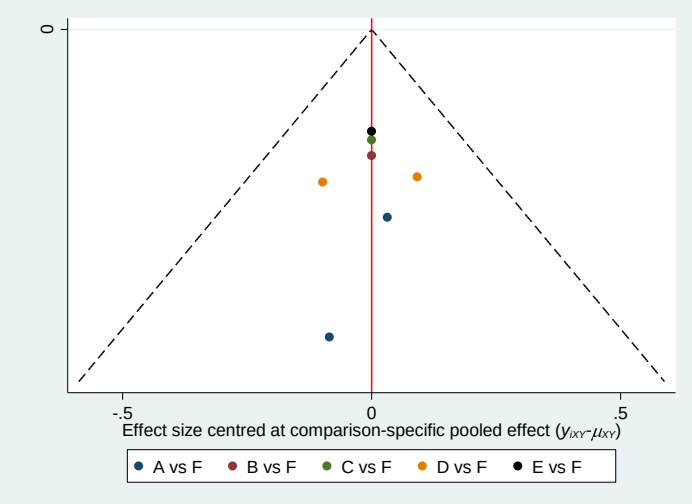
ii. All RCTs reported long-term CRC incidence with follow-up 0-20 years or more



A, ASA-HD; B, ASA-LD; C, ASA-VLD; D, ASA-VLD+Antiox; E, Antiox; F, B6; G, Calcium+VitD; H, Folic+B12; I, Folic+B12+B6; J, PCB.

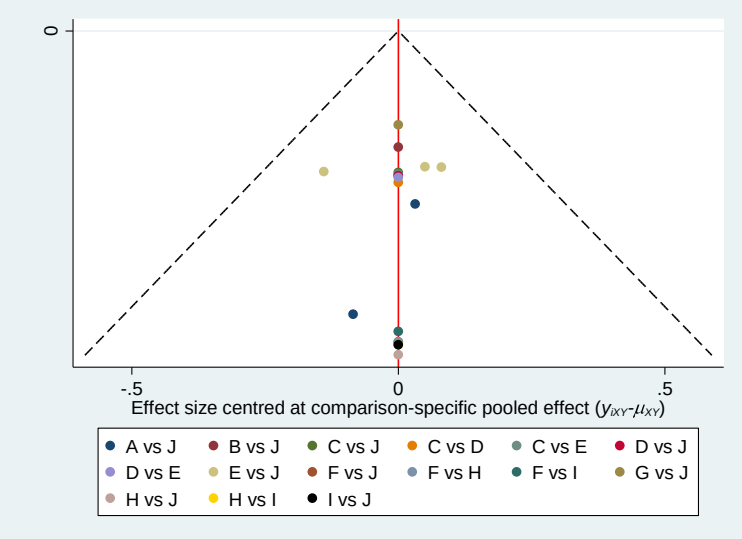
Figure S10.3 Comparison-adjusted funnel plots from the network meta-analyses: long-term risk of CRC mortality

i. RCTs reported long-term CRC incidence with follow-up more than 10 years



A, ASA-HD; B, ASA-LD; C, ASA-VLD; D, Antiox; E, Calcium+VitD; F, PCB.

ii. All RCTs reported long-term CRC incidence with follow-up 0-20 years or more



A, ASA-HD; B, ASA-LD; C, ASA-VLD; D, ASA-VLD+Antiox; E, Antiox; F, B6; G, Calcium+VitD; H, Folic+B12; I, Folic+B12+B6; J, PCB.

Figure S10.4 Comparison-adjusted funnel plots from the network meta-analyses: major GI bleeding events

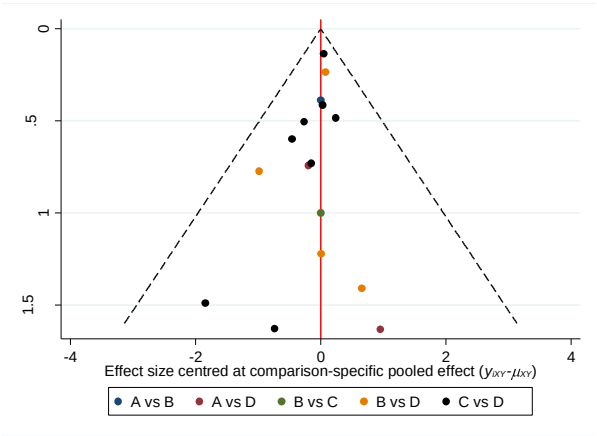
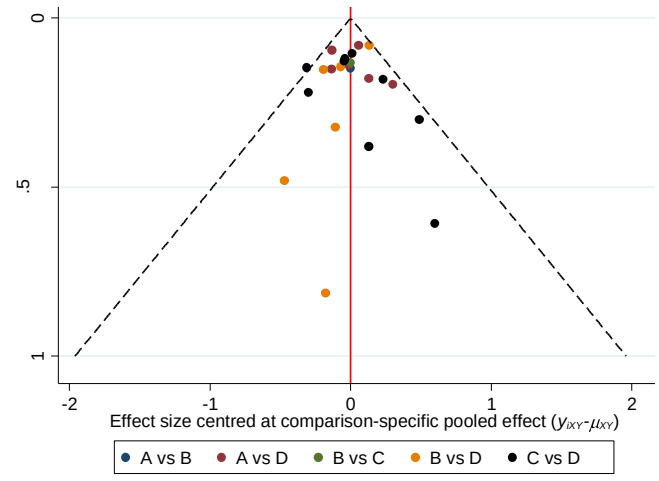


Figure S10.5 Comparison-adjusted funnel plots from the network meta-analyses: CV mortality



Supplement 11: GRADE Summary of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach adapted to network meta-analysis was used to rate the quality of evidence into four levels [21]: high, moderate, low and very low quality. In this approach, direct estimates from RCTs rated at high quality and can be graded down to moderate, low and very-low quality based on risk of bias, indirectness, imprecision, inconsistency and publication bias. The rating of the quality of the indirect estimates starts at the lowest rating of the two direct estimates that contribute to the indirect estimate of the comparison of interest as first order loops. In the presence of intransitivity, indirect estimate can be further rate down from the lower of the confidence ratings of the contributing direct comparisons. Finally, if both direct and indirect evidence are available then the higher of the two quality ratings can be assigned to the quality rating for NMA estimates.

Comparisons	**Direct evidence (from pairwise meta-analysis)**		**Indirect evidence (from node-splitting)**		**Difference**	**Network meta-analysis**	
Long-term CRC incidence	**RR [95% CI]**	**Quality of evidence**	**RR [95% CI]**	**Quality of evidence**	**P value**	**RR [95% CI]**	**Quality of evidence**
ASA-HD vs. Placebo	0.74 [0.57, 0.97]	Very low[a]	NA	NA	-	0.74 [0.57, 0.97]	Very low
ASA-LD vs. Placebo	1.03 [0.83, 1.27]	Very low[b]	NA	NA	-	1.03 [0.83, 1.27]	Very low
ASA-VLD vs. Placebo	0.81 [0.67, 0.98]	Low[c]	NA	NA	-	0.81 [0.67, 0.98]	Low
ASA-HD vs ASA-LD	NA	NA	0.72 [0.51,1.01]	Very low[d]	-	0.72 [0.51,1.01]	Very low
ASA-HD vs ASA-VLD	NA	NA	0.91 [0.66, 1.26]	Very low[d]	-	0.91 [0.66, 1.26]	Very low
ASA-LD vs ASA-VLD	NA	NA	1.27 [0.96,1.68]	Very low[d]	-	1.27 [0.96,1.68]	Very low
Long-term CRC mortality	**RR [95% CI]**	**Quality of evidence**	**RR [95% CI]**	**Quality of evidence**	**P value**	**RR [95% CI]**	**Quality of evidence**
ASA-HD vs. Placebo	0.72 [0.51, 1.03]	Very low[a]	0.26 [0.02, 3.65]	Very low[d]	0.45	0.71 [0.50, 1.01]	Very low
ASA-LD vs. Placebo	0.50 [0.22, 1.17]	Low[e]	0.37 [0.15, 0.90]	Very Low[d,f]	0.66	0.43 [0.23, 0.81]	Low
ASA-VLD vs. Placebo	0.63 [0.43, 0.93]	Moderate[g]	1.04 [0.30, 3.65]	Very low[d,f]	0.45	0.66 [0.45, 0.95]	Moderate

ASA-HD vs. ASA-LD	1.35 [0.55, 3.33]	Low[h]	2.08 [0.78, 5.55]	Very low[d,f]	0.54	1.66 [0.84, 3.29]	Low
ASA-HD vs. ASA-VLD	NA	NA	1.08 [0.66, 1.79]	Very low[d,f]	-	1.08 [0.66, 1.79]	Very low
ASA-LD vs. ASA-VLD	0.49 [0.19, 1.32]	Low[h]	0.82 [0.34, 1.98]	Very Low [d,f]	0.45	0.65 [0.34, 1.25]	Very low

Randomized controlled trials (RCTs) without important limitations are rated high on the GRADE scale. However, the above results are from long term observational follow-up of RCTs with proper random sequence generation during intervention phase. Hence the initial quality rating starts with moderate level.

a. Risk of bias (One RCT is open control); indirectness (dose and treatment duration variation); imprecision (close to null effect)
b. Short duration of follow-up; only 12 years; imprecision
c. Imprecision (close to null effect)
d. Based on rating of the two pairwise estimates that contributes to the indirect estimate (first order loop)
e. Imprecision
f. Intransitivity
g. Indirectness (dose 30-75 mg/day and treatment duration variation)
h. Indirectness (treatment duration and follow-up)

Long-term CRC incidence: No triangular or quadratic loops found for node-splitting.

Supplement 12: Net clinical benefit analysis

Table S12.1 Pooled risk estimates and net clinical benefit of treatment options compared with placebo

Treatment	Pooled risk estimates (%)			Risk ratio (network meta-analysis)			Net survival gain (%)
	Mortality due to CRC	Mortality due to CV	Major GIB	Mortality due to CRC	Mortality due to CV	Major GIB	
ASA-HD	1.473 (0.853, 2.462)	4.741 (3.438, 6.315)	1.385 (0.307, 4.564)	0.714 (0.503, 1.013)	0.928 (0.826, 1.043)	4.037 (1.861, 8.760)	0.908 (0.416, 1.342)
ASA-LD	0.885 (0.385, 1.967)	4.528 (3.206, 6.173)	0.635 (0.201, 1.465)	0.429 (0.227, 0.809)	0.886 (0.770, 1.020)	1.851 (1.218, 2.812)	1.736 (1.010, 2.434)
ASA-VLD	1.360 (0.772, 2.321)	4.708 (3.420, 6.258)	0.495 (0.190, 0.942)	0.659 (0.455, 0.955)	0.922 (0.821, 1.034)	1.442 (1.150, 1.808)	1.091 (0.614, 1.573)
PCB (reference)†	2.063 (1.696, 2.430)	5.109 (4.164, 6.053)	0.343 (0.165, 0.521)	1	1	1	-

1. All of treatment was significantly better than placebo.
2. ASA-LD seems to be the most effective regimen.

† Pooled risk estimate of the treatment with PCB (reference) was calculated by using meta-analyses of proportions (calculated by using meta-analyses of proportions in Stata with metaprop command).

Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; ASA-VLD, very low-dose aspirin; CRC, colorectal cancer; CV, cardiovascular; GIB, gastrointestinal bleeding; PCB, placebo.

Table S12.2 Combined risk estimates of mortality from CRC and CV and pooled risk estimates of major GI bleeding (for scatter plot).

Treatment	Risk estimates for CRC mortality (%)	Risk estimates for CV mortality (%)	Risk estimates for CRC and CV mortality (%)	Risk estimates for GI bleeding (%)
ASA-HD	1.467	4.738	6.205	1.400
ASA-LD	0.894	4.529	5.422	0.640
ASA-VLD	1.370	4.705	6.076	0.499
PCB	2.066	2.066	7.176	0.346

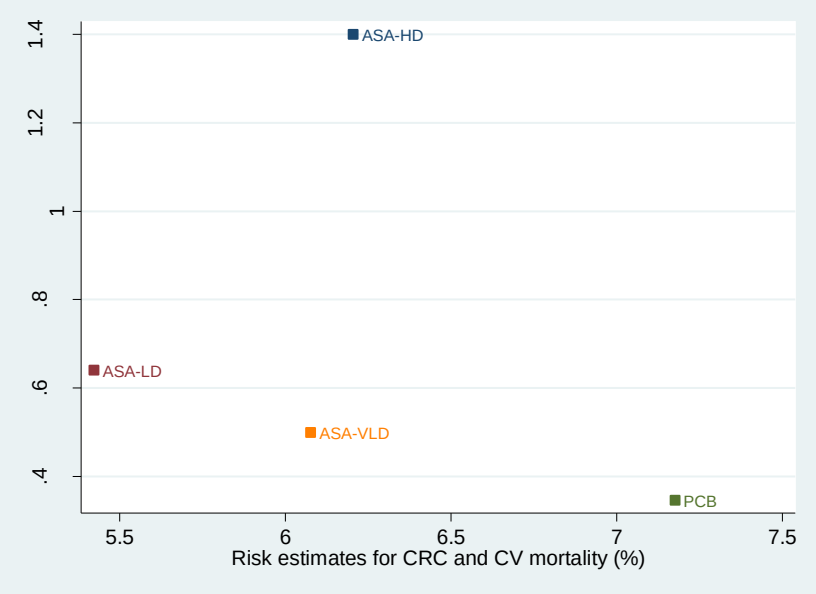
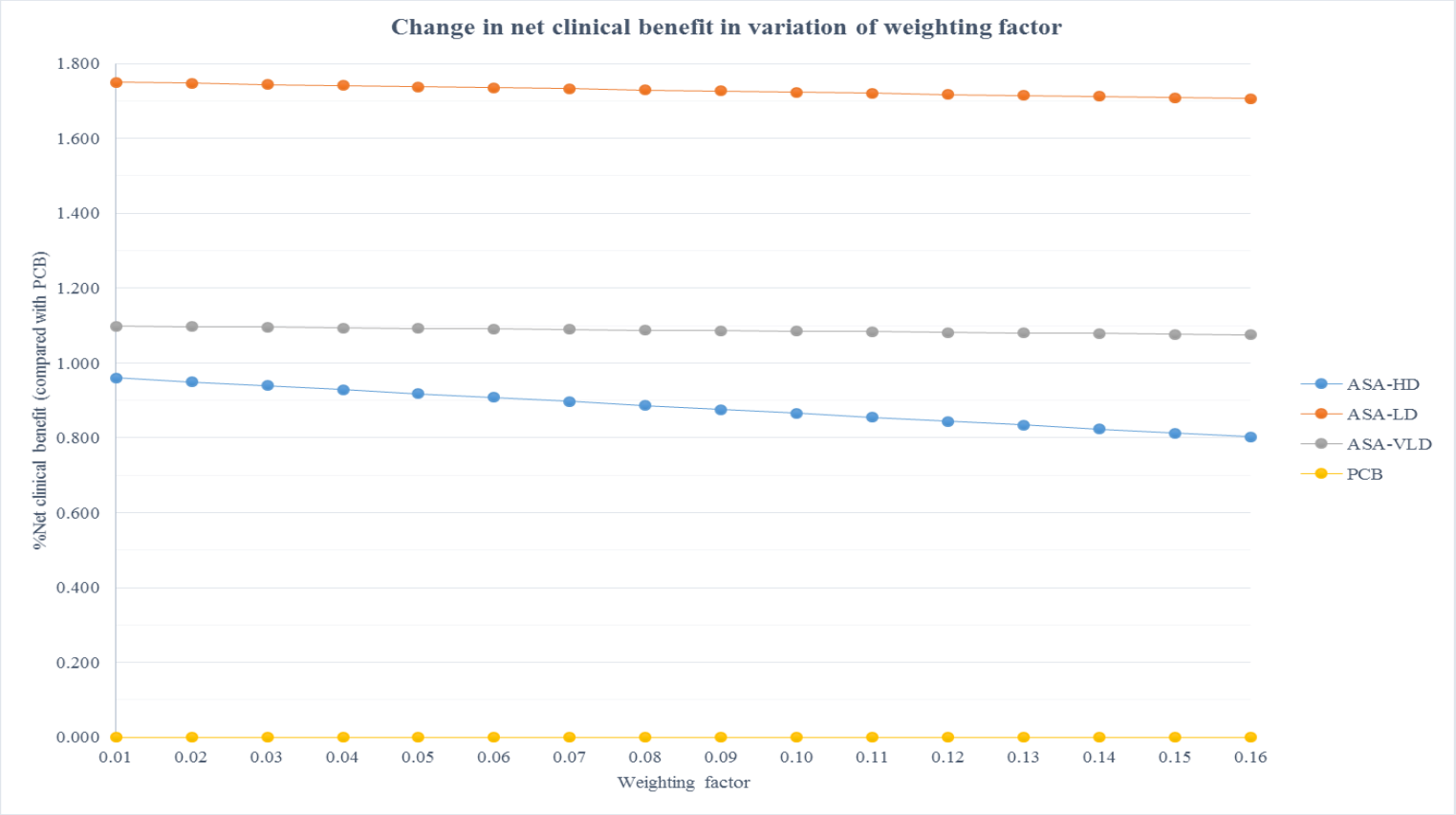


Figure S12.1 Sensitivity analyses of net clinical benefit by varying weighting factors from 0.01 to 0.16



Note: Based on the sensitivity analysis, the benefit declines when increasing of weighting factor (which indicates that the benefit from mortality prevention will not be warrant if severe bleeding occurs).

Method S12.1 Explanation why low-dose aspirin was gained the most clinical benefit?

First, although there is no significant difference in the efficacy of mortality prevention from CRC (RR 0.65; 95% CI 0.34, 1.25) and CV cause (RR 0.96; 95% CI 0.81, 1.14) between low and very-low dose aspirin, low-dose aspirin has better ranking than very low-dose aspirin in our network comparison for aforementioned outcomes. Second, the difference of major GI bleeding between these two regimens was small. As seen in eTable 12.1, the pooled risk estimates of major GI bleeding for low-dose aspirin and very low-dose aspirin were 0.635 (95% CI 0.201, 1.465) and 0.495 (95% CI 0.190, 0.942), respectively. Therefore, the magnitude of benefit gain from mortality prevention from CRC and CV cause are much higher than death from GI bleeding. Previous meta-analysis [96] conducted by the Antithrombotic Trialists' Collaboration to investigate effects of antiplatelet therapy among patients at high risk of occlusive vascular events also demonstrated that aspirin in doses from 75 to 325 mg daily appears to be the effective dose for the prevention of vascular events without differences in risk of major extracranial bleeding across dose ranges. However, we caution the reader to carefully interpret and apply our result in the current practice since it does not clear that low-dose aspirin provide a significance level of benefit gain than very low-dose aspirin (%Net survival gain for low-dose and very low-dose aspirin were 1.736 [95% CI 1.010, 2.434] and 1.091 [95% CI 0.614, 1.573], respectively).

Figure S12.2 Threshold analyses by varying the weight for case-fatality ratio of GI bleeding

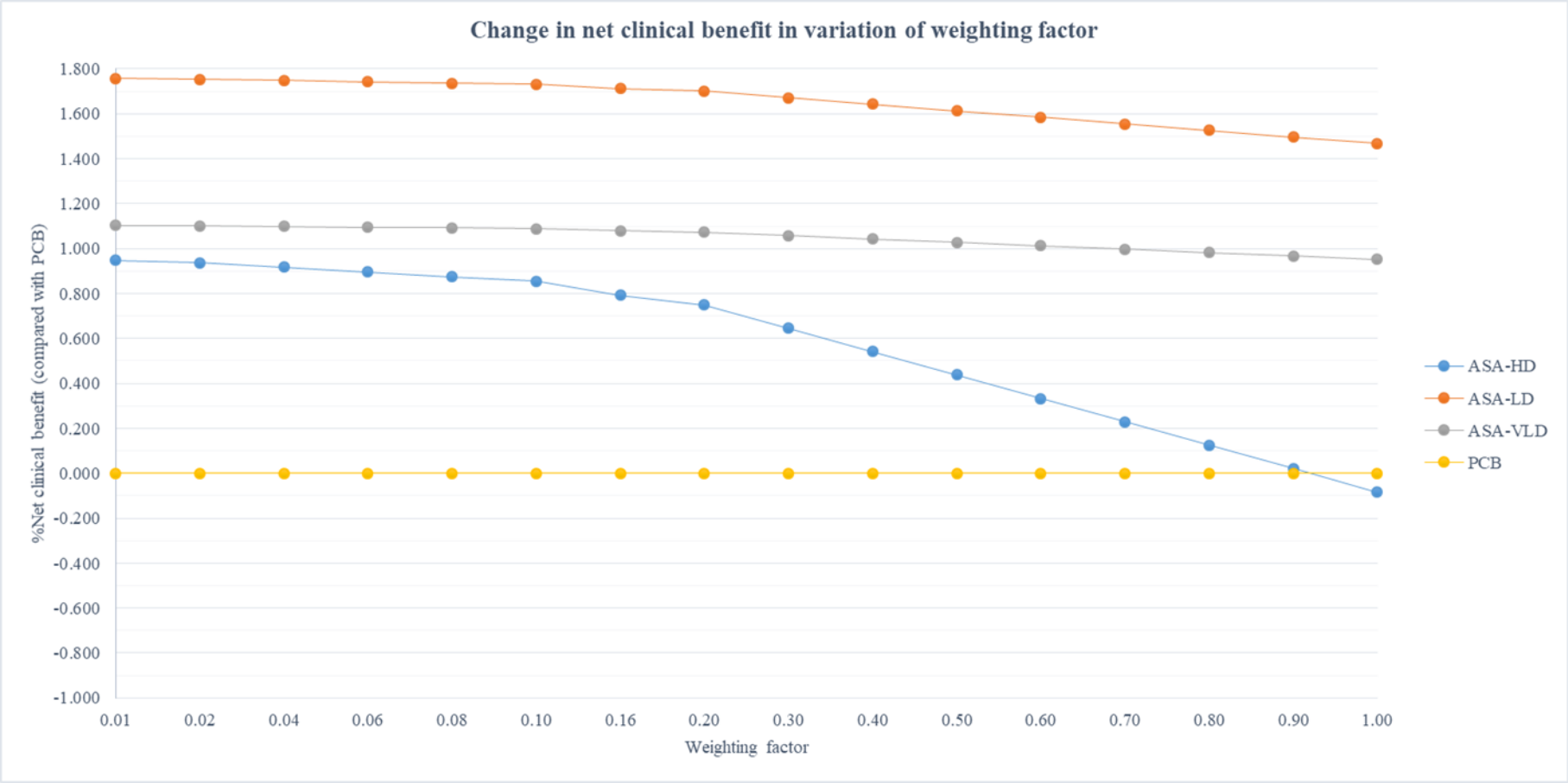
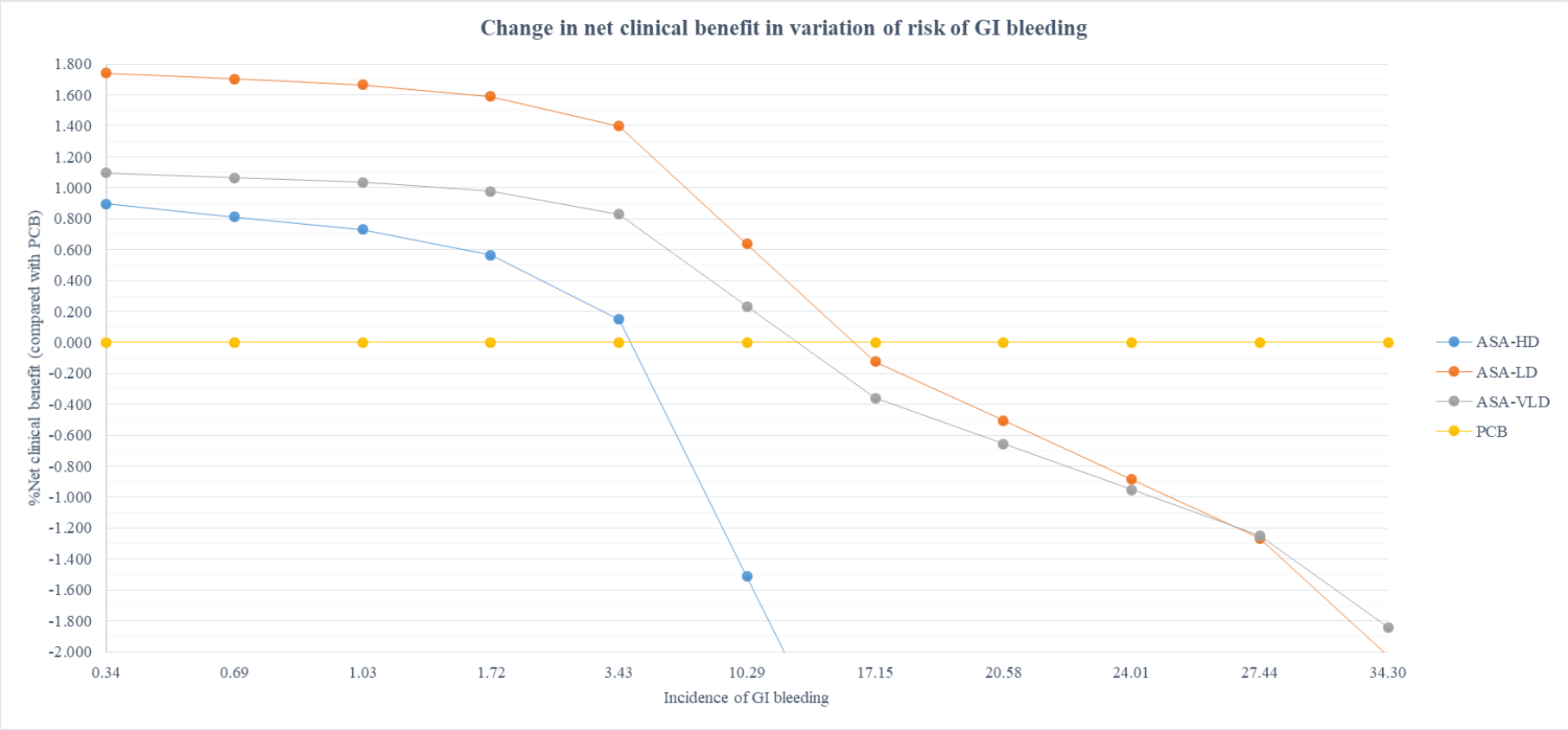


Figure S12.3 Threshold analyses by varying the incidence of GI bleeding.



Reference

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