

Appendix 3

Sensitivity analyses

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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 ARR 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 gastrointestinal 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.

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

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

Model for prediction of 15-year colorectal cancer risk

$(1 - \exp(- (0.00674 * \exp(B - 6.96952)))) * 100\%$, where

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

Model for prediction of 15-year non-colorectal cancer risk

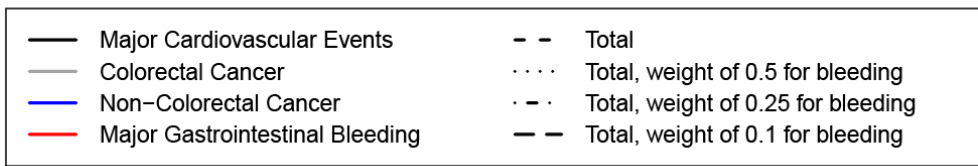
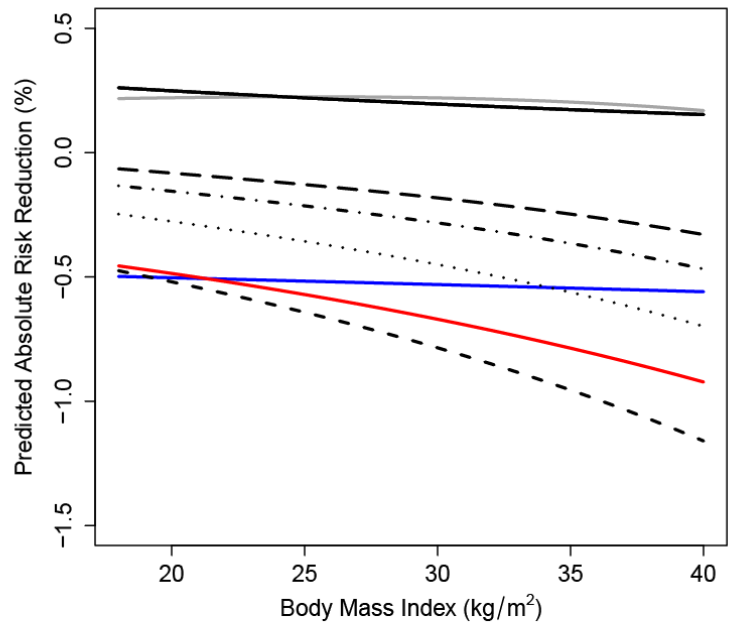
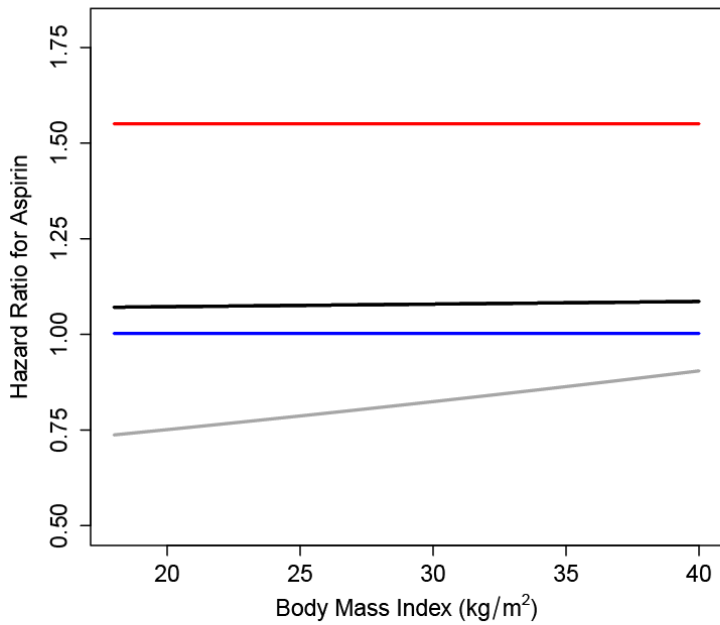
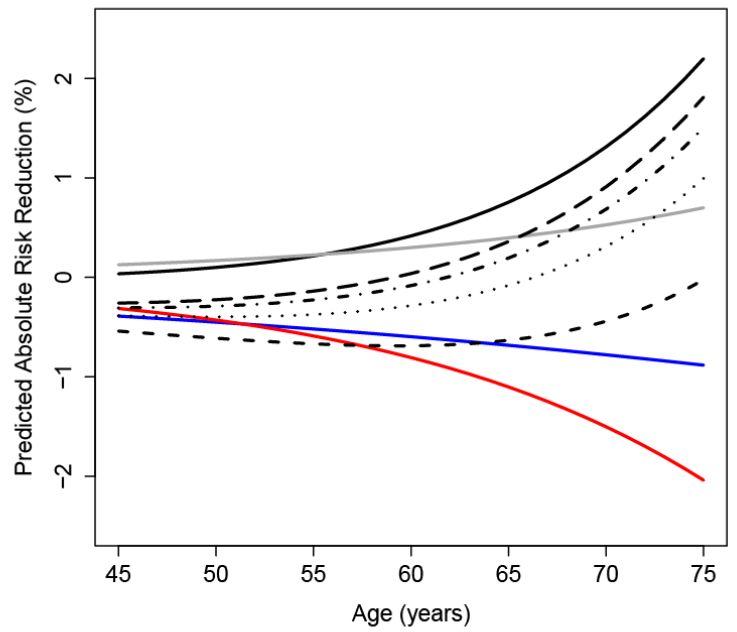
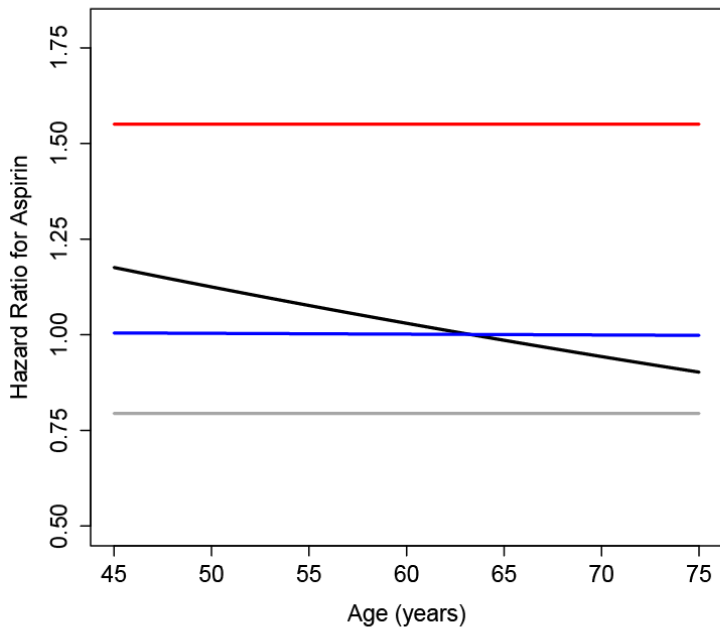
$(1 - \exp(- (0.0677 * \exp(C - 3.46478)))) * 100\%$, where

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

Model for prediction of 15-year major gastro-intestinal bleeding risk

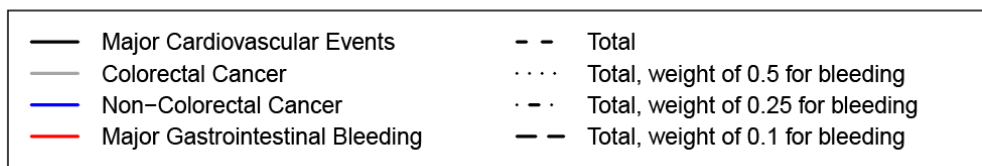
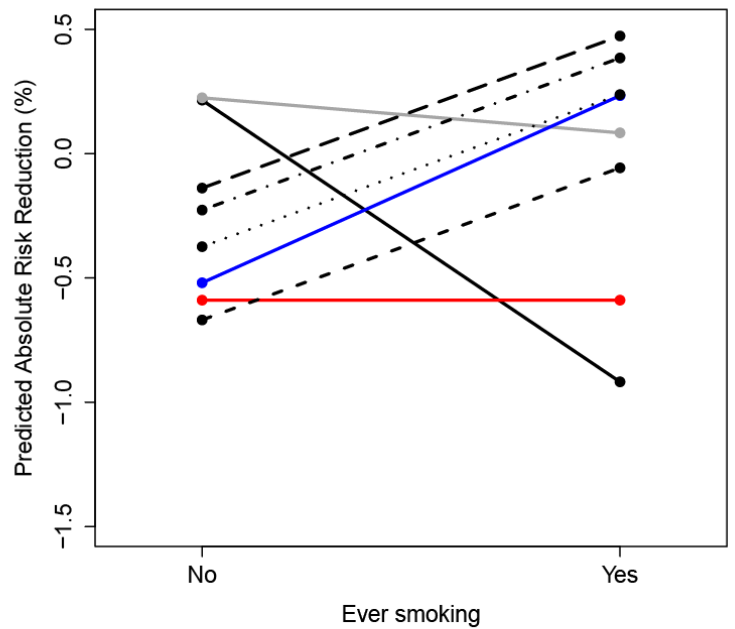
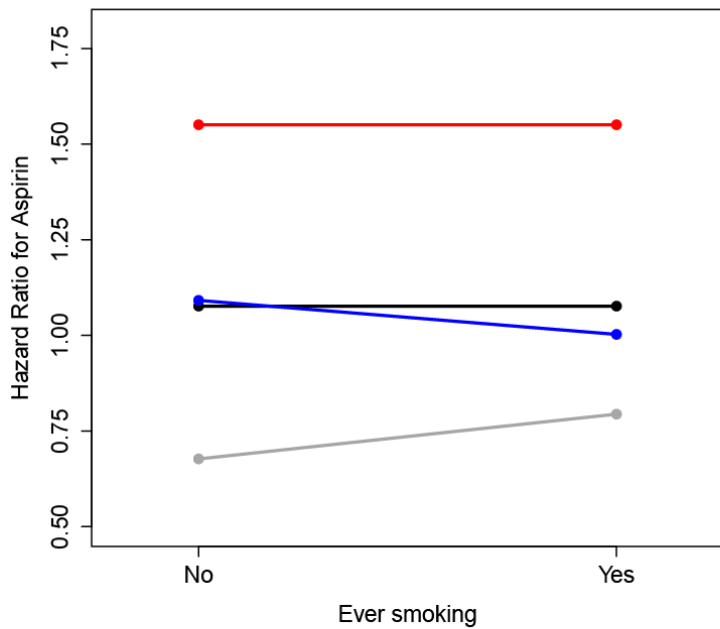
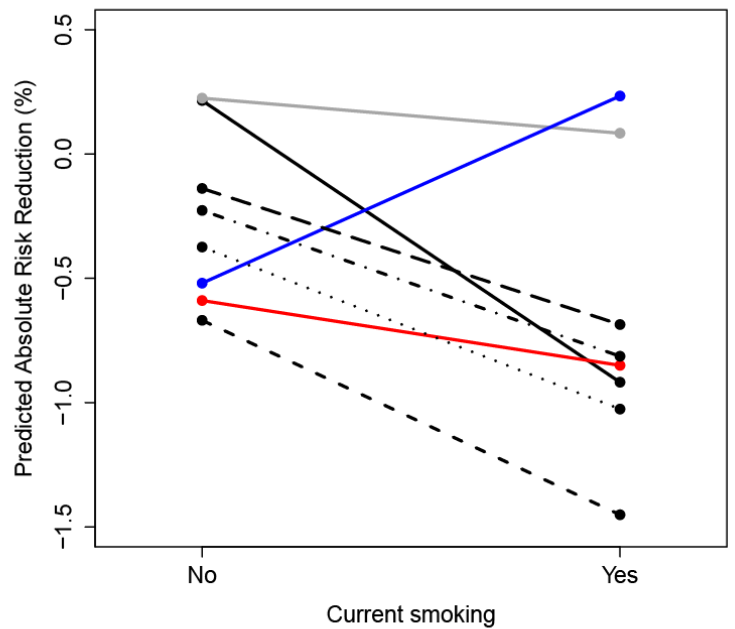
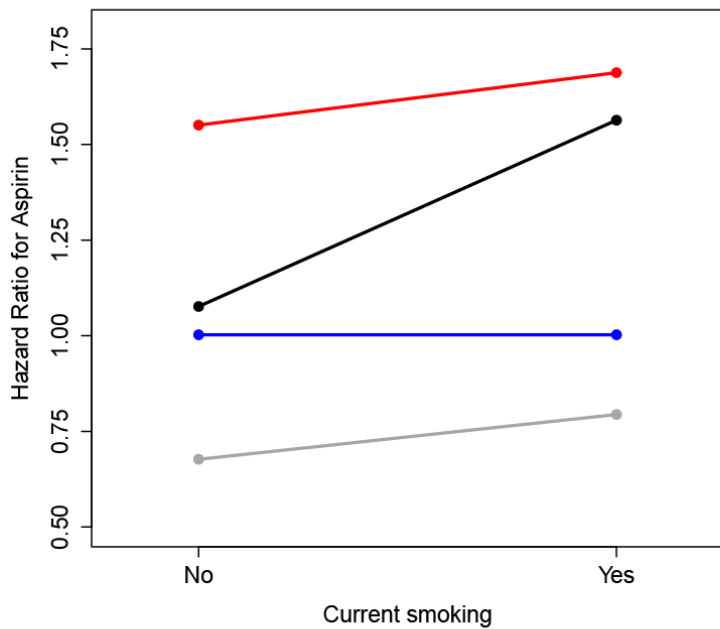
$(1 - \exp(- (0.01094 * \exp(D - 4.38127)))) * 100\%$, where

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



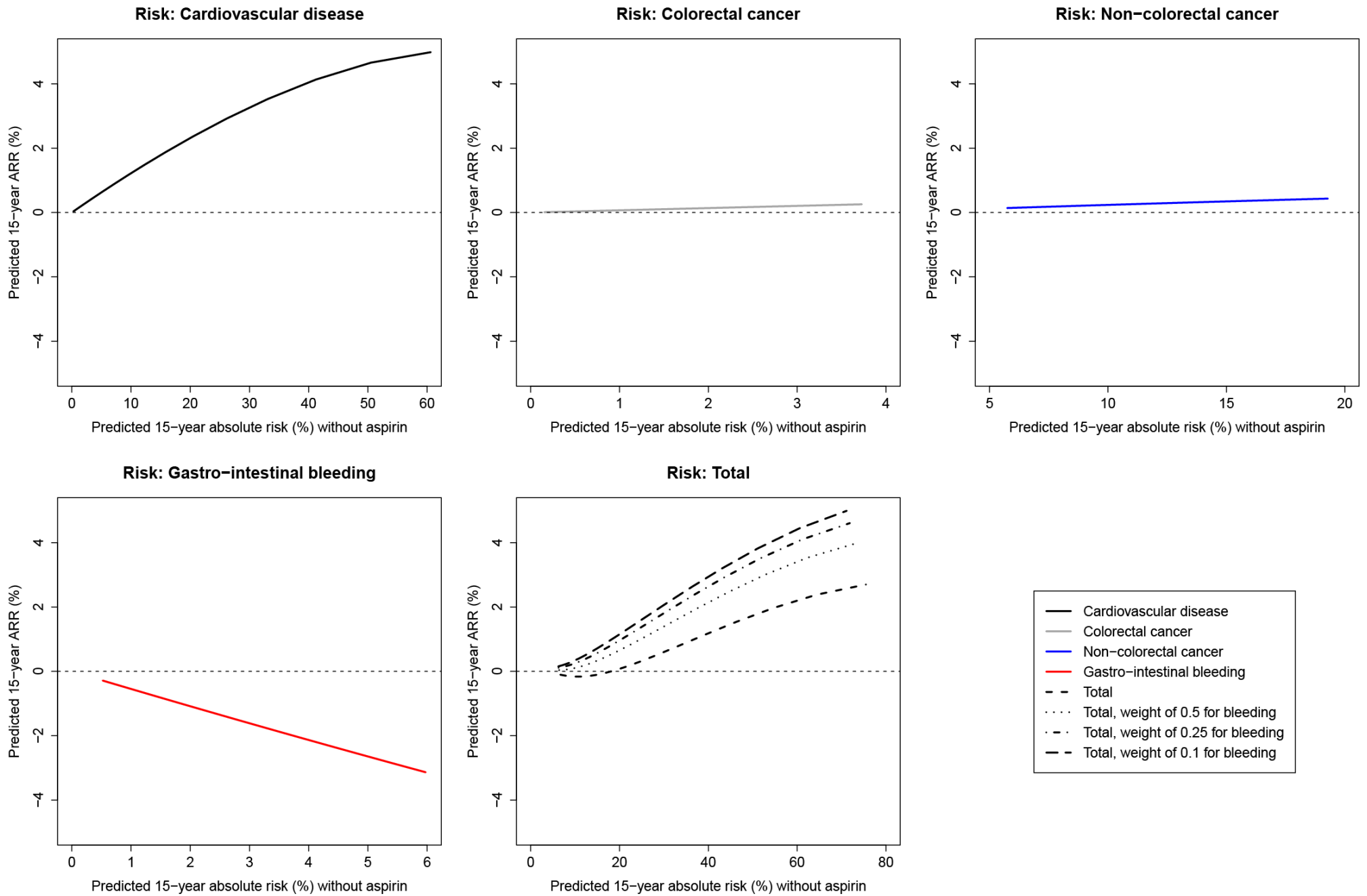
Appendix 3A (2) | Sensitivity analysis - Effect of treatment interactions with age and body mass index on hazard ratio's and predicted 15-year absolute risk reductions for aspirin.

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).

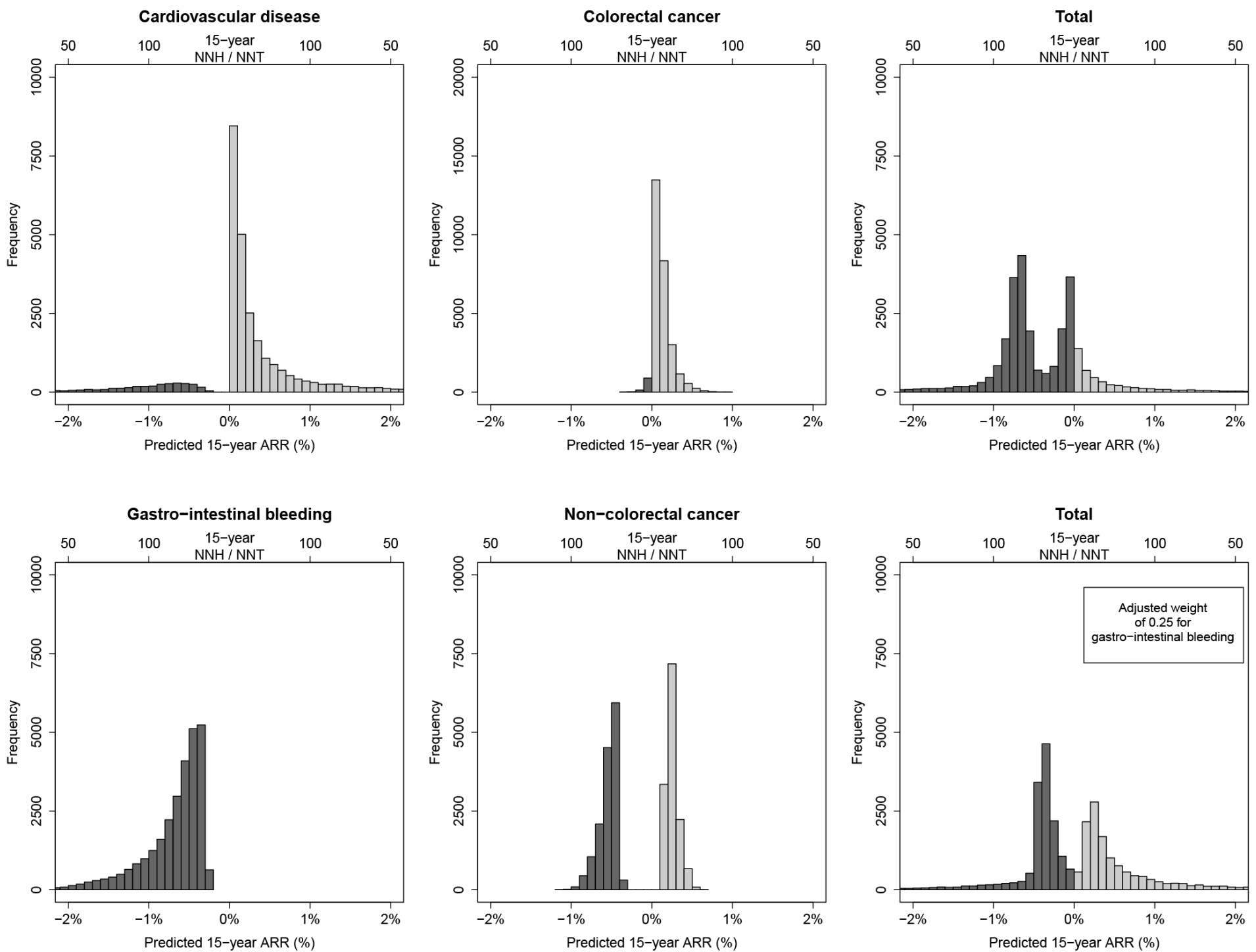


Appendix 3A (2) | Sensitivity analysis - Effect of treatment interactions with smoking status on hazard ratio's and predicted 15-year absolute risk reductions for aspirin.

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

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

Model for prediction of 15-year colorectal cancer risk

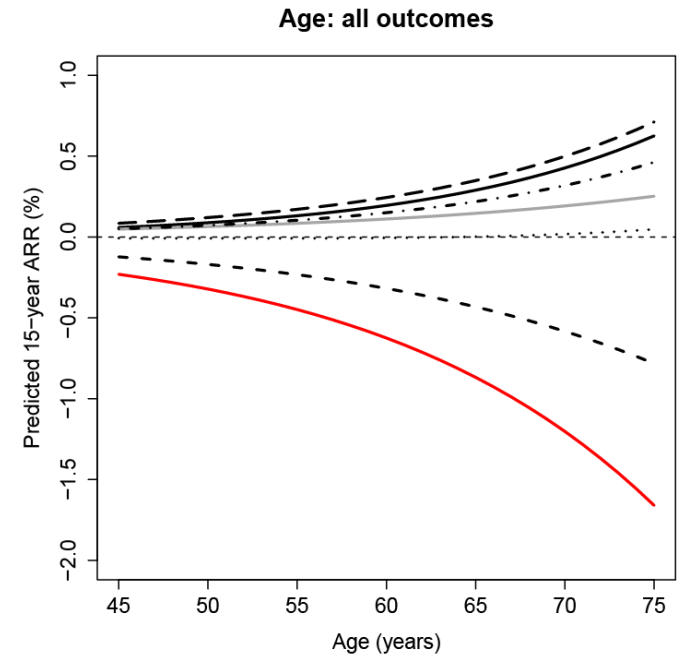
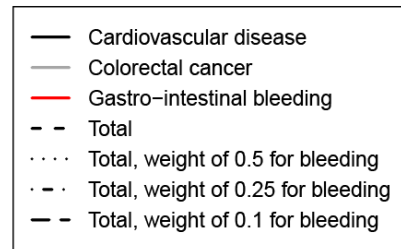
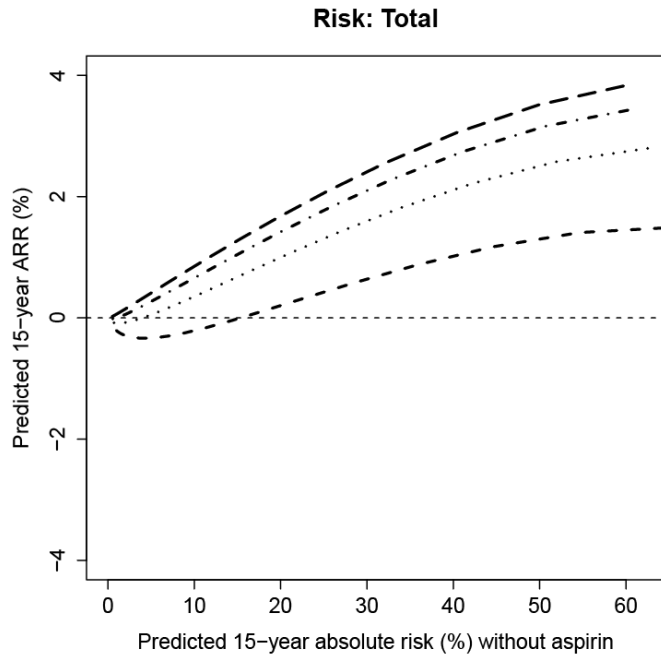
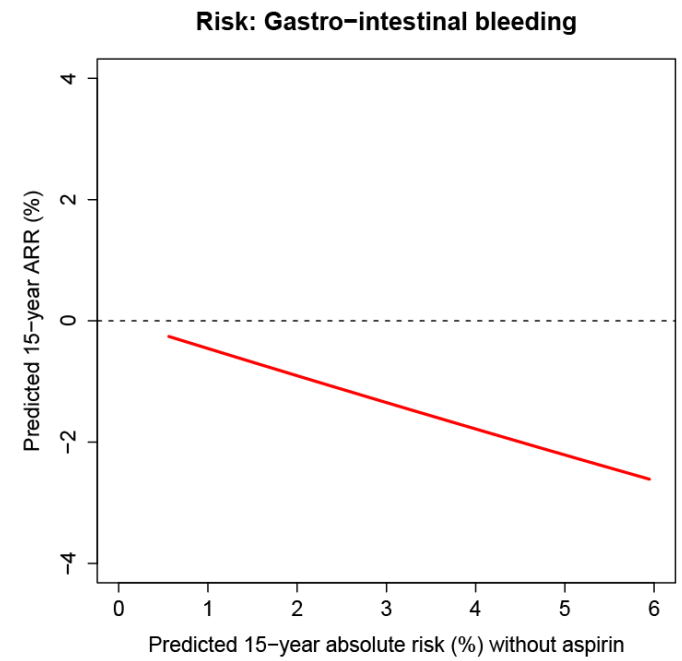
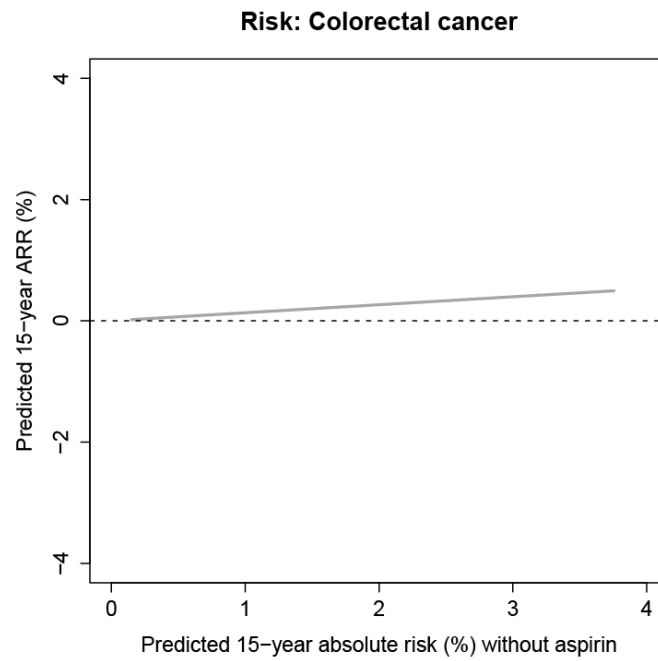
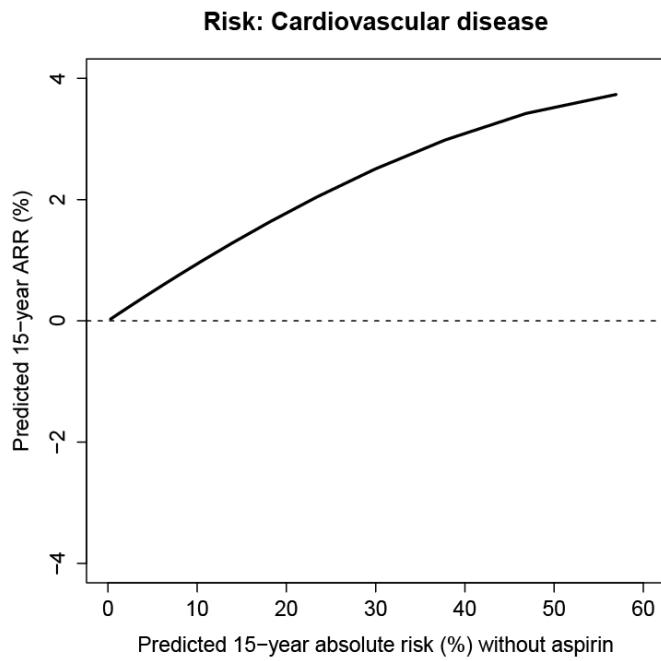
$(1 - \exp(- (0.00454 * \exp(B - 6.95442)))) * 100\%$, where

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

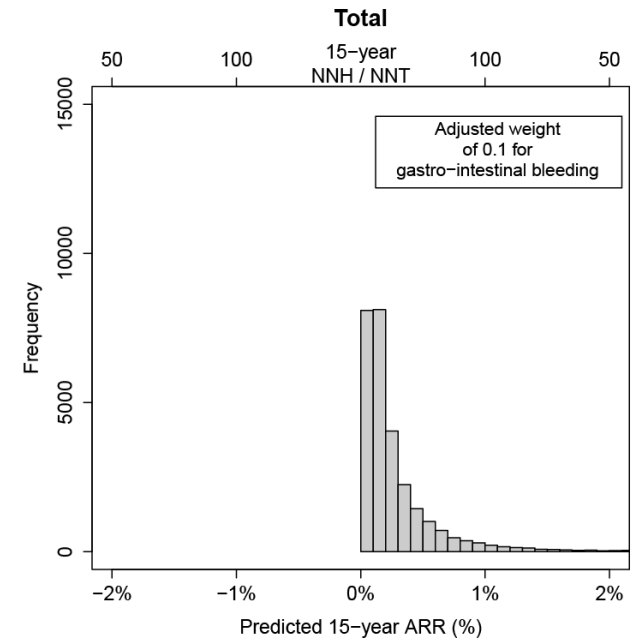
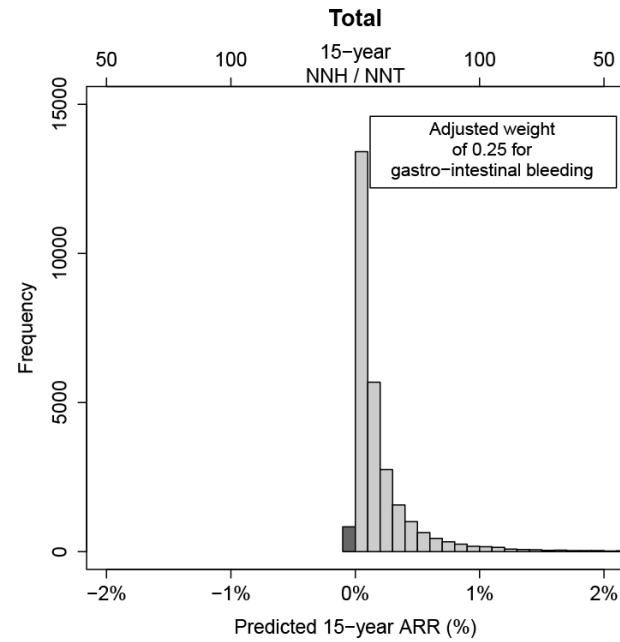
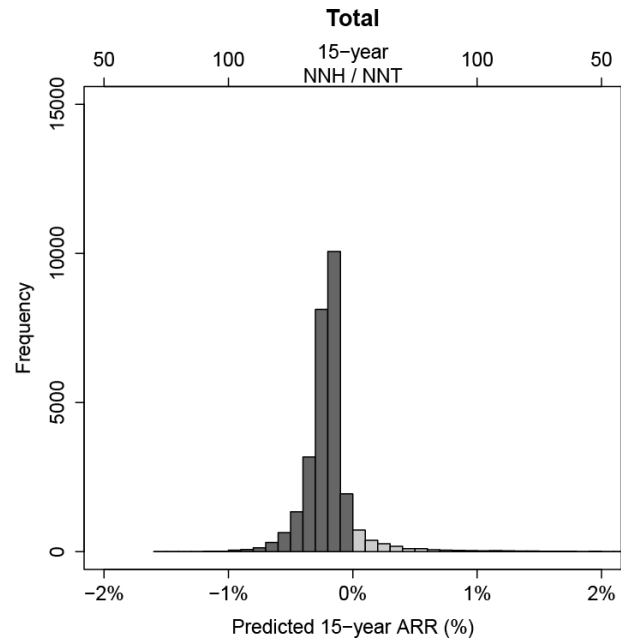
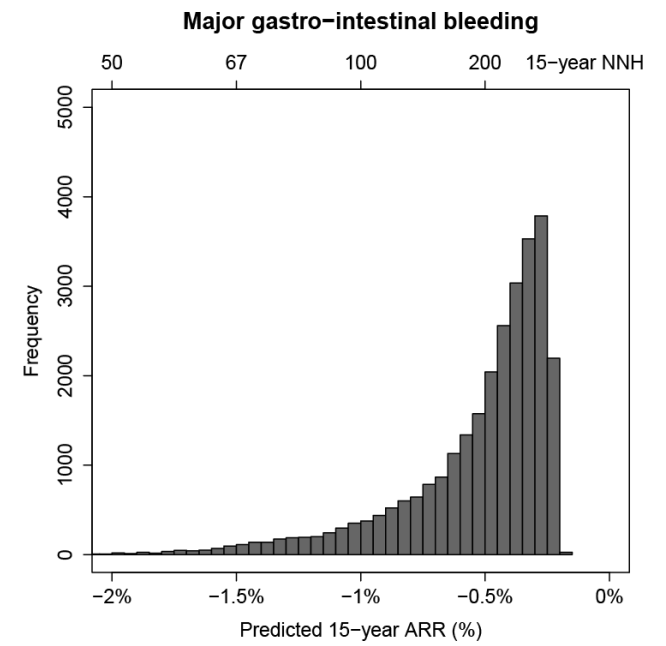
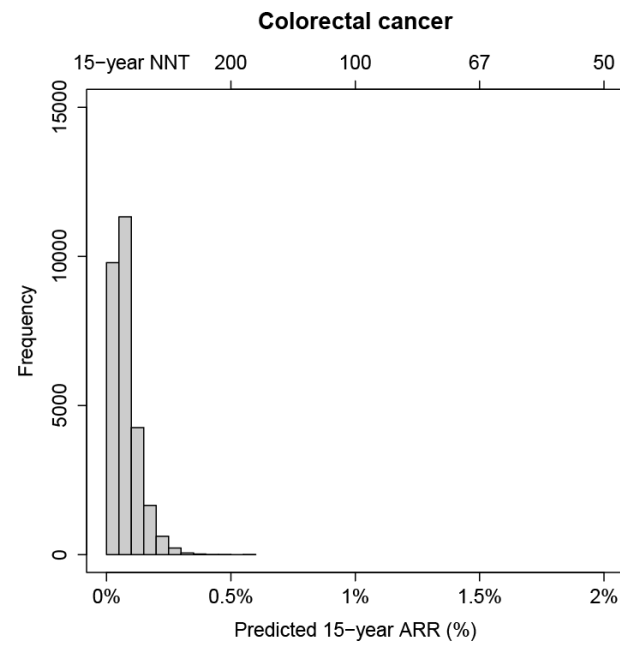
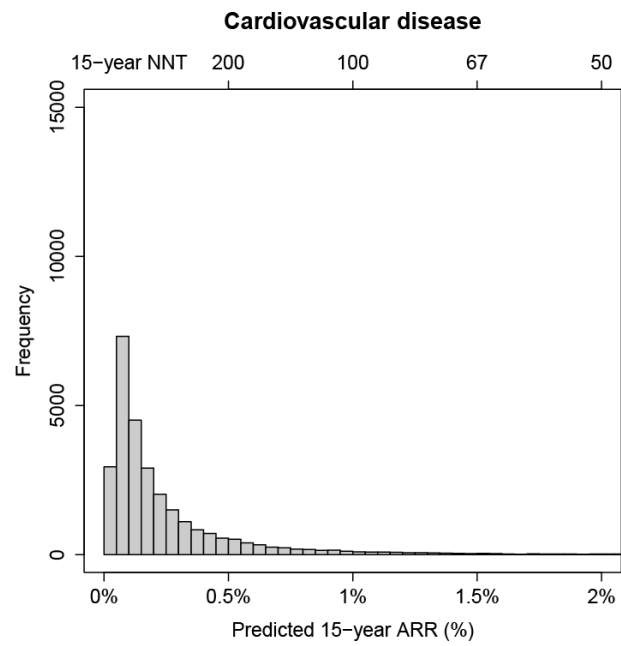
Model for prediction of 15-year major gastro-intestinal bleeding risk

$(1 - \exp(- (0.01238 * \exp(D - 4.70541)))) * 100\%$, where

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



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.