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ORIGINAL ARTICLE

Individualised prediction of alternate-day aspirin treatment effects on the combined risk of cancer, cardiovascular disease and gastrointestinal bleeding in healthy women

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ABSTRACT

Background The value of aspirin in primary prevention of cancer and cardiovascular disease (CVD) remains unclear. The aim of this study was to identify women who benefit from alternate-day aspirin with regard to all relevant outcomes, including cancer, CVD and major gastrointestinal bleeding.

Methods Long term follow-up data of 27 939 healthy women with baseline plasma samples in the Women's Health Study, a randomised trial of 100 mg alternate-day aspirin versus placebo, were used to develop competing risks models for individualised prediction of absolute risk reduction of the combination of CVD, cancer and major gastrointestinal bleeding by aspirin.

Results Although aspirin was associated with a modestly decreased 15-year risk of colorectal cancer, CVD, and in some women non-colorectal cancer, aspirin treatment resulted in a negative treatment effect in the majority of women if gastrointestinal bleeding was also taken into account. The excess risk of major gastrointestinal bleeding by aspirin increased with age, but the benefits for colorectal cancer and CVD risk were also greater at higher age. Decision curves indicated that selective treatment of women ≥65 years may improve net benefit compared to treating all, none and prediction-based treatment. The observed 15-year number needed to treat to prevent one event among women ≥65 years was 29 (95% CI 12 to 102).

Conclusions Concurrent evaluation of the absolute effects on cancer, CVD and major gastrointestinal bleeding showed that alternate-day use of low-dose aspirin is ineffective or harmful in the majority of women in primary prevention. Selective treatment of women ≥65 years with aspirin may improve net benefit.

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INTRODUCTION

Emerging data convincingly show that aspirin, in addition to its effects on cardiovascular risk, reduces cancer risk.[1–4] Recent meta-analyses of individual patient data from randomised trials of daily aspirin showed a notable decrease in both cancer incidence and mortality, particularly for colorectal cancer.[2 3 5] The protective effects were more pronounced in trials with longer duration of treatment and emerged only after a delay of 5–10 years, depending on the dose used.[1–3 5 6] In contrast to daily aspirin, no effect of alternate-day aspirin on cancer risk was observed in previous analyses of the two largest randomised trials of aspirin, the Women's Health Study (WHS) and the Physicians' Health Study (PHS).[7 8] Recently, however, analysis of long term observational follow-up data of the WHS revealed a reduction in colorectal cancer risk in the aspirin group, emerging after a median follow-up of 18 years (HR 0.80, 95% CI 0.67 to 0.97).[9]

Despite these findings, the role of aspirin in primary prevention remains unclear, as it is uncertain whether the combined benefits for cancer and cardiovascular disease (CVD) outweigh the increase in major bleeding events.[4 10] The US Food and Drug Administration recently published a consumer update in which the use of aspirin for primary prevention of CVD is discouraged,[11] whereas current guidelines, focusing on CVD, recommend to consider use of aspirin prophylaxis for individuals at high cardiovascular risk[12] and in those ≥65 years of age, if the benefit for CVD prevention is likely to outweigh the risk of bleeding events.[13 14] However, for whom the latter is the case, especially if the potential benefits for cancer prevention are also considered, remains to be established.

As treatment effect may be determined by multiple patient characteristics, using models to predict treatment effect for individuals could help to select patients for aspirin treatment.[15–20] This would enable clinicians to estimate the response of an individual to aspirin prophylaxis and only treat those who are expected to benefit.

Using data from the WHS, we developed models for predicting aspirin treatment effect (ie, 15-year absolute risk reduction (ARR) of the combination of CVD, cancer and major bleeding events), aimed at identifying initially healthy women who could benefit from aspirin. Moreover, we evaluated which of the following aspirin treatment strategies would lead to the most favourable clinical outcome: treat none, treat everyone, treat only women ≥65 years, and prediction-based treatment.

METHODS

The WHS was a randomised trial evaluating the effect of 100 mg alternate-day aspirin compared with placebo for primary prevention of CVD and cancer in 39 876 women ≥45 years of age, without a history of CVD or cancer. Detailed methods and

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outcomes have been described previously.[7 9 21 22] Written informed consent was obtained from all participants and the trial was approved by the Institutional Review Board of Brigham and Women's Hospital. After the end of randomised treatment on 31 March 2004, with an average 10 years of follow-up, participants were invited for further observational follow-up.[9] A detailed description of the post-trial follow-up and endpoint ascertainment is provided in online supplementary appendix 1. The present analyses include endpoints accrued and confirmed through 14 March 2012, using data of women who provided an adequate baseline plasma sample (n=27 939).

Model derivation

To obtain individualised predictions of treatment effect of aspirin, proportional subdistribution hazards models[23] for four outcomes were developed: (1) CVD (ie, non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes), (2) invasive colorectal cancer; (3) non-colorectal cancer (ie, any invasive neoplasm, excluding colorectal and non-melanoma skin cancer); and (4) major gastrointestinal bleeding. The latter was defined as gastrointestinal bleeding events requiring hospitalisation. Reports of cancer were confirmed by pathology or cytology reports or, rarely, were based on strong clinical and radiologic or laboratory marker evidence.[7 9] Given that the evidence of a preventive effect of aspirin is most abundant for colorectal cancer, this outcome was modelled apart from other cancers, so that any specific effects of aspirin on colorectal cancer risk could be evaluated separately. To avoid non-additivity of risks for individual endpoints, outcomes were modelled in a competing risks framework, mutually accounting for the events of interest, as well as for death by causes other than CVD, cancer or gastrointestinal bleeding (see online supplementary appendix 2.1).[23 24] Models were developed for treatment effect prediction at 10 and 15 years. To reduce overfitting, predictors that were deemed to be easily available in clinical practice, including age, smoking status, body mass index, systolic blood pressure, use of blood pressure lowering medication, total cholesterol, high density lipoprotein cholesterol, high sensitivity C-reactive protein, family history of premature coronary heart disease, haemoglobin A1c if diabetic, height, diabetes mellitus, alcohol use, menopausal status, hormone replacement therapy use, family history of cancer and history of dyspepsia, were preselected based on existing literature (see online supplementary appendix 1). The relative treatment effect of aspirin was assumed constant in the main analysis. Findings of effect modification by any risk factors are inconsistent in previous studies[3 7 9 21 25] although significant effect modification was found by age and smoking for CVD in the WHS.[21] To evaluate these potential relative subgroup effects, sensitivity analyses were performed in which treatment interactions were considered (see online supplementary appendix 1).

To obtain individualised ARRs, the models were used to predict the absolute risk of all individual outcomes with and

Table 1 Baseline characteristics of the total study population and according to predicted 15-year ARR of major cardiovascular events, colorectal cancer, non-colorectal cancer, and major gastrointestinal bleeding with aspirin treatment

	Total study population (n=27 939)	<0% predicted ARR (n=18 524)	≥0% and <1% predicted ARR (n=8943)	≥1% predicted ARR (n=472)
Age (years)	54.7±7	52.3±5	59.0±7	64.9±7
Age >65 years	2968 (11)	582 (3)	2130 (24)	256 (54)
Caucasian ethnicity	26 401 (95)	17 664 (95)	8526 (95)	441 (93)
Current smoking	3252 (12)	818 (4)	2220 (25)	217 (46)
Past smoking	10 239 (37)	7399 (40)	2750 (31)	98 (21)
Never smoking	14 424 (52)	10 307 (56)	3973 (44)	157 (33)
Alcohol use (≥1 drink/week)	11 327 (41)	8012 (43)	3184 (36)	133 (28)
Peri- or postmenopausal	20 210 (72)	11 609 (63)	8173 (91)	465 (99)
Hormone replacement therapy use	14 353 (51)	9336 (50)	4819 (54)	219 (46)
Body mass index (kg/m^2)	25.9±5.0	25.4±4.7	26.9±4.9	28.1±5.2
High density lipoprotein (mg/dL)	53.7±15.0	56.5±14.4	48.3±13.1	41.8±11.4
Total cholesterol (mg/dL)	211.8±41.8	204.5±37.9	225.1±40.8	234.3±40.4
High sensitivity C-reactive protein (mg/L)	2.0 [0.8–4.4]	1.5 [0.6–3.5]	3.1 [1.5–5.8]	5.3 [2.7–8.6]
Systolic blood pressure (mm Hg)	124±14	118±10	134±13	148±14
Blood pressure lowering medication use	3739 (13)	812 (4)	2640 (30)	292 (62)
Lipid lowering medication use	893 (3)	319 (2)	516 (6)	58 (12)
Diabetes mellitus	685 (2)	35 (0)	425 (5)	227 (48)
Family history of premature CHD	3959 (14)	2177 (12)	1753 (20)	93 (20)
Family history of cancer*	4966 (18)	3205 (17)	1701 (19)	101 (21)
History of dyspepsia	2575 (9)	1836 (10)	703 (8)	36 (8)
Randomised to aspirin use	13 976 (50)	9239 (50)	4498 (50)	239 (51)
15-year predicted risk (%) of:				
Major cardiovascular events	1.78 [0.96–3.70]	1.17 [0.77–1.77]	4.95 [3.45–7.58]	26.91 [22.11–33.59]
Colorectal cancer	0.81 [0.50–1.28]	0.64 [0.43–0.96]	1.27 [0.84–1.88]	1.85 [1.27–2.55]
Non-colorectal cancer	9.72 [8.29–11.84]	9.09 [7.94–10.63]	11.50 [9.51–14.05]	14.51 [12.09–16.87]
Major gastrointestinal bleeding	1.01 [0.75–1.51]	0.85 [0.68–1.14]	1.53 [1.10–2.18]	2.91 [2.22–3.67]

Data are presented as mean ±SD, median [IQ] or n (%).
A weight of 0.25 was applied for major gastrointestinal bleeding when calculating the predicted total ARR.
*History of breast, colorectal or ovarian cancer in a parent or sibling. Data in first column represent data before imputation of missing values, whereas data in the other columns are based on imputed data.
ARR, absolute risk reduction; CHD, coronary heart disease.

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without aspirin. Subsequently, the ARRs were calculated as the difference between the predicted absolute risk with and without aspirin treatment and the ARRs of the individual outcomes were summed to get a total ARR. As some women and/or physicians may consider CVD or cancer diagnosis to be more important than gastrointestinal bleeding, the total ARR was also calculated applying different weights (ie, 0.5, 0.25 and 0.1) for gastrointestinal bleeding.

Model validation

To adjust for overfitting, bootstrap-based uniform shrinkage was applied for the models[26] (see online supplementary appendix 1). Discriminatory ability of each model was evaluated using an optimism-corrected estimate of the c-index that is adapted for competing risks.[27] Calibration was assessed graphically using calibration plots.

Decision curve analysis[20] was used to evaluate whether use of the models for selecting women for aspirin prophylaxis would improve the clinical outcome compared to other treatment strategies, including treating no one, treating all, and treating only women ≥65 years. This method focuses on the effects of (changes in) treatment decisions that result from a treatment strategy and is based on calculation of 'net benefit'. Calculation of net benefit starts with choosing a treatment threshold, that is the smallest treatment effect (expressed as ARR) at which one would opt for treatment. This treatment threshold can also be expressed as the number-willing-to-treat (NWT), which is the reciprocal of the treatment threshold and can be interpreted as the maximum acceptable number needed to treat (NNT).[17 19] Subsequently, this threshold is used for weighing the reduction in event rate by a certain treatment strategy against the harms of treatment. As the appropriate NWT is subjective and can vary among different patients and clinicians, net benefit was calculated for 15-year NWT values ranging from infinite to 20 (ie, treatment threshold of 0–5%). The net benefit results were presented graphically as decision curves. Given that no effect of cancers other than colorectal cancer was observed in previous analysis of the WHS, sensitivity analysis were performed in which the treatment effect of aspirin on non-colorectal cancer was assumed null. Further details on the model development and validation are provided in online supplementary appendix 1.

RESULTS

Baseline characteristics of the present study population (n=27 939) are shown in table 1. During the trial (median follow-up of 10.1 years, IQR 9.5–10.8), 604 cases of CVD, 168 colorectal cancer diagnoses, 1832 non-colorectal cancer diagnosis, and 302 gastrointestinal bleedings requiring hospitalisation were recorded. An additional 107 colorectal and 1388 non-colorectal cancer cases were confirmed during the post-trial period (median follow-up:7.2 years, IQR 4.6–7.3).

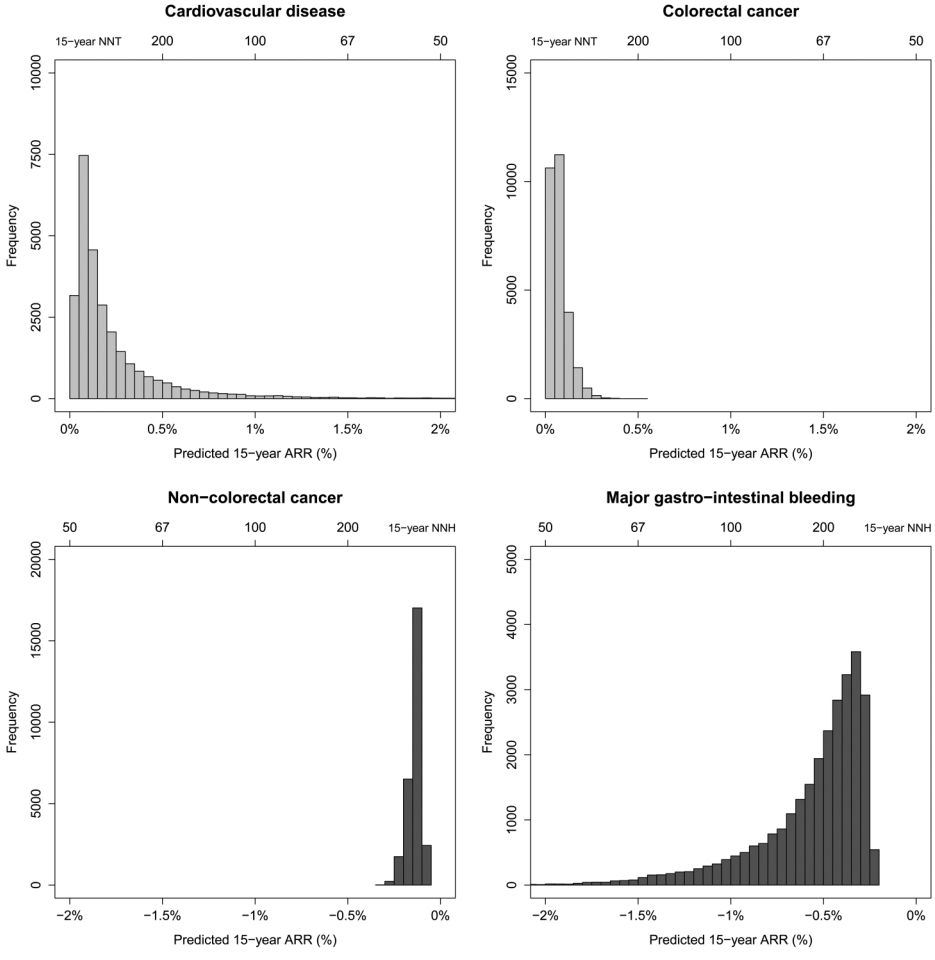

Figure 1 Distribution of predicted 15-year ARR for major cardiovascular events, colorectal cancer, non-colorectal cancer, and major gastrointestinal bleeding with aspirin treatment in the study population. ARR, absolute risk reduction; NNT/NNH, number needed to treat/harm.

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Model derivation and validation

The computational formulas for 10- and 15-year treatment effect of aspirin are provided in online supplementary appendix 2.2 and 2.3. Discrimination of the 10-year CVD model was good (c-index0.785), whereas the discrimination of the model for colorectal cancer (c-index 0.65), non-colorectal cancer (c-index 0.59), and gastrointestinal bleeding (c-index 0.641) was moderate. The models for 15-year predictions of colorectal and non-colorectal cancer showed similar discriminatory power (c-index 0.655 and 0.582, respectively). Model calibration was generally well balanced (see online supplementary appendix 2.4).

ARR by aspirin

The WHS participants had a median predicted 15-year risk of 11.4% for all adverse outcomes combined (1.5% for CVD, 0.5% for colorectal cancer, 8.7% for non-colorectal cancer, and 0.8% for major gastrointestinal bleeding). The distribution of individualised 15-year ARRs of aspirin are shown in figures 1 and 2 and the ARRs with NNTs with 95% CIs observed in the WHS population and specific subgroups are shown in online supplementary appendix 2.5 and table 2. Overall, there was a small benefit from aspirin treatment with regard to CVD (15-year ARR 0.27%, 95% CI 0.06% to 0.86%, NNT 371) and colorectal cancer (15-year ARR 0.14%, 95% CI 0.02% to 0.59%, NNT 709). No effect on non-colorectal cancer was observed (15-year absolute risk increase (ARI) 0.08%, 95% CI −0.64% to 0.80%, number needed to harm (NNH) 709) and aspirin increased the risk of gastrointestinal bleeding in all women (15-year ARI 0.75%, 95% CI 0.50% to 1.00%, NNH 133). Consequently, aspirin non-significantly increased the median 15-year risk for all outcomes combined by 0.42% (95% CI −0.45% to 1.29%). However, a more beneficial distribution of ARRs was observed if a weight was applied for gastrointestinal bleeding. The 10-year estimates were largely similar, although effects of aspirin were closer to the null (see online supplementary appendix 2.5 and 2.6). A stronger protective effect of aspirin on CVD was observed in women ≥65 years (15-year ARR 3.11%, 95% CI 1.67% to 5.27%, NNT 29). The risk of gastrointestinal bleeding was also increased in this group, but this increase was relatively smaller than the decrease in CVD, especially if bleeding is given less weight than CVD and cancer (see online supplementary appendix 2.7).

The predicted ARR of CVD and, to a lesser degree, of colorectal cancer increased with higher baseline CVD and colorectal cancer risk (see online supplementary appendix 2.8). In contrast, the absolute risk of gastrointestinal bleeding increased notably in women with high baseline risk when on aspirin. Only women with a total baseline risk of >40% for all outcomes would derive benefit from aspirin, although at which baseline risk aspirin yields benefit is dependent on the weight that is applied for bleeding. A similar effect of age on the

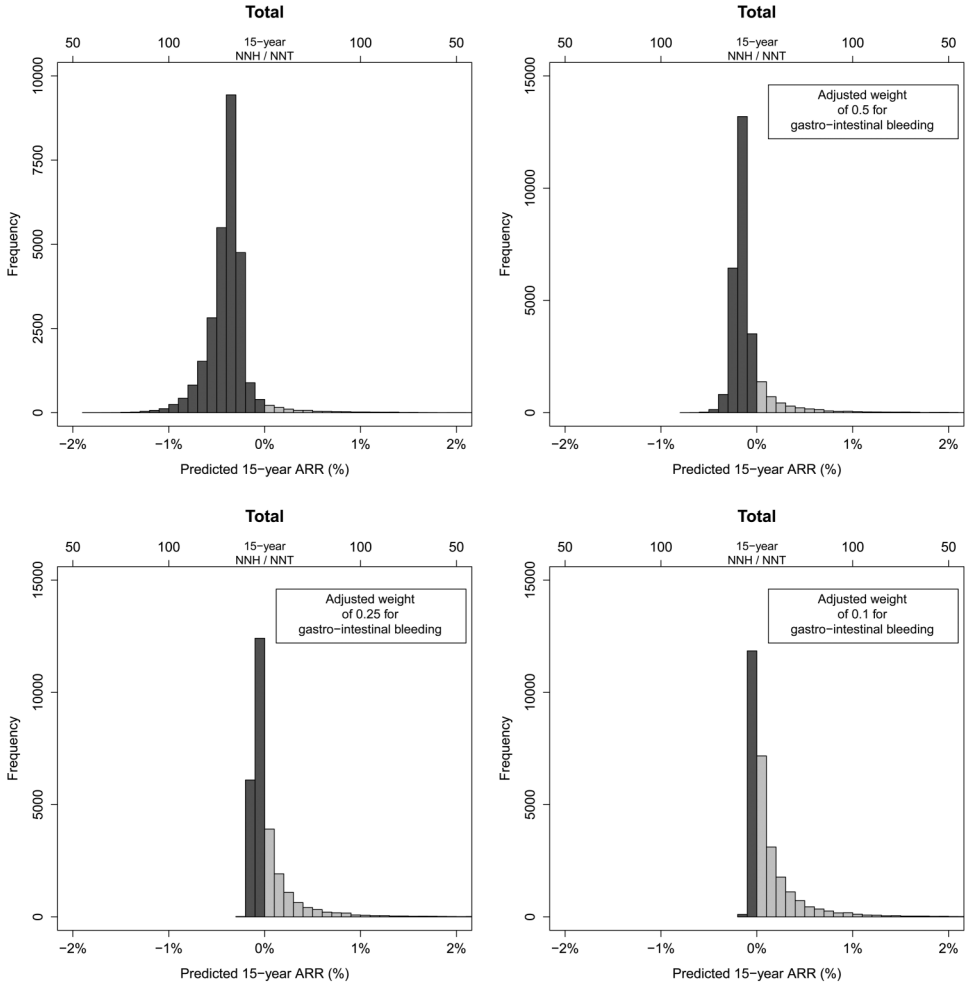

Figure 2 Distribution of predicted 15-year ARR for the total of all outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer, and major gastrointestinal bleeding) applying different weights for gastrointestinal bleeding, in participants in the Women's Health Study. ARR, absolute risk reduction; NNT/NNH, number needed to treat/harm.

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predicted 15-year ARR was observed, with increasing benefit for CVD and colorectal cancer with higher age. However, the increase in absolute risk of bleeding by aspirin was also stronger in older individuals.

Table 1 displays the characteristics of the study participants by predicted 15-year ARR for the combination of all adverse outcome (<0%, between 0–1%, and ≥1%), calculated with a weight of 0.25 for bleedings. Notably, 66% of women had a negative overall treatment effect. Older age was an important determinant for treatment effect—of the women with a predicted overall treatment effect of ≥1% ARR (NNT 100), 54% were ≥65 years.

Net benefit assessment

Decision curves for evaluating the net benefit of different aspirin treatment strategies with regard to the total outcome, with different weights for gastrointestinal bleeding, are shown in figure 3. Treating all women of ≥65 years is the most favourable treatment strategy if the 15-year NWT is >32 (ie, one is willing to treat 32 women to prevent one event), but the limit is lower if gastrointestinal bleeding is given less weight. If treatment would be reserved for women ≥65 years, the NNT to prevent one adverse event would be 29 (95% CI 12 to 102). Because the models predicted only a small benefit or even harm for the vast majority, and thus almost no women would be selected for treatment, prediction-based treatment yielded similar benefit as treating none over the whole range of treatment thresholds. Decision curves for the individual outcomes (see online supplementary appendix 2.9) show that treating all women ≥65 years results in the highest net benefit for CVD and non-colorectal cancer, although treating none would be the optimal strategy if the NWT is lower than 30 and 50, respectively.

Sensitivity analyses

Results of sensitivity analyses are provided in online supplementary appendix 3. The predicted ARRs from the models with treatment interactions were more widely distributed, particularly for non-colorectal cancer, with benefit in 48% of the study population and harm caused in the other 52%. When the effect of aspirin on non-colorectal cancer was assumed null, the total ARR tended to be slightly higher. Overall, however, the results from the sensitivity analysis were similar to the main results and, in both scenarios, decision curve analysis indicated that prediction-based treatment was inferior to treating none or treating only women ≥65 years.

DISCUSSION

In the present study, data of the WHS were used to develop models for treatment effect prediction of alternate-day aspirin on the combination of CVD, cancer and major gastrointestinal bleeding in initially healthy women. Although aspirin was associated with a modestly decreased 15-year risk of CVD and colorectal cancer, aspirin treatment resulted in small benefit or even harm in the majority of women if gastrointestinal bleeding were also taken into account. Age was the most important determinant for benefit of aspirin treatment; this was also reflected by the observation that treating only women ≥65 years of age resulted in a higher net benefit with regard to the combined outcomes compared to other treatment strategies, including prediction-based treatment.

Recent findings that both daily and alternate-day aspirin can reduce cancer risk, particularly for colorectal cancer, have reignited the debate on aspirin in primary prevention. Given that aspirin only modestly lowers cardiovascular risk, while

Table 2 Observed 15-year ARRs and numbers needed to treat/harm for aspirin

	Total study population		Women <65 years		Women ≥65 years	
	ARR (95% CI)	NNT* or NNH† (95% CI)	ARR (95% CI)	NNT* or NNH† (95% CI)	ARR (95% CI)	NNT* or NNH† (95% CI)
Major cardiovascular event	0.27 (0.06 to 0.86)	371 (116 to >1000)*	−0.06 (−0.39 to 0.26)	>1000† (259† to 382*)	3.11 (1.67 to 5.27)	32 (19 to 60)*
Colorectal cancer	0.14 (0.02 to 0.59)	709 (170 to >1000)*	0.17 (0.04 to 0.55)	581 (181 to >1000)*	−0.11 (−1.15 to 0.93)	924† (87† to 107*)
Non-colorectal cancer	−0.08 (−0.80 to 0.64)	>1000† (124† to 156*)	−0.32 (−1.06 to 0.42)	312† (94† to 237*)	2.05 (0.43 to 6.28)	49 (16 to 235)*
Major gastrointestinal bleeding	−0.75 (−0.50 to −1.00)	133 (100 to 198)†	−0.64 (−0.40 to −0.87)	157 (114 to 251)†	−1.66 (−0.50 to −2.82)	60 (35 to 199)†
Total	−0.42 (−1.29 to 0.45)	238† (78† to 223*)	−0.85 (−1.72 to 0.03)	118† (58† to >1000*)	3.39 (0.98 to 8.42)	29 (12 to 102)*
Total, adjusted weight of 0.5 for gastrointestinal bleeding	−0.05 (−0.92 to 0.82)	>1000† (109† to 121*)	−0.53 (−1.40 to 0.34)	189† (71† to 291*)	4.22 (1.59 to 8.90)	24 (11 to 63)*
Total, adjusted weight of 0.25 for gastrointestinal bleeding	0.14 (0.00 to 7.59)	703 (13 to >1000)*	−0.37 (−1.24 to 0.50)	271† (81† to 199*)	4.64 (1.92 to 9.19)	22 (11 to 52)*
Total, adjusted weight of 0.1 for gastrointestinal bleeding	0.25 (0.00 to 3.43)	393 (29 to >1000)*	−0.27 (−1.15 to 0.60)	365† (87† to 167*)	4.89 (2.13 to 9.38)	20 (11 to 47)*

Risks were estimated based on the cumulative incidence function, accounting for competing risk.
*NNT, number needed to treat.
†NNH, number needed to harm.
ARR, absolute risk reduction (in %).

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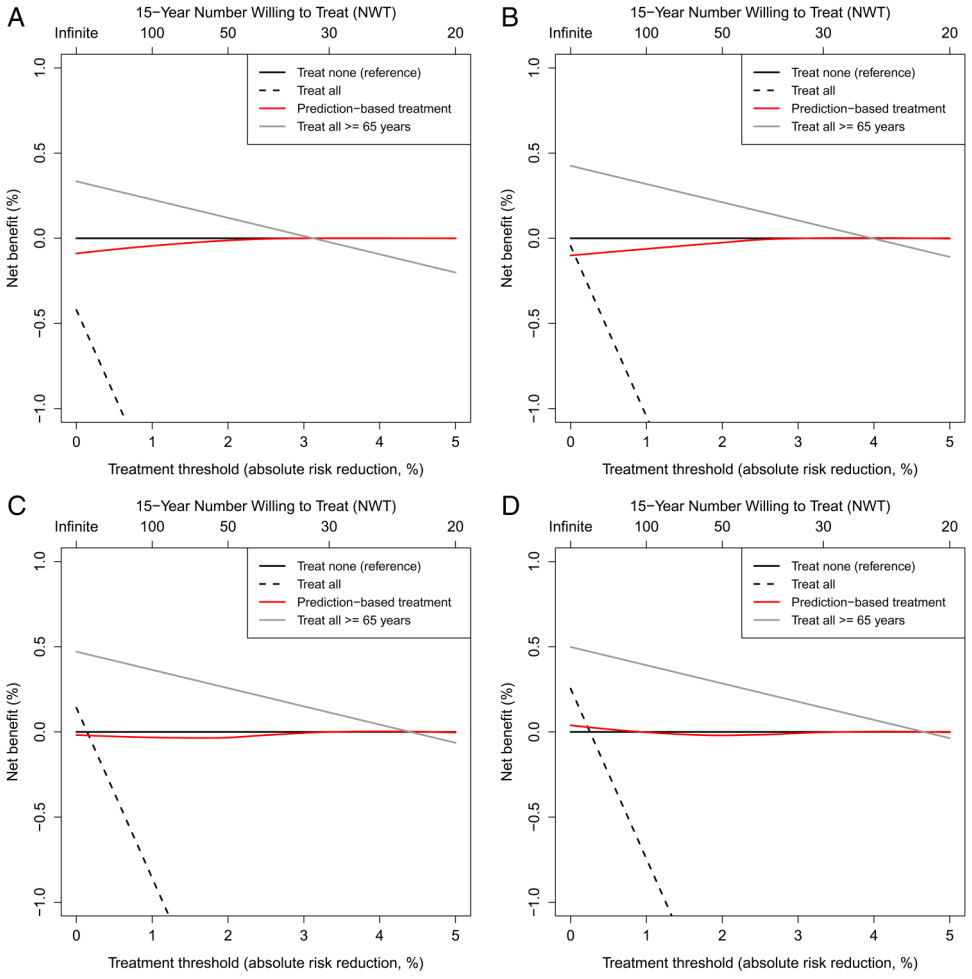

Figure 3 Decision curves for different aspirin treatment strategies, with different weights applied to major gastrointestinal bleeding. (A) No weight (one bleeding is equal to one cardiovascular event or cancer diagnosis). (B) Weight of 0.5 (two bleedings are equal to one cardiovascular event or cancer diagnosis). (C) Weight of 0.25 (four bleedings are equal to one cardiovascular event or cancer diagnosis). (D) Weight of 0.1 (10 bleedings are equal to one cardiovascular event or cancer diagnosis). Reading the net benefit plot starts with choosing a treatment threshold, that is the absolute risk reduction (ARR) at which one would opt for treatment, or number willing to treat (NWT). An NWT of 30 implies that one is willing to treat 30 women to prevent at least 1 event. Since major gastrointestinal bleeding is already incorporated in the total outcome, the treatment threshold is mainly chosen depending on how important one would deem less serious complications, inconvenience of taking pills, and costs. Positive net benefit means that the treatment strategy led to a more favourable trade-off between benefits (observed decrease in event rate) and harms (the proportion of patients receiving treatment weighted by the reciprocal of the treatment threshold). For example, when using a weight of 0.25 for bleeding (C) and an NWT of 30 (treatment of all women with predicted risk reduction of 3.3% or more, ie, a threshold of 3.3%), treating only women ≥65 years of age yields a positive net benefit of observed reduction in event rate—(proportion receiving treatment×treatment threshold) =0.03748−(0.11×0.033)=0.12%—and would be the optimal treatment strategy, whereas prediction-based treatment gives a net benefit of zero (predicted ARR are below the treatment threshold for all women, so equal to treating none) and treating all worsens clinical outcome (negative net benefit).

increasing the risk of major gastrointestinal bleeding,[10 25] the benefits for cancer could tip the balance in favour of aspirin in primary prevention. Moreover, it is important to correctly identify those for whom these benefits of aspirin prophylaxis outweigh the harms, and vice versa. Our results indicate that selectively treating women ≥65 years of age may yield the most favourable clinical outcome, given that the harms (ie, minor adverse effects, inconvenience and costs) of treating 32 (or fewer, if one considers CVD or cancer to be more important than major gastrointestinal bleeding) women with aspirin during 15 years are considered to be acceptable to prevent one case of CVD or cancer.This finding is notable, especially since older age was associated with higher bleeding risk on aspirin treatment. However, in many women ≥65 years of age the benefits of aspirin with regard to cancer and particularly CVD risk outweigh the increased bleeding risk, especially if bleeding events are considered to be less important. The finding that the protective effect of aspirin with regard to CVD risk increases with age is in line with results in men from the PHS.[28]

A previous cost-effectiveness study, evaluating the benefits of daily aspirin with regard to CVD, showed that aspirin could yield net benefit in individuals with a high CVD risk.[29] Although we observed that the benefits of aspirin were dependent on CVD risk, selective treatment of women with >10% 10-year CVD risk did not improve overall net benefit and was inferior to selective treatment of women of ≥65 years when the effects on cancer and bleeding were also taken into account.

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As the predicted net benefit of aspirin treatment for most women is small, less serious side effects (ie, minor bleeding and peptic ulcers) become important in aspirin treatment decisions. Extrapolating the combined incidence rates of minor gastrointestinal bleeding and peptic ulcers during the trial period results in a 15-year ARR of −3.4%. This means that for every 29 women using alternate-day aspirin during 15 years, one experiences a minor gastrointestinal bleeding or peptic ulcer.

Treatment based on predictions from multivariable models resulted in lower net benefit than treating women ≥65 years of age. This is possibly due to the usage of multiple models, which might increase the probability of misclassification. In particular, the prediction model for non-colorectal cancer showed a slightly unsatisfactory performance. This outcome comprises a heterogeneous group of cancers, which might have led to the introduction of noise by some of the predictors other than age. This unexpected finding emphasises the importance of evaluating different treatment strategies based on their clinical benefit with regard to all relevant outcomes (eg, by means of decision curve analysis). In the sensitivity analysis, no important changes in treatment effect predictions were observed, indicating that the results are robust.

Study limitations

Some study limitations need to be considered. First, the participants of the WHS are generally at low risk due to selection criteria (eg, all female health professionals). This might limit extrapolation of the results to the general population. Secondly, the present analyses only included first events, meaning that, for example, when a participant experienced both CVD and major gastrointestinal bleeding during the study, only the first event was used. In our view, however, this is similar to clinical practice, where, after non-fatal CVD, bleeding or cancer diagnosis the changes in one's medical condition usually call for a new aspirin treatment decision moment. Thirdly, we presented results with differing weights for major gastrointestinal bleeding, because some might consider bleeding events to be less important than CVD or cancer, but, of course, any weight would be arbitrary. However, if the 15-year NWT would be 32 or higher, the weight for bleeding is irrelevant, as for any lower NWT selective treatment of women ≥65 years of age would be the optimal treatment strategy. Lastly, our results may not apply for daily aspirin as the effects on cancer risk occur earlier than those on alternate-day low-dose aspirin use.[1 3 6]

Whether aspirin prophylaxis could indeed be beneficial in the elderly is currently being evaluated in a randomised trial (NCT01038583). Meanwhile, simultaneous evaluation of absolute treatment effects on all relevant outcomes on an individual patient level such as presented in this study, rather than evaluating each outcome at a time on a group level, could provide a sensible approach to determine the value of aspirin in primary prevention.

CONCLUSIONS

Alternate-day use of low-dose aspirin for primary prevention is ineffective or harmful in the majority of women with regard to the combined risk of CVD, cancer and major gastrointestinal bleeding. Age is the most important determinant of aspirin treatment effect, and the protective effects of aspirin with regard to CVD increased with age. Although the excess risk of major gastrointestinal bleeding by aspirin is higher in women ≥65 years of age, selective treatment of this group is may improve net benefit.

Key messages

What is known on this subject?

Recent evidence suggests that long term use of alternate-day low-dose aspirin may reduce risk for colorectal cancer in healthy women. The value of aspirin in primary prevention, however, remains uncertain, as it is unclear for whom the benefits for the combination of cancer and cardiovascular disease (CVD) outweigh the increase in major bleeding risk.

What might this study add?

This study shows that although aspirin is associated with a modestly decreased 15-year risk of CVD and colorectal cancer, aspirin treatment results in small overall benefit or even harm in the majority of women if gastrointestinal bleeding is also taken into account. Age is the most important determinant for benefit of aspirin treatment. Treating only women ≥65 years of age yielded the highest net benefit with regard to the combined outcomes when compared to treating all women, treating none, and prediction-based treatment.

How might this impact on clinical practice?

For the majority of women in primary prevention, the long term benefits of alternate-day low-dose aspirin with regard to cancer and CVD do not outweigh the increase in major gastrointestinal bleeding. Selective treatment of women ≥65 years of age with aspirin may improve net benefit.

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Contributors RCMvK conceived the research question, designed and carried out the data analyses, interpreted the results and drafted the manuscript. FLJV conceived the research question, designed the data analyses, interpreted the results and revised the manuscript for important intellectual content. PMR conceived the research question, collected the data, designed the data analyses, interpreted the results and revised the manuscript for important intellectual content. JAND conceived the research question, designed the data analyses, interpreted the results and revised the manuscript for important intellectual content. JEB is the principal investigator of the Women's' Health Study, collected the data and revised the manuscript for important intellectual content. YvdG conceived the research question, designed the data analyses, interpreted the results and revised the manuscript for important intellectual content. NRC conceived the research question, collected the data, designed the data analyses, interpreted the results and revised the manuscript for important intellectual content.

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Competing interests PMR receives investigator initiated research support from the National Institutes of Health, Amgen, Novartis, Pfizer, and AstraZeneca; has served as a consultant to ISIS, Vascular Biogenics, Boston Heart, Jannson, and Genzyme; and is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to Siemens and AstraZeneca. FLJV's department receives grant support from the Netherlands Organisation for Health Research and Development, and the Catharijne Foundation Utrecht; and speaker fees from Merck.

Ethics approval The Institutional Review Board of Brigham and Women's Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data set: not available. Study protocol and statistical code: available from the authors upon written request. The authors have written an R-function for decision curve analyses for models that apply the results of a clinical trial[20] which is also available on request (email: R.C.M.vanKruijsdijk@umcutrecht.nl).

Patient Consent Obtained.

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Appendix 1 | Detailed description of methods

Design overview

The WHS was a randomized trial evaluating the effect of 100mg of aspirin on alternate days compared with placebo for primary prevention of CVD and cancer in 39,876 women of 45 years of age or older, without a history of cardiovascular disease or cancer. Detailed methods and outcomes have been described previously[1-4]. Written informed consent was obtained from all participants and the trial was approved by the Institutional Review Board of Brigham and Women's Hospital and was monitored by an external data and safety monitoring board. Endpoints were ascertained using yearly questionnaires and were confirmed using medical records. All relevant information was reviewed by an endpoints committee comprising physicians blinded to treatment allocation[1, 2]. After the end of randomized treatment on 31 March 2004, with an average 10 years of follow-up, participants were invited for further observational follow-up[4]. Of the survivors 33,682 (88.6%) women agreed to continue participation. During the posttrial follow-up, use of aspirin was allowed for women from both study arms. The posttrial use of aspirin for at least three days per month was higher in the randomized aspirin group (46%) compared to the placebo group (43%). Women who used nonstudy aspirin during the posttrial follow-up used aspirin for a median of three years (IQR: 2-5 years)[4]. Information on outcomes was collected and confirmed in a similar manner as during the trial period. End point review is complete for 95% of reported cancer cases, 95% of myocardial infarctions, and 94% of strokes. The confirmation rate among participants with records is 82% for cancer, 61% for myocardial infarction, and 68% for stroke. For the present study, only events confirmed by medical records and deaths with confirmed cause were used. Reports of gastrointestinal bleeding were collected intermittently during posttrial follow-up and were not confirmed[4]. The present analyses include end points accrued and confirmed through 14 March 2012, using data of participants who provided an adequate baseline plasma sample (n=27,939).

Model development

Data of women who provided a baseline plasma sample (n=27,939) were used for model development. For the 10-year predictions, endpoints that occurred during the trial period were used. In order to capture any delayed effects of aspirin on cancer risk[4, 5], the cancer outcomes were also modeled using cases ascertained during the entire follow-up, for prediction of 15-year treatment effect. Since the effects of aspirin on CVD and bleeding seem to be more immediate[4, 6] and the randomized aspirin intervention stopped after 31 March 2004, modeling these outcomes using posttrial data would likely lead to underestimation of the treatment effect. Hence, 15-year predictions for CVD and bleeding were obtained by extrapolating the 10-year risk estimates under the assumption of exponential risk over time, to mimic the effects of taking aspirin for a duration of 15-years. As the CVD endpoint included all strokes, hemorrhagic strokes were not evaluated separately.

To minimize over-fitting, predictors for each outcome were selected based on existing risk scores and/or literature[7-11]. Only predictors that were deemed to be easily available in clinical practice were selected. As a result, the following predictors, besides aspirin treatment, were used for major cardiovascular events (CVD): age, current smoking, body mass index (BMI), systolic blood pressure (SBP), use of blood pressure lowering medication, total cholesterol, high density lipoprotein cholesterol (HDLc), high sensitivity C-reactive protein (hs-CRP), family history of premature coronary heart disease (CHD) and hemoglobin A1c (HbA1c) if diabetic; for colorectal cancer: age, ever smoking, BMI, height, diabetes mellitus, alcohol use (no. of drinks per day), menopausal status, hormone replacement therapy use, family history of colorectal cancer; for non-colorectal cancer: age, ever smoking, BMI, height, diabetes mellitus, alcohol use, menopausal status, hormone replacement therapy use, family history of breast, colorectal, or ovarian cancer; for major bleeding events: age, current smoking, BMI, alcohol use, diabetes mellitus, history of dyspepsia.

The relative treatment effect of aspirin was assumed constant in the main analysis. Findings of effect modification by any risk factors are inconsistent in previous studies[1, 2, 12-14], although significant effect modification was found by age and smoking for CVD in the WHS[2]. To evaluate these potential relative subgroup effects, sensitivity analyses were performed in which treatment interactions with age, smoking status and BMI were considered. These interactions terms were chosen based on previous findings of interaction[1, 2, 15] and/or strong pathophysiological evidence[16, 17]. To avoid including non-relevant treatment interactions, estimation of model coefficients with implicit variable selection was done using component-wise likelihood-based boosting[18]. Aspirin use was included as an mandatory (unpenalized) covariable, whereas the other candidate predictors and treatment interactions were subjected to penalization in penalized partial likelihood estimation. The optimal number of boosting steps was determined by 10-fold cross-validation[19].

Similar to previous analysis of the WHS[1, 4], no effect of aspirin on non-colorectal cancer was observed in the present competing risks analysis (HR 1.02, 95%CI 0.95-1.09). Since the incidence of non-colorectal cancer is high compared to the other competing outcomes, even a small non-significant coefficient could potentially have considerable effects on the overall treatment effect predictions. To evaluate these effects

and to test the robustness of the results, sensitivity analysis were performed in which the treatment effect of aspirin on non-colorectal cancer was assumed null. Accordingly, the competing risks endpoint was adjusted in these analyses.

One or more covariable data were missing in 865 (3.1%) participants and these were singly imputed using bootstrapping and predictive mean matching (aregImpute-algorithm in R, Hmisc-package)[20]: family history of premature CHD (n=464), SBP (n=292), HbA1c (n=140), hormone replacement therapy use (n=55), menopausal status (n=51), smoking status (n=36), BMI (n=23), blood pressure lowering medication use (n=18), diabetes mellitus (n=15), total cholesterol (n=1), HDLc (n=1), alcohol use (n=6), family history of cancer (n=865) and height (n=18). To limit the effect of outliers, continuous predictors were truncated at the 1st and 99th percentile. Continuous predictors that were not linearly associated to the outcome were transformed to optimize model fit[21]. Accordingly, HDLc, total cholesterol, systolic blood pressure and hsCRP were log-transformed.

Model validation

An estimate of the optimism in the calibration slope was obtained for all models by repeating the complete modeling process in 500 bootstrap samples. The optimism was 0.9% for the CVD model, 9.7% for the 10-year colorectal cancer model, 7.7% for the 15-year colorectal cancer model, 4.1% for the 10-year non-colorectal cancer model, 3.2% for the 15-year non-colorectal cancer model and 4.9% for the bleeding model. Subsequently, the obtained uniform shrinkage factors were applied to the models to adjust for overfitting[21].

The proportional subdistribution hazards assumptions were assessed graphically by plotting the scaled Schoenfeld residuals against failure time and formally by a Wald test of the interaction term of a specific covariable with the logarithm of time. Some non-proportionality was observed for age and family history of cancer in the 15-year model for non-colorectal cancer (p-values: <0.001 and 0.039, respectively). In addition, the proportionality assumption appeared to be violated for history of dyspepsia in the gastro-intestinal bleeding model (p-value: 0.044). Hence, the reported coefficients for these predictors should be interpreted as the weighted average effect over follow-up[22].

Discriminatory ability of each model was evaluated using an inverse probability of censoring weighted estimate of the c-index that is adapted for competing risks[23]. C-indices were truncated at 10 or 15-year and corrected for optimism by repeating the complete modeling process in 500 bootstrap samples. Calibration was assessed graphically using calibration plots.

Net benefit assessment

To evaluate the clinical value of prediction-based treatment with aspirin in a primary prevention setting, a decision analytic approach as proposed by Vickers et al. [24] was used. This method focuses on the effects of (changes in) treatment decisions that result from a treatment strategy (e.g. prediction-based treatment) and is based on calculation of 'net benefit'. Net benefit is defined as the treatment benefit (reduction in event rate) minus the treatment harm (adverse effects, costs, etc.), where the relative weighting of treatment harm is given by a treatment threshold (*i.e.* ARR at which one would opt for treatment). This treatment threshold is the reciprocal of the maximum acceptable number-needed-to-treat (NNT) to prevent one event or 'number-willing-to-treat' (NWT)[7, 25]. Consequently, the net benefit of a certain treatment strategy is calculated as the observed decrease in event rate minus the treatment rate multiplied by the treatment threshold. Using the aggregated ARRs of all outcomes for each individual, the clinical value of the combination of the benefit and harm models can be assessed.Net benefit was calculated for the following treatment strategies: (I) treat no one (reference, *i.e.* net benefit equals zero), (II) treat everyone, (III) treat according to guidelines[26] , *i.e.* women ≥65 years and (IV) prediction-based treatment. Since major gastro-intestinal bleeding is already incorporated in the total ARR, the treatment threshold for aspirin is mainly determined by less serious complications, inconvenience of taking pills and costs. As the appropriate treatment threshold (or NWT) is subjective and can vary among different patients and clinicians, the net benefit was calculated for threshold values ranging from 0 to 5% (10-/15-year NWT between infinite and 20). Net benefit for the different treatment strategies was also calculated applying a weight of 0.5, 0.25 and 0.1 for gastro-intestinal bleeding. The net benefit results were presented graphically as decision curves after local polynomial regression fitting.

All analyses were performed in R, version 3.0.2 (R Core Team, Vienna, Austria; packages: 'Hmisc', 'pec', 'riskRegression').

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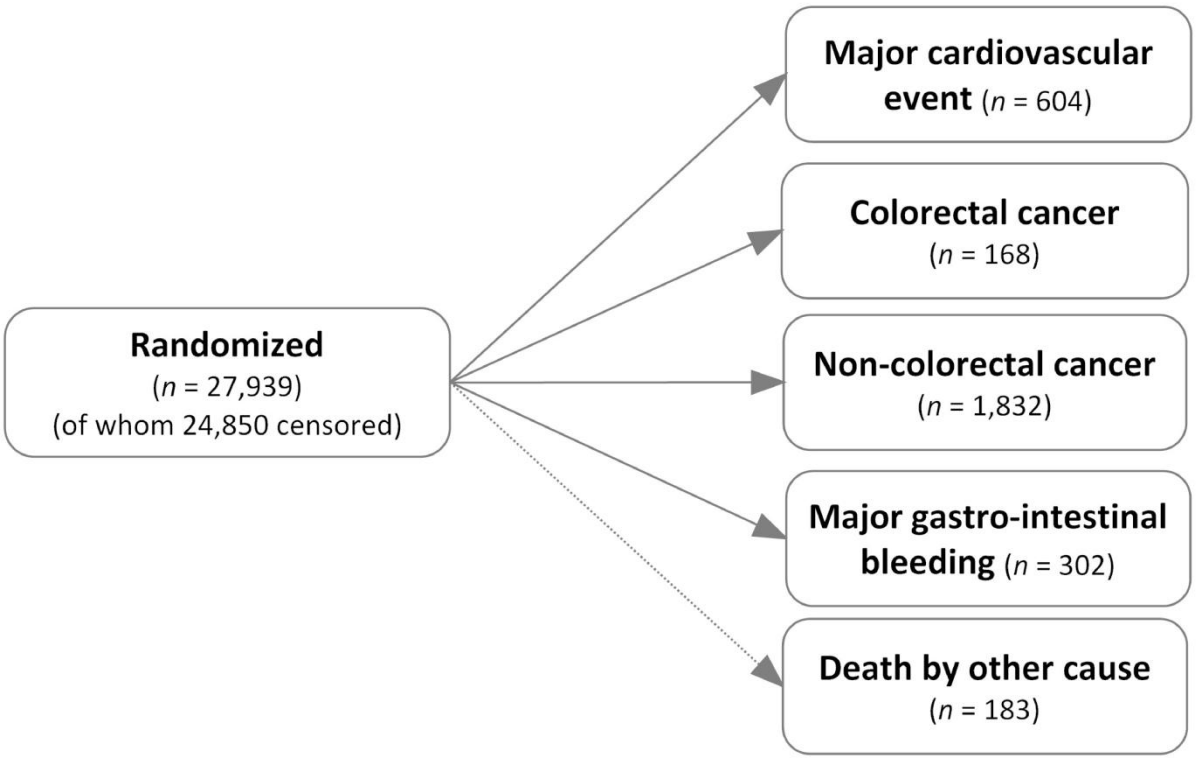
Appendix 2

Supplemental figures



Appendix 2.1 | Competing risks framework with number of events during trial period (*i.e.* from baseline through 31 March 2004, average follow-up of 10.1 years) in women included in the Women's Health Study who provided an adequate baseline plasma sample. Models for the prediction of absolute effects of aspirin on major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding were developed. No separate model was developed for prediction of the effects on death by other causes, since no effects of aspirin on this outcome was expected, given that all relevant outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding) are already taken into account. Death by other causes was taken into account as competing risks outcome when modelling the other outcomes, because not taking competing risks into account may lead to bias in predictions of absolute risks.

Appendix 2.2 | Models for prediction of 10-year absolute risk reduction with aspirin treatment

Predicted 10-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.*
Total risk on aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.*

Model for prediction of 10-year major cardiovascular event risk
(1 - exp(- (0.01068 * exp(A – 20.51836)))) * 100%, where

A = 0.07750 * age (years) + 0.91719 [if current smoker] – 0.02174* body mass index (kg/m^2) + 3.27143 * natural logarithm(systolic blood pressure, mmHg) + 0.25540 [if using blood pressure lowering medication] + 0.28204 [if family history of premature myocardial infarction] + 0.83017 * natural logarithm(total cholesterol, mg/dL) – 0.90235 * natural logarithm(high-density lipoprotein cholesterol, mg/dL) + 0.11419 * natural logarithm(high-sensitivity C-reactive protein, mg/L) + 0.17444 * hemoglobin A1c (%) [if diabetic] –0.09592 [if using aspirin]

Model for prediction of 10-year colorectal cancer risk
(1 - exp(- (0.00287 * exp(B – 4.854)))) * 100%, where

B = 0.06907 * age (years) + 0.15647 [if ever smoker] + 0.03173 * body mass index (kg/m^2) + 0.00180 * height (inches) – 0.01487 [if diabetic] + 0.03258 * no. of alcoholic drinks per day + 0.28102 [if peri- / postmenopausal] – 0.26464 [if ever used hormone replacement therapy] + 0.12076 [if family history of colorectal cancer] – 0.05372 [if using aspirin]

Model for prediction of 10-year non-colorectal cancer risk
(1 - exp(- (0.05554 * exp(C – 3.40691)))) * 100%, where

C = 0.04287 * age (years) + 0.14222 [if ever smoker] + 0.00125 * body mass index (kg/m^2) + 0.01469 * height (inches) – 0.14474 [if diabetic] + 0.07571 * no. of alcoholic drinks per day – 0.14239 [if peri- / postmenopausal] + 0.04985 [if ever used hormone replacement therapy] + 0.00181 [if family history of cancer] + 0.046578 [if using aspirin]

Model for prediction of 10-year major gastro-intestinal bleeding risk
(1 - exp(- (0.00742 * exp(D – 4.53537)))) * 100%, where

D = 0.06209 * age (years) + 0.22339 [if current smoker] + 0.03316 * body mass index (kg/m^2) + 0.26552 [if diabetic] + 0.00652 * no. of alcoholic drinks per day + 0.21780 [if history of dyspepsia] + 0.45399 [if using aspirin]

Outcomes were modelled in a competing risks framework, mutually accounting for all outcomes as well as death by other causes (Appendix 2.1), because not taking competing risks into account may lead to bias in predictions of absolute risks and non-additivity of risks for the individual outcomes[23 24]. No separate model was developed for prediction of the effects of aspirin on death by other causes, since no effects of aspirin on this outcome was expected, given that all relevant outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding) are already taken into account.

Appendix 2.3 | Models for prediction of 15-year absolute risk reduction with aspirin treatment

Predicted 15-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.*
Total risk on aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.*

Model for prediction of 15-year major cardiovascular event risk
(1 - exp(- (0.01602 * exp(A – 20.51836)))) * 100%, where

A = 0.07750 * age (years) + 0.91719 [if current smoker] – 0.02174* body mass index (kg/m^2) + 3.27143 * natural logarithm(systolic blood pressure, mmHg) + 0.25540 [if using blood pressure lowering medication] + 0.28204 [if family history of premature myocardial infarction] + 0.83017 * natural logarithm(total cholesterol, mg/dL) – 0.90235 * natural logarithm(high-density lipoprotein cholesterol, mg/dL) + 0.11419 * natural logarithm(high-sensitivity C-reactive protein, mg/L) + 0.17444 * hemoglobin A1c (%) [if diabetic] –0.09592 [if using aspirin]

Model for prediction of 15-year colorectal cancer risk
(1 - exp(- (0.00428 * exp(B – 6.89174)))) * 100%, where

B = 0.05465 * age (years) + 0.18407 [if ever smoker] + 0.03713 * body mass index (kg/m^2) + 0.03973 * height (inches) – 0.27643 [if diabetic] + 0.15733 * no. of alcoholic drinks per day + 0.62717 [if peri- / postmenopausal] – 0.29949 [if ever used hormone replacement therapy] + 0.14094 [if family history of colorectal cancer] – 0.14483 [if using aspirin]

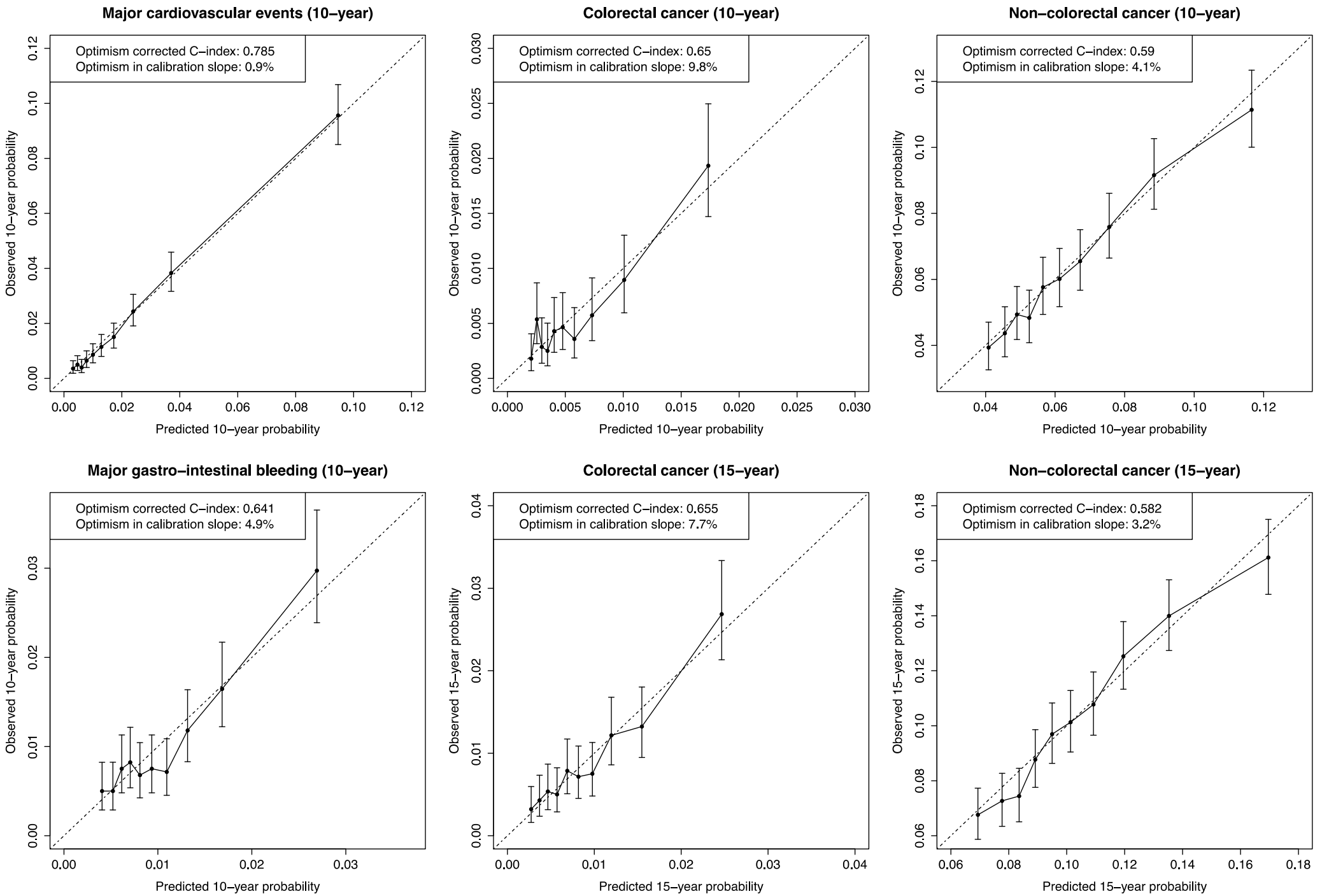
Model for prediction of 15-year non-colorectal cancer risk
(1 - exp(- (0.09493 * exp(C – 3.61989)))) * 100%, where

C = 0.03598 * age (years) + 0.17283 [if ever smoker] + 0.00735 * body mass index (kg/m^2) + 0.02162 * height (inches) – 0.03080 [if diabetic] + 0.09586 * no. of alcoholic drinks per day – 0.13779 [if peri- / postmenopausal] + 0.06473 [if ever used hormone replacement therapy] + 0.06062 [if family history of cancer] + 0.01568 [if using aspirin]

Model for prediction of 15-year major gastro-intestinal bleeding risk
(1 - exp(- (0.01113 * exp(D – 4.53537)))) * 100%, where

D = 0.06209 * age (years) + 0.22339 [if current smoker] + 0.03316 * body mass index (kg/m^2) + 0.26552 [if diabetic] + 0.00652 * no. of alcoholic drinks per day + 0.21780 [if history of dyspepsia] + 0.45399 [if using aspirin]

Outcomes were modelled in a competing risks framework, mutually accounting for all outcomes as well as death by other causes (Appendix 2.1), because not taking competing risks into account may lead to bias in predictions of absolute risks and non-additivity of risks for the individual outcomes[23 24]. No separate model was developed for prediction of the effects of aspirin on death by other causes, since no effects of aspirin on this outcome was expected, given that all relevant outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding) are already taken into account.



Appendix 2.4 | Calibration plots. Axis scales differ between plots. Plots were created with R-code adjusted from: *N.P. Bleda. Interval-censored semi-competing risks data : a novel approach for modelling bladder cancer. Thesis, Universitat Politècnica de Catalunya, Barcelona, June 2010.*

Appendix 2.5 (A) | Observed absolute risks, absolute risk reductions and numbers needed to treat/harm for aspirin

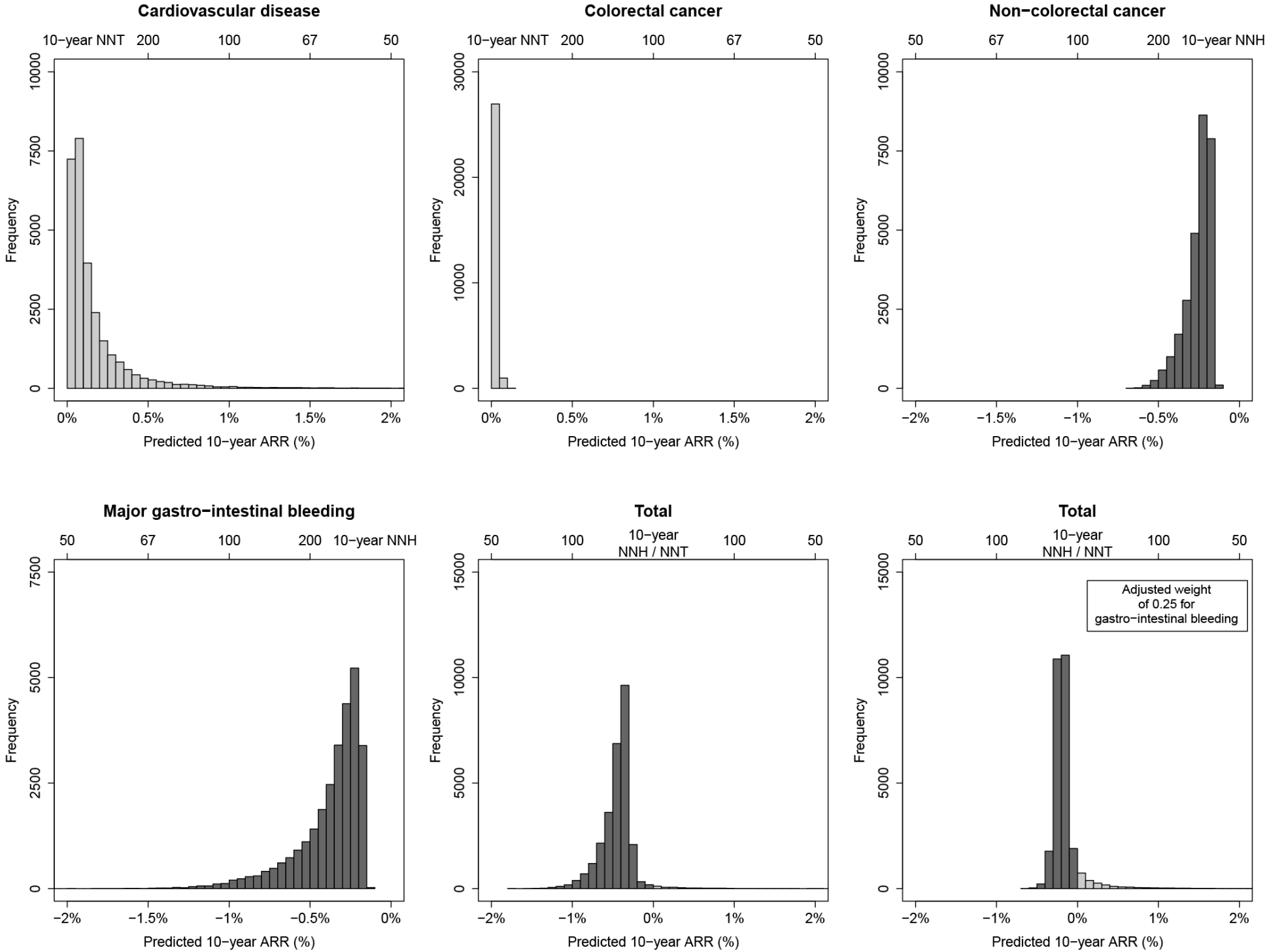
		Major cardiovascular disease	Colorectal cancer	Non-colorectal cancer	Major gastro-intestinal bleeding
		Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Total study population					
10-year	AR without aspirin (%)	2.27 (2.03 to 2.53)	0.61 (0.49 to 0.75)	6.40 (6.00 to 6.82)	0.83 (0.69 to 0.99)
	AR with aspirin (%)	2.09 (1.86 to 2.34)	0.60 (0.48 to 0.74)	6.67 (6.26 to 7.10)	1.33 (1.15 to 1.53)
	ARR (%)	0.18 (0.02 to 0.95)	0.01 (0.00 to 32.05)	-0.27 (-0.86 to 0.32)	-0.50 (-0.26 to -0.75)
	[a]NNT or [b]NNH	550 (106 to >1000) [a]	>1000 (3 to >1000) [a]	370[b] (117[b] to 317[a])	199 (134 to 390) [b]
15-year	AR without aspirin (%)	3.38 (3.14 to 3.64)	1.01 (0.85 to 1.18)	10.44 (9.93 to 10.96)	1.24 (1.09 to 1.40)
	AR with aspirin (%)	3.11 (2.88 to 3.36)	0.86 (0.72 to 1.03)	10.52 (10.01 to 11.04)	1.99 (1.80 to 2.19)
	ARR (%)	0.27 (0.06 to 0.86)	0.14 (0.02 to 0.59)	-0.08 (-0.80 to 0.64)	-0.75 (-0.50 to -1.00)
	[a]NNT or [b]NNH	371 (116 to >1000) [a]	709 (170 to >1000) [a]	>1000[b] (124[b] to 156[a])	133 (100 to 198) [b]
Women <65 years					
10-year	AR without aspirin (%)	1.66 (1.45 to 1.90)	0.51 (0.40 to 0.65)	5.75 (5.34 to 6.17)	0.69 (0.55 to 0.85)
	AR with aspirin (%)	1.70 (1.49 to 1.95)	0.47 (0.36 to 0.60)	6.23 (5.82 to 6.67)	1.11 (0.94 to 1.31)
	ARR (%)	-0.04 (-0.37 to 0.28)	0.05 (0.00 to 0.96)	-0.49 (-1.08 to 0.11)	-0.43 (-0.19 to -0.66)
	[a]NNT or [b]NNH	>1000[b] (273[b] to 354[a])	>1000 (105 to >1000) [a]	205[b] (92[b] to 937[a])	235 (151 to 531) [b]
15-year	AR without aspirin (%)	2.48 (2.26 to 2.72)	0.88 (0.73 to 1.06)	9.62 (9.11 to 10.15)	1.03 (0.89 to 1.18)
	AR with aspirin (%)	2.55 (2.32 to 2.78)	0.71 (0.57 to 0.87)	9.94 (9.42 to 10.48)	1.66 (1.48 to 1.86)
	ARR (%)	-0.06 (-0.39 to 0.26)	0.17 (0.04 to 0.55)	-0.32 (-1.06 to 0.42)	-0.64 (-0.40 to -0.87)
	[a]NNT or [b]NNH	>1000[b] (259[b] to 382[a])	581 (181 to >1000) [a]	312[b] (94[b] to 237[a])	157 (114 to 251) [b]
Women ≥65 years					
10-year	AR without aspirin (%)	7.39 (6.12 to 8.82)	1.43 (0.92 to 2.15)	11.93 (10.32 to 13.66)	2.02 (1.39 to 2.86)
	AR with aspirin (%)	5.25 (4.18 to 6.49)	1.71 (1.13 to 2.47)	10.29 (8.81 to 11.91)	3.15 (2.34 to 4.14)
	ARR (%)	2.14 (0.85 to 4.52)	-0.27 (-1.17 to 0.63)	1.64 (0.31 to 5.34)	-1.12 (-2.28 to 0.04)
	[a]NNT or [b]NNH	47 (22 to 118) [a]	369[b] (85[b] to 158[a])	61 (19 to 321) [a]	89[b] (44[b] to >1000[a])
15-year	AR without aspirin (%)	10.88 (9.58 to 12.28)	2.06 (1.42 to 2.89)	17.44 (15.52 to 19.45)	3.02 (2.35 to 3.82)
	AR with aspirin (%)	7.77 (6.67 to 8.97)	2.17 (1.51 to 3.01)	15.39 (13.59 to 17.30)	4.68 (3.84 to 5.64)
	ARR (%)	3.11 (1.67 to 5.27)	-0.11 (-1.15 to 0.93)	2.05 (0.43 to 6.28)	-1.66 (-0.50 to -2.82)
	[a]NNT or [b]NNH	32 (19 to 60) [a]	924[b] (87[b] to 107[a])	49 (16 to 235) [a]	60 (35 to 199) [b]
Never smokers					
10-year	AR without aspirin (%)	1.85 (1.55 to 2.18)	0.57 (0.42 to 0.77)	5.43 (4.92 to 5.97)	0.69 (0.52 to 0.91)
	AR with aspirin (%)	1.53 (1.26 to 1.84)	0.54 (0.39 to 0.73)	6.63 (6.06 to 7.22)	1.16 (0.93 to 1.43)
	ARR (%)	0.32 (0.07 to 1.05)	0.03 (0.00 to 3.86)	-1.20 (-0.41 to -1.98)	-0.46 (-0.15 to -0.78)
	[a]NNT or [b]NNH	314 (95 to >1000) [a]	>1000 (26 to >1000) [a]	83 (50 to 242) [b]	215 (128 to 685) [b]
15-year	AR without aspirin (%)	2.76 (2.46 to 3.09)	0.92 (0.72 to 1.16)	9.05 (8.40 to 9.73)	1.04 (0.86 to 1.25)
	AR with aspirin (%)	2.29 (2.01 to 2.59)	0.72 (0.55 to 0.94)	9.90 (9.22 to 10.61)	1.73 (1.49 to 2.00)
	ARR (%)	0.47 (0.18 to 1.09)	0.20 (0.04 to 0.75)	-0.85 (-1.81 to 0.11)	-0.69 (-0.37 to -1.01)
	[a]NNT or [b]NNH	211 (92 to 565) [a]	509 (134 to >1000) [a]	117[b] (55[b] to 911[a])	144 (99 to 267) [b]
Past smokers					
10-year	AR without aspirin (%)	2.27 (1.88 to 2.71)	0.76 (0.55 to 1.03)	7.01 (6.33 to 7.75)	1.00 (0.75 to 1.30)
	AR with aspirin (%)	1.96 (1.60 to 2.37)	0.74 (0.53 to 1.01)	6.08 (5.44 to 6.76)	1.50 (1.19 to 1.86)
	ARR (%)	0.31 (0.04 to 1.48)	0.02 (0.00 to 24.90)	0.94 (0.30 to 2.37)	-0.50 (-0.07 to -0.93)
	[a]NNT or [b]NNH	321 (68 to >1000) [a]	>1000 (4 to >1000) [a]	107 (42 to 339) [a]	200 (107 to >1000) [b]
15-year	AR without aspirin (%)	3.38 (2.99 to 3.81)	1.21 (0.94 to 1.54)	11.50 (10.64 to 12.40)	1.49 (1.23 to 1.78)
	AR with aspirin (%)	2.92 (2.55 to 3.32)	1.06 (0.81 to 1.37)	10.28 (9.46 to 11.13)	2.24 (1.92 to 2.59)
	ARR (%)	0.46 (0.12 to 1.38)	0.15 (0.01 to 1.40)	1.22 (0.40 to 2.98)	-0.75 (-0.31 to -1.18)
	[a]NNT or [b]NNH	216 (72 to 853) [a]	662 (71 to >1000) [a]	82 (34 to 250) [a]	134 (85 to 322) [b]
Current smokers					
10-year	AR without aspirin (%)	4.12 (3.22 to 5.18)	0.31 (0.12 to 0.69)	8.72 (7.41 to 10.16)	0.89 (0.51 to 1.47)
	AR with aspirin (%)	4.98 (3.99 to 6.14)	0.44 (0.20 to 0.87)	8.75 (7.43 to 10.20)	1.57 (1.04 to 2.27)
	ARR (%)	-0.86 (-2.31 to 0.59)	-0.13 (-0.55 to 0.29)	-0.03 (-1.99 to 1.92)	-0.68 (-1.44 to 0.09)
	[a]NNT or [b]NNH	-116 (-43 to 169) [a]	-758 (-181 to 348) [a]	<-1000 (50 to 52) [b]	148 (-69 to >1000) [b]
15-year	AR without aspirin (%)	6.12 (5.19 to 7.15)	0.75 (0.41 to 1.28)	13.28 (11.66 to 14.99)	1.33 (0.93 to 1.87)
	AR with aspirin (%)	7.38 (6.36 to 8.50)	0.88 (0.51 to 1.44)	14.06 (12.40 to 15.83)	2.34 (1.79 to 3.01)
	ARR (%)	-1.26 (-2.71 to 0.19)	-0.13 (-0.75 to 0.50)	-0.79 (-3.18 to 1.60)	-1.01 (-0.24 to -1.78)
	[a]NNT or [b]NNH	-79 (-37 to 524) [a]	-783 (-133 to 201) [a]	127 (31 to 62) [b]	99 (56 to 420) [b]

CI: Confidence interval ; AR: Absolute risk ; ARR: Absolute risk reduction ; [a]NNT: Number needed to treat ; [b]NNH: Number needed to harm. Risks were estimated based on the cumulative incidence function, accounting for competing risks.

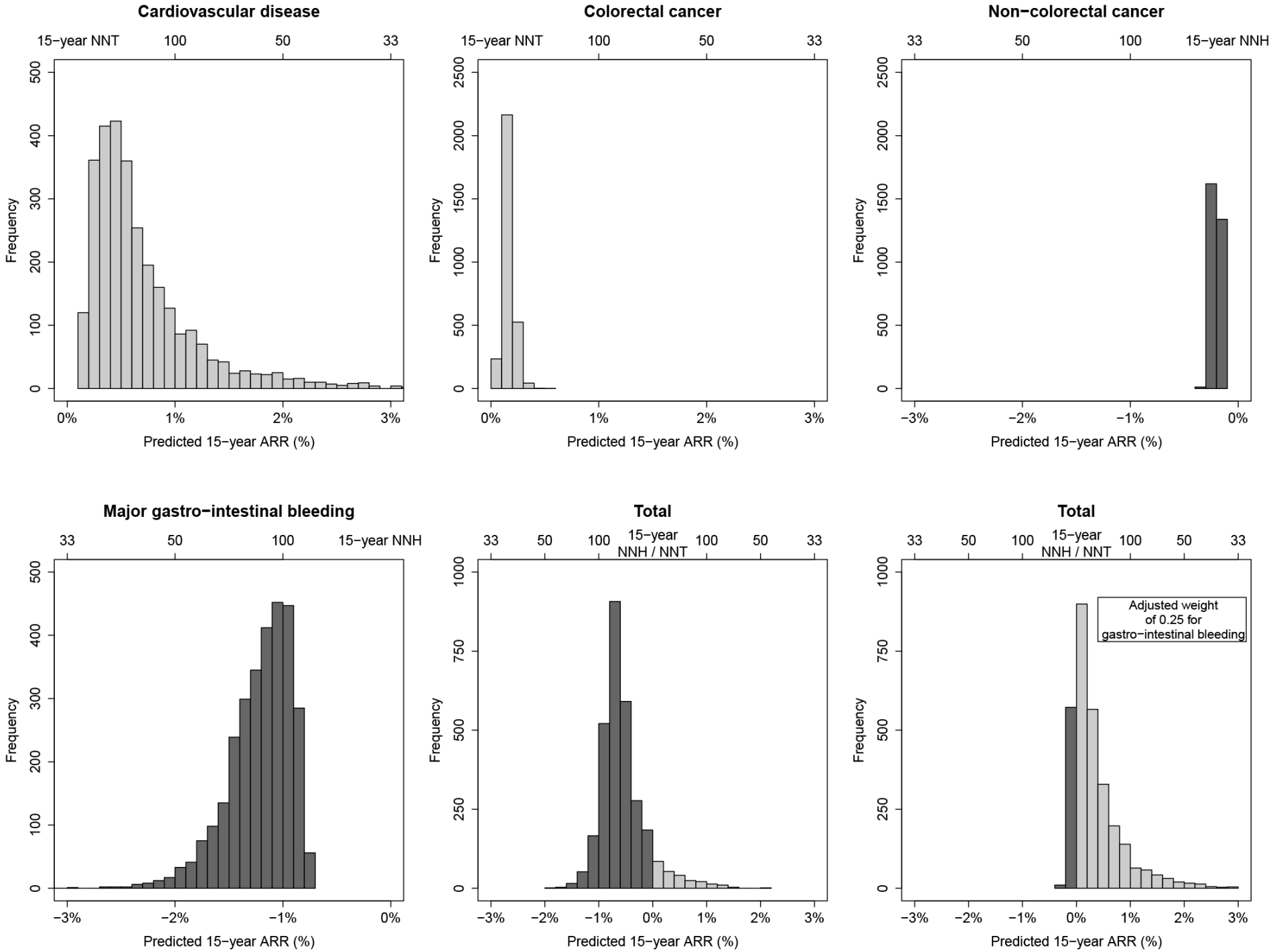
Appendix 2.5 (B) | Observed absolute risks, absolute risk reductions and numbers needed to treat/harm for aspirin

		Total	Total adjusted weight of 0.5 for gastro-intestinal bleeding	Total adjusted weight of 0.25 for gastro-intestinal bleeding	Total adjusted weight of 0.1 for gastro-intestinal bleeding
		Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Total study population					
10-year	AR without aspirin (%)	10.11 (9.59 to 10.64)	9.69 (9.18 to 10.22)	9.49 (8.97 to 10.01)	9.36 (8.85 to 9.89)
	AR with aspirin (%)	10.69 (10.16 to 11.23)	10.02 (9.50 to 10.57)	9.69 (9.16 to 10.23)	9.49 (8.96 to 10.03)
	ARR (%)	-0.58 (-1.33 to 0.17)	-0.33 (-1.08 to 0.42)	-0.20 (-0.95 to 0.54)	-0.13 (-0.88 to 0.62)
	[a]iNNT or [b]iNNH	172[b] (605[b] to 75[a])	302[b] (93[b] to 240[a])	488[b] (105[b] to 184[a])	772[b] (114[b] to 162[a])
15-year	AR without aspirin (%)	16.07 (15.46 to 16.68)	15.45 (14.84 to 16.07)	15.14 (14.53 to 15.76)	14.95 (14.35 to 15.57)
	AR with aspirin (%)	16.49 (15.87 to 17.11)	15.49 (14.88 to 16.12)	15.00 (14.38 to 15.62)	14.70 (14.09 to 15.32)
	ARR (%)	-0.42 (-1.29 to 0.45)	-0.05 (-0.92 to 0.82)	0.14 (0.00 to 7.59)	0.25 (0.00 to 3.43)
	[a]iNNT or [b]iNNH	238[b] (223[b] to 78[a])	>1000[b] (109[b] to 121[a])	703 (13 to >1000) [a]	393 (29 to >1000) [a]
Women <65 years					
10-year	AR without aspirin (%)	8.61 (8.11 to 9.13)	8.26 (7.76 to 8.78)	8.09 (7.59 to 8.61)	7.99 (7.49 to 8.51)
	AR with aspirin (%)	9.52 (8.99 to 10.06)	8.96 (8.44 to 9.51)	8.68 (8.16 to 9.23)	8.52 (7.99 to 9.06)
	ARR (%)	-0.91 (-0.17 to -1.65)	-0.70 (-1.44 to 0.04)	-0.59 (-1.33 to 0.15)	-0.53 (-1.27 to 0.21)
	[a]iNNT or [b]iNNH	110 (61 to 583) [b]	143[b] (70[b] to >1000[a])	169[b] (75[b] to 676[a])	190[b] (79[b] to 472[a])
15-year	AR without aspirin (%)	14.02 (13.41 to 14.63)	13.50 (12.90 to 14.12)	13.25 (12.64 to 13.86)	13.09 (12.49 to 13.71)
	AR with aspirin (%)	14.86 (14.25 to 15.49)	14.03 (13.41 to 14.66)	13.62 (13.00 to 14.25)	13.37 (12.75 to 14.00)
	ARR (%)	-0.85 (-1.72 to 0.03)	-0.53 (-1.40 to 0.34)	-0.37 (-1.24 to 0.50)	-0.27 (-1.15 to 0.60)
	[a]iNNT or [b]iNNH	118[b] (58[b] to >1000[a])	189[b] (71[b] to 291[a])	271[b] (81[b] to 199[a])	365[b] (87[b] to 167[a])
Women ≥65 years					
10-year	AR without aspirin (%)	22.78 (20.47 to 25.17)	21.77 (19.46 to 24.16)	21.26 (18.96 to 23.66)	20.96 (18.66 to 23.36)
	AR with aspirin (%)	20.39 (18.21 to 22.67)	18.82 (16.64 to 21.10)	18.03 (15.86 to 20.32)	17.56 (15.39 to 19.85)
	ARR (%)	2.39 (0.46 to 7.46)	2.95 (0.81 to 7.58)	3.23 (1.01 to 7.71)	3.40 (1.13 to 7.81)
	[a]iNNT or [b]iNNH	42 (13 to 215) [a]	34 (13 to 123) [a]	31 (13 to 99) [a]	29 (13 to 89) [a]
15-year	AR without aspirin (%)	33.40 (30.81 to 36.01)	31.89 (29.30 to 34.50)	31.13 (28.55 to 33.75)	30.68 (28.10 to 33.30)
	AR with aspirin (%)	30.01 (27.55 to 32.50)	27.67 (25.22 to 30.16)	26.50 (24.05 to 29.00)	25.79 (23.35 to 28.30)
	ARR (%)	3.39 (0.98 to 8.42)	4.22 (1.59 to 8.90)	4.64 (1.92 to 9.19)	4.89 (2.13 to 9.38)
	[a]iNNT or [b]iNNH	29 (12 to 102) [a]	24 (11 to 63) [a]	22 (11 to 52) [a]	20 (11 to 47) [a]
Never smokers					
10-year	AR without aspirin (%)	8.54 (7.89 to 9.23)	8.20 (7.54 to 8.88)	8.02 (7.37 to 8.71)	7.92 (7.27 to 8.61)
	AR with aspirin (%)	9.85 (9.15 to 10.59)	9.27 (8.57 to 10.01)	8.99 (8.29 to 9.72)	8.81 (8.11 to 9.54)
	ARR (%)	-1.31 (-0.33 to -2.29)	-1.08 (-0.10 to -2.06)	-0.96 (-1.94 to 0.02)	-0.89 (-1.87 to 0.09)
	[a]iNNT or [b]iNNH	76 (44 to 304) [b]	93 (49 to >1000) [b]	104[b] (52[b] to >1000[a])	112[b] (53[b] to >1000[a])
15-year	AR without aspirin (%)	13.77 (12.99 to 14.57)	13.25 (12.47 to 14.05)	12.99 (12.21 to 13.79)	12.83 (12.05 to 13.64)
	AR with aspirin (%)	14.64 (13.84 to 15.47)	13.78 (12.97 to 14.60)	13.34 (12.54 to 14.17)	13.08 (12.28 to 13.91)
	ARR (%)	-0.87 (-2.01 to 0.26)	-0.53 (-1.67 to 0.61)	-0.36 (-1.49 to 0.78)	-0.25 (-1.39 to 0.89)
	[a]iNNT or [b]iNNH	114[b] (50[b] to 380[a])	189[b] (60[b] to 164[a])	282[b] (67[b] to 128[a])	398[b] (72[b] to 113[a])
Past smokers					
10-year	AR without aspirin (%)	11.04 (10.16 to 11.96)	10.54 (9.66 to 11.46)	10.29 (9.41 to 11.21)	10.14 (9.26 to 11.06)
	AR with aspirin (%)	10.26 (9.42 to 11.15)	9.52 (8.67 to 10.41)	9.14 (8.30 to 10.03)	8.92 (8.08 to 9.81)
	ARR (%)	0.77 (0.11 to 3.06)	1.02 (0.25 to 2.99)	1.15 (0.33 to 3.02)	1.22 (0.39 to 3.04)
	[a]iNNT or [b]iNNH	130 (33 to 885) [a]	98 (33 to 398) [a]	87 (33 to 300) [a]	82 (33 to 259) [a]
15-year	AR without aspirin (%)	17.58 (16.54 to 18.65)	16.84 (15.79 to 17.91)	16.46 (15.42 to 17.54)	16.24 (15.20 to 17.31)
	AR with aspirin (%)	16.49 (15.49 to 17.53)	15.38 (14.37 to 16.41)	14.82 (13.81 to 15.85)	14.48 (13.48 to 15.52)
	ARR (%)	1.09 (0.23 to 3.49)	1.46 (0.47 to 3.57)	1.65 (0.61 to 3.67)	1.76 (0.70 to 3.74)
	[a]iNNT or [b]iNNH	92 (29 to 442) [a]	68 (28 to 213) [a]	61 (27 to 164) [a]	57 (27 to 144) [a]
Current smokers					
10-year	AR without aspirin (%)	14.04 (12.32 to 15.87)	13.60 (11.88 to 15.43)	13.37 (11.66 to 15.20)	13.24 (11.53 to 15.07)
	AR with aspirin (%)	15.74 (13.91 to 17.68)	14.96 (13.13 to 16.90)	14.57 (12.74 to 16.51)	14.33 (12.51 to 16.27)
	ARR (%)	-1.70 (-4.29 to 0.89)	-1.36 (-3.95 to 1.23)	-1.19 (-3.78 to 1.40)	-1.09 (-3.68 to 1.50)
	[a]iNNT or [b]iNNH	59[b] (23[b] to 112[a])	73[b] (25[b] to 82[a])	84 (26 to 72)	92[b] (27[b] to 67[a])
15-year	AR without aspirin (%)	21.48 (19.49 to 23.55)	20.82 (18.82 to 22.88)	20.48 (18.49 to 22.55)	20.28 (18.29 to 22.35)
	AR with aspirin (%)	24.67 (22.53 to 26.85)	23.50 (21.37 to 25.69)	22.91 (20.78 to 25.10)	22.56 (20.43 to 24.75)
	ARR (%)	-3.18 (-0.21 to -6.15)	-2.68 (-5.65 to 0.29)	-2.43 (-5.39 to 0.54)	-2.28 (-5.24 to 0.69)
	[a]iNNT or [b]iNNH	31 (16 to 466) [b]	37[b] (18[b] to 346[a])	41 (19 to 185) [a]	44[b] (19[b] to 145[a])

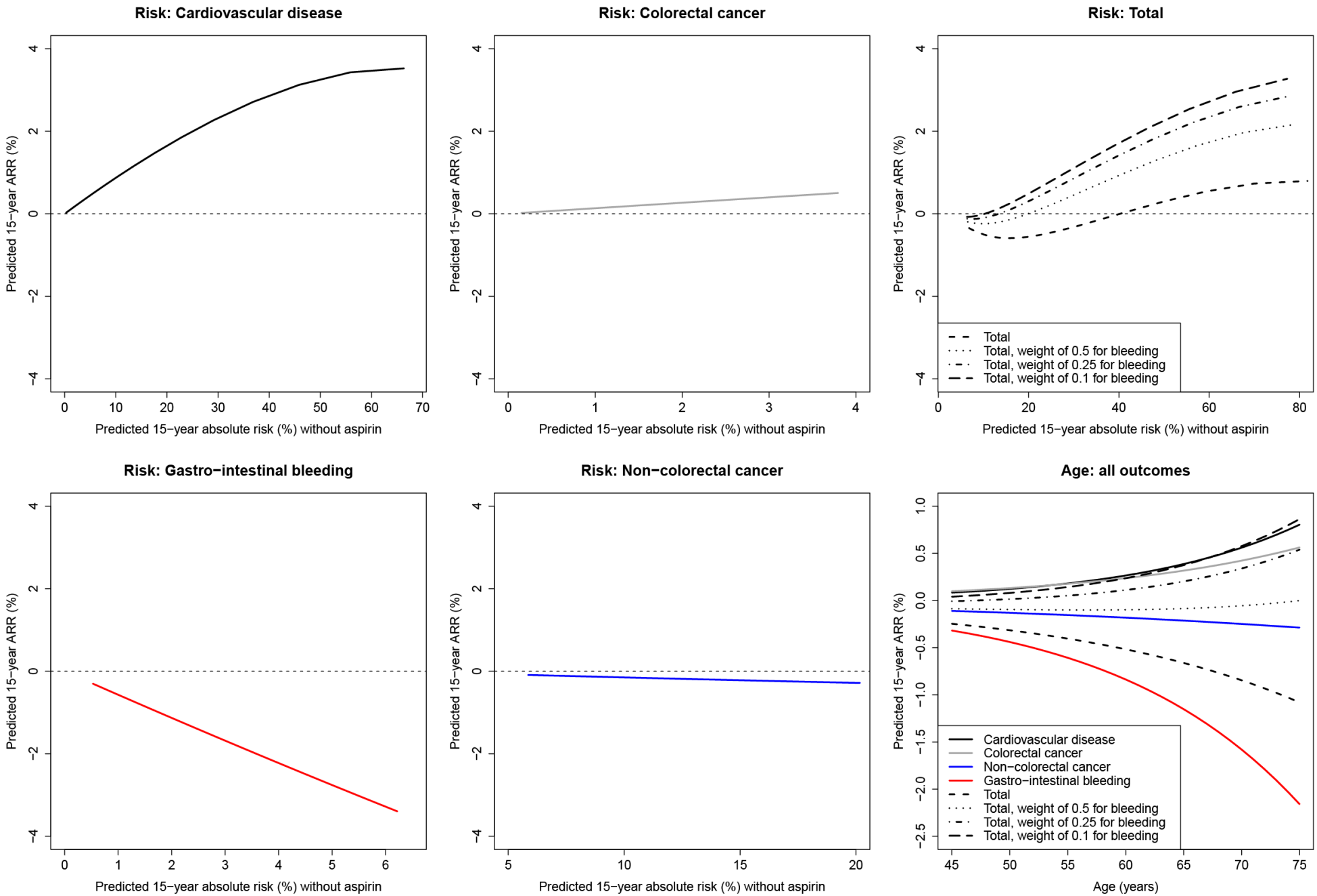
CI: Confidence interval ; AR: Absolute risk ; ARR: Absolute risk reduction ; [a]NNT: Number needed to treat ; [b]NNH: Number needed to harm. Risks were estimated based on the cumulative incidence function, accounting for competing risks.



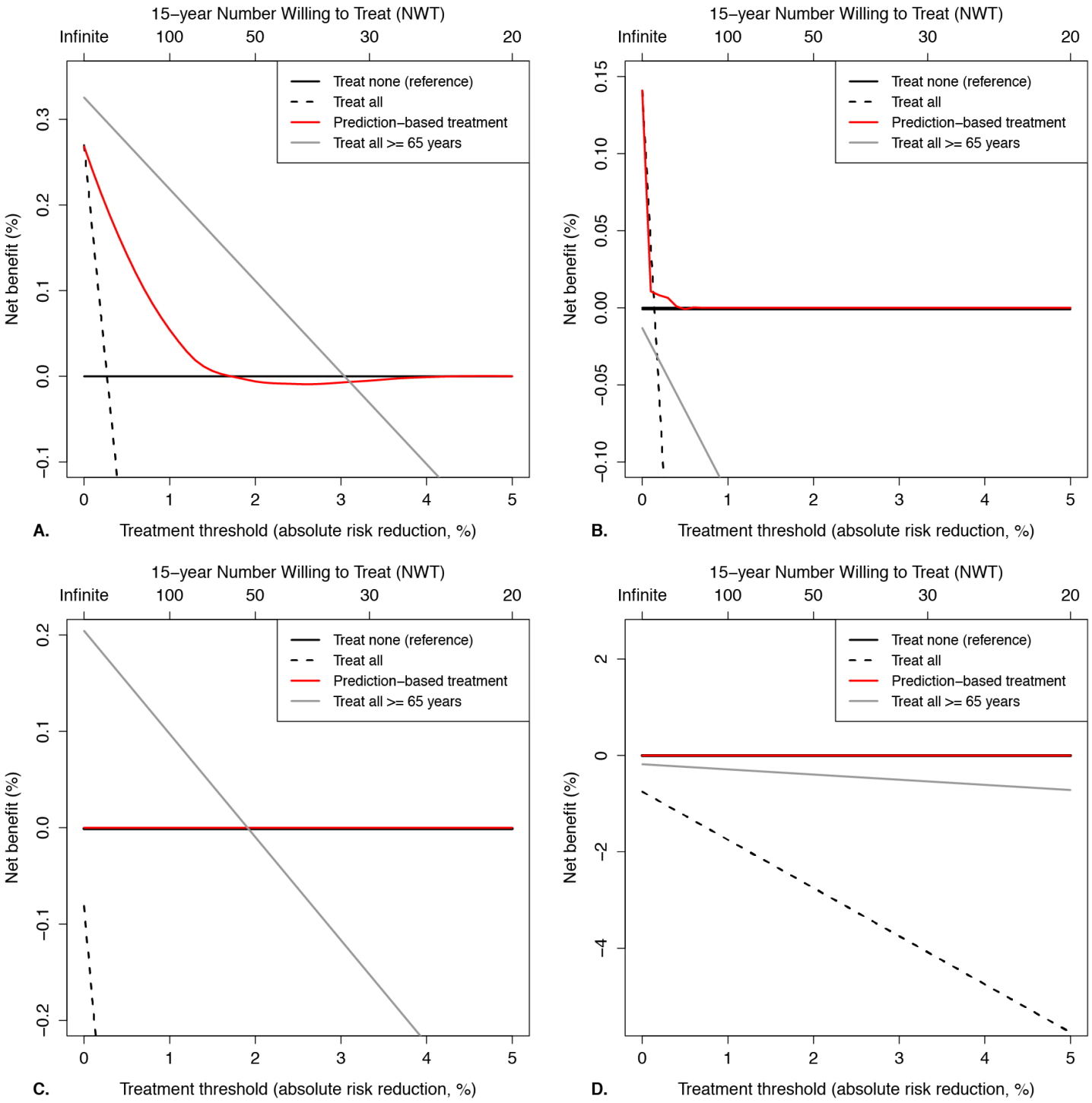
Appendix 2.6 | Distribution of predicted 10-year absolute risk reduction for major cardiovascular events, colorectal cancer and major gastro-intestinal bleeding with aspirin



Appendix 2.7 | Distribution of predicted 15-year absolute risk reduction for major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding with aspirin treatment in participants of the Women's Health Study of 65 years and older. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.



Appendix 2.8 | Effect of baseline risk and age on predicted 15-year absolute risk reduction. ARR: absolute risk reduction. ARR in plot for age apply to an average participant of the Women's Health Study (i.e. a 55-year old postmenopausal woman who never smoked, does not have diabetes, history of dyspepsia or a family no family history of premature myocardial infarction or cancer, has a height of 65 inches, a BMI of 26 kg/m2 and a systolic blood pressure of 124 mmHg and does not receive treatment for hypertension, with a serum level of high sensitivity C-reactive protein of 2·0 mg/L, total cholesterol of 212 mg/dL and a HDL-cholesterol of 54 mg/dL, drinks 2 alcoholic beverages per week and has never received hormone replacement therapy) with alternating age.



Appendix 2.9 | Decision curves for different aspirin treatment strategies for the individual outcomes: **A.** Major cardiovascular events ; **B.** Colorectal cancer ; **C**. Non-colorectal cancer ; **D.** Major gastro-intestinal bleeding. Reading the net benefit plot starts with choosing a treatment threshold, that is the absolute risk reduction (ARR) at which one would opt for treatment, or number-willing-to-treat (NWT). A NWT of 30 implies that one is willing to treat 30 women to prevent at least 1 event. Positive net benefit means that the treatment strategy led to a more favourable trade-off between benefits (observed decrease in event rate) and harms (the proportion of patients receiving treatment weighted by the reciprocal of the treatment threshold). Since for non-colorectal cancer and major gastro-intestinal bleeding all patients had a negative predicted absolute risk prediction (meaning that their risk of those outcomes increases with aspirin), none will selected for treatment over the full range of threshold values when applying prediction-based treatment and the net benefit for this treatment strategy is equal to zero.

Appendix 3

Sensitivity analyses

Appendix 3.1 | Summary of results

Using the models with treatment interactions, the protective effect of aspirin for CVD increased with age, whereas current smoking attenuated the benefits of aspirin (*appendix 3A*). BMI and ever smoking were inversely related to treatment effect on colorectal cancer. The HR of aspirin for non-colorectal cancer risk slightly decreased with higher age and was lower for ever smokers. Current smoking increased the risk of major bleeding when using aspirin. Compared to the main results, the predicted ARRs from the models with treatment interactions were more widely distributed, particularly for non-colorectal cancer, as aspirin was associated with benefit in 48% of the study population and caused harm in the other 52%. If a weight was applied for gastro-intestinal bleeding, the models with treatment interactions yielded a higher net benefit compared to the models without interaction, but treating only women ≥65 years was still the most favourable treatment strategy.

When the effect of aspirin on non-colorectal cancer was assumed null in sensitivity analysis, the total ARR tended to be slightly higher (*appendix 3B*). When a weight of 0.25 was applied for bleeding, 3.1% of the women had a predicted 15-year ARR of >1% (iNNT:100) versus 1.7% in the main analysis. Although some improvement in the net benefit of prediction-based treatment was observed, treating only women ≥65 years was still superior if the 15-year NWT was >60, whereas treating none was the most favorable treatment strategy for lower ranges of NWT.

Appendix 3A (1) | Models for prediction of 15-year absolute risk reduction with aspirin treatment

Predicted 15-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.*
Total risk on aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.*

Model for prediction of 15-year major cardiovascular event risk
(1 - exp(- (0.01597 * exp(A – 20.78737)))) * 100%, where

A = 0.08225 * age (years) – 0.00883 * age (years) [if using aspirin] + 0.75154 [if current smoker] + 0.37331 [if current smoker and using aspirin] – 0.02022 * body mass index (kg/m^2) + 0.00063 * body mass index (kg/m^2) [if using aspirin] + 3.28886 * natural logarithm(systolic blood pressure, mmHg) + 0.25407 [if using blood pressure lowering medication] + 0.82587 * natural logarithm(total cholesterol, mg/dL) – 0.87803 * natural logarithm(high-density lipoprotein cholesterol, mg/dL) + 0.10963 * natural logarithm(high-sensitivity C-reactive protein, mg/L) + 0.17672 * hemoglobin A1c (%) [if diabetic] + 0.27403 [if family history of premature myocardial infarction] + 0.33118 [if using aspirin]

Model for prediction of 15-year colorectal cancer risk
(1 - exp(- (0.00674 * exp(B – 6.96952)))) * 100%, where

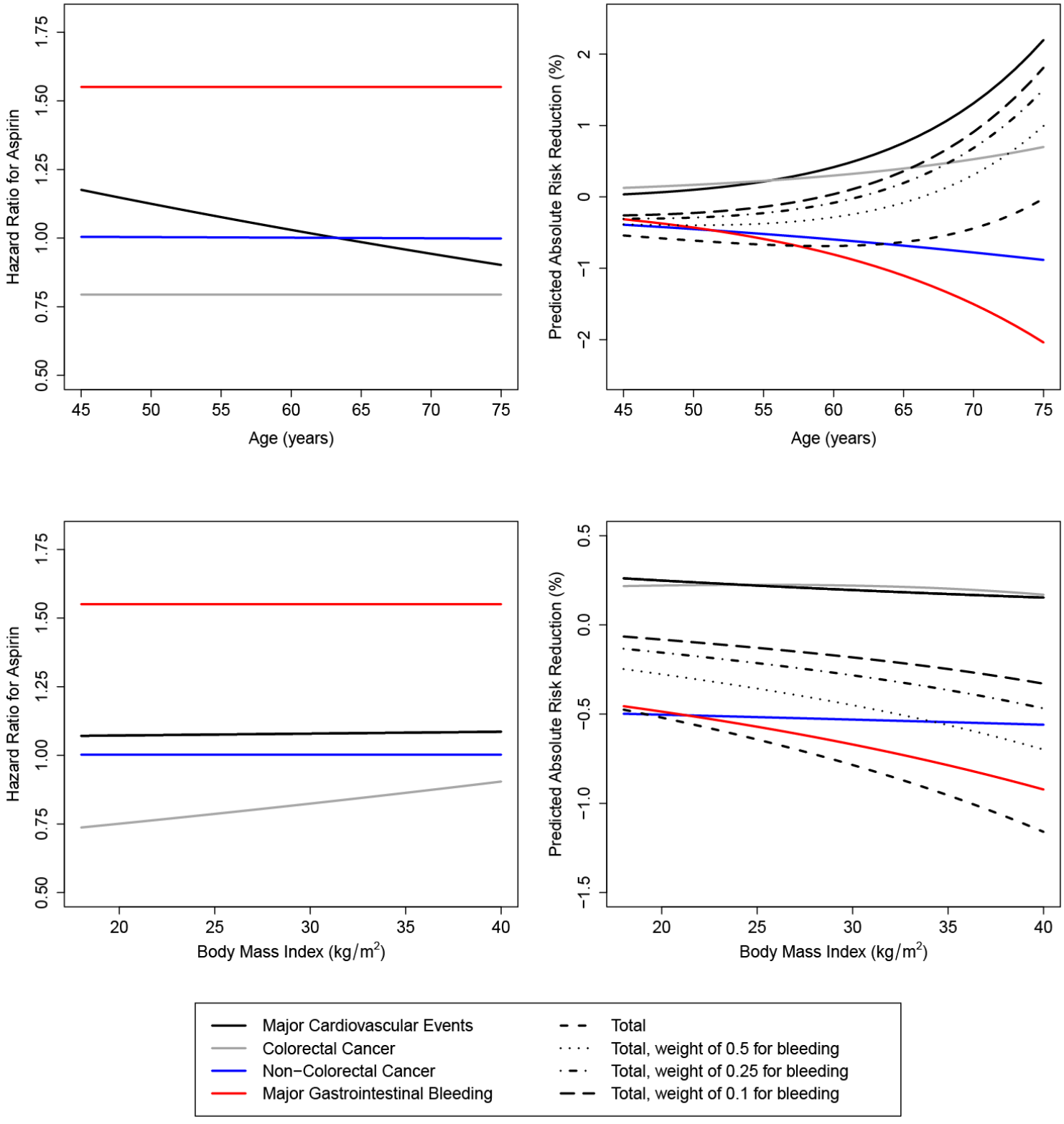
B = 0.05783 * age (years) + 0.10755 [if ever smoker] + 0.15955 [if ever smoker and using aspirin] + 0.03632 * height (inches) + 0.03483 * body mass index (kg/m^2) + 0.00930 * body mass index (kg/m^2) [if using aspirin] – 0.20511 [if diabetic] + 0.15214 * no. of alcoholic drinks per day + 0.59635 [if peri- / postmenopausal] – 0.27149 [if ever used hormone replacement therapy] + 0.11092 [if family history of colorectal cancer] – 0.47292 [if using aspirin]

Model for prediction of 15-year non-colorectal cancer risk
(1 - exp(- (0.0677 * exp(C – 3.46478)))) * 100%, where

C = 0.03481 * age (years) – 0.00021 * age (years) [if using aspirin] + 0.21150 [if ever smoker] – 0.08502 [if ever smoker and using aspirin] + 0.02085 * height (inches) + 0.00585 * body mass index (kg/m^2) – 0.02323 [if diabetic] + 0.09414 * no. of alcoholic drinks per day – 0.10978 [if peri- / postmenopausal] + 0.0535 [if ever used hormone replacement therapy] + 0.05403 [if family history of cancer] + 0.07276 [if using aspirin]

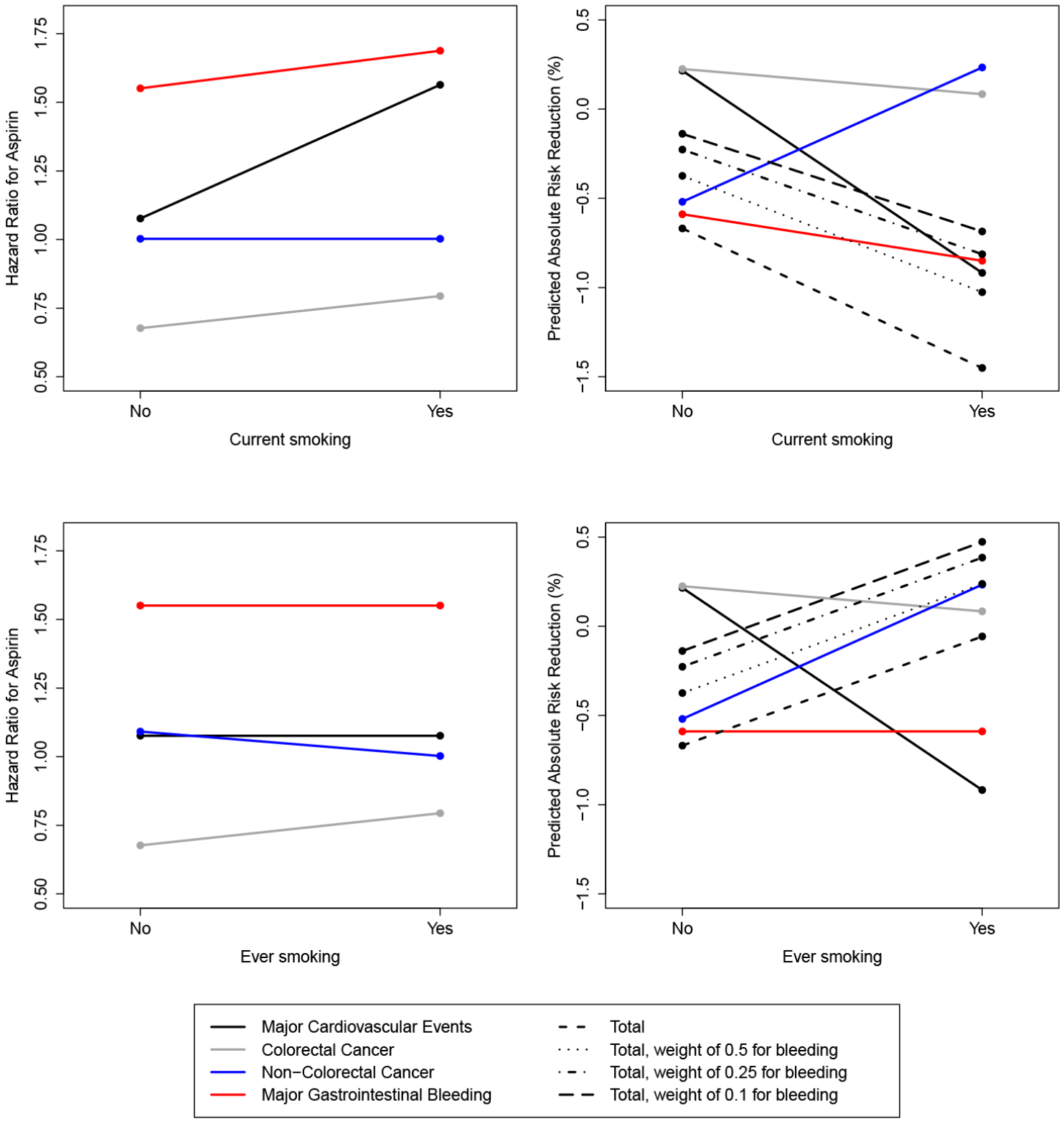
Model for prediction of 15-year major gastro-intestinal bleeding risk
(1 - exp(- (0.01094 * exp(D – 4.38127)))) * 100%, where

D = 0.06386 * age (years) + 0.14899 [if current smoker] + 0.08470 [if current smoker and using aspirin] + 0.03257 * body mass index (kg/m^2) + 0.24747 [if diabetic] + 0.19232 [if history of dyspepsia] + 0.44374 [if using aspirin]



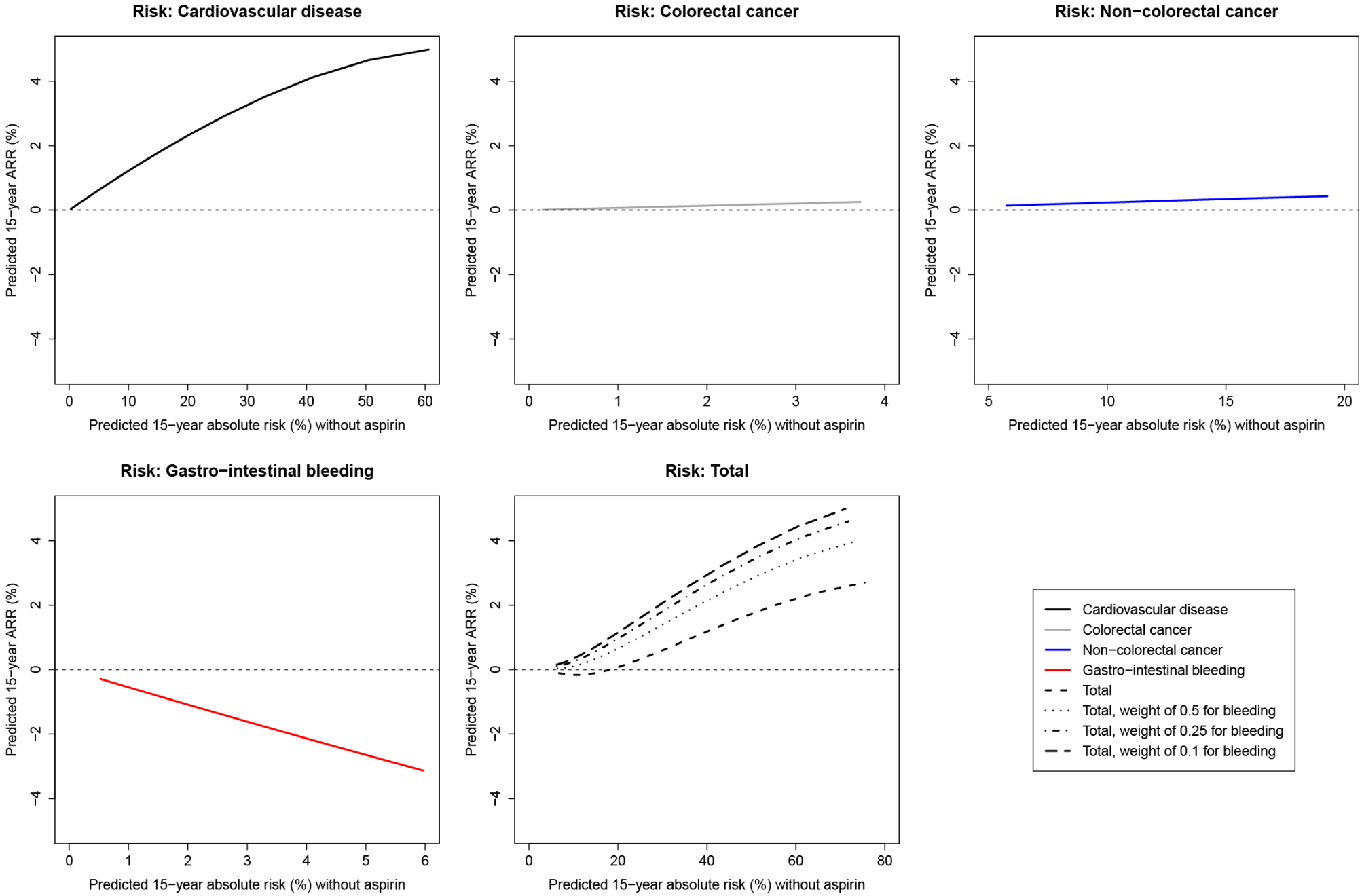
Appendix 3A (2) | Sensitivity analysis - Effect of treatment interactions with age and body mass index on hazard ratio's and predicted 15-year absolute risk reductions for aspirin.

Presented hazard ratio's and absolute risk reductions apply to an average participant of the Women's Health Study (i.e. a 55-year old postmenopausal woman who never smoked, does not have diabetes, history of dyspepsia or a family no family history of premature myocardial infarction or cancer, has a height of 65 inches, a BMI of 26 kg/m2 and a systolic blood pressure of 124 mmHg and does not receive treatment for hypertension, with a serum level of high sensitivity C-reactive protein of 2.0 mg/L, total cholesterol of 212 mg/dL and a HDL-cholesterol of 54 mg/dL, drinks 2 alcoholic beverages per week and has never received hormone replacement therapy). For the specific plots, all the above characteristics were kept constant with the exception of the characteristic displayed on the x-axis (e.g. for the age-plot, a women with the aforementioned average characteristics with age alternating from 45 to 75 years).

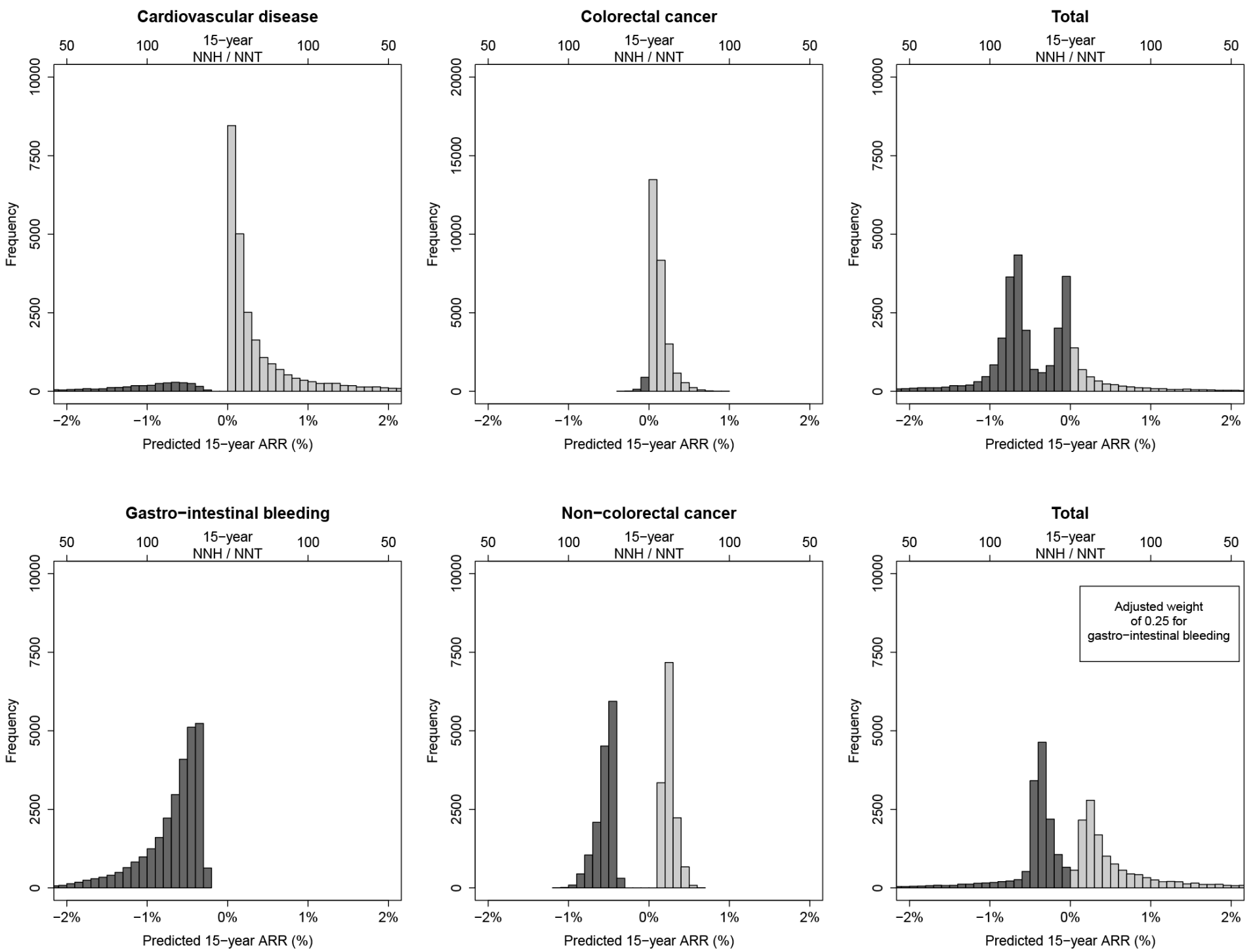


Appendix 3A (2) | Sensitivity analysis - Effect of treatment interactions with smoking status on hazard ratio's and predicted 15-year absolute risk reductions for aspirin.

Presented hazard ratio's and absolute risk reductions apply to an average participant of the Women's Health Study (i.e. a 55-year old postmenopausal woman who never smoked, does not have diabetes, history of dyspepsia or a family no family history of premature myocardial infarction or cancer, has a height of 65 inches, a BMI of 26 kg/m2 and a systolic blood pressure of 124 mmHg and does not receive treatment for hypertension, with a serum level of high sensitivity C-reactive protein of 2.0 mg/L, total cholesterol of 212 mg/dL and a HDL-cholesterol of 54 mg/dL, drinks 2 alcoholic beverages per week and has never received hormone replacement therapy). For the specific plots, all the above characteristics were kept constant with the exception of the characteristic displayed on the x-axis (e.g. for the current smoking-plot, a women with the aforementioned average characteristics with current smoking set to no/yes).



Appendix 3A (3)| Sensitivity analysis - Effect of baseline risk on predicted 15-year absolute risk reduction for aspirin using models with treatment interactions.
ARR: Absolute risk reduction.



Appendix 3A (4)| Sensitivity analysis - Distribution of predicted 15-year absolute risk reduction with aspirin treatment in participants of the Women's Health Study based on models with treatment interactions. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.

Appendix 3B (1) | Models for prediction of 15-year absolute risk reduction with aspirin treatment

Predicted 15-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.*
Total risk on aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.*

Model for prediction of 15-year major cardiovascular event risk
(1 - exp(- (0.01539 * exp(A – 19.9348)))) * 100%, where

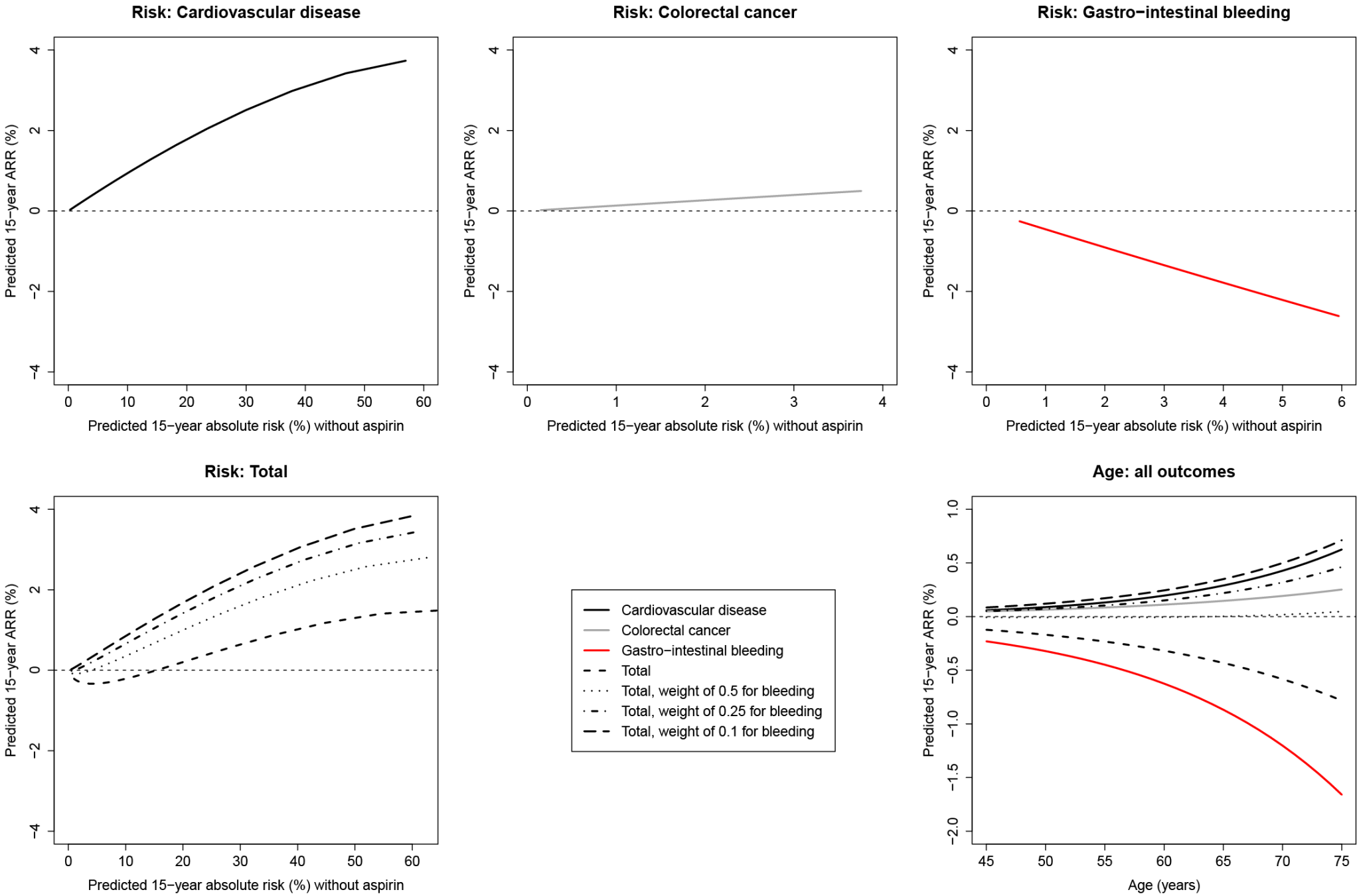
A = 0.08057 * age (years) + 0.95481 [if current smoker] – 0.02471* body mass index (kg/m^2) + 3.16178 * natural logarithm(systolic blood pressure, mmHg) + 0.28377 [if using blood pressure lowering medication] + 0.30422 [if family history of premature myocardial infarction] + 0.79060 * natural logarithm(total cholesterol, mg/dL) – 0.88894 * natural logarithm(high-density lipoprotein cholesterol, mg/dL) + 0.12118 * natural logarithm(high-sensitivity C-reactive protein, mg/L) + 0.17274 * hemoglobin A1c (%) [if diabetic] – 0.10389 [if using aspirin]

Model for prediction of 15-year colorectal cancer risk
(1 - exp(- (0.00454 * exp(B – 6.95442)))) * 100%, where

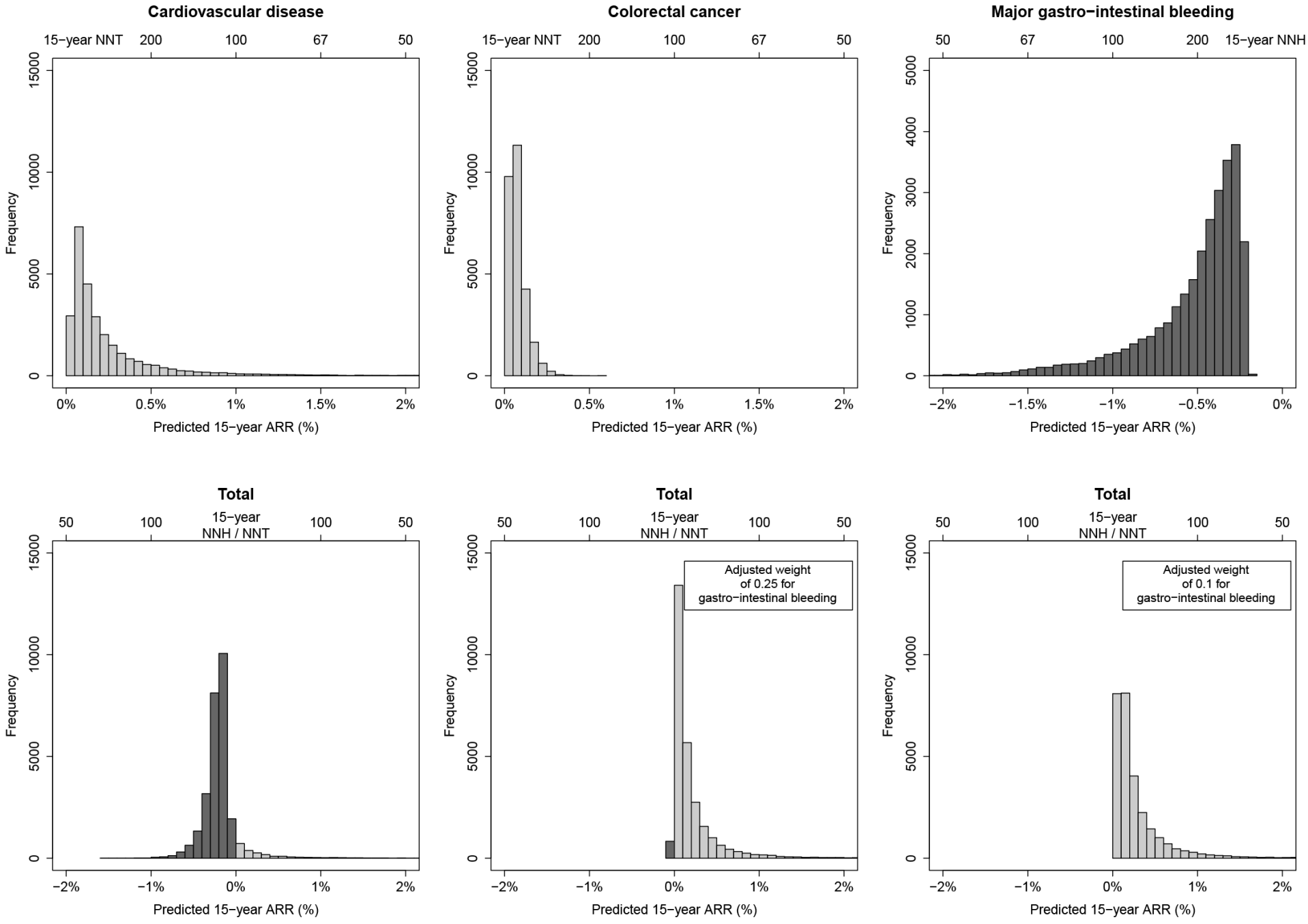
B = 0.05519 * age (years) + 0.18649 [if ever smoker] + 0.03746 * body mass index (kg/m^2) + 0.04004 * height (inches) – 0.27782 [if diabetic] + 0.15837 * no. of alcoholic drinks per day + 0.63234 [if peri- / postmenopausal] – 0.30225 [if ever used hormone replacement therapy] + 0.14242 [if family history of colorectal cancer] – 0.14411 [if using aspirin]

Model for prediction of 15-year major gastro-intestinal bleeding risk
(1 - exp(- (0.01238 * exp(D – 4.70541)))) * 100%, where

D = 0.06713 * age (years) + 0.31456 [if current smoker] + 0.03054 * body mass index (kg/m^2) + 0.32720 [if diabetic] + 0.01474 * no. of alcoholic drinks per day + 0.16382 [if history of dyspepsia] + 0.37788 [if using aspirin]



Appendix 3B (2)| Sensitivity analysis – Effect of baseline risk and age on predicted 15-year absolute risk reduction using models for prediction of treatment effect of aspirin on major cardiovascular events, colorectal cancer and major gastro-intestinal bleeding, while assuming no effect of aspirin on non-colorectal cancer. ARR: absolute risk reduction. Absolute risk reductions in plot for age apply to an average participant of the Women's Health Study (see page 3).



Appendix 3B (3)| Sensitivity analysis - Distribution of predicted 15-year absolute risk reduction with aspirin treatment in participants of the Women's Health Study assuming no effect of aspirin on non-colorectal cancer. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.

HEART

Cons of regular low dose aspirin to stave off serious illness in women outweigh pros

But limiting to over-65s may boost net health gain, suggest researchers

[Individualised prediction of alternate-day aspirin treatment effects on the combined risk of cancer, cardiovascular disease and gastrointestinal bleeding Online First doi 10.1136/heartjnl-2014-306342]
[Editorial: Aspirin use in women for primary prevention Online First doi 10.1136/heartjnl-2014-306770]

The pros of giving healthy women regular low dose aspirin to stave off serious illness, such as cancer and heart disease, are outweighed by the cons, suggests a large study published online in the journal ***Heart.***

But the balance begins to shift with increasing age, and limiting this form of primary prevention to women aged 65 and above, was better than not taking aspirin at all, or treating women from the age of 45 onwards, say the researchers.

They base their findings on almost 30,000 healthy women, who were at least 45 years old and taking part in the Women's Health Study.

Participants were randomly assigned to take either 100 mg of aspirin or a dummy tablet (placebo) every other day, to see whether aspirin curbed their risk of heart disease, stroke, and cancer.

During the trial period, which lasted 10 years, 604 cases of cardiovascular disease, 168 cases of bowel cancer, 1832 cases of other cancers, and 302 major gastrointestinal bleeds requiring admission to hospital were diagnosed.

Over the subsequent seven years, a further 107 cases of bowel cancer and 1388 other cancers were diagnosed.

Compared with placebo, regular aspirin was linked to a lower risk of heart disease, stroke, bowel cancer, and in some women, other cancers, but only marginally so.

And this slight health gain was trumped by the prevalence of internal gastrointestinal bleeding, which affected two thirds of the women taking the non-steroidal anti-inflammatory drug.

The risk of gastrointestinal bleeding rose with age, but so too did the drug's impact on lowering the risk of bowel cancer and cardiovascular disease, with the balance appearing to tip in favour of the drug for women aged 65 and above.

The researchers calculated that over 15 years, 29 over-65s would need to be treated with aspirin to prevent one case of cancer or heart disease/stroke.

"Recent findings that both daily and alternate day aspirin can reduce cancer risk, particularly for colorectal cancer, have re-ignited the debate on aspirin in primary prevention," write the researchers.

But they conclude that blanket treatment "is ineffective or harmful in the majority of women with regard to the combined risk of cardiovascular disease, cancer and major gastrointestinal bleeding."

Appendix 1 | Detailed description of methods

Design overview

The WHS was a randomized trial evaluating the effect of 100mg of aspirin on alternate days compared with placebo for primary prevention of CVD and cancer in 39,876 women of 45 years of age or older, without a history of cardiovascular disease or cancer. Detailed methods and outcomes have been described previously[1-4]. Written informed consent was obtained from all participants and the trial was approved by the Institutional Review Board of Brigham and Women's Hospital and was monitored by an external data and safety monitoring board. Endpoints were ascertained using yearly questionnaires and were confirmed using medical records. All relevant information was reviewed by an endpoints committee comprising physicians blinded to treatment allocation[1, 2]. After the end of randomized treatment on 31 March 2004, with an average 10 years of follow-up, participants were invited for further observational follow-up[4]. Of the survivors 33,682 (88.6%) women agreed to continue participation. During the posttrial follow-up, use of aspirin was allowed for women from both study arms. The posttrial use of aspirin for at least three days per month was higher in the randomized aspirin group (46%) compared to the placebo group (43%). Women who used nonstudy aspirin during the posttrial follow-up used aspirin for a median of three years (IQR: 2-5 years)[4]. Information on outcomes was collected and confirmed in a similar manner as during the trial period. End point review is complete for 95% of reported cancer cases, 95% of myocardial infarctions, and 94% of strokes. The confirmation rate among participants with records is 82% for cancer, 61% for myocardial infarction, and 68% for stroke. For the present study, only events confirmed by medical records and deaths with confirmed cause were used. Reports of gastrointestinal bleeding were collected intermittently during posttrial follow-up and were not confirmed[4]. The present analyses include end points accrued and confirmed through 14 March 2012, using data of participants who provided an adequate baseline plasma sample (n=27,939).

Model development

Data of women who provided a baseline plasma sample (n=27,939) were used for model development. For the 10-year predictions, endpoints that occurred during the trial period were used. In order to capture any delayed effects of aspirin on cancer risk[4, 5], the cancer outcomes were also modeled using cases ascertained during the entire follow-up, for prediction of 15-year treatment effect. Since the effects of aspirin on CVD and bleeding seem to be more immediate[4, 6] and the randomized aspirin intervention stopped after 31 March 2004, modeling these outcomes using posttrial data would likely lead to underestimation of the treatment effect. Hence, 15-year predictions for CVD and bleeding were obtained by extrapolating the 10-year risk estimates under the assumption of exponential risk over time, to mimic the effects of taking aspirin for a duration of 15-years. As the CVD endpoint included all strokes, hemorrhagic strokes were not evaluated separately.

To minimize over-fitting, predictors for each outcome were selected based on existing risk scores and/or literature[7-11]. Only predictors that were deemed to be easily available in clinical practice were selected. As a result, the following predictors, besides aspirin treatment, were used for major cardiovascular events (CVD): age, current smoking, body mass index (BMI), systolic blood pressure (SBP), use of blood pressure lowering medication, total cholesterol, high density lipoprotein cholesterol (HDLc), high sensitivity C-reactive protein (hs-CRP), family history of premature coronary heart disease (CHD) and hemoglobin A1c (HbA1c) if diabetic; for colorectal cancer: age, ever smoking, BMI, height, diabetes mellitus, alcohol use (no. of drinks per day), menopausal status, hormone replacement therapy use, family history of colorectal cancer; for non-colorectal cancer: age, ever smoking, BMI, height, diabetes mellitus, alcohol use, menopausal status, hormone replacement therapy use, family history of breast, colorectal, or ovarian cancer; for major bleeding events: age, current smoking, BMI, alcohol use, diabetes mellitus, history of dyspepsia.

The relative treatment effect of aspirin was assumed constant in the main analysis. Findings of effect modification by any risk factors are inconsistent in previous studies[1, 2, 12-14], although significant effect modification was found by age and smoking for CVD in the WHS[2]. To evaluate these potential relative subgroup effects, sensitivity analyses were performed in which treatment interactions with age, smoking status and BMI were considered. These interactions terms were chosen based on previous findings of interaction[1, 2, 15] and/or strong pathophysiological evidence[16, 17]. To avoid including non-relevant treatment interactions, estimation of model coefficients with implicit variable selection was done using component-wise likelihood-based boosting[18]. Aspirin use was included as an mandatory (unpenalized) covariable, whereas the other candidate predictors and treatment interactions were subjected to penalization in penalized partial likelihood estimation. The optimal number of boosting steps was determined by 10-fold cross-validation[19].

Similar to previous analysis of the WHS[1, 4], no effect of aspirin on non-colorectal cancer was observed in the present competing risks analysis (HR 1.02, 95%CI 0.95-1.09). Since the incidence of non-colorectal cancer is high compared to the other competing outcomes, even a small non-significant coefficient could potentially have considerable effects on the overall treatment effect predictions. To evaluate these effects

and to test the robustness of the results, sensitivity analysis were performed in which the treatment effect of aspirin on non-colorectal cancer was assumed null. Accordingly, the competing risks endpoint was adjusted in these analyses.

One or more covariable data were missing in 865 (3.1%) participants and these were singly imputed using bootstrapping and predictive mean matching (aregImpute-algorithm in R, Hmisc-package)[20]: family history of premature CHD (n=464), SBP (n=292), HbA1c (n=140), hormone replacement therapy use (n=55), menopausal status (n=51), smoking status (n=36), BMI (n=23), blood pressure lowering medication use (n=18), diabetes mellitus (n=15), total cholesterol (n=1), HDLc (n=1), alcohol use (n=6), family history of cancer (n=865) and height (n=18). To limit the effect of outliers, continuous predictors were truncated at the 1st and 99th percentile. Continuous predictors that were not linearly associated to the outcome were transformed to optimize model fit[21]. Accordingly, HDLc, total cholesterol, systolic blood pressure and hsCRP were log-transformed.

Model validation

An estimate of the optimism in the calibration slope was obtained for all models by repeating the complete modeling process in 500 bootstrap samples. The optimism was 0.9% for the CVD model, 9.7% for the 10-year colorectal cancer model, 7.7% for the 15-year colorectal cancer model, 4.1% for the 10-year non-colorectal cancer model, 3.2% for the 15-year non-colorectal cancer model and 4.9% for the bleeding model. Subsequently, the obtained uniform shrinkage factors were applied to the models to adjust for overfitting[21].

The proportional subdistribution hazards assumptions were assessed graphically by plotting the scaled Schoenfeld residuals against failure time and formally by a Wald test of the interaction term of a specific covariable with the logarithm of time. Some non-proportionality was observed for age and family history of cancer in the 15-year model for non-colorectal cancer (p-values: <0.001 and 0.039, respectively). In addition, the proportionality assumption appeared to be violated for history of dyspepsia in the gastro-intestinal bleeding model (p-value: 0.044). Hence, the reported coefficients for these predictors should be interpreted as the weighted average effect over follow-up[22].

Discriminatory ability of each model was evaluated using an inverse probability of censoring weighted estimate of the c-index that is adapted for competing risks[23]. C-indices were truncated at 10 or 15-year and corrected for optimism by repeating the complete modeling process in 500 bootstrap samples. Calibration was assessed graphically using calibration plots.

Net benefit assessment

To evaluate the clinical value of prediction-based treatment with aspirin in a primary prevention setting, a decision analytic approach as proposed by Vickers et al. [24] was used. This method focuses on the effects of (changes in) treatment decisions that result from a treatment strategy (e.g. prediction-based treatment) and is based on calculation of 'net benefit'. Net benefit is defined as the treatment benefit (reduction in event rate) minus the treatment harm (adverse effects, costs, etc.), where the relative weighting of treatment harm is given by a treatment threshold (*i.e.* ARR at which one would opt for treatment). This treatment threshold is the reciprocal of the maximum acceptable number-needed-to-treat (NNT) to prevent one event or 'number-willing-to-treat' (NWT)[7, 25]. Consequently, the net benefit of a certain treatment strategy is calculated as the observed decrease in event rate minus the treatment rate multiplied by the treatment threshold. Using the aggregated ARRs of all outcomes for each individual, the clinical value of the combination of the benefit and harm models can be assessed.Net benefit was calculated for the following treatment strategies: (I) treat no one (reference, *i.e.* net benefit equals zero), (II) treat everyone, (III) treat according to guidelines[26] , *i.e.* women ≥65 years and (IV) prediction-based treatment. Since major gastro-intestinal bleeding is already incorporated in the total ARR, the treatment threshold for aspirin is mainly determined by less serious complications, inconvenience of taking pills and costs. As the appropriate treatment threshold (or NWT) is subjective and can vary among different patients and clinicians, the net benefit was calculated for threshold values ranging from 0 to 5% (10-/15-year NWT between infinite and 20). Net benefit for the different treatment strategies was also calculated applying a weight of 0.5, 0.25 and 0.1 for gastro-intestinal bleeding. The net benefit results were presented graphically as decision curves after local polynomial regression fitting.

All analyses were performed in R, version 3.0.2 (R Core Team, Vienna, Austria; packages: 'Hmisc', 'pec', 'riskRegression').

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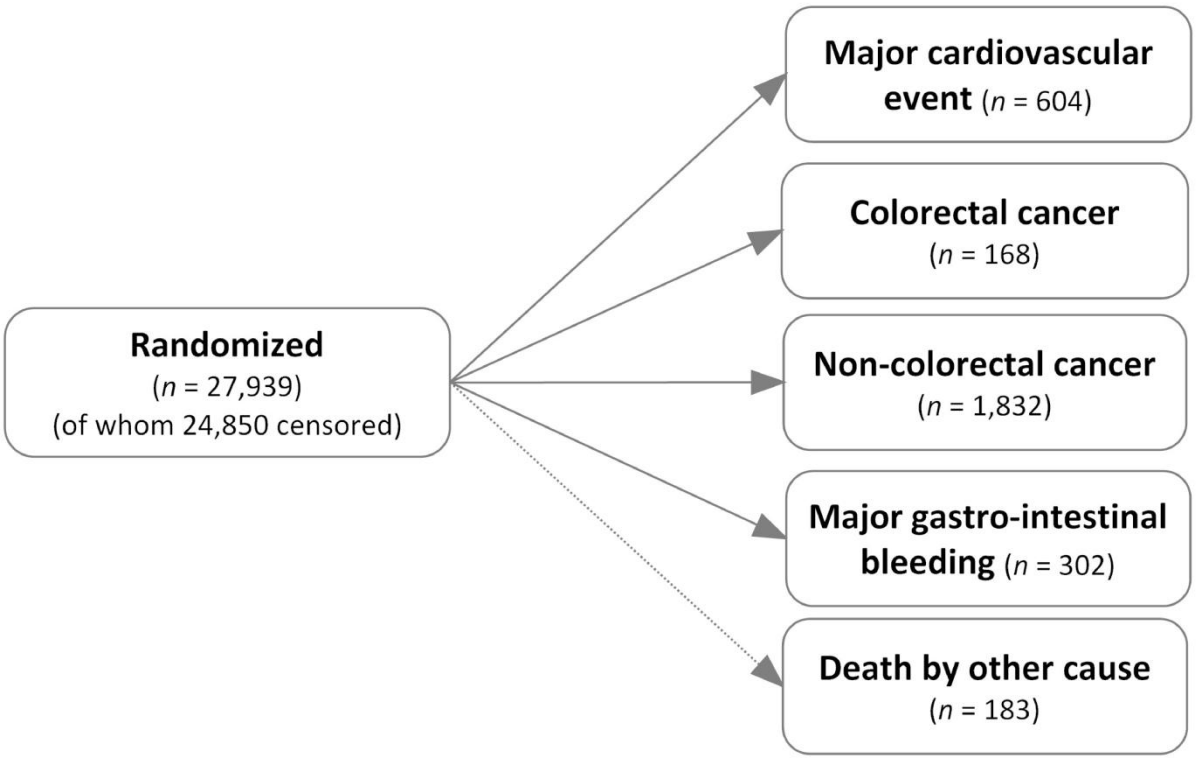
Appendix 2

Supplemental figures



Appendix 2.1 | Competing risks framework with number of events during trial period (*i.e.* from baseline through 31 March 2004, average follow-up of 10.1 years) in women included in the Women's Health Study who provided an adequate baseline plasma sample. Models for the prediction of absolute effects of aspirin on major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding were developed. No separate model was developed for prediction of the effects on death by other causes, since no effects of aspirin on this outcome was expected, given that all relevant outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding) are already taken into account. Death by other causes was taken into account as competing risks outcome when modelling the other outcomes, because not taking competing risks into account may lead to bias in predictions of absolute risks.

Appendix 2.2 | Models for prediction of 10-year absolute risk reduction with aspirin treatment

Predicted 10-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.*
Total risk on aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.*

Model for prediction of 10-year major cardiovascular event risk
(1 - exp(- (0.01068 * exp(A – 20.51836)))) * 100%, where

A = 0.07750 * age (years) + 0.91719 [if current smoker] – 0.02174* body mass index (kg/m^2) + 3.27143 * natural logarithm(systolic blood pressure, mmHg) + 0.25540 [if using blood pressure lowering medication] + 0.28204 [if family history of premature myocardial infarction] + 0.83017 * natural logarithm(total cholesterol, mg/dL) – 0.90235 * natural logarithm(high-density lipoprotein cholesterol, mg/dL) + 0.11419 * natural logarithm(high-sensitivity C-reactive protein, mg/L) + 0.17444 * hemoglobin A1c (%) [if diabetic] –0.09592 [if using aspirin]

Model for prediction of 10-year colorectal cancer risk
(1 - exp(- (0.00287 * exp(B – 4.854)))) * 100%, where

B = 0.06907 * age (years) + 0.15647 [if ever smoker] + 0.03173 * body mass index (kg/m^2) + 0.00180 * height (inches) – 0.01487 [if diabetic] + 0.03258 * no. of alcoholic drinks per day + 0.28102 [if peri- / postmenopausal] – 0.26464 [if ever used hormone replacement therapy] + 0.12076 [if family history of colorectal cancer] – 0.05372 [if using aspirin]

Model for prediction of 10-year non-colorectal cancer risk
(1 - exp(- (0.05554 * exp(C – 3.40691)))) * 100%, where

C = 0.04287 * age (years) + 0.14222 [if ever smoker] + 0.00125 * body mass index (kg/m^2) + 0.01469 * height (inches) – 0.14474 [if diabetic] + 0.07571 * no. of alcoholic drinks per day – 0.14239 [if peri- / postmenopausal] + 0.04985 [if ever used hormone replacement therapy] + 0.00181 [if family history of cancer] + 0.046578 [if using aspirin]

Model for prediction of 10-year major gastro-intestinal bleeding risk
(1 - exp(- (0.00742 * exp(D – 4.53537)))) * 100%, where

D = 0.06209 * age (years) + 0.22339 [if current smoker] + 0.03316 * body mass index (kg/m^2) + 0.26552 [if diabetic] + 0.00652 * no. of alcoholic drinks per day + 0.21780 [if history of dyspepsia] + 0.45399 [if using aspirin]

Outcomes were modelled in a competing risks framework, mutually accounting for all outcomes as well as death by other causes (Appendix 2.1), because not taking competing risks into account may lead to bias in predictions of absolute risks and non-additivity of risks for the individual outcomes[23 24]. No separate model was developed for prediction of the effects of aspirin on death by other causes, since no effects of aspirin on this outcome was expected, given that all relevant outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding) are already taken into account.

Appendix 2.3 | Models for prediction of 15-year absolute risk reduction with aspirin treatment

Predicted 15-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.*
Total risk on aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.*

Model for prediction of 15-year major cardiovascular event risk
(1 - exp(- (0.01602 * exp(A – 20.51836)))) * 100%, where

A = 0.07750 * age (years) + 0.91719 [if current smoker] – 0.02174* body mass index (kg/m^2) + 3.27143 * natural logarithm(systolic blood pressure, mmHg) + 0.25540 [if using blood pressure lowering medication] + 0.28204 [if family history of premature myocardial infarction] + 0.83017 * natural logarithm(total cholesterol, mg/dL) – 0.90235 * natural logarithm(high-density lipoprotein cholesterol, mg/dL) + 0.11419 * natural logarithm(high-sensitivity C-reactive protein, mg/L) + 0.17444 * hemoglobin A1c (%) [if diabetic] –0.09592 [if using aspirin]

Model for prediction of 15-year colorectal cancer risk
(1 - exp(- (0.00428 * exp(B – 6.89174)))) * 100%, where

B = 0.05465 * age (years) + 0.18407 [if ever smoker] + 0.03713 * body mass index (kg/m^2) + 0.03973 * height (inches) – 0.27643 [if diabetic] + 0.15733 * no. of alcoholic drinks per day + 0.62717 [if peri- / postmenopausal] – 0.29949 [if ever used hormone replacement therapy] + 0.14094 [if family history of colorectal cancer] – 0.14483 [if using aspirin]

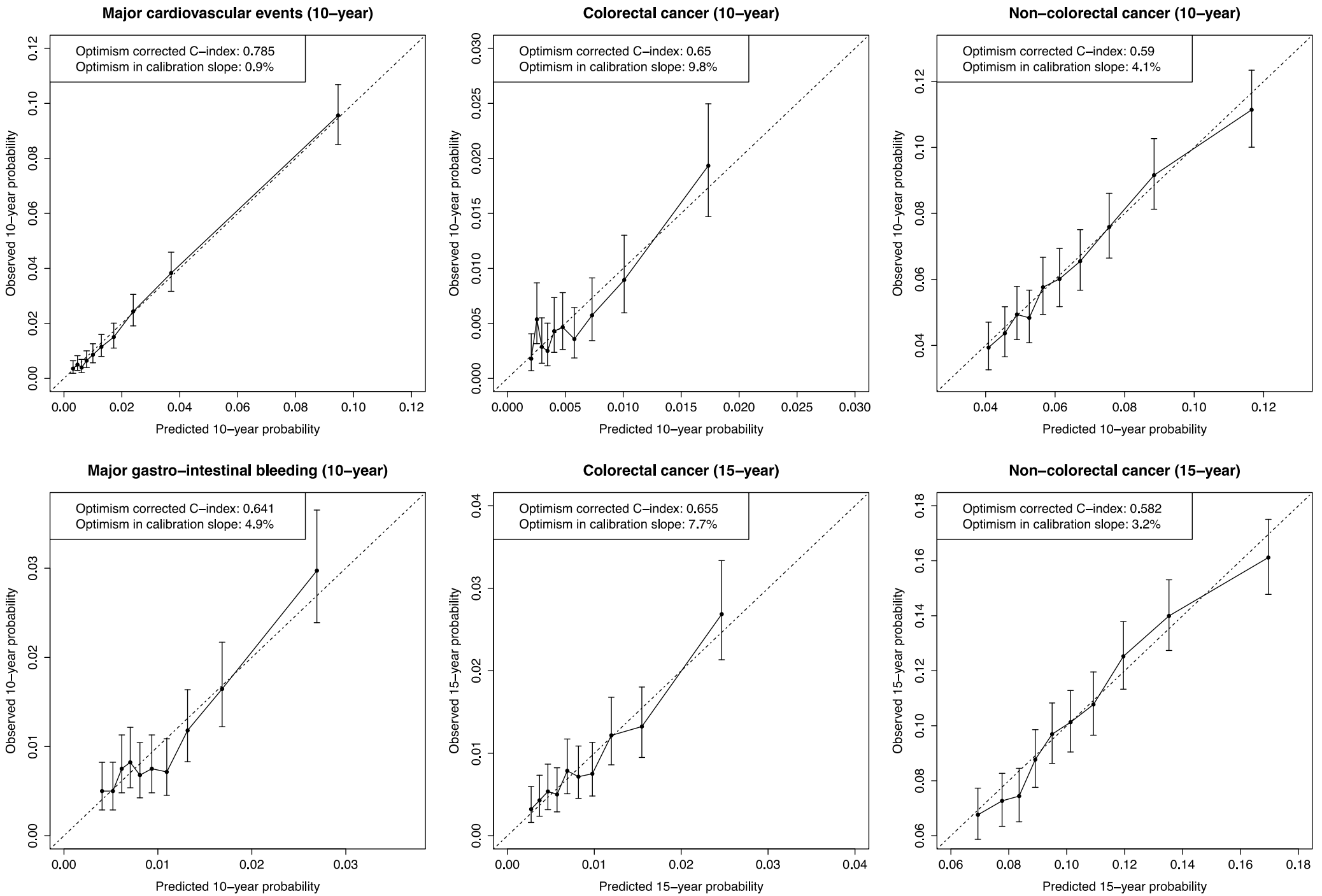
Model for prediction of 15-year non-colorectal cancer risk
(1 - exp(- (0.09493 * exp(C – 3.61989)))) * 100%, where

C = 0.03598 * age (years) + 0.17283 [if ever smoker] + 0.00735 * body mass index (kg/m^2) + 0.02162 * height (inches) – 0.03080 [if diabetic] + 0.09586 * no. of alcoholic drinks per day – 0.13779 [if peri- / postmenopausal] + 0.06473 [if ever used hormone replacement therapy] + 0.06062 [if family history of cancer] + 0.01568 [if using aspirin]

Model for prediction of 15-year major gastro-intestinal bleeding risk
(1 - exp(- (0.01113 * exp(D – 4.53537)))) * 100%, where

D = 0.06209 * age (years) + 0.22339 [if current smoker] + 0.03316 * body mass index (kg/m^2) + 0.26552 [if diabetic] + 0.00652 * no. of alcoholic drinks per day + 0.21780 [if history of dyspepsia] + 0.45399 [if using aspirin]

Outcomes were modelled in a competing risks framework, mutually accounting for all outcomes as well as death by other causes (Appendix 2.1), because not taking competing risks into account may lead to bias in predictions of absolute risks and non-additivity of risks for the individual outcomes[23 24]. No separate model was developed for prediction of the effects of aspirin on death by other causes, since no effects of aspirin on this outcome was expected, given that all relevant outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding) are already taken into account.



Appendix 2.4 | Calibration plots. Axis scales differ between plots. Plots were created with R-code adjusted from: *N.P. Bleda. Interval-censored semi-competing risks data : a novel approach for modelling bladder cancer. Thesis, Universitat Politècnica de Catalunya, Barcelona, June 2010.*

Appendix 2.5 (A) | Observed absolute risks, absolute risk reductions and numbers needed to treat/harm for aspirin

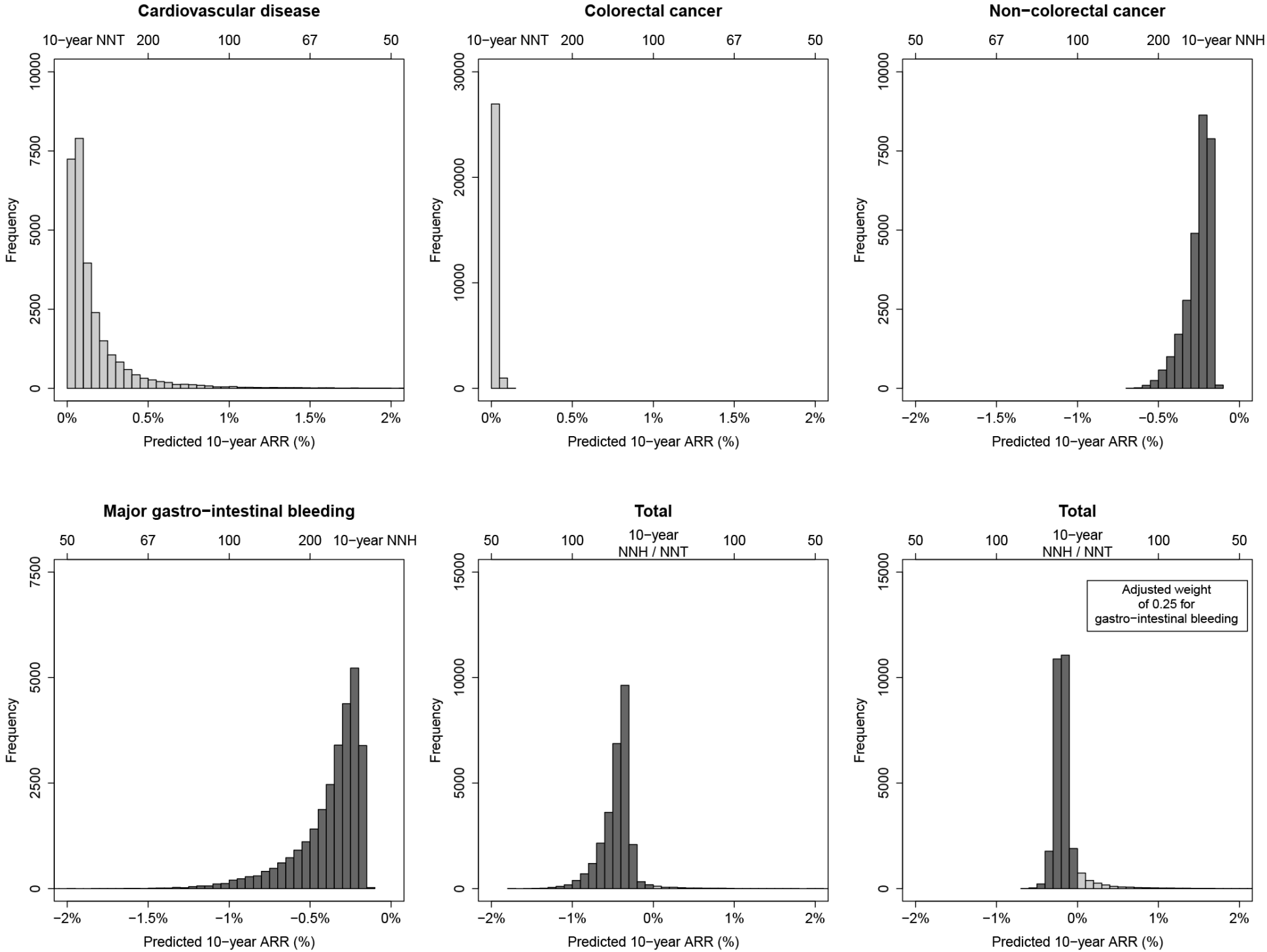
		Major cardiovascular disease	Colorectal cancer	Non-colorectal cancer	Major gastro-intestinal bleeding
		Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Total study population					
10-year	AR without aspirin (%)	2.27 (2.03 to 2.53)	0.61 (0.49 to 0.75)	6.40 (6.00 to 6.82)	0.83 (0.69 to 0.99)
	AR with aspirin (%)	2.09 (1.86 to 2.34)	0.60 (0.48 to 0.74)	6.67 (6.26 to 7.10)	1.33 (1.15 to 1.53)
	ARR (%)	0.18 (0.02 to 0.95)	0.01 (0.00 to 32.05)	-0.27 (-0.86 to 0.32)	-0.50 (-0.26 to -0.75)
	[a]NNT or [b]NNH	550 (106 to >1000) [a]	>1000 (3 to >1000) [a]	370[b] (117[b] to 317[a])	199 (134 to 390) [b]
15-year	AR without aspirin (%)	3.38 (3.14 to 3.64)	1.01 (0.85 to 1.18)	10.44 (9.93 to 10.96)	1.24 (1.09 to 1.40)
	AR with aspirin (%)	3.11 (2.88 to 3.36)	0.86 (0.72 to 1.03)	10.52 (10.01 to 11.04)	1.99 (1.80 to 2.19)
	ARR (%)	0.27 (0.06 to 0.86)	0.14 (0.02 to 0.59)	-0.08 (-0.80 to 0.64)	-0.75 (-0.50 to -1.00)
	[a]NNT or [b]NNH	371 (116 to >1000) [a]	709 (170 to >1000) [a]	>1000[b] (124[b] to 156[a])	133 (100 to 198) [b]
Women <65 years					
10-year	AR without aspirin (%)	1.66 (1.45 to 1.90)	0.51 (0.40 to 0.65)	5.75 (5.34 to 6.17)	0.69 (0.55 to 0.85)
	AR with aspirin (%)	1.70 (1.49 to 1.95)	0.47 (0.36 to 0.60)	6.23 (5.82 to 6.67)	1.11 (0.94 to 1.31)
	ARR (%)	-0.04 (-0.37 to 0.28)	0.05 (0.00 to 0.96)	-0.49 (-1.08 to 0.11)	-0.43 (-0.19 to -0.66)
	[a]NNT or [b]NNH	>1000[b] (273[b] to 354[a])	>1000 (105 to >1000) [a]	205[b] (92[b] to 937[a])	235 (151 to 531) [b]
15-year	AR without aspirin (%)	2.48 (2.26 to 2.72)	0.88 (0.73 to 1.06)	9.62 (9.11 to 10.15)	1.03 (0.89 to 1.18)
	AR with aspirin (%)	2.55 (2.32 to 2.78)	0.71 (0.57 to 0.87)	9.94 (9.42 to 10.48)	1.66 (1.48 to 1.86)
	ARR (%)	-0.06 (-0.39 to 0.26)	0.17 (0.04 to 0.55)	-0.32 (-1.06 to 0.42)	-0.64 (-0.40 to -0.87)
	[a]NNT or [b]NNH	>1000[b] (259[b] to 382[a])	581 (181 to >1000) [a]	312[b] (94[b] to 237[a])	157 (114 to 251) [b]
Women ≥65 years					
10-year	AR without aspirin (%)	7.39 (6.12 to 8.82)	1.43 (0.92 to 2.15)	11.93 (10.32 to 13.66)	2.02 (1.39 to 2.86)
	AR with aspirin (%)	5.25 (4.18 to 6.49)	1.71 (1.13 to 2.47)	10.29 (8.81 to 11.91)	3.15 (2.34 to 4.14)
	ARR (%)	2.14 (0.85 to 4.52)	-0.27 (-1.17 to 0.63)	1.64 (0.31 to 5.34)	-1.12 (-2.28 to 0.04)
	[a]NNT or [b]NNH	47 (22 to 118) [a]	369[b] (85[b] to 158[a])	61 (19 to 321) [a]	89[b] (44[b] to >1000[a])
15-year	AR without aspirin (%)	10.88 (9.58 to 12.28)	2.06 (1.42 to 2.89)	17.44 (15.52 to 19.45)	3.02 (2.35 to 3.82)
	AR with aspirin (%)	7.77 (6.67 to 8.97)	2.17 (1.51 to 3.01)	15.39 (13.59 to 17.30)	4.68 (3.84 to 5.64)
	ARR (%)	3.11 (1.67 to 5.27)	-0.11 (-1.15 to 0.93)	2.05 (0.43 to 6.28)	-1.66 (-0.50 to -2.82)
	[a]NNT or [b]NNH	32 (19 to 60) [a]	924[b] (87[b] to 107[a])	49 (16 to 235) [a]	60 (35 to 199) [b]
Never smokers					
10-year	AR without aspirin (%)	1.85 (1.55 to 2.18)	0.57 (0.42 to 0.77)	5.43 (4.92 to 5.97)	0.69 (0.52 to 0.91)
	AR with aspirin (%)	1.53 (1.26 to 1.84)	0.54 (0.39 to 0.73)	6.63 (6.06 to 7.22)	1.16 (0.93 to 1.43)
	ARR (%)	0.32 (0.07 to 1.05)	0.03 (0.00 to 3.86)	-1.20 (-0.41 to -1.98)	-0.46 (-0.15 to -0.78)
	[a]NNT or [b]NNH	314 (95 to >1000) [a]	>1000 (26 to >1000) [a]	83 (50 to 242) [b]	215 (128 to 685) [b]
15-year	AR without aspirin (%)	2.76 (2.46 to 3.09)	0.92 (0.72 to 1.16)	9.05 (8.40 to 9.73)	1.04 (0.86 to 1.25)
	AR with aspirin (%)	2.29 (2.01 to 2.59)	0.72 (0.55 to 0.94)	9.90 (9.22 to 10.61)	1.73 (1.49 to 2.00)
	ARR (%)	0.47 (0.18 to 1.09)	0.20 (0.04 to 0.75)	-0.85 (-1.81 to 0.11)	-0.69 (-0.37 to -1.01)
	[a]NNT or [b]NNH	211 (92 to 565) [a]	509 (134 to >1000) [a]	117[b] (55[b] to 911[a])	144 (99 to 267) [b]
Past smokers					
10-year	AR without aspirin (%)	2.27 (1.88 to 2.71)	0.76 (0.55 to 1.03)	7.01 (6.33 to 7.75)	1.00 (0.75 to 1.30)
	AR with aspirin (%)	1.96 (1.60 to 2.37)	0.74 (0.53 to 1.01)	6.08 (5.44 to 6.76)	1.50 (1.19 to 1.86)
	ARR (%)	0.31 (0.04 to 1.48)	0.02 (0.00 to 24.90)	0.94 (0.30 to 2.37)	-0.50 (-0.07 to -0.93)
	[a]NNT or [b]NNH	321 (68 to >1000) [a]	>1000 (4 to >1000) [a]	107 (42 to 339) [a]	200 (107 to >1000) [b]
15-year	AR without aspirin (%)	3.38 (2.99 to 3.81)	1.21 (0.94 to 1.54)	11.50 (10.64 to 12.40)	1.49 (1.23 to 1.78)
	AR with aspirin (%)	2.92 (2.55 to 3.32)	1.06 (0.81 to 1.37)	10.28 (9.46 to 11.13)	2.24 (1.92 to 2.59)
	ARR (%)	0.46 (0.12 to 1.38)	0.15 (0.01 to 1.40)	1.22 (0.40 to 2.98)	-0.75 (-0.31 to -1.18)
	[a]NNT or [b]NNH	216 (72 to 853) [a]	662 (71 to >1000) [a]	82 (34 to 250) [a]	134 (85 to 322) [b]
Current smokers					
10-year	AR without aspirin (%)	4.12 (3.22 to 5.18)	0.31 (0.12 to 0.69)	8.72 (7.41 to 10.16)	0.89 (0.51 to 1.47)
	AR with aspirin (%)	4.98 (3.99 to 6.14)	0.44 (0.20 to 0.87)	8.75 (7.43 to 10.20)	1.57 (1.04 to 2.27)
	ARR (%)	-0.86 (-2.31 to 0.59)	-0.13 (-0.55 to 0.29)	-0.03 (-1.99 to 1.92)	-0.68 (-1.44 to 0.09)
	[a]NNT or [b]NNH	-116 (-43 to 169) [a]	-758 (-181 to 348) [a]	<-1000 (50 to 52) [b]	148 (-69 to >1000) [b]
15-year	AR without aspirin (%)	6.12 (5.19 to 7.15)	0.75 (0.41 to 1.28)	13.28 (11.66 to 14.99)	1.33 (0.93 to 1.87)
	AR with aspirin (%)	7.38 (6.36 to 8.50)	0.88 (0.51 to 1.44)	14.06 (12.40 to 15.83)	2.34 (1.79 to 3.01)
	ARR (%)	-1.26 (-2.71 to 0.19)	-0.13 (-0.75 to 0.50)	-0.79 (-3.18 to 1.60)	-1.01 (-0.24 to -1.78)
	[a]NNT or [b]NNH	-79 (-37 to 524) [a]	-783 (-133 to 201) [a]	127 (31 to 62) [b]	99 (56 to 420) [b]

CI: Confidence interval ; AR: Absolute risk ; ARR: Absolute risk reduction ; [a]NNT: Number needed to treat ; [b]NNH: Number needed to harm. Risks were estimated based on the cumulative incidence function, accounting for competing risks.

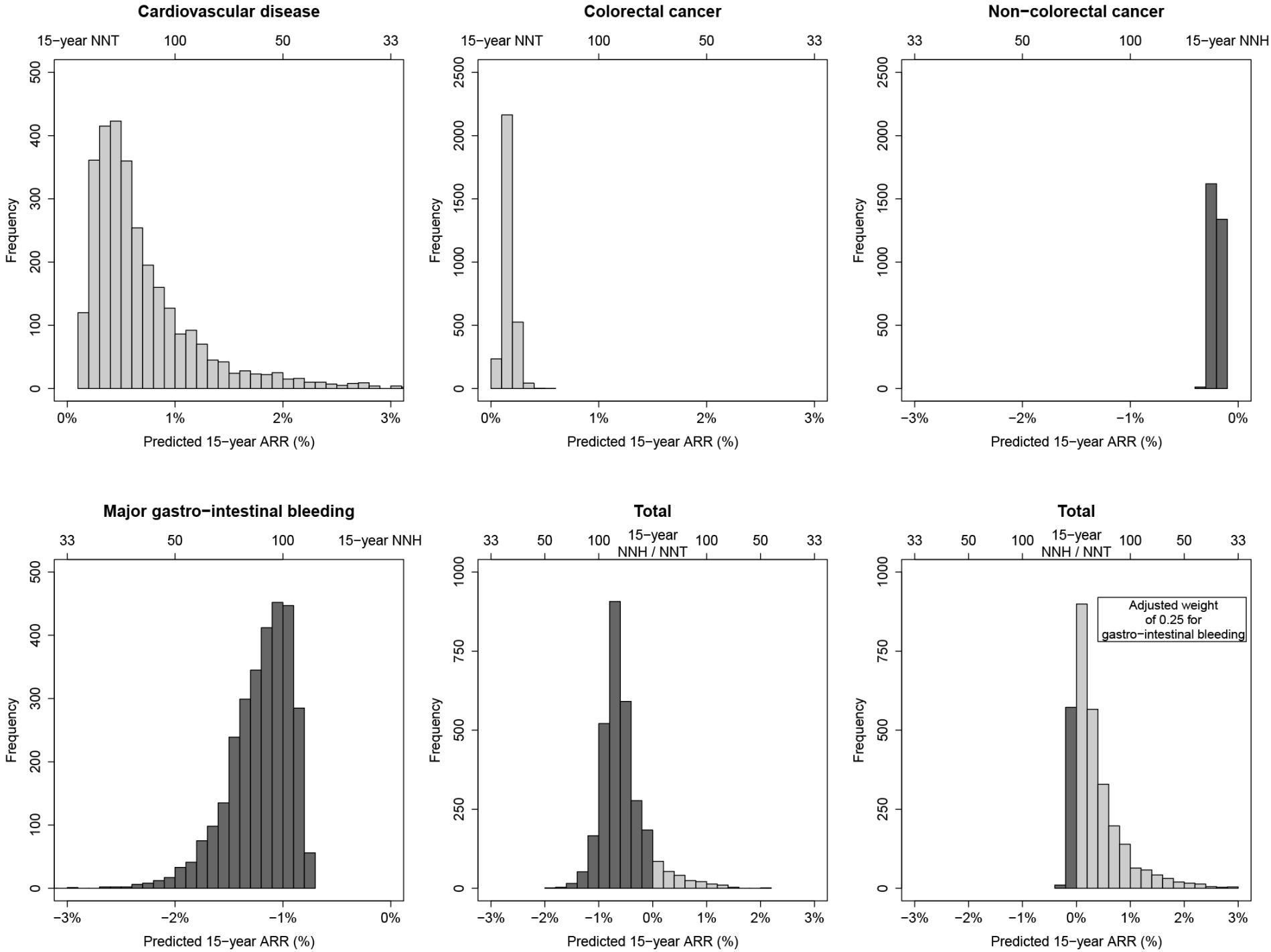
Appendix 2.5 (B) | Observed absolute risks, absolute risk reductions and numbers needed to treat/harm for aspirin

		Total	Total adjusted weight of 0.5 for gastro-intestinal bleeding	Total adjusted weight of 0.25 for gastro-intestinal bleeding	Total adjusted weight of 0.1 for gastro-intestinal bleeding
		Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Total study population					
10-year	AR without aspirin (%)	10.11 (9.59 to 10.64)	9.69 (9.18 to 10.22)	9.49 (8.97 to 10.01)	9.36 (8.85 to 9.89)
	AR with aspirin (%)	10.69 (10.16 to 11.23)	10.02 (9.50 to 10.57)	9.69 (9.16 to 10.23)	9.49 (8.96 to 10.03)
	ARR (%)	-0.58 (-1.33 to 0.17)	-0.33 (-1.08 to 0.42)	-0.20 (-0.95 to 0.54)	-0.13 (-0.88 to 0.62)
	[a]iNNT or [b]iNNH	172[b] (605[b] to 75[a])	302[b] (93[b] to 240[a])	488[b] (105[b] to 184[a])	772[b] (114[b] to 162[a])
15-year	AR without aspirin (%)	16.07 (15.46 to 16.68)	15.45 (14.84 to 16.07)	15.14 (14.53 to 15.76)	14.95 (14.35 to 15.57)
	AR with aspirin (%)	16.49 (15.87 to 17.11)	15.49 (14.88 to 16.12)	15.00 (14.38 to 15.62)	14.70 (14.09 to 15.32)
	ARR (%)	-0.42 (-1.29 to 0.45)	-0.05 (-0.92 to 0.82)	0.14 (0.00 to 7.59)	0.25 (0.00 to 3.43)
	[a]iNNT or [b]iNNH	238[b] (223[b] to 78[a])	>1000[b] (109[b] to 121[a])	703 (13 to >1000) [a]	393 (29 to >1000) [a]
Women <65 years					
10-year	AR without aspirin (%)	8.61 (8.11 to 9.13)	8.26 (7.76 to 8.78)	8.09 (7.59 to 8.61)	7.99 (7.49 to 8.51)
	AR with aspirin (%)	9.52 (8.99 to 10.06)	8.96 (8.44 to 9.51)	8.68 (8.16 to 9.23)	8.52 (7.99 to 9.06)
	ARR (%)	-0.91 (-0.17 to -1.65)	-0.70 (-1.44 to 0.04)	-0.59 (-1.33 to 0.15)	-0.53 (-1.27 to 0.21)
	[a]iNNT or [b]iNNH	110 (61 to 583) [b]	143[b] (70[b] to >1000[a])	169[b] (75[b] to 676[a])	190[b] (79[b] to 472[a])
15-year	AR without aspirin (%)	14.02 (13.41 to 14.63)	13.50 (12.90 to 14.12)	13.25 (12.64 to 13.86)	13.09 (12.49 to 13.71)
	AR with aspirin (%)	14.86 (14.25 to 15.49)	14.03 (13.41 to 14.66)	13.62 (13.00 to 14.25)	13.37 (12.75 to 14.00)
	ARR (%)	-0.85 (-1.72 to 0.03)	-0.53 (-1.40 to 0.34)	-0.37 (-1.24 to 0.50)	-0.27 (-1.15 to 0.60)
	[a]iNNT or [b]iNNH	118[b] (58[b] to >1000[a])	189[b] (71[b] to 291[a])	271[b] (81[b] to 199[a])	365[b] (87[b] to 167[a])
Women ≥65 years					
10-year	AR without aspirin (%)	22.78 (20.47 to 25.17)	21.77 (19.46 to 24.16)	21.26 (18.96 to 23.66)	20.96 (18.66 to 23.36)
	AR with aspirin (%)	20.39 (18.21 to 22.67)	18.82 (16.64 to 21.10)	18.03 (15.86 to 20.32)	17.56 (15.39 to 19.85)
	ARR (%)	2.39 (0.46 to 7.46)	2.95 (0.81 to 7.58)	3.23 (1.01 to 7.71)	3.40 (1.13 to 7.81)
	[a]iNNT or [b]iNNH	42 (13 to 215) [a]	34 (13 to 123) [a]	31 (13 to 99) [a]	29 (13 to 89) [a]
15-year	AR without aspirin (%)	33.40 (30.81 to 36.01)	31.89 (29.30 to 34.50)	31.13 (28.55 to 33.75)	30.68 (28.10 to 33.30)
	AR with aspirin (%)	30.01 (27.55 to 32.50)	27.67 (25.22 to 30.16)	26.50 (24.05 to 29.00)	25.79 (23.35 to 28.30)
	ARR (%)	3.39 (0.98 to 8.42)	4.22 (1.59 to 8.90)	4.64 (1.92 to 9.19)	4.89 (2.13 to 9.38)
	[a]iNNT or [b]iNNH	29 (12 to 102) [a]	24 (11 to 63) [a]	22 (11 to 52) [a]	20 (11 to 47) [a]
Never smokers					
10-year	AR without aspirin (%)	8.54 (7.89 to 9.23)	8.20 (7.54 to 8.88)	8.02 (7.37 to 8.71)	7.92 (7.27 to 8.61)
	AR with aspirin (%)	9.85 (9.15 to 10.59)	9.27 (8.57 to 10.01)	8.99 (8.29 to 9.72)	8.81 (8.11 to 9.54)
	ARR (%)	-1.31 (-0.33 to -2.29)	-1.08 (-0.10 to -2.06)	-0.96 (-1.94 to 0.02)	-0.89 (-1.87 to 0.09)
	[a]iNNT or [b]iNNH	76 (44 to 304) [b]	93 (49 to >1000) [b]	104[b] (52[b] to >1000[a])	112[b] (53[b] to >1000[a])
15-year	AR without aspirin (%)	13.77 (12.99 to 14.57)	13.25 (12.47 to 14.05)	12.99 (12.21 to 13.79)	12.83 (12.05 to 13.64)
	AR with aspirin (%)	14.64 (13.84 to 15.47)	13.78 (12.97 to 14.60)	13.34 (12.54 to 14.17)	13.08 (12.28 to 13.91)
	ARR (%)	-0.87 (-2.01 to 0.26)	-0.53 (-1.67 to 0.61)	-0.36 (-1.49 to 0.78)	-0.25 (-1.39 to 0.89)
	[a]iNNT or [b]iNNH	114[b] (50[b] to 380[a])	189[b] (60[b] to 164[a])	282[b] (67[b] to 128[a])	398[b] (72[b] to 113[a])
Past smokers					
10-year	AR without aspirin (%)	11.04 (10.16 to 11.96)	10.54 (9.66 to 11.46)	10.29 (9.41 to 11.21)	10.14 (9.26 to 11.06)
	AR with aspirin (%)	10.26 (9.42 to 11.15)	9.52 (8.67 to 10.41)	9.14 (8.30 to 10.03)	8.92 (8.08 to 9.81)
	ARR (%)	0.77 (0.11 to 3.06)	1.02 (0.25 to 2.99)	1.15 (0.33 to 3.02)	1.22 (0.39 to 3.04)
	[a]iNNT or [b]iNNH	130 (33 to 885) [a]	98 (33 to 398) [a]	87 (33 to 300) [a]	82 (33 to 259) [a]
15-year	AR without aspirin (%)	17.58 (16.54 to 18.65)	16.84 (15.79 to 17.91)	16.46 (15.42 to 17.54)	16.24 (15.20 to 17.31)
	AR with aspirin (%)	16.49 (15.49 to 17.53)	15.38 (14.37 to 16.41)	14.82 (13.81 to 15.85)	14.48 (13.48 to 15.52)
	ARR (%)	1.09 (0.23 to 3.49)	1.46 (0.47 to 3.57)	1.65 (0.61 to 3.67)	1.76 (0.70 to 3.74)
	[a]iNNT or [b]iNNH	92 (29 to 442) [a]	68 (28 to 213) [a]	61 (27 to 164) [a]	57 (27 to 144) [a]
Current smokers					
10-year	AR without aspirin (%)	14.04 (12.32 to 15.87)	13.60 (11.88 to 15.43)	13.37 (11.66 to 15.20)	13.24 (11.53 to 15.07)
	AR with aspirin (%)	15.74 (13.91 to 17.68)	14.96 (13.13 to 16.90)	14.57 (12.74 to 16.51)	14.33 (12.51 to 16.27)
	ARR (%)	-1.70 (-4.29 to 0.89)	-1.36 (-3.95 to 1.23)	-1.19 (-3.78 to 1.40)	-1.09 (-3.68 to 1.50)
	[a]iNNT or [b]iNNH	59[b] (23[b] to 112[a])	73[b] (25[b] to 82[a])	84 (26 to 72)	92[b] (27[b] to 67[a])
15-year	AR without aspirin (%)	21.48 (19.49 to 23.55)	20.82 (18.82 to 22.88)	20.48 (18.49 to 22.55)	20.28 (18.29 to 22.35)
	AR with aspirin (%)	24.67 (22.53 to 26.85)	23.50 (21.37 to 25.69)	22.91 (20.78 to 25.10)	22.56 (20.43 to 24.75)
	ARR (%)	-3.18 (-0.21 to -6.15)	-2.68 (-5.65 to 0.29)	-2.43 (-5.39 to 0.54)	-2.28 (-5.24 to 0.69)
	[a]iNNT or [b]iNNH	31 (16 to 466) [b]	37[b] (18[b] to 346[a])	41 (19 to 185) [a]	44[b] (19[b] to 145[a])

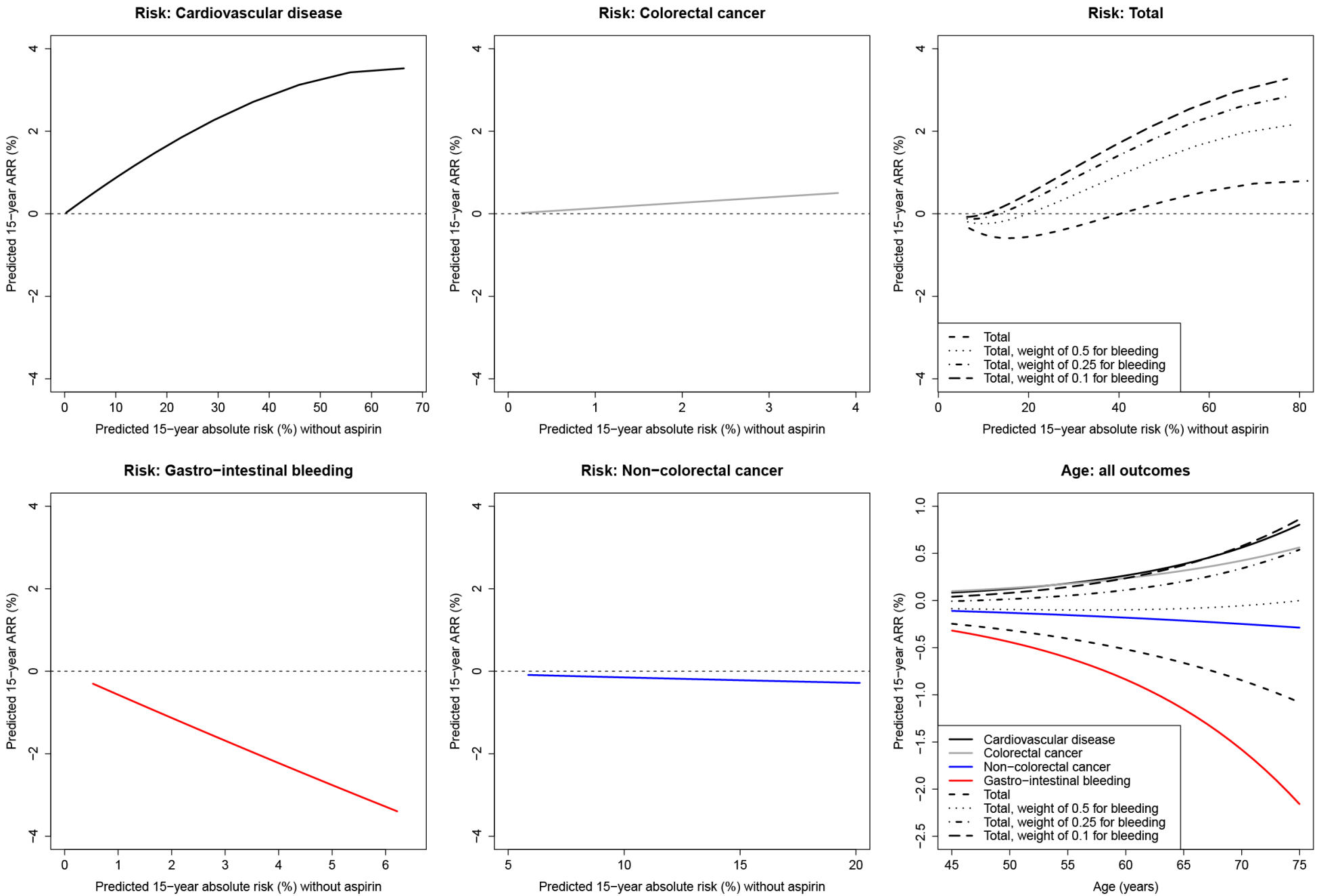
CI: Confidence interval ; AR: Absolute risk ; ARR: Absolute risk reduction ; [a]NNT: Number needed to treat ; [b]NNH: Number needed to harm. Risks were estimated based on the cumulative incidence function, accounting for competing risks.



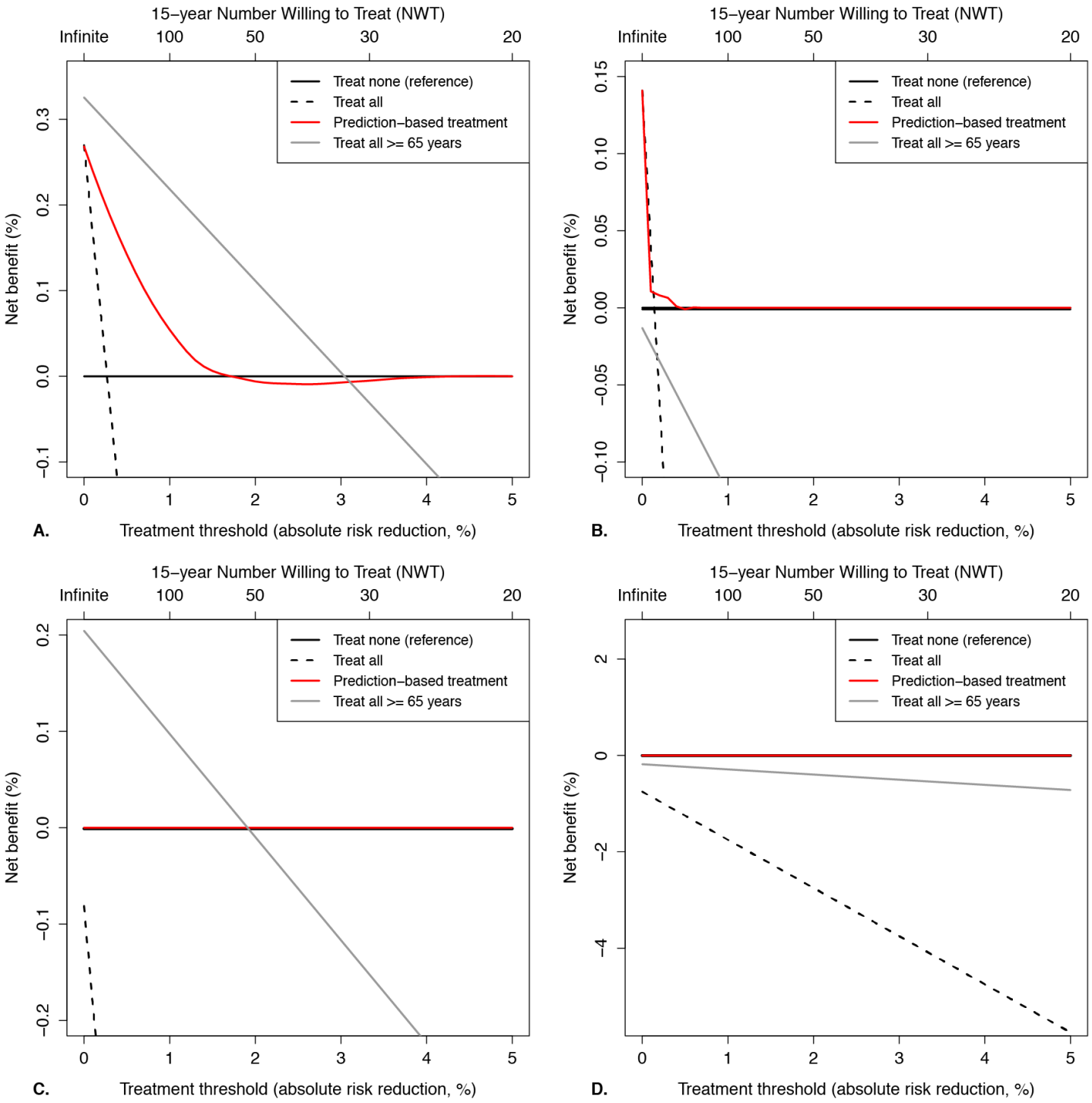
Appendix 2.6 | Distribution of predicted 10-year absolute risk reduction for major cardiovascular events, colorectal cancer and major gastro-intestinal bleeding with aspirin



Appendix 2.7 | Distribution of predicted 15-year absolute risk reduction for major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding with aspirin treatment in participants of the Women's Health Study of 65 years and older. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.



Appendix 2.8 | Effect of baseline risk and age on predicted 15-year absolute risk reduction. ARR: absolute risk reduction. ARR in plot for age apply to an average participant of the Women's Health Study (i.e. a 55-year old postmenopausal woman who never smoked, does not have diabetes, history of dyspepsia or a family no family history of premature myocardial infarction or cancer, has a height of 65 inches, a BMI of 26 kg/m2 and a systolic blood pressure of 124 mmHg and does not receive treatment for hypertension, with a serum level of high sensitivity C-reactive protein of 2·0 mg/L, total cholesterol of 212 mg/dL and a HDL-cholesterol of 54 mg/dL, drinks 2 alcoholic beverages per week and has never received hormone replacement therapy) with alternating age.



Appendix 2.9 | Decision curves for different aspirin treatment strategies for the individual outcomes: **A.** Major cardiovascular events ; **B.** Colorectal cancer ; **C**. Non-colorectal cancer ; **D.** Major gastro-intestinal bleeding. Reading the net benefit plot starts with choosing a treatment threshold, that is the absolute risk reduction (ARR) at which one would opt for treatment, or number-willing-to-treat (NWT). A NWT of 30 implies that one is willing to treat 30 women to prevent at least 1 event. Positive net benefit means that the treatment strategy led to a more favourable trade-off between benefits (observed decrease in event rate) and harms (the proportion of patients receiving treatment weighted by the reciprocal of the treatment threshold). Since for non-colorectal cancer and major gastro-intestinal bleeding all patients had a negative predicted absolute risk prediction (meaning that their risk of those outcomes increases with aspirin), none will selected for treatment over the full range of threshold values when applying prediction-based treatment and the net benefit for this treatment strategy is equal to zero.

Appendix 3

Sensitivity analyses

Appendix 3.1 | Summary of results

Using the models with treatment interactions, the protective effect of aspirin for CVD increased with age, whereas current smoking attenuated the benefits of aspirin (*appendix 3A*). BMI and ever smoking were inversely related to treatment effect on colorectal cancer. The HR of aspirin for non-colorectal cancer risk slightly decreased with higher age and was lower for ever smokers. Current smoking increased the risk of major bleeding when using aspirin. Compared to the main results, the predicted ARRs from the models with treatment interactions were more widely distributed, particularly for non-colorectal cancer, as aspirin was associated with benefit in 48% of the study population and caused harm in the other 52%. If a weight was applied for gastro-intestinal bleeding, the models with treatment interactions yielded a higher net benefit compared to the models without interaction, but treating only women ≥65 years was still the most favourable treatment strategy.

When the effect of aspirin on non-colorectal cancer was assumed null in sensitivity analysis, the total ARR tended to be slightly higher (*appendix 3B*). When a weight of 0.25 was applied for bleeding, 3.1% of the women had a predicted 15-year ARR of >1% (iNNT:100) versus 1.7% in the main analysis. Although some improvement in the net benefit of prediction-based treatment was observed, treating only women ≥65 years was still superior if the 15-year NWT was >60, whereas treating none was the most favorable treatment strategy for lower ranges of NWT.

Appendix 3A (1) | Models for prediction of 15-year absolute risk reduction with aspirin treatment

Predicted 15-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.*
Total risk on aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.*

Model for prediction of 15-year major cardiovascular event risk
(1 - exp(- (0.01597 * exp(A – 20.78737)))) * 100%, where

A = 0.08225 * age (years) – 0.00883 * age (years) [if using aspirin] + 0.75154 [if current smoker] + 0.37331 [if current smoker and using aspirin] – 0.02022 * body mass index (kg/m^2) + 0.00063 * body mass index (kg/m^2) [if using aspirin] + 3.28886 * natural logarithm(systolic blood pressure, mmHg) + 0.25407 [if using blood pressure lowering medication] + 0.82587 * natural logarithm(total cholesterol, mg/dL) – 0.87803 * natural logarithm(high-density lipoprotein cholesterol, mg/dL) + 0.10963 * natural logarithm(high-sensitivity C-reactive protein, mg/L) + 0.17672 * hemoglobin A1c (%) [if diabetic] + 0.27403 [if family history of premature myocardial infarction] + 0.33118 [if using aspirin]

Model for prediction of 15-year colorectal cancer risk
(1 - exp(- (0.00674 * exp(B – 6.96952)))) * 100%, where

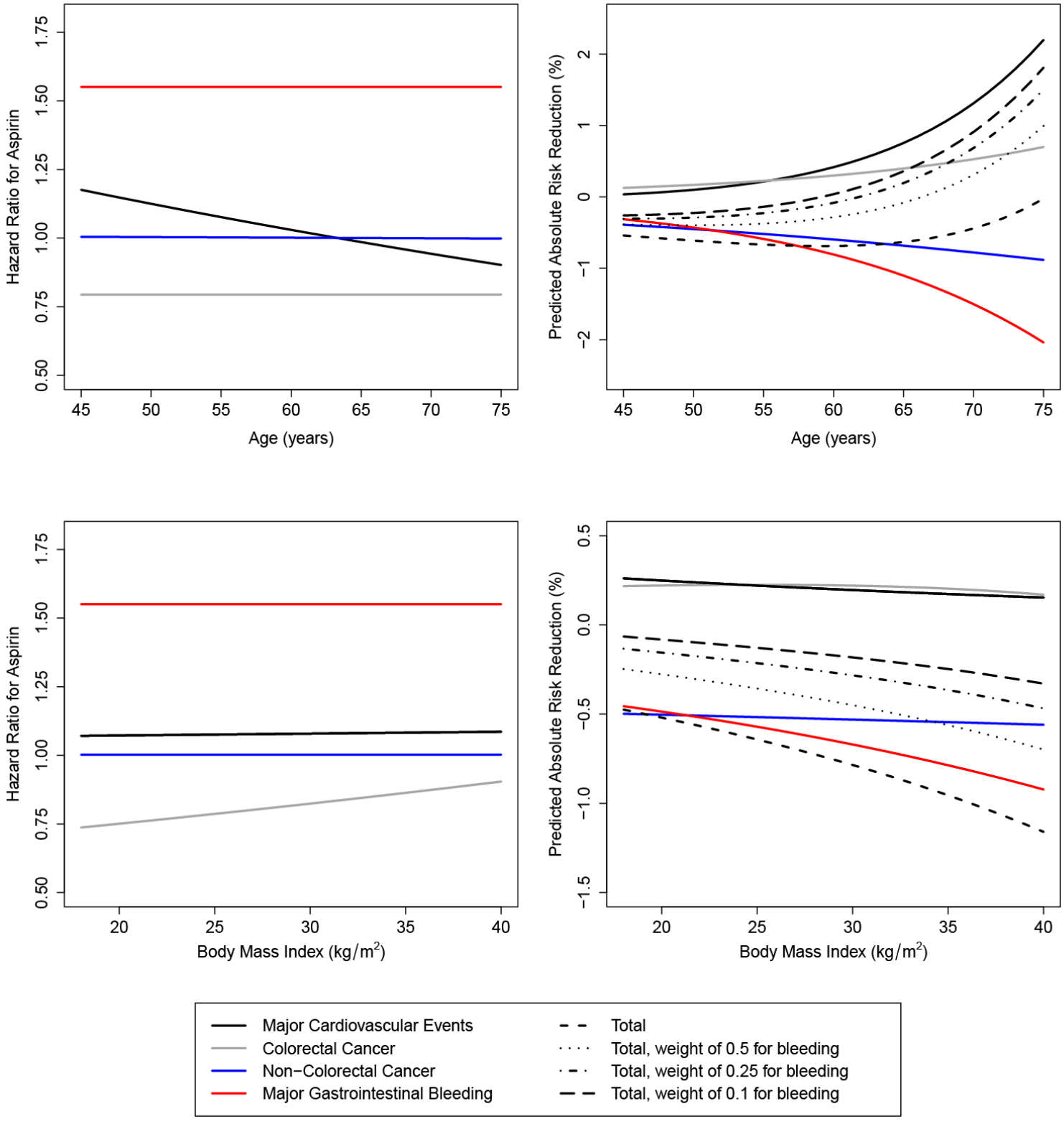
B = 0.05783 * age (years) + 0.10755 [if ever smoker] + 0.15955 [if ever smoker and using aspirin] + 0.03632 * height (inches) + 0.03483 * body mass index (kg/m^2) + 0.00930 * body mass index (kg/m^2) [if using aspirin] – 0.20511 [if diabetic] + 0.15214 * no. of alcoholic drinks per day + 0.59635 [if peri- / postmenopausal] – 0.27149 [if ever used hormone replacement therapy] + 0.11092 [if family history of colorectal cancer] – 0.47292 [if using aspirin]

Model for prediction of 15-year non-colorectal cancer risk
(1 - exp(- (0.0677 * exp(C – 3.46478)))) * 100%, where

C = 0.03481 * age (years) – 0.00021 * age (years) [if using aspirin] + 0.21150 [if ever smoker] – 0.08502 [if ever smoker and using aspirin] + 0.02085 * height (inches) + 0.00585 * body mass index (kg/m^2) – 0.02323 [if diabetic] + 0.09414 * no. of alcoholic drinks per day – 0.10978 [if peri- / postmenopausal] + 0.0535 [if ever used hormone replacement therapy] + 0.05403 [if family history of cancer] + 0.07276 [if using aspirin]

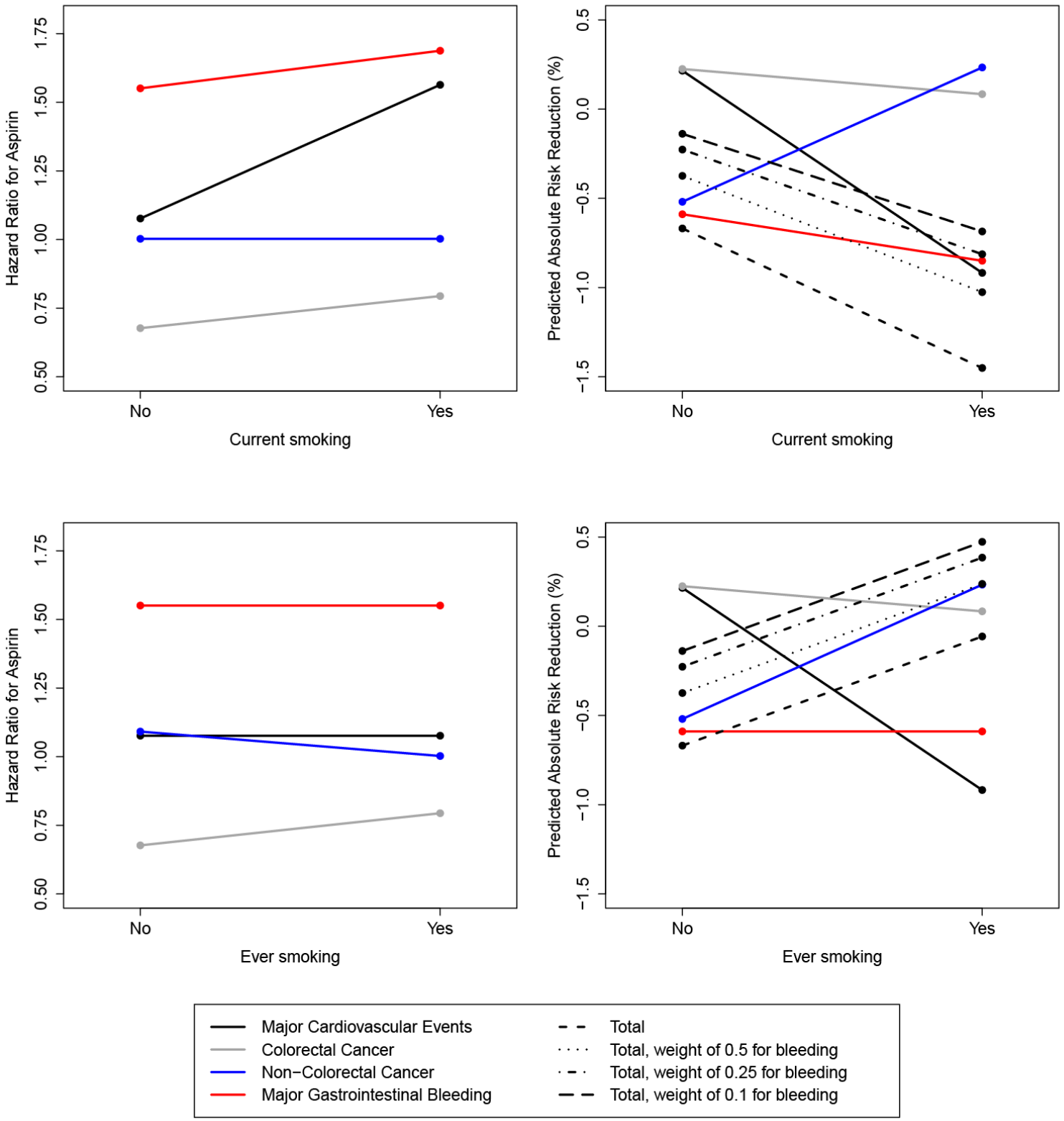
Model for prediction of 15-year major gastro-intestinal bleeding risk
(1 - exp(- (0.01094 * exp(D – 4.38127)))) * 100%, where

D = 0.06386 * age (years) + 0.14899 [if current smoker] + 0.08470 [if current smoker and using aspirin] + 0.03257 * body mass index (kg/m^2) + 0.24747 [if diabetic] + 0.19232 [if history of dyspepsia] + 0.44374 [if using aspirin]



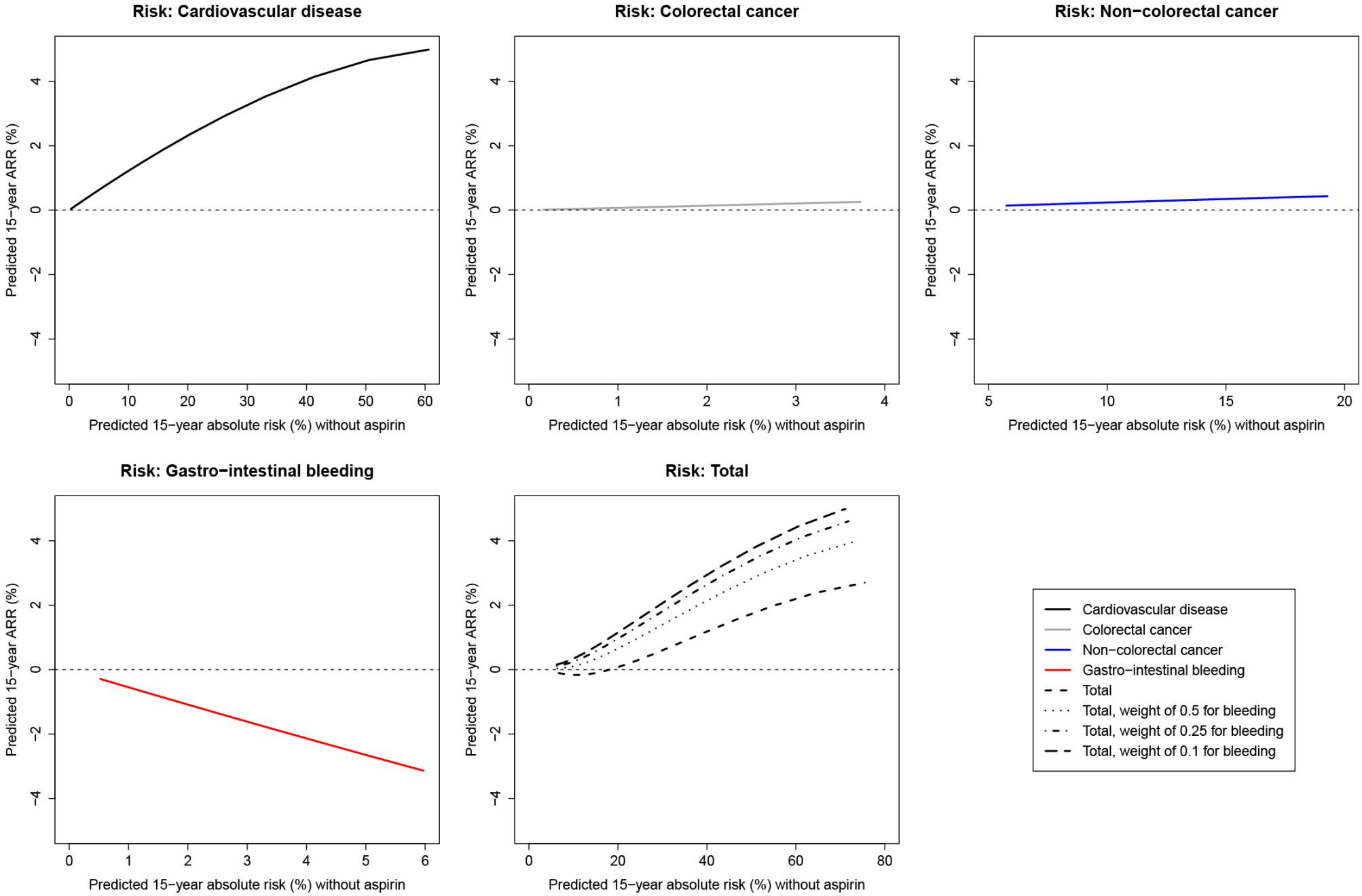
Appendix 3A (2) | Sensitivity analysis - Effect of treatment interactions with age and body mass index on hazard ratio's and predicted 15-year absolute risk reductions for aspirin.

Presented hazard ratio's and absolute risk reductions apply to an average participant of the Women's Health Study (i.e. a 55-year old postmenopausal woman who never smoked, does not have diabetes, history of dyspepsia or a family no family history of premature myocardial infarction or cancer, has a height of 65 inches, a BMI of 26 kg/m2 and a systolic blood pressure of 124 mmHg and does not receive treatment for hypertension, with a serum level of high sensitivity C-reactive protein of 2.0 mg/L, total cholesterol of 212 mg/dL and a HDL-cholesterol of 54 mg/dL, drinks 2 alcoholic beverages per week and has never received hormone replacement therapy). For the specific plots, all the above characteristics were kept constant with the exception of the characteristic displayed on the x-axis (e.g. for the age-plot, a women with the aforementioned average characteristics with age alternating from 45 to 75 years).

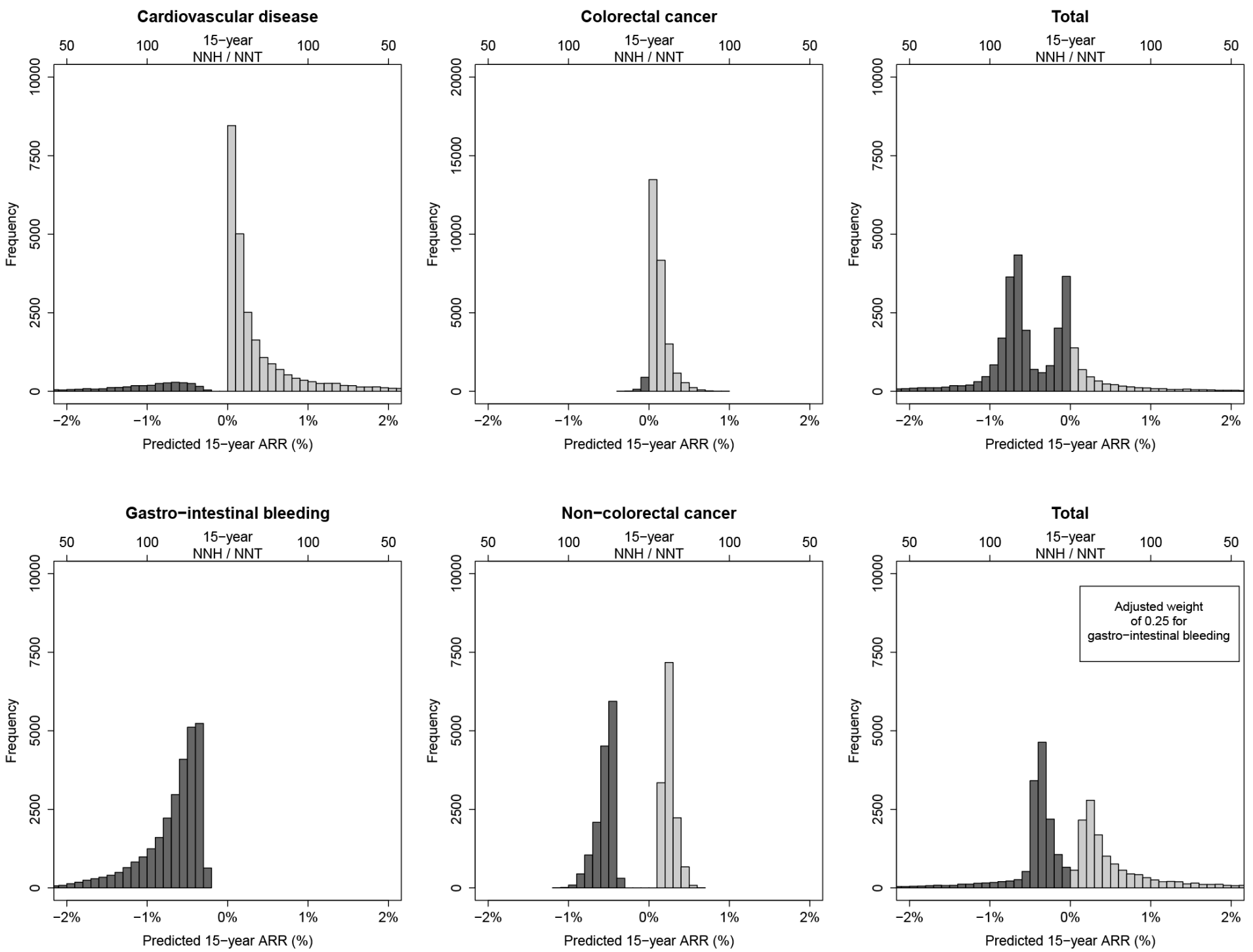


Appendix 3A (2) | Sensitivity analysis - Effect of treatment interactions with smoking status on hazard ratio's and predicted 15-year absolute risk reductions for aspirin.

Presented hazard ratio's and absolute risk reductions apply to an average participant of the Women's Health Study (i.e. a 55-year old postmenopausal woman who never smoked, does not have diabetes, history of dyspepsia or a family no family history of premature myocardial infarction or cancer, has a height of 65 inches, a BMI of 26 kg/m2 and a systolic blood pressure of 124 mmHg and does not receive treatment for hypertension, with a serum level of high sensitivity C-reactive protein of 2.0 mg/L, total cholesterol of 212 mg/dL and a HDL-cholesterol of 54 mg/dL, drinks 2 alcoholic beverages per week and has never received hormone replacement therapy). For the specific plots, all the above characteristics were kept constant with the exception of the characteristic displayed on the x-axis (e.g. for the current smoking-plot, a women with the aforementioned average characteristics with current smoking set to no/yes).



Appendix 3A (3)| Sensitivity analysis - Effect of baseline risk on predicted 15-year absolute risk reduction for aspirin using models with treatment interactions.
ARR: Absolute risk reduction.



Appendix 3A (4)| Sensitivity analysis - Distribution of predicted 15-year absolute risk reduction with aspirin treatment in participants of the Women's Health Study based on models with treatment interactions. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.

Appendix 3B (1) | Models for prediction of 15-year absolute risk reduction with aspirin treatment

Predicted 15-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.*
Total risk on aspirin treatment:	*Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.*

Model for prediction of 15-year major cardiovascular event risk
(1 - exp(- (0.01539 * exp(A – 19.9348)))) * 100%, where

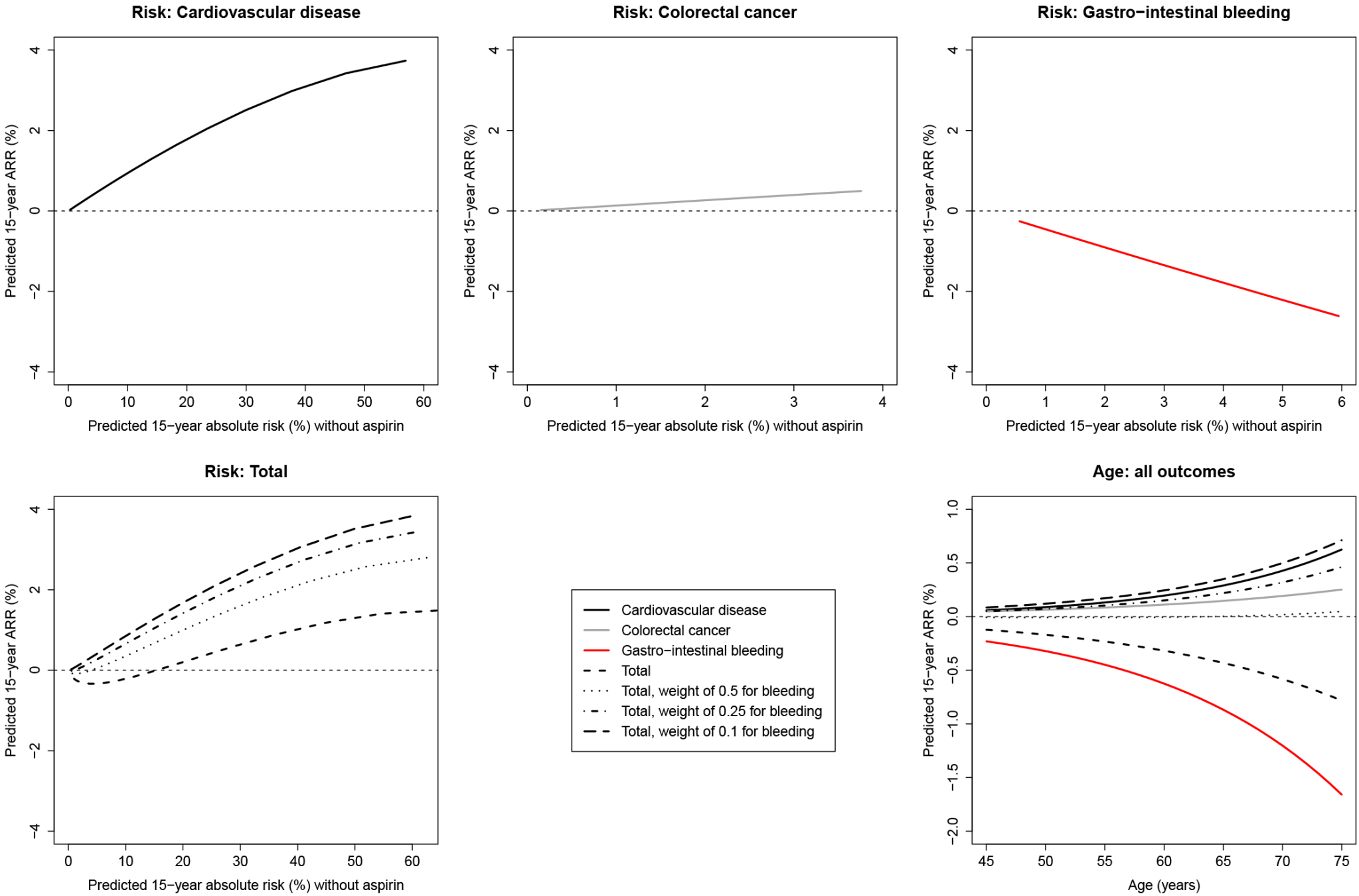
A = 0.08057 * age (years) + 0.95481 [if current smoker] – 0.02471* body mass index (kg/m^2) + 3.16178 * natural logarithm(systolic blood pressure, mmHg) + 0.28377 [if using blood pressure lowering medication] + 0.30422 [if family history of premature myocardial infarction] + 0.79060 * natural logarithm(total cholesterol, mg/dL) – 0.88894 * natural logarithm(high-density lipoprotein cholesterol, mg/dL) + 0.12118 * natural logarithm(high-sensitivity C-reactive protein, mg/L) + 0.17274 * hemoglobin A1c (%) [if diabetic] – 0.10389 [if using aspirin]

Model for prediction of 15-year colorectal cancer risk
(1 - exp(- (0.00454 * exp(B – 6.95442)))) * 100%, where

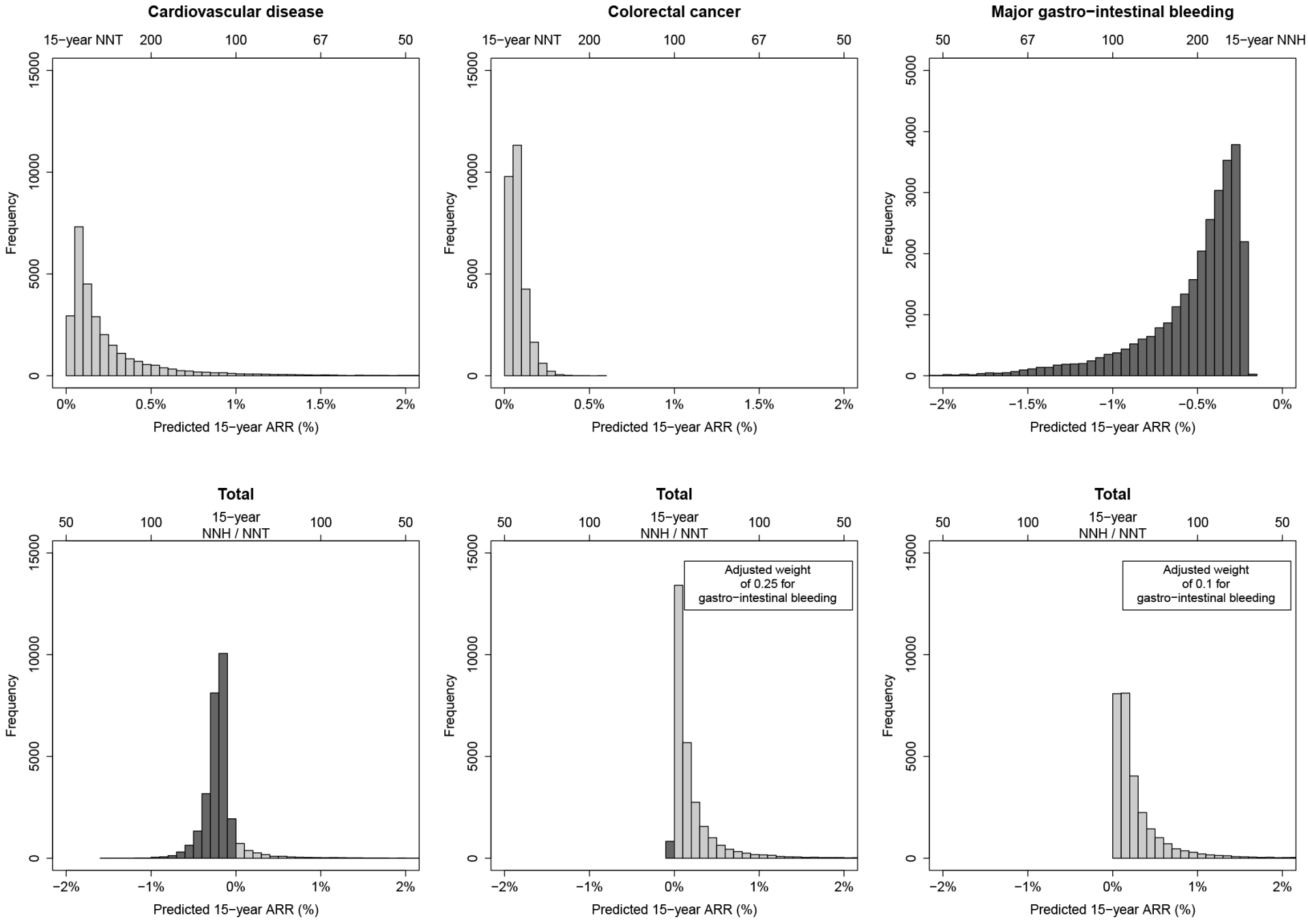
B = 0.05519 * age (years) + 0.18649 [if ever smoker] + 0.03746 * body mass index (kg/m^2) + 0.04004 * height (inches) – 0.27782 [if diabetic] + 0.15837 * no. of alcoholic drinks per day + 0.63234 [if peri- / postmenopausal] – 0.30225 [if ever used hormone replacement therapy] + 0.14242 [if family history of colorectal cancer] – 0.14411 [if using aspirin]

Model for prediction of 15-year major gastro-intestinal bleeding risk
(1 - exp(- (0.01238 * exp(D – 4.70541)))) * 100%, where

D = 0.06713 * age (years) + 0.31456 [if current smoker] + 0.03054 * body mass index (kg/m^2) + 0.32720 [if diabetic] + 0.01474 * no. of alcoholic drinks per day + 0.16382 [if history of dyspepsia] + 0.37788 [if using aspirin]



Appendix 3B (2)| Sensitivity analysis – Effect of baseline risk and age on predicted 15-year absolute risk reduction using models for prediction of treatment effect of aspirin on major cardiovascular events, colorectal cancer and major gastro-intestinal bleeding, while assuming no effect of aspirin on non-colorectal cancer. ARR: absolute risk reduction. Absolute risk reductions in plot for age apply to an average participant of the Women's Health Study (see page 3).



Appendix 3B (3)| Sensitivity analysis - Distribution of predicted 15-year absolute risk reduction with aspirin treatment in participants of the Women's Health Study assuming no effect of aspirin on non-colorectal cancer. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.