Estimates of benefits and harms of prophylactic use of aspirin in the general population.

J. Cuzick, M. A. Thorat, C. Bosetti, P. H. Brown, J. Burn, N. R. Cook, L. G. Ford, E. J. Jacobs, J. A. Jankowski, C. La Vecchia, M. Law, F. Meyskens, P. M. Rothwell, H. J. Senn, A. Umar

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Supplementary material:

Section A:

Supplementary tables

Section B:

Supplementary text

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Section A:

Sensitivity analyses: The results of benefit-harm analyses under different assumptions are presented.

Overall benefits and harms of aspirin prophylaxis in the general population assessed with 5 years of aspirin use

Tables 4 and 5 in the main paper display benefits and harms associated with 10 years of aspirin use. Here we show the benefits and harms associated with **5 years** of aspirin use. The incidence of major events (cancer, myocardial infarction, stroke, major bleeding) and mortality are summarized in Supplementary Tables W1 and W2, respectively. We also show benefits and harms associated with 10 years of aspirin use if the effect of aspirin is restricted to only three gastrointestinal cancers (colorectal, oesophageal and gastric cancers) in Supplementary Tables W3 and W4.

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Supplementary Table W1: Benefits and harms of 5 years of aspirin use on the incidence of major events by age and sex.

Baseline probabilities of an event and aspirin-related reductions (per 100 individuals in 10 years) using best (and conservative)estimates for prophylactic use of aspirin for 5 years on the incidence of major events viz. cancer, myocardial infarction, stroke, and major bleeding according to sex and age at starting use. All estimates are adjusted for intercurrent mortality.

Effects on cardiovascular and bleeding events are assumed to occur only during active treatment (5 years) and those for cancer do not start until after 3 years of use but persist for an additional 5 years after treatment completion. Baseline rates are for the entire 10 year period. Figures in parentheses are conservative estimates.

Age at starting		50 years		55 years		60 years		65 years	
Incidence		Baseline	Reduction	Baseline	Reduction	Baseline	Reduction	Baseline	Reduction
Cancer	Men	4.86	0.37 (0.26)	8.28	0.69 (0.48)	12.77	1.11 (0.77)	17.11	1.42 (0.99)
	Women	6.08	0.37 (0.23)	8.02	0.51 (0.33)	10.25	0.70 (0.46)	11.95	0.81 (0.56)
MI	Men	2.99	0.23	3.96	0.31	5.27	0.40	6.91	0.54
	Women	0.83	0.06	1.30	0.09	2.14	0.15	3.55	0.24
Stroke	Men	1.16	0.02	1.71	0.04	2.56	0.05	3.86	0.08
	Women	0.93	0.02	1.36	0.03	2.03	0.04	3.15	0.06
TOTAL	Men	9.01	**0.62 (0.51)**	13.95	**1.03 (0.82)**	20.59	**1.56 (1.23)**	27.87	**2.04 (1.61)**
	Women	7.84	**0.45 (0.31)**	10.68	**0.63 (0.45)**	14.43	**0.88 (0.65)**	18.64	**1.12 (0.86)**
Adverse events		Baseline	Excess	Baseline	Excess	Baseline	Excess	Baseline	Excess
Major extracranial bleeding	Men	0.60	0.12 (0.15)	0.93	0.21 (0.27)	1.24	0.30 (0.39)	1.54	0.39 (0.50)
	Women	0.30	0.06 (0.08)	0.47	0.10 (0.14)	0.63	0.15 (0.19)	0.80	0.20 (0.26)
Net Benefit	Men	9.61	**0.50 (0.36)**	14.88	**0.82 (0.55)**	21.83	**1.26 (0.84)**	29.41	**1.66 (1.11)**
	Women	8.14	**0.39 (0.23)**	11.15	**0.53 (0.31)**	15.06	**0.73 (0.45)**	19.44	**0.92 (0.60)**

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Supplementary Table W2: Benefits and harms of 5 years of aspirin use on mortality by age and sex.

Baseline 15-year event specific mortality probabilities and aspirin-related reductions (per 100 individuals) using best (and conservative)estimates for prophylactic use of aspirin for 5 years on mortality due to cancer, myocardial infarction, stroke, and aspirin-related adverse events (peptic ulcer and gastrointestinal bleeding) according to sex and age at starting use.

Effects on cardiovascular and bleeding events are assumed to occur only during active treatment (5 years) and those for cancer do not start until after 5 years of use but persist for an additional 10 years after treatment completion. Baseline rates are for the entire 15 year period. Figures in parentheses are conservative estimates.

Age at starting		**50 years**		**55 years**		**60 years**		**65 years**	
Mortality		Baseline	Reduction	Baseline	Reduction	Baseline	Reduction	Baseline	Reduction
Cancer	Men	4.08	0.50 (0.40)	6.93	0.82 (0.66)	10.63	1.20 (0.96)	14.97	1.61 (1.28)
	Women	3.62	0.28 (0.20)	5.48	0.43 (0.32)	7.81	0.62 (0.46)	10.60	0.86 (0.65)
MI	Men	2.78	0.02	4.69	0.04	7.45	0.08	10.85	0.13
	Women	0.84	0.01	1.70	0.01	3.28	0.03	5.72	(0.05
TOTAL	Men	6.87	**0.52 (0.43)**	11.62	**0.86 (0.70)**	18.09	**1.28 (1.04)**	25.82	**1.74 (1.41)**
	Women	4.45	**0.29 (0.21)**	7.17	**0.44 (0.33)**	11.10	**0.65 (0.49)**	16.31	**0.91 (0.70)**
Adverse events		Baseline	Excess	Baseline	Excess	Baseline	Excess	Baseline	Excess
Stroke	Men	0.54	0.02	0.94	0.04	1.73	0.06	3.10	0.11
	Women	0.38	0.02	0.66	0.03	1.37	0.04	2.82	0.08
GI bleeding	Men	0.12	0.02 (0.02)	0.16	0.02 (0.02)	0.32	0.04 (0.04)	0.54	0.05 (0.06)
	Women	0.07	0.01 (0.01)	0.11	0.01 (0.02)	0.21	0.02 (0.02)	0.37	0.03 (0.04)
Peptic Ulcer	Men	0.06	0.01 (0.01)	0.07	0.01 (0.01)	0.11	0.01 (0.02)	0.14	0.02 (0.02)
	Women	0.05	0.01 (0.01)	0.06	0.01 (0.01)	0.09	0.01 (0.01)	0.12	0.01 (0.02)
TOTAL	Men	0.71	**0.05 (0.06)**	1.17	**0.06 (0.07)**	2.16	**0.11 (0.12)**	3.77	**0.18 (0.19)**
	Women	0.50	**0.04 (0.04)**	0.82	**0.05 (0.05)**	1.67	**0.07 (0.07)**	3.31	**0.13 (0.14)**
All-cause Deaths	Men	10.34	**0.47 (0.37)**	16.23	**0.80 (0.63)**	25.20	**1.17 (0.92)**	38.92	**1.56 (1.22)**
	Women	6.82	**0.25 (0.17)**	10.52	**0.39 (0.27)**	16.77	**0.58 (0.41)**	27.46	**0.78 (0.56)**

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Supplementary Table W3: Benefits and harms of 10 years of aspirin use on the incidence of major events by age and sex (effects on only 3 GI cancers**).**

Baseline probabilities of an event and aspirin-related reductions (per 100 individuals in 15 years) using best (and conservative)estimates for prophylactic use of aspirin for 10 years on the incidence of major events viz. cancer, myocardial infarction, stroke, and major bleeding according to sex and age at starting use. All estimates are adjusted for intercurrent mortality.

Effects on cardiovascular and bleeding events are assumed to occur only during active treatment (10 years) and those for cancer do not start until after 3 years of use but persist for an additional 5 years after treatment completion. The effect of aspirin is restricted to only three gastrointestinal cancers (colorectal, oesophageal and gastric cancers). Baseline rates are for the entire 15 year period. Figures in parentheses are conservative estimates.

Age at starting		**50 years**		**55 years**		**60 years**		**65 years**	
Incidence		Baseline	Reduction	Baseline	Reduction	Baseline	Reduction	Baseline	Reduction
Cancer	Men	9.70	0.63 (0.53)	15.20	1.02 (0.87)	20.75	1.39 (1.18)	25.39	1.69 (1.44)
	Women	10.41	0.36 (0.31)	13.19	0.56 (0.47)	15.78	0.77 (0.65)	18.08	0.99 (0.84)
MI	Men	5.13	0.52	6.75	0.68	8.72	0.89	10.92	1.15
	Women	1.62	0.15	2.59	0.23	4.22	0.37	6.69	0.61
Stroke	Men	2.14	0.06	3.16	0.08	4.66	0.12	6.66	0.18
	Women	1.71	0.05	2.54	0.07	3.84	0.10	5.75	0.15
TOTAL	Men	16.97	**1.21 (1.11)**	25.11	**1.79 (1.63)**	34.13	**2.41 (2.20)**	42.97	**3.03 (2.78)**
	Women	13.74	**0.56 (0.50)**	18.32	**0.85 (0.77)**	23.83	**1.24 (1.13)**	30.53	**1.75 (1.60)**
Adverse events		Baseline	Excess	Baseline	Excess	Baseline	Excess	Baseline	Excess
Major extra-cranial bleeding	Men	1.12	0.32 (0.42)	1.58	0.49 (0.64)	2.00	0.66 (0.85)	2.37	0.81 (1.05)
	Women	0.57	0.16 (0.21)	0.81	0.25 (0.32)	1.05	0.34 (0.44)	1.30	0.43 (0.55)
Net Benefit	Men	18.09	**0.88 (0.70)**	26.70	**1.29 (0.99)**	36.13	**1.75 (1.35)**	45.34	**2.22 (1.72)**
	Women	14.31	**0.40 (0.29)**	19.13	**0.60 (0.45)**	24.88	**0.90 (0.69)**	31.83	**1.32 (1.05)**

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Supplementary Table W4: Benefits and harms of 10 years of aspirin use on mortality by age and sex (effects on only 3 GI cancers**).**

Baseline 20-year event specific mortality probabilities and aspirin-related reductions (per 100 individuals) using best (and conservative)estimates for prophylactic use of aspirin for 10 years on mortality due to cancer, myocardial infarction, stroke, and aspirin-related adverse events (peptic ulcer and gastrointestinal bleeding) according to sex and age at starting use.

Effects on cardiovascular and bleeding events are assumed to occur only during active treatment (10 years) and those for cancer do not start until after 5 years of use but persist for an additional 10 years after treatment completion. The effect of aspirin is restricted to only three gastrointestinal cancers (colorectal, oesophageal and gastric cancers). Baseline rates are for the entire 20 year period. Figures in parentheses are conservative estimates.

Age at starting		**50 years**		**55 years**		**60 years**		**65 years**	
Mortality		Baseline	Reduction	Baseline	Reduction	Baseline	Reduction	Baseline	Reduction
Cancer	Men	7.45	0.64 (0.57)	11.59	0.92 (0.81)	16.40	1.23 (1.08)	20.53	1.43 (1.25)
	Women	6.12	0.29 (0.26)	8.80	0.44 (0.39)	12.04	0.64 (0.56)	15.26	0.87 (0.76)
MI	Men	5.08	0.07	8.05	0.12	11.80	0.20	15.13	0.31
	Women	1.80	0.02	3.44	0.04	6.02	0.08	9.33	0.14
TOTAL	Men	12.53	**0.71 (0.63)**	19.64	**1.04 (0.93)**	28.19	**1.43 (1.28)**	35.66	**1.74 (1.57)**
	Women	7.92	**0.31 (0.28)**	12.24	**0.48 (0.43)**	18.06	**0.71 (0.64)**	24.60	**1.01 (0.91)**
Adverse events		Baseline	Excess	Baseline	Excess	Baseline	Excess	Baseline	Excess
Stroke	Men	1.03	0.06	1.85	0.09	3.21	0.17	4.83	0.32
	Women	0.74	0.04	1.47	0.06	2.90	0.11	5.12	0.26
GI bleeding	Men	0.19	0.04 (0.04)	0.34	0.05 (0.06)	0.57	0.08 (0.09)	0.74	0.17 (0.19)
	Women	0.12	0.02 (0.03)	0.22	0.03 (0.04)	0.39	0.05 (0.06)	0.59	0.11 (0.13)
Peptic Ulcer	Men	0.08	0.02 (0.02)	0.12	0.03 (0.03)	0.15	0.03 (0.04)	0.17	0.05 (0.06)
	Women	0.07	0.02 (0.02)	0.10	0.02 (0.02)	0.13	0.03 (0.03)	0.16	0.04 (0.05)
TOTAL	Men	1.29	**0.11 (0.12)**	2.31	**0.17 (0.18)**	3.93	**0.28 (0.30)**	5.73	**0.54 (0.58)**
	Women	0.93	**0.09 (0.09)**	1.79	**0.11 (0.12)**	3.42	**0.19 (0.21)**	5.86	**0.41 (0.44)**
All-cause Deaths	Men	18.02	**0.59 (0.51)**	27.67	**0.87 (0.75)**	41.99	**1.15 (0.98)**	58.74	**1.20 (0.99)**
	Women	11.82	**0.23 (0.18)**	18.55	**0.37 (0.30)**	29.86	**0.52 (0.43)**	47.45	**0.60 (0.47)**

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Section B:

METHODS:

Measurement of harmful effects of aspirin

Systematic MEDLINE searches were carried out to determine i) magnitude of increase in harms caused by aspirin ii) age and sex-specific baseline rates of gastrointestinal bleeding, peptic ulcer and major extracranial bleeding (Table 2 in the main text) iii) and the proportion of UGIC attributable to *H. pylori* infection in the UK general population. The estimates of mortality due to peptic ulcer and gastrointestinal bleeding were based on applying age-specific case-fatality rates (5% below and 10% above 70 years of age) to the respective incidence rates. Case-fatality rates were also derived from several studies [s1-7] identified through a systematic MEDLINE search.

Derivation of effect sizes (Table 3 in the main text) used for modelling

Effect sizes for cardiovascular disease:

All effect sizes used are directly taken from ATT Collaborators' review [s8].

Effect sizes for bleeding and ulcer harms:

Effect sizes derived as reported elsewhere [s9].

Effect sizes for cancer: Based on data presented in Table 1 (main text)

General rules:

- Data from case-control studies are based on a very large number of cancer incidence events, and these are generally consistent with data from RCTs [s10]. Therefore, derivation of effect sizes for cancer incidence is based on data from RCTs, case-control studies and cohort studies.
- On the other hand, data from case-control studies for cancer mortality events are sparse Therefore, derivation of effect sizes for cancer mortality is based on data from RCTs and cohort studies.
- All effect sizes are assumed in steps of 5%.
- Estimates for >5 years of aspirin use are considered where available
- Effect sizes are based on a non-weighted average of estimates from different study types.*
- Non-weighted average thus obtained is rounded to the closest 5% step on the side of unity. For example, non-weighted average estimates of 0.62 and 0.88 yield best estimate RRs of 0.65 and 0.90 respectively.

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- Conservative estimates assume a 5% smaller effect than best estimates. For example, if best estimate is 0.75, conservative estimate is taken as 0.80.

* In case of colorectal cancer, substantial heterogeneity in estimates exists across different study types, non-weighted average of estimates from consistent study types (i.e. case-control studies and RCTs) is taken.

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FINDINGS:

Bleeding and other side effects

Without a doubt increased bleeding is the most important side effect of aspirin [s9]. Haemorrhagic stroke, although rare, is the most serious and potentially fatal side effect. Estimates suggest a relative increase of 32-36% in haemorrhagic strokes in aspirin users from a baseline rate of 0.03%/year [s8, 11-14].

Much commoner are the extracranial (predominantly gastro-intestinal) bleeds, where the risk for major events is increased by about 30-70% from an overall baseline risk of 0.7 per 1000 per year [s8, 11, 12, 14-16] with low or standard-dose aspirin treatment [s9]. Absolute risks differ substantially across the population (Table 2 in the main text). Aspirin-related gastro-intestinal bleeding is frequently a result of either aspirin-induced acute erosive gastritis or haemorrhagic complication of peptic ulcer. Different studies [s8, 17-20] report different baseline major bleeding rates due to differences in the definitions and populations. We use rates estimated from ATT data and the basis for this is fully discussed elsewhere [s9]. The baseline risk of uncomplicated peptic ulcer in the general population increases from 0.5 per 1000 per year in women and 0.6 per 1000 per year in men aged 50-54 years to 1.0 and 1.2, respectively per 1000 per year at age 65-69 years [s21]. However, these events may be under-reported as higher rates were seen in some trials [s22, 23]. RCTs report a 30-60% increase in peptic ulcers associated with aspirin use [s22-24]. The incidence of peptic ulcer in the developed world is declining [s21, 25], perhaps due to the decline in prevalence of *H. pylori* infection [s26, 27] and the increasing use of proton pump inhibitors for treating peptic ulceration [s21, 28]. Other frequent bleeding events like epistaxis and haematuria are rarely serious, but can limit population utilization and aspirin increases the risk of these by 5-15% [s22]. Overall, the rates of gastro-intestinal complications increase steeply beyond age 70y [s19, 29, 30] and fatality rates show a similar trend [s5], but the rates and fatality ratios are low below 70 years of age.

Aspirin use after cancer diagnosis, effect on metastasis and survival.

Aspirin appears to have an impact on mortality that exceeds its effect on incidence [s31]. Aspirin may reduce metastatic spread through its effect on platelets [s32, 33], but it may also act through other mechanisms [s34-37]. RCTs show larger effect sizes for cancer mortality reduction than those for cancer incidence reduction [s38]. RCTs have also shown a lower proportion of cancers with metastases at presentation in those taking aspirin and lower propensity to develop metastases in those who continue aspirin after cancer diagnosis [s39]. Observational studies in breast cancer [s40], and colorectal cancer [s41, 42] have shown similar observations of reduced metastasis and improved survival in patients taking or continuing aspirin after the diagnosis of cancer. Recent evidence from the Nurses' Health Study and the Health Professionals Follow-up Study suggests that *PIK3CA* mutation may be a predictive biomarker for aspirin efficacy in adjuvant treatment [s43]. Therapeutic use of aspirin in colorectal cancer is currently being investigated in the ASCOLT trial [s44] whereas the Big A trial [s45] will investigate aspirin as an adjuvant treatment in non-small cell lung cancer. Another trial (ADD-Aspirin) is being set up in the UK to investigate role of aspirin in adjuvant treatment of colorectal, gastro-oesophageal, breast and prostate cancers [s37].

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