Supplementary Appendix

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

Supplement to: McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018;379:1519-28. DOI: 10.1056/NEJMoa1803955

The ASPREE (ASPirin in Reducing events in the Elderly) trial

SUPPLEMENTARY APPENDIX

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SUPPLEMENTARY MATERIALS

ASPREE END POINT DEFINITIONS & ADJUDICATION CRITERIA

(ASPREE Protocol www.aspree.org)

ALL-CAUSE and CAUSE-SPECIFIC MORTALITY

Definitions and processes for death confirmation and cause of death

Confirmation of death - Reported deaths were considered to be confirmed upon verification with two independent sources (*e.g.* family or PCP report, or clinical record, or public death notice).

Cause of death - Cause of death was defined as the disease responsible for trajectory to death.

Source information from hospitals/medical centers, treating physicians, government bodies (e.g. Government registers) autopsy reports, death certificates, medical records, and information obtained from the next of kin or other family members where relevant were collected, sent to the ASPREE Data Management Center and presented to adjudicators of the Death EAC.

Adjudicators were blinded to participant identity and treatment arm. Adjudicators considered the progression of disease and disability over the course of the study and then assigned cause of death based on trajectory to death.

Adjudication of fatal and non-fatal secondary end points occurred independently by disease-specific EACs and results of these adjudications were available to those adjudicating cause of death. When relevant records could not be obtained, cases were assigned a cause of death based on NDI ICD-10 codes.

Time-to-event for death was taken as the date of death recorded on death certification. Each blinded case was sent to two adjudicators and if there was discordance in the outcome, the case was discussed at a meeting and the outcome agreed by both adjudicators.

CARDIOVASCULAR DISEASE

Definitions and process for adjudication of fatal and non-fatal cardiovascular events

Cardiovascular events included a) Coronary heart disease death, b) non-fatal myocardial infarction (MI), c) fatal and non-fatal stroke, d) non-coronary cardiac or vascular death and e) hospitalization for heart failure.

Source information from hospitals/medical centers, treating physicians, death certificates, medical records, hospital information obtained from the next of kin or other family members where relevant was collected, sent to the ASPREE Data Management Center and presented to adjudicators of the Death, Cardiac or Stroke EACs as appropriate. Adjudicators were blinded to participant identity and treatment arm.

a) Coronary heart disease death was defined as death from MI, sudden cardiac death, rapid cardiac death (death after possible MI), cardiac failure death (with coronary cause) and other coronary death.

- MI - Autopsy or death certificate diagnosis, with definitive or suspected diagnosis of MI within 4 weeks of death.
- Sudden cardiac death - Death occurring within one hour of the onset of new cardiac symptoms (ischemic chest symptoms or sudden collapse) or unwitnessed death after last being seen without new cardiac symptoms, and in each case, without any coronary disease (clinically or at autopsy) that could have been rapidly fatal.
- Rapid cardiac death (death after possible MI) - Death within 1-24 hours of the onset of severe cardiac symptoms unrelated to other known causes. Death in hospital with possible MI (i.e. participants who have had typical ischemic pain and whose ECG and enzyme results fulfil the criteria for definitive MI and in whom there was no good evidence for another diagnosis for the event).
- Cardiac failure death - Death due to heart failure (prior NYHA Class III-IV dyspnea), without any defined non-coronary cause.
- Other coronary death - Any death where the underlying cause was certified as coronary (and where there is no evidence of non-coronary cause of death, clinically or at autopsy).

The Death EAC was responsible for determining if events met this definition. Time-to-event for coronary heart disease death was taken as the date of death recorded on death certification.

b) Non-fatal MI was defined according to the American College of Cardiology & European Society of Cardiology definition [1] and classified as either acute evolving or recent MI, or established MI.

Criteria for acute, evolving or recent MI include either one of the following:

1. Typical rise in troponin or CK-MB as biochemical markers of myocardial necrosis with at least one of the following:
   - ischemic symptoms;
   - development of pathologic Q waves on the ECG;
   - ECG changes indicative of ischemia (ST segment elevation or depression);
   - coronary artery intervention (e.g. coronary angioplasty).

2. Pathologic findings of an acute MI. Criteria for established MI include either one of the following:
   - Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
   - Pathologic findings of a healed or healing MI.

The Cardiac EAC was responsible for determining if events met this definition. Time-to-event for non-fatal MI was taken as the date of troponin rise for acute, evolving or recent MI, and the date of ECG or pathology report for established MI.

c) Fatal and non-fatal stroke were defined according to the World Health Organization (WHO) definition as rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin [2]. This definition excluded cases of primary cerebral tumor, cerebral metastasis, subdural hematoma, post seizure palsy, brain trauma, and transient ischemic attack.
Fatal stroke was defined as any death due to the rapid onset of a new neurological deficit attributed to obstruction or rupture in the intra-cranial or extra-cranial cerebral arterial system.
The Stroke EAC was responsible for determining if events met this definition. Time-to-event for stroke was taken as the date of first evidence of disturbance of cerebral function.

Confirmed strokes were further classified as:

- Ischemic stroke (included in cardiovascular end point)
- Ischemic stroke with hemorrhagic transformation (included in cardiovascular end point)
- Stroke type uncertain (included in cardiovascular end point)
- Hemorrhagic stroke (included in major hemorrhage end point)
- Sub-arachnoid hemorrhage stroke (included in major hemorrhage end point)

Ischemic stroke sub-classification - Cerebral infarction could be confirmed by autopsy. The TOAST classification for subtype of acute ischemic stroke was utilized, in which both clinical features and ancillary tests (laboratory, radiology, and ultrasonography) were used to categorize five subtypes [3]

1. large artery atherosclerosis (embolus/thrombosis);
2. cardio embolism (high risk/medium risk);
3. small-vessel occlusion (lacunae);
4. stroke of other determined etiology;
5. stroke of undetermined etiology:
    (a) two or more causes identified;
    (b) negative evaluation;
    (c) incomplete evaluation.

Distinction between ischemic and hemorrhagic stroke could be made only with appropriate imaging as outlined in the table below:

	CT	MRI
Ischemic stroke	An area of low attenuation or a normal appearance in the vascular territory that corresponded to the recent symptoms and signs	A critically relevant area of increased signal on diffusion weighted imaging, a slight hypointensity with or without mass effect on T1-weighted images, a bright area of hyper-intensity with or without mass effect on T2-weighted images, or evidence of recent infarction on diffusion weighted MRI
Hemorrhagic stroke	An area of hyperdensity within the brain parenchyma with or without extension into the ventricles or subarachnoid space or, for scans performed beyond 1 week, an area of attenuation with ring enhancement after injection of contrast	An area of hypointensity or isointensity on T1-weighted images or an area of marked hypointensity on gradient echo and T2-weighted images, or by autopsy demonstrating the origin of the hemorrhage as the cerebral parenchyma

NB: Rarer causes and sites of intracerebral hemorrhage such as underlying arteriovenous malformation and spinal cord hemorrhage were documented.

Hemorrhagic stroke sub-classification – Sub-classification was used for hemorrhagic strokes based on imaging information, as described in the table above. To complement the use of the TOAST classification for thrombo-embolic stroke, the extent of intracerebral hemorrhage was qualtified by assessing hemorrhage site and volume by CT or MRI. Volume was assessed by utilizing the ABC/2 formula with hemorrhage sites as lobar, basal ganglionic or brain stem. [4]

Sub-arachnoid hemorrhages (SAH) – These were reviewed by the Stroke EAC. SAH must have satisfied all the criteria above to be considered as stroke. SAH that did not meet the above criteria were adjudicated as 'Not stroke end point – intracranial bleed present but event did not meet the stroke criteria.' Events with this outcome were sent to the neurologist on the Clinically Significant Bleeding (CSB) EAC who determined whether the event met the CSB criteria.

d) Non-coronary cardiac or vascular death – Health or coronial records of death or sudden death attributable to cardiac-related or vascular-related origins that were not due to coronary or myocardial ischemic were provided to the Death E8AC for consideration. If considered appropriate, other EACs such as the Cardiac or Stroke EACs adjudicated the event. Such deaths may have included those attributed to AAA rupture, large vessel atherosclerosis, cardiomyopathy, cardiomegaly, myocarditis, peripheral vascular disease.

The Death EAC was responsible for determining if events met this definition. Time-to-event for non-coronary or vascular death was taken as the date of death recorded on death certification.

e) Hospitalization due to cardiac failure - Hospital discharge diagnosis of cardiac failure triggered an assessment by the Cardiac EAC. Hospitalization for heart failure was defined as an unplanned overnight stay, or longer, in a hospital environment (emergency room, observation unit or inpatient care) or similar facility. Heart failure was defined as a patient having typical symptoms (e.g., dyspnea, fatigue) that occurred at rest or on effort that was characterized by objective evidence of an underlying structural abnormality or cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood (particularly during exercise). The diagnosis of heart failure may have been further strengthened by a beneficial clinical response to treatment(s) directed towards amelioration of symptoms associated with this condition. Where possible, heart failure diagnosis was confirmed by demonstrated pulmonary congestion or edema on chest imaging. If chest imaging was not available, documented evidence of clinical signs of pulmonary oedema (e.g. rales > 1/3 up the lung fields thought to be of cardiac causes), pulmonary capillary wedge pressure >18 mmHg or B-type natriuretic peptide of >500pg/ml were utilised to confirm the diagnosis of heart failure.

The Cardiac EAC was responsible for determining if events met this definition. Time-to-event for hospitalization for heart failure was taken as the date of hospitalization. Each blinded case was sent to two adjudicators and if there was discordance in the outcome, the case was sent to a third adjudicator for a decision. Any case could be taken to a meeting of the EAC for discussion if an adjudicator needed to seek clarification in interpreting the notes or applying the decision rules.

CANCER – FATAL AND NON-FATAL

Definitions and processes for adjudication

Fatal and non-fatal cancer was defined as incident non-metastatic cancer (cancer type not present prior to randomization), or incident metastatic cancer. Incident metastatic cancer included: incident cancer that was metastatic at presentation, incident metastasis of a non-metastatic cancer present at baseline, or incident blood cancer.

Non-melantoma skin cancer was excluded from the fatal and non-fatal cancer end point, as was local recurrence of a previous cancer.

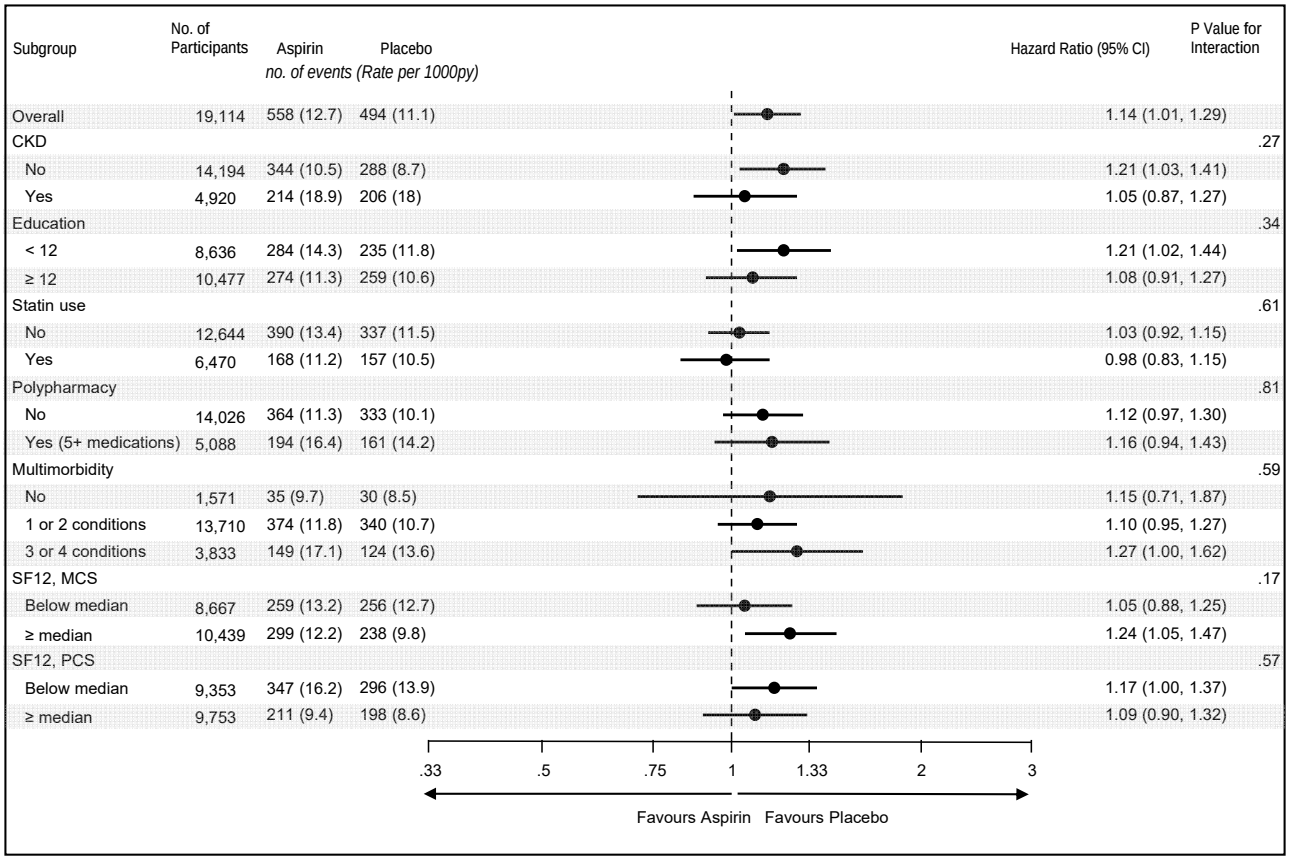
Specific decision rules developed by the Cancer EAC included:

- ASPREE cancers must be histopathologically confirmed, unless histology was not performed, in which case confirmation on imaging or through strong clinical evidence was accepted (e.g. currently receiving treatment for cancer).
- Where there was no evidence of metastatic disease patients were coded as not having metastatic disease.
- Presentation of local (local or regional) nodal disease was not considered metastatic disease, whilst distant nodal disease represented metastatic disease.
- Presentation of metastasis without a prior diagnosis of the primary cancer was considered metastatic on presentation and thus only one ASPREE cancer end point - 'Metastatic cancer end point'
- Presentation of metastasis within 3 months of the primary diagnosis was considered metastatic on presentation and thus only one ASPREE cancer end point - 'Metastatic cancer end point'.
- Presentation with metastasis greater than 3 months after the primary diagnosis was considered metastatic spread following an initial non-metastatic presentation. Consequently, the event was linked with two ASPREE end points, one non-metastatic (i.e. the initial presentation) and one metastatic. Cases of this nature were presented to the EAC in two parts, once for the initial presentation and once for the metastatic spread. The summary document alerted adjudicators as to the part being presented for adjudication.
- Exception rule: non-melanoma cancers of the skin were considered as a primary cancer if they were reported as either the primary or secondary cause of death.
- Exception rule for non-melanoma cancers of the skin that progressed to metastasis. All cases were considered as a metastatic cancer event.

Source information from clinical case notes and hospital medical records related to these events were collected, sent to the ASPREE Data Management Center and presented to adjudicators on the Cancer EAC. Adjudicators were blinded to participant identity and treatment arm. Each blinded case was sent to two adjudicators and if there was discordance in the outcome, the case was sent to a third adjudicator for a decision. Any case could be taken to a meeting of the EAC for discussion if an adjudicator needed to seek clarification in interpreting the notes or applying the decision rules.

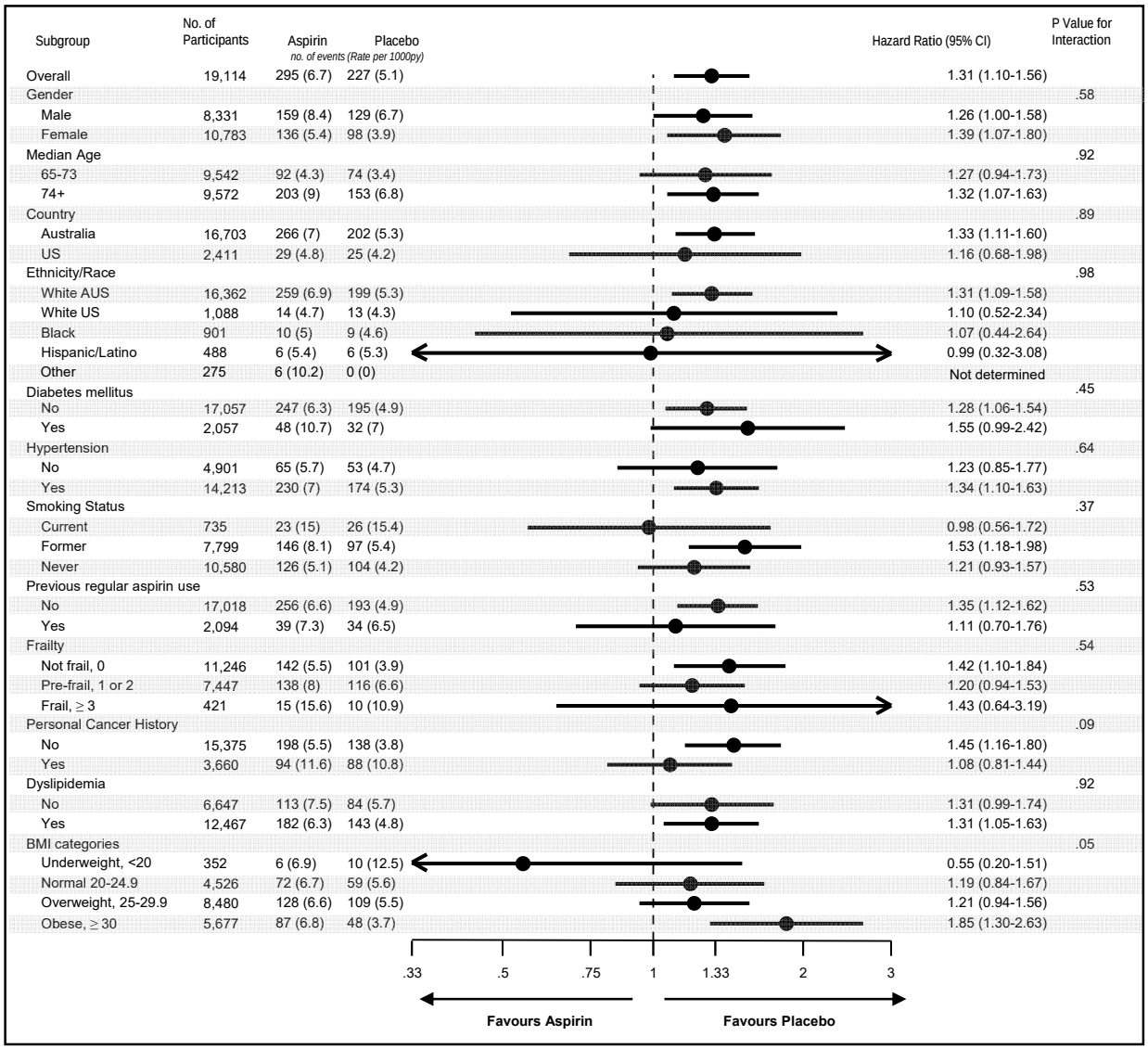
SUPPLEMENTARY FIGURES

Figure S1: Forest Plot for All-cause Mortality in Subgroups Not Prespecified



CKD (Chronic kidney disease) defined as eGFR < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3mg/mmol; Statin use included 483 individuals (247 aspirin and 236 placebo) on non-statin lipid lowering therapies; Multi-morbidity includes the following conditions: hypertension, diabetes, dyslipidemia and CKD; SF12 (Short-Form 12) is a quality of life questionnaire, MCS = mental component score, PCS = physical component score.

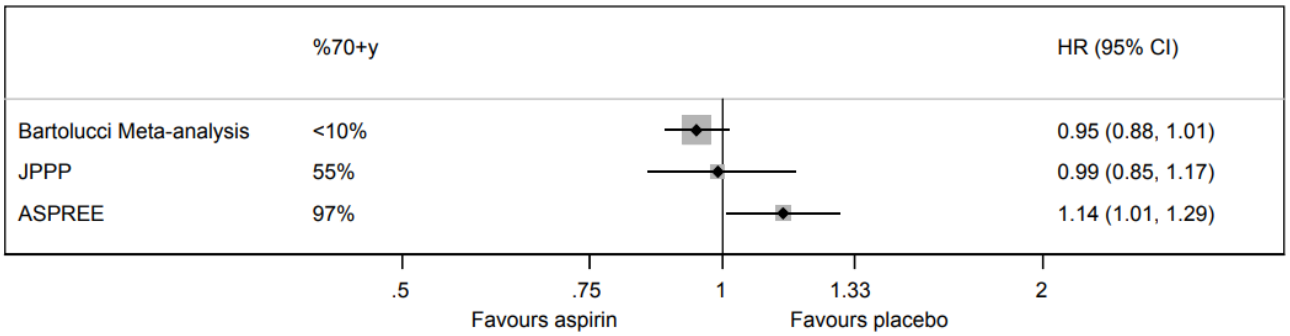
Figure S2: Forest Plot for Cancer-related Mortality in Prespecified Subgroups



Ethnicity/Race 'Other' is defined as any category with <200 participants overall, which includes Aboriginal/Torres Strait Islander (12), Native American (6), More than one race (64), Native Hawaiian / Pacific Islander (11) and those who were not Hispanic and who did not state their ethnicity/race (18); Diabetes mellitus is defined from self-report or fasting glucose ≥126mg/dL (≥7 mmol/L) or on treatment for diabetes; Hypertension is defined as 'on treatment' for high BP or BP > 140/90 mmHg at study entry; Dyslipidemia defined as those taking cholesterol-lowering medications or serum cholesterol ≥212 mg/dL (≥5 mmol/L; Australia) and ≥240 mg/dL (≥6.2 mmol/L; U.S.) or LDL>160 mg/dL (>4.1 mmol/L); Previous regular aspirin use was self-reported regular use of aspirin

immediately prior to first baseline visit with a one-month washout prior to randomization to study medication; ‘Pre-frail’ included anyone with 1 or 2 criteria and ‘Frail’ included anyone with 3 or more criteria of the adapted Fried frailty criteria, including body weight, strength, exhaustion, walking speed and physical activity.[5]

Figure S3: Forest Plot for All-cause Mortality in ASPREE Compared with Other Aspirin Prevention Trials



Meta-analysis from Bartolucci[6] with an additional study, the Japanese Primary Prevention Project (JPPP)[7] compared with ASPREE. The sizes of the symbols are proportional to the estimated numbers of subjects in the trials or meta-analysis.

SUPPLEMENTARY TABLES

Table S1: ASPREE Eligibility Criteria

Inclusion criteria
- able to give informed consent
- able to attend a study visit
- men and women
- aged 70 years and older (no upper age limit) except for U.S. blacks and Hispanics who were aged 65 years and older (no upper age limit)
Exclusion criteria
- a past history of cardiovascular or cerebrovascular event or established CVD, defined as myocardial infarction (MI), heart failure, angina pectoris, stroke, transient ischemic attack, >50% carotid stenosis or previous carotid endarterectomy or stenting, coronary artery angioplasty or stenting, coronary artery bypass grafting, abdominal aortic aneurysm
- a clinical diagnosis of atrial fibrillation
- a clinical diagnosis of dementia or score of <78 out of 100 on Modified Mini-Mental State (3MS) examination[8] administered by trained study staff
- physical disability as defined by severe difficulty or inability to perform independently any of the 6 Katz basic activities of daily living (ADLs) which include bathing, transferring from chair or bed, toileting, dressing, eating, walking across a room[9]
- a condition with a high current or recurrent risk of bleeding, anemia (hemoglobin <12 g/dl males, <11 g/dl females)
- a condition likely to cause death within 5 years (opinion of the general practitioner or primary care physician)
- current continuous use of other antiplatelet or anticoagulant medication
- current use of aspirin for secondary prevention
- uncontrolled high blood pressure (systolic BP ≥180 mmHg and/or diastolic BP ≥105 mmHg)
- unwilling to cease regular aspirin being taken for primary prevention
- pill taking compliance of <80% during a 4-week placebo run-in phase
- current participation in another clinical trial

Eligibility: Participants were generally healthy individuals aged 65 years and older (U.S. blacks and Hispanic) or 70 years and older (all other groups). The age differential was permitted to ensure that black and Hispanic populations could be represented in the trial, given evidence of higher burden of disease necessitating aspirin use. Interested potential community-dwelling participants were screened by phone for suitability and eligibility. After obtaining informed consent, study eligibility was determined at 'in person' study visits utilizing the inclusion/exclusion criteria shown above and previously described [10, 11].

Table S2: ASPREE health measures and definitions

Annual health measures
- demographics and lifestyle factors
- blood pressure, heart rate
- weight, waist circumference
- cardiovascular & renal biomarkers (fasting lipids, hemoglobin, blood glucose, creatinine, urinary albumin:creatinine ratio or ACR)
- depression screen (CES-D-10) [12]
- LIFE disability questionnaire [13] including the Katz basic Activities of Daily Living [9] (including walking across a room, bathing, dressing, transferring from a bed or chair, using the toilet, and eating); participants selected one of the following options for completing these tasks with 'no difficulty', 'a little difficulty' 'some difficulty', 'a lot of difficulty' or 'unable to perform independently'; and as a check, answered whether assistance from another person was required to complete.
- quality of life questionnaire (SF-12) including calculations of MCS (Mental Component Score) and PCS (Physical Component Score) [14]
- clinical events
6 month phone calls
- confirmation of living circumstances
- administration of the Katz basic Activities of Daily Living
- questions regarding daily study medication adherence
- clinical and adverse events reports
Biennial health measures
- neurocognitive assessments included Modified Mini-Mental State examination (3MS) [8], Hopkins Verbal Learning Test – Revised (HVLT-R) [15], Controlled Oral Word Association Test (COWAT) [16], Symbol Digit Modalities Test (SDMT) [17]
- physical function tests (3m gait speed [18], handgrip strength [19])

Baseline/final visit health measure
- height
Health definitions
- diabetes mellitus - self report of diabetes mellitus or fasting glucose ≥126 mg/dL (≥7 mmol/L) or on treatment for diabetes.
- hypertension - on treatment for high BP or BP > 140/90 mmHg at study entry
- dyslipidemia - taking cholesterol-lowering medications or serum cholesterol ≥212 mg/dL (≥5 mmol/L) (Australia) and ≥ 240 mg/dL (≥6.2 mmol/L; U.S.) or LDL>160 mg/dL (>4.1 mmol/L).
- CKD (Chronic kidney disease) - eGFR < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3 mg/mmol
- Smoking status – current smoker, former smoker or never smoked
- Ethnicity / race – all participants self-identified as Hispanic or not and then selected one category from the following: White/Caucasian, Black/African American, Aboriginal or Torres Strait Islander, Native American, Asian, Native Hawaiian/Other Pacific Islander/Maori, more than one race or other. The category white includes those who did not identify as Hispanic and identified as White/Caucasian.
- Multi-morbidity for the purposes of this report includes the following conditions: hypertension, diabetes, dyslipidemia and CKD
- Frailty - 'Pre-frail' included anyone with 1 or 2 criteria and 'Frail' included anyone with 3 or more criteria of the adapted Fried frailty criteria. These included body weight (BMI <20kg/m^2), strength (hand grip in lowest 20% of participants by sex and Fried-defined sex-specific BMI categories), exhaustion (taken from the self-reported CES-D-10 responses, indicating at least one of the following conditions was present for 3 days or more during the last week, (a) "I felt that everything I did was an effort" or (b) "I could not get going") walking speed (3m gait speed in lowest 20% of participants by sex and Fried-defined sex-specific height categories) and physical activity (taken from the self reported Life questionnaire, indicating yes to "In the last 2 weeks, no walking outside the home, or walked outside home but longest amount of time walked without sitting down to rest was less than 10 minutes") [5]

Further details of these health measures and how they were assessed or recorded can be found in [10, 11] and www.aspree.org (Protocol)

Table S3: The Effect of Trial Group on Cancer-related Mortality and According to Subgroups

	Aspirin		Placebo		Aspirin v. Placebo			
	No. events	**Rate per 1000 PY**	**No. events**	**Rate per 1000 PY**	**Hazard ratio**	**95% CI**	**P-value**	**Test of interaction P-value**
Cancer-related deaths	295	6.7	227	5.1	1.31	1.10, 1.56	0.002	
Subgroups prespecified in trial protocol								
Males	159	8.4	129	6.7	1.26	1.00, 1.58	0.06	0.56
Females	136	5.4	98	3.9	1.39	1.07, 1.80	0.01	
Age below median (65-73y)	92	4.3	74	3.4	1.27	0.94, 1.73	0.12	0.83
Age at or above median (74+y)	203	9.0	153	6.8	1.32	1.07, 1.63	0.01	
Australia	266	7.0	202	5.3	1.33	1.11, 1.60	0.002	0.63
U.S.	29	4.8	25	4.2	1.16	0.68, 1.98	0.59	
White Australian	259	6.9	199	5.3	1.31	1.09, 1.58	0.004	0.91
White U.S.	14	4.7	13	4.3	1.10	0.52, 2.34	0.81	
Black	10	5.0	9	4.6	1.07	0.44, 2.64	0.88	
Hispanic/Latino	6	5.4	6	5.3	0.99	0.32, 3.08	0.99	
Other *	6	10.2	0		ND			
No diabetes	247	6.3	195	4.9	1.28	1.06, 1.54	0.01	0.43
Diabetes mellitus†	48	10.7	32	7.0	1.55	0.99, 2.42	0.06	
No hypertension	65	5.7	53	4.7	1.23	0.85, 1.77	0.27	0.69
Hypertension‡	230	7.0	174	5.3	1.34	1.10, 1.63	0.004	
Current smoker	23	15.0	26	15.4	0.98	0.56, 1.72	0.95	0.25
Former smoker	146	8.1	97	5.4	1.53	1.18, 1.98	0.001	
Never smoker	126	5.1	104	4.2	1.21	0.93, 1.57	0.15	
No regular aspirin use prior	256	6.6	193	4.9	1.35	1.12, 1.62	0.002	0.46
Prior regular aspirin use§	39	7.3	34	6.5	1.11	0.70, 1.76	0.64	
Subgroups prespecified in statistical analysis plan								
Not frail	142	5.5	101	3.9	1.42	1.10, 1.84	0.01	0.62
Pre-frail ‖	138	8.0	116	6.6	1.20	0.94, 1.53	0.15	
Frail ‖	15	15.6	10	10.9	1.43	0.64, 3.19	0.38	

No personal cancer history	198	5.5	138	3.8	1.45	1.16, 1.80	0.001	0.11
History of cancer (excluding non-melanoma skin cancer)	94	11.6	88	10.8	1.08	0.81, 1.44	0.61	
No Dyslipidemia	113	7.5	84	5.7	1.31	0.99, 1.74	0.06	0.10
Dyslipidemia¶	182	6.3	143	4.8	1.31	1.05, 1.63	0.02	
BMI underweight (<20kg/m^2)	6	6.9	10	12.5	0.55	0.20, 1.51	0.25	0.07
Normal weight (20-24 kg/m^2)	72	6.7	59	5.6	1.19	0.84, 1.67	0.33	
Overweight (25-29 kg/m^2)	128	6.6	109	5.5	1.21	0.94, 1.56	0.15	
Obese (30+ kg/m^2)	87	6.8	48	3.7	1.85	1.30, 2.63	0.001	
Subgroups not prespecified								
No Chronic Kidney Disease	178	5.4	146	4.4	1.23	0.99, 1.53	0.06	0.35
Chronic Kidney Disease**	117	10.3	81	7.1	1.46	1.10, 1.94	0.01	
Education, <12 years	148	7.5	110	5.5	1.35	1.05, 1.73	0.02	0.76
Education 12+ years	147	6.1	117	4.8	1.28	1.00, 1.63	0.05	
No polypharmacy	201	6.2	164	5.0	1.26	1.02, 1.55	0.03	0.51
Polypharmacy: 5+ medications	94	7.9	63	5.6	1.43	1.04, 1.97	0.03	
None of diabetes, hypertension, dyslipidemia, CKD	12	3.3	13	3.7	0.91	0.41, 1.99	0.81	0.13
1 or 2 of these conditions	201	6.3	165	5.2	1.22	0.99, 1.50	0.06	
3 or 4 of these conditions	82	9.4	49	5.4	1.77	1.24, 2.52	0.002	
SF12 MCS <57	129	6.6	104	5.2	1.28	0.99, 1.66	0.06	0.82
SF12 MCS ≥57	166	6.8	123	5.1	1.33	1.06, 1.69	0.02	
SF12 PCS <50	175	8.2	119	5.6	1.47	1.16, 1.85	0.001	0.15
SF12 PCS ≥50	120	5.3	108	4.7	1.13	0.87, 1.47	0.34	

For details of acronyms, abbreviations or further definitions, see Supplementary Table S2 for study measures.

Body Mass Index (BMI) categories <20, 20-24.9, 25-29.9, 30+ kg/m^2 are described in the Statistical Analysis Plan [5] and closely match the WHO definitions of underweight, normal weight, overweight and obese.

*Other is defined as any category with <200 participants overall, which includes Aboriginal/Torres Strait Islander (12), Native American (6), More than one race (64), Native Hawaiian / Pacific Islander (11) and those who were not Hispanic and who did not state their ethnicity/race (18).

† Self-report of diabetes mellitus or fasting glucose ≥126 mg/dL (≥7 mmol/L) or on treatment for diabetes

‡ On treatment for high BP or BP > 140/90 mmHg at study entry

§ Self-reported regular use of aspirin immediately prior to first baseline visit with a one-month washout prior to randomization to study medication.

‖ 'Pre-frail' included anyone with 1 or 2 criteria and 'Frail' included anyone with 3 or more criteria of the adapted Fried frailty criteria [5]

¶ Dyslipidemia defined as those taking cholesterol-lowering medications or serum cholesterol ≥212 mg/dL (≥5.5 mmol/L; Australia) and ≥240 mg/dL (≥6.2 mmol/L; U.S.) or LDL>160 mg/dL (>4.1 mmol/L)

** Chronic kidney disease (CKD) defined as eGFR < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3 mg/mmol

Table S4: Mode (Proximal Cause) of Death for All-cause Mortality By Trial Group

All deaths			
	Treatment		
Mode of Death*	**Aspirin, N (%)**	**Placebo, N (%)**	**Total, N (%)**
Cancer & metastasis†	131 (23%)	114 (23%)	245 (23%)
Hemorrhage	15 (3%)	9 (2%)	24 (2%)
Heart failure & myocardial infarction	22 (4%)	23 (5%)	45 (4%)
Infection	57 (10%)	52 (11%)	109 (10%)
Stroke	27 (5%)	19 (4%)	46 (4%)
Thrombosis/thromboembolus	2 (0%)	2 (0%)	4 (0%)
Other‡	67 (12%)	57 (12%)	124 (12%)
Undetermined§	10 (2%)	5 (1%)	15 (1%)
No clinical information around death ‖	227 (41%)	213 (43%)	440 (42%)
Total	**558 (100%)**	**494 (100%)**	**1052 (100%)**

* Mode of death was the immediate cause of death (e.g. pneumonia) as distinct from the underlying cause of death (e.g. lung cancer)

† Cancer includes local disease, metastasis and adverse outcomes from cancer treatment

‡ Other includes COPD, renal failure, accidental death, suicide, dementia (but excludes other listed categories)

§ Undetermined: documentation available but does not contain a mode of death

‖ No clinical information around death means there were no documents available

Table S5: Mode (Proximal Cause) of Death in Those Who Were Adjudicated as Cancer-related Deaths

Cancer-related Deaths			
	Trial Group		
Mode of Death*	**Aspirin, N (%)**	**Placebo, N (%)**	**Total, N (%)**
Cancer†	131 (45%)	112 (50%)	243 (47%)
Hemorrhage	3 (1%)	1 (0%)	4 (1%)
Heart failure & myocardial infarction	0 (0%)	4 (2%)	4 (1%)
Infection	27 (9%)	13 (6%)	40 (8%)
Stroke	1 (0%)	2 (1%)	3 (1%)
Thrombosis/thromboembolus	2 (1%)	0 (0%)	2 (0%)
Other‡	21 (7%)	16 (7%)	37 (7%)
Undetermined§	6 (2%)	3 (1%)	9 (2%)
No clinical information around death‖	102 (35%)	71 (32%)	173 (34%)
Total¶	**293 (100%)**	**222 (100%)**	**515 (100%)**

* Mode of death was the immediate cause of death (e.g. pneumonia) as distinct from trajectory adjudicated cause of death (e.g. lung cancer)

† Cancer includes local disease, metastasis and adverse outcomes from cancer treatment

‡ Other includes COPD, renal failure, accidental death, suicide, dementia (but excludes other listed categories)

§ Undetermined: documentation available but do not contain a mode of death

‖ No clinical information around death means there were no contemporary documents available

¶ A further 7 cancer-related deaths (2 in the aspirin arm and 5 in the placebo arm) were not included in this table of adjudicated cancer-related deaths because the cause of death was obtained solely from NDI search.

Table S6: The Effect of Trial Group on All-cause Mortality and According to Subgroups

	Aspirin		Placebo		Aspirin v. Placebo			
	No. events	**Rate per 1000 PY**	**No. events**	**Rate per 1000 PY**	**Hazard ratio**	**95% CI**	**P-value**	**Test of interaction P-value**
All-cause mortality	**558**	**12.7**	**494**	**11.1**	**1.14**	**1.01,1.29**	**0.03**	
Subgroups prespecified in trial protocol								
Males	314	16.6	269	14.1	1.19	1.01,1.40	0.04	0.46
Females	244	9.7	225	8.9	1.09	0.91,1.30	0.37	
Age below median (65-73y)	154	7.2	145	6.6	1.09	0.87,1.36	0.48	0.66
Age at or above median (74+y)	404	18.0	349	15.6	1.15	1.00,1.33	0.05	
Australia	496	13.1	416	10.8	1.21	1.06,1.37	0.005	0.02
U.S.	62	10.3	78	13.0	0.79	0.57,1.11	0.17	
White Australian	486	13.0	410	10.9	1.20	1.05,1.36	0.008	0.19
White U.S.	29	9.7	35	11.5	0.84	0.52,1.38	0.50	
Black	24	12.0	30	15.3	0.78	0.45,1.33	0.36	
Hispanic/Latino	10	9.0	14	12.3	0.72	0.32,1.61	0.42	
Other *	9	15.3	5	7.2	2.05	0.69,6.13	0.20	
No diabetes	471	11.9	426	10.7	1.11	0.98,1.27	0.11	0.31
Diabetes mellitus†	87	19.4	68	15.0	1.33	0.97,1.82	0.08	
No hypertension	125	11.0	109	9.6	1.15	0.89,1.49	0.28	0.94
Hypertension‡	433	13.3	385	11.7	1.14	0.99,1.31	0.07	
Current smoker	43	28.0	52	30.8	0.91	0.61,1.37	0.66	0.23
Former smoker	272	15.2	217	12.0	1.28	1.07,1.53	0.007	
Never smoker	243	9.9	225	9.1	1.08	0.90,1.29	0.41	
No regular aspirin use prior	488	12.6	415	10.6	1.19	1.05,1.36	0.008	0.07
Prior regular aspirin use§	70	13.1	79	15.2	0.86	0.62,1.19	0.36	
Subgroups prespecified in statistical analysis plan								
Not frail	228	8.9	183	7.0	1.26	1.04,1.53	0.02	0.22
Pre-frail ‖	289	16.7	282	16.1	1.03	0.88,1.22	0.70	
Frail ‖	41	42.6	29	31.6	1.36	0.85,2.19	0.20	

No personal cancer history	398	11.1	353	9.8	1.14	0.99,1.31	0.08	0.97
History of cancer (excluding non-melanoma skin cancer)	157	19.3	139	17.0	1.14	0.91,1.44	0.25	
No Dyslipidemia	224	14.9	196	13.4	1.11	0.92,1.35	0.28	0.78
Dyslipidemia¶	334	11.5	298	10.0	1.15	0.99,1.35	0.08	
BMI underweight (<20kg/m^2)	29	33.5	20	25.0	1.33	0.75,2.35	0.33	0.22
Normal weight (20-24 kg/m^2)	148	13.8	147	14.0	0.98	0.78,1.23	0.84	
Overweight (25-29 kg/m^2)	228	11.7	213	10.7	1.10	0.91,1.33	0.31	
Obese (30+ kg/m^2)	150	11.7	111	8.5	1.38	1.08,1.77	0.01	
Nonprespecified subgroups								
No Chronic Kidney Disease	344	10.5	288	8.7	1.21	1.03,1.41	0.02	0.27
Chronic Kidney Disease**	214	18.9	206	18.0	1.05	0.87,1.27	0.61	
Education, <12 years	284	14.3	235	11.8	1.21	1.02,1.44	0.03	0.34
Education 12+ years	274	11.3	259	10.6	1.08	0.91,1.27	0.40	
No polypharmacy	364	11.3	333	10.1	1.12	0.97,1.30	0.13	0.81
Polypharmacy: 5+ medications	194	16.4	161	14.2	1.16	0.94,1.43	0.17	
None of diabetes, hypertension, dyslipidemia, CKD	35	9.7	30	8.5	1.15	0.71,1.87	0.58	0.59
1 or 2 of these conditions	374	11.8	340	10.7	1.10	0.95,1.27	0.21	
3 or 4 of these conditions	149	17.1	124	13.6	1.27	1.00,1.62	0.05	
SF12 MCS <57	259	13.2	256	12.7	1.05	0.88,1.25	0.58	0.17
SF12 MCS ≥57	299	12.2	238	9.8	1.24	1.05,1.47	0.01	
SF12 PCS <50	347	16.2	296	13.9	1.17	1.00,1.37	0.05	0.57
SF12 PCS ≥50	211	9.4	198	8.6	1.09	0.90,1.32	0.40	

For details of acronyms, abbreviations or further definitions, see Supplementary Table S2 of study measures.

Body Mass Index (BMI) categories <20, 20-24.9, 25-29.9, 30+ kg/m^2 are described in the Statistical Analysis Plan [5] and closely match the WHO definitions of underweight, normal weight, overweight and obese.

*Other is defined as any category with <200 participants overall, which includes Aboriginal/Torres Strait Islander (12), Native American (6), More than one race (64), Native Hawaiian / Pacific Islander (11) and those who were not Hispanic and who did not state their ethnicity/race (18).

† Self report of diabetes mellitus or fasting glucose ≥ 126mg/dL (≥7 mmol/L) or on treatment for diabetes

‡ On treatment for high BP or BP > 140/90 mmHg at study entry

§ Self-reported regular use of aspirin immediately prior to first baseline visit with a one-month washout prior to randomization to study medication.

‖ 'Pre-frail' included anyone with 1 or 2 criteria and 'Frail' included anyone with 3 or more criteria of the adapted Fried frailty criteria [5]

¶ Dyslipidemia defined as those taking cholesterol-lowering medications or serum cholesterol ≥212 mg/dL (≥5.5 mmol/L; Australia) and ≥240 mg/dL (≥6.2 mmol/L; U.S.) or LDL>160 mg/dL (>4.1 mmol/L)

** Chronic kidney disease (CKD) defined as eGFR < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3 mg/mmol

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