Supplementary Appendix

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

Supplement to: McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med 2018;379:1499-508. DOI: 10.1056/NEJMoa1800722

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)

ASPREE PRIMARY END POINT

Details of 'time-to-event' data capture for the components of the primary end point and secondary end points are included below. In summary, persistent physical disability end point was taken as the first reported date of an Activities of Daily Living loss that was confirmed approximately 6 months later (+/- 1 month). A dementia trigger occurred when there was a reduction in 3MS (<78 or 10.15-point age and education level adjusted fall from baseline; administered at years 1, 3, 5, 7 or close-out visit) or a report of clinical diagnosis of dementia or a report of a prescription of cholinesterase inhibitor for dementia (Australia only). The latter two triggers could occur at any annual visit or 6-month phone call (dementia diagnosis only). The event date for a dementia end point was taken as the trigger date prompting a dementia assessment, which subsequently was confirmed as dementia by the end point adjudication committee.

For the analysis of secondary end points, all participants experiencing the event were included, not just the subset for whom the event was their first, thereby contributing to the primary end point.

DEMENTIA

Definition and process for adjudication

Dementia was defined according to the Diagnostic and Statistical Manual for Mental Disorders, American Psychiatric Association (DSM-IV) criteria [1].

Diagnostic features included:

A. Memory impairment and
B. At least one of the following: Aphasia, apraxia, agnosia, disturbances in executive functioning.

In addition, the cognitive impairments must have been severe enough to cause impairment in social and occupational functioning, the decline must have represented a decline from a previously higher level of functioning, and the diagnosis of dementia should not have been made if the cognitive deficits occured exclusively during the course of a delirium.

A 3MS [2] (Modified Mini-Mental State examination; scored out of 100) score of below 78, a fall in 3MS score of more than 10.15 points compared with the individual's base line score after adjustment for age and level of education, a diagnosis of dementia, a report of thinking / memory concerns to a specialist, or prescription of a cholinesterase inhibitor (Australia only, where Pharmaceutical Benefits Scheme supports prescription only after a clinical diagnosis of cognitive impairment) triggered completion of additional and uniformly applied cognitive and functional testing (described in detail in the ASPREE Protocol available https://aspree.org/aus/wp-content/uploads/sites/2/2014/04/ASPREE-Protocol-AUS-Version-9-Nov-2014-Monash-approved.pdf). These tests were conducted by trained and accredited research staff. Collection of ancillary data (laboratory tests and a CT or MRI) was sought for end point ascertainment.

Source information from dementia assessments, clinical case notes and hospital medical records related to these events was collected, sent to the ASPREE Data Management Center and presented to adjudicators of the Dementia End Point Adjudication Committee (EAC). Adjudicators were blinded to

participant identity and treatment arm. Cases were sent to two adjudicators and if there was discordance in the decision, the case was taken to a meeting of the EAC that had to be unanimous in the final 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.

Time-to-event for dementia was taken as the time between randomization and the date of the trigger (low 3MS, dementia diagnosis or cholinesterase inhibitor prescription) that was confirmed by the dementia EAC.

PERSISTENT PHYSICAL DISABILITY

Definition and process for assessment/adjudication

Persistent loss of physical activities of daily living was defined as inability or severe difficulty with performance of one or more of the six Katz Activities of Daily Living (ADLs) [3] or, if the Katz ADL questions could not be administered, admission to a nursing care facility for a physical disability.

- The Katz ADLs include walking, bathing, dressing, transferring from a bed or chair, using the toilet, and eating.
- The following response options were used: (1) no difficulty, (2) a little difficulty, (3) some difficulty, (4) a lot of difficulty, or (5) unable to perform. An additional question was asked for each Katz ADL about usually requiring assistance from another person.

For participants who were unable to answer due to illness, a proxy was permitted to answer these same questions on behalf of the participant. The instrument was administered by interview at baseline and every six months. Persistent loss of the same Katz ADL was a primary end point.

In 2016, the ASPREE DSMB approved the expansion of the definition of persistent physical disability end point to include adjudicated admission to a nursing care facility for physical disability in those cases where it was not possible to obtain Katz ADL information.

The Physical Disability EAC was responsible for determining if events should be considered a physical disability end point *in lieu* of information regarding the persistent loss of physical function as defined by a report of 'a lot of difficulty', 'unable to perform', or as a check, needing assistance with completing the ADL.

Source information from clinical case notes, nursing home facility records, and other medical records related to these events was collected, sent to the ASPREE Data Management Center and presented to adjudicators of the Physical Disability EAC. Adjudicators were blinded to participant identity and treatment arm.

Time-to-event for the persistent Katz ADL loss was taken as the first reported date of the ADL loss, that was confirmed approximately 6 months later (+/- 1 month), or time to the date of admission to a nursing care facility for a physical disability.

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 [4] 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 [5]. 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 [6]

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. [7]

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 EAC 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, or 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.

MAJOR HEMORRHAGE

Definition and processes for adjudication

Major hemorrhage includes

a) hemorrhagic stroke and

b) non-stroke clinically significant bleeding.

a) Hemorrhagic stroke definition and adjudication

Refer to the stroke section c) of Cardiovascular Disease, above.

b) Clinically significant bleeding (CSB) definition and adjudication

Clinically significant bleeding was defined as non-stroke intracranial bleeding and extracranial bleeding at gastrointestinal or other sites that required transfusion, hospitalization for more than 24 hours, prolonged hospitalization by more than 24 hours with bleeding as the principal reason, surgery, or was fatal. [8]

The ASPREE definition of clinically significant bleeding required that bleeding was substantiated by the documentation of one of the following on the medical record:

- Observed bleeding (e.g., bleeding observed on gastroscope / cystoscope etc.)
- Reasonable report of symptoms of bleeding (e.g., melena or hematemesis)
- Medical, nursing or paramedical report
- Imaging evidence such as CT/MRI for intracerebral hemorrhage

Note: Low hemoglobin or drop in hemoglobin without one of the above did not satisfy the criteria of substantiated bleeding.

Specific decision rules developed by the CSB EAC included:

- If hospitalization criterion was to be utilized, bleeding must have been the principal reason for hospitalization, prolongation of hospitalization or surgery and must be substantiated.
- Additional adjudication occurred on whether the event was spontaneous (e.g., bleeding esophageal varices or gastric ulcer) or induced (e.g., trauma).
- Elective in-patient surgical procedure (included therapeutic endoscopic procedures) with prolonged stay, repeat surgery, or transfusion: ‘Case does not meet CSB defintion’
- Elective in-patient surgical procedure (included therapeutic endoscopic procedures) readmitted after discharge primarily for bleeding:- ‘Case meets CSB definition’

- Elective out-patient procedure (included therapeutic endoscopic procedures) readmitted, prolonged stay, repeat surgery, or transfusion:- 'Case meets CSB definition'
- Non-elective inpatient procedure (included therapeutic endoscopic procedures) readmitted, prolonged stay, repeat surgery, or transfusion:- 'Case meets CSB defintion'
- A positive fecal occult blood test was insufficient to substantiate observed CSB:- 'Case does not meet CSB definition'

Source information from clinical case notes and hospital medical records related to these events was collected, sent to the ASPREE Data Management Center and presented to adjudicators on the CSB EAC. Adjudictors 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.

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-melanoma 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. Adjudictors 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.

TESTING THE IDENTITY OF ASPIRIN AND PLACEBO TABLETS (MASKED ANALYSIS)

For the ASPREE Study, aspirin and placebo tablets were manufactured by Bayer, Germany and sent to PT Bayer, Indonesia and then to Fisher Clinical Services in India for packaging. Tablets were packaged into unlabelled high-density polyethylene bottles and then these bottles were packaged into boxes that were labelled as containing either aspirin or placebo. The shipments were received at Pharmaceutical Packaging Professionals (PPP) in Adelaide then Port Melbourne, Australia, accompanied by a batch-specific product certificate of analysis specifying the identity, concentration and purity of aspirin and placebo tablets. Upon receipt of each shipment, 1 bottle of each tablet type from each batch was sent to Chemical Analysis (Croydon, Australia) for identity testing by liquid chromatography – mass spectrometry method. In all cases, the correct identity of the tablets was confirmed by this method.

At PPP, the medications were stored in their original packaging in a dedicated holding room. At the appropriate time, they were taken into a separate room for labelling. Bottles from only one tablet type were removed and labelled at any one time. Labelled bottles with study ID were shipped directly to the U.S. sites and to the ASPREE Co-ordinating Center in Melbourne or other study sites in Australia.

At the ASPREE Co-ordinating Center (Monash University, Australia), correct labelling and allocation of bottles to the correct tablet type were tested by selecting bottles from each batch that, for various reasons, were not distributed to participants (for example, the participant had to cease meds due to an adverse event, or the participant had withdrawn) and conducting blinded analyses. None of the bottles had previously been opened prior to testing.

The bottles of study medication were 'blinded' by covering the original bottle labels and allocation of a new code number. The codes were provided to the un-blinded biostatistician by the coding staff member. A different staff member then tested one tablet from each of the bottles together with known control samples with the following tests:

- pH determination (pH <3.0 indicates ASPIRIN, pH >4.0 indicates NO ASPIRIN)
- Iron III Chloride test (color change to purple indicates the presence of ASPIRIN, no color change indicates NO ASPIRIN) which detects the presence of phenol (such as present in salicylic acid) by a color change after addition of iron chloride.

All test samples produced concordant results for the two tests, i.e., pH<3.0 and color change to purple (Aspirin) OR pH>4.0 and no color change (Placebo). The second staff member then independently sent the results to the biostatistician who matched the results with the coded list and verified that the identity of all bottles tested were correct. The number of bottles tested was dependent on the size of each batch. The controls were from known bottles of aspirin and placebo which were requested as a labelled-bottle of each tablet type from PPP for this purpose. We ran a known aspirin and placebo tablet every 20 samples of study tablets.

Results of testing

All quality control samples (N=186 for Australian tests and N=18 for U.S tests) were verified as correct. There were tested 1649 Australian and 169 U.S. study medication bottles from 7 batches of medication across all years of the study. Of these, approximately 52% were supposed to be aspirin. After confirming the identity of each bottle, 100% of tablets tested contained the correct ingredient – aspirin or no aspirin (placebo).

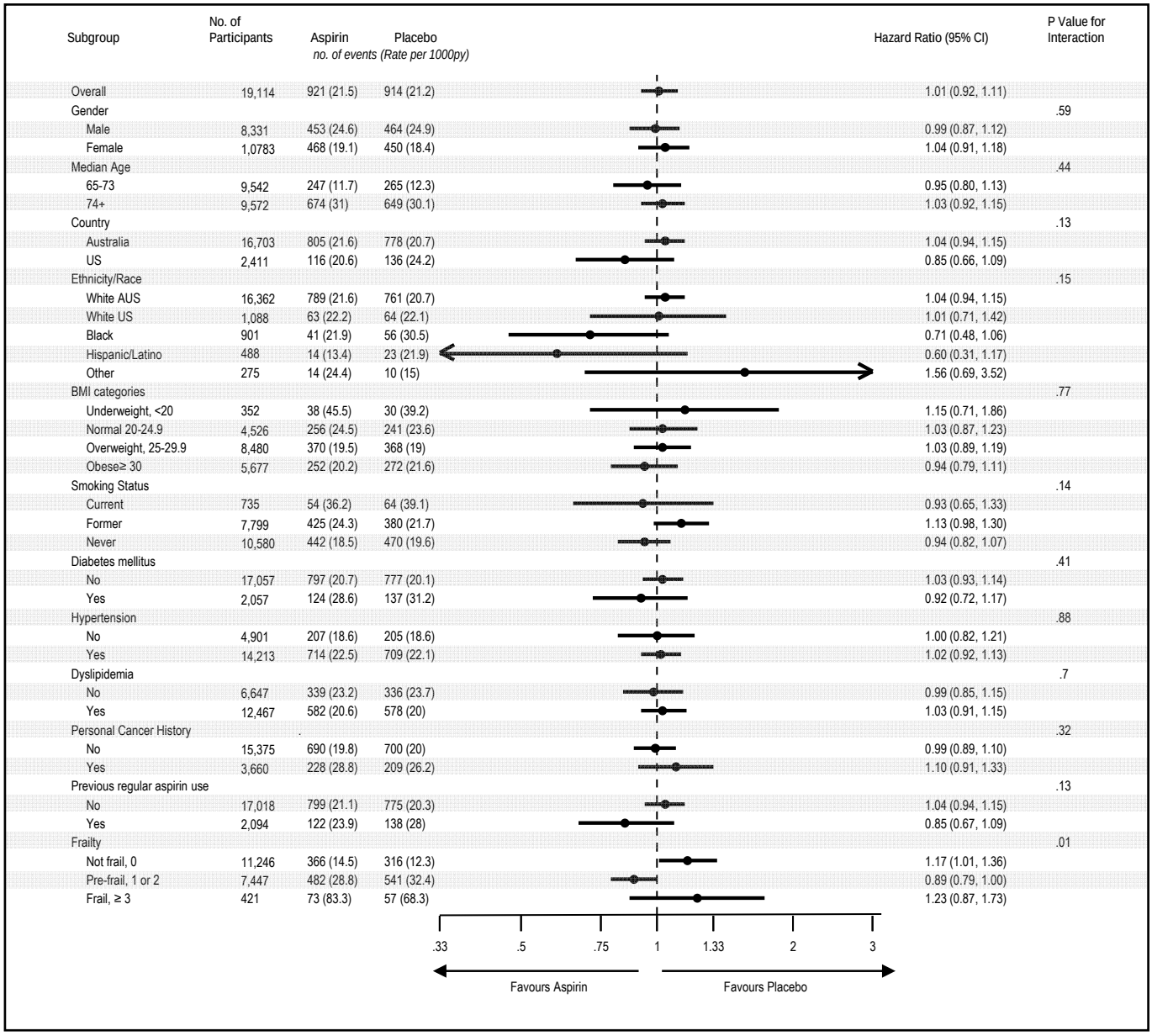
STATISTICAL ANALYSES FOR ASPREE END POINTS AND SUBGROUPS

The target sample size of 19,000 participants was based on the intention to identify a 10% reduction in the number of primary end-point events by aspirin (i.e., hazard ratio 0.90) [9,10]. Only events that occurred on or prior to 12th June 2017 (date of cessation of study medication) were included. In summary, we estimated the probability of remaining event-free using the Kaplan-Meier method and its complement, cumulative incidence, was used for plots. Cox proportional-hazards models were used in intention-to-treat analyses to compare aspirin and placebo arms on time-to-event end points and to evaluate effects in subgroups through use of interaction terms. Individuals were censored in the analysis of each end point at the latest time that an end-point event could have been identified. Uninformative censoring was assumed.

In subgroup analyses, individuals with missing subgroup information were omitted since this occurrence was rare. Subgroups specified in the trial protocol or the statistical analysis plan included gender, age, country of residence, ethnicity, prior regular use of aspirin, frailty category, personal history of cancer, and baseline presences of diabetes, hypertension, smoking or smoking history, and dyslipidemia [9,10]. The ASPREE protocol stated that each report of secondary end points would indicate the statistical significance of the primary end point, and would indicate the total number of secondary end points examined, but would not apply a statistical adjustment for multiplicity. A post-hoc procedure to account for multiplicity of secondary end points, with a Bonferroni-adjusted significance level of 0.007, was applied to any claim for benefit in the secondary end points. For measures reflecting safety, including death and major hemorrhage, a significance level of 0.05 was applied.

SUPPLEMENTARY FIGURES

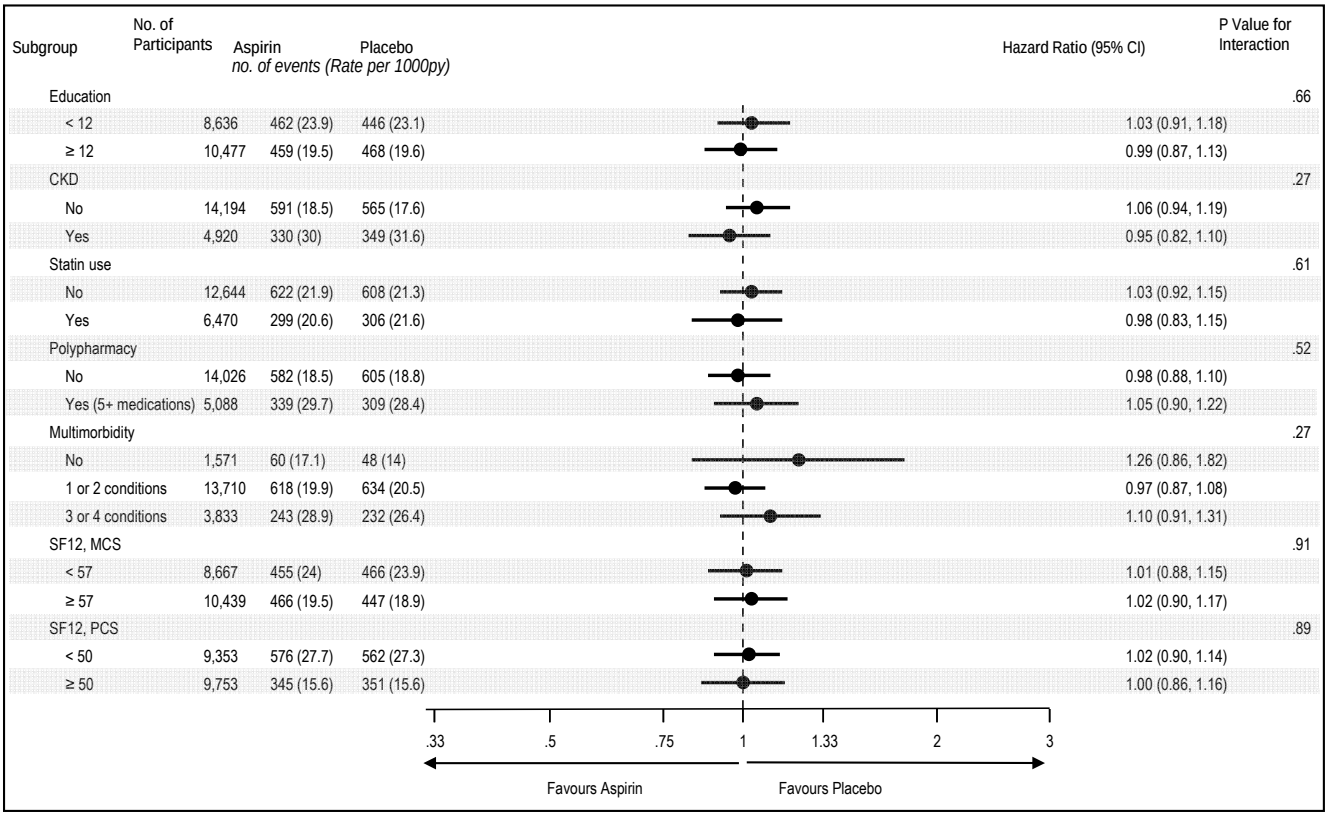
Figure S1: Forest Plot for the Primary Composite End Point in Prespecified Subgroups



Ethnicity/Race 'Other' is defined as any category with <200 participants overall, which includes Aboriginal/Torres Strait Islanders (12), Native Americans (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 ≥126 mg/dL (≥7 mmol/L) or on treatment for diabetes mellitus; 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 (≥5.5 mmol/L; Australia) and ≥240 mg/dL (≥6.2 mmol/L; U.S.) or LDL>160 mg/dL (>4.1 mmol/L) [10,11]; 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. [10]

Figure S2: Forest Plot for the Primary Composite End Point in Subgroups Not Prespecified



CKD (Chronic kidney disease) defined as eGFR < 60 ml/min/1.73m^2 or 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.

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 [2] 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 [3]
- 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 Hispanics) 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 [9]. 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 [9,11].

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 [3] (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) [11,14]
- 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) [2], 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 (≥5.5 mmol/L; Australia) and ≥240 mg/dL (≥6.2 mmol/L; U.S.) or LDL>160 mg/dL (>4.1 mmol/L) [10,11]
- CKD (Chronic kidney disease) - eGFR < 60 ml/min/1.73m^2 or albumin to creatinine ratio ≥3mg/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") [10]

Further details of these health measures and how they were assessed or recorded can be found in [9,11] and www.aspree.org (Protocol)

Table S3: Additional Baseline Demographic and Clinical Characteristics of ASPREE Participants by Trial Group

Baseline Characteristic		Aspirin (N=9525)		Placebo (N=9589)	
Age, years					
65-69	n, %	284	3.0	280	2.9
70-74	n, %	5243	55.0	5356	55.9
75-84	n, %	3618	38.0	3601	37.5
85+	n, %	380	4.0	352	3.7
Female gender	n, %	5373	56.4	5410	56.4
Education 12+ years	n, %	5217	54.8	5260	54.9
Height, meters	Mean, SD	1.65	0.09	1.65	0.09
Weight, Kg	Mean, SD	76.9	15.2	77	14.8
Waist circumference, cm; n=18,921	Mean, SD	97.1	13.0	97.2	12.8
BMI, kg/m^2					
<20	n, %	182	1.9	170	1.8
20-24.9	n, %	2282	24.1	2244	23.5
25-29.9	n, %	4201	44.3	4279	44.8
30+	n, %	2820	29.7	2857	29.9
Smoking status					
Current	n, %	352	3.7	383	4.0
Former	n, %	3909	41.0	3890	40.6
Never	n, %	5264	55.3	5316	55.4
Current alcohol consumption	n, %	7309	76.7	7333	76.5
Living alone	n, %	3097	32.5	3155	32.9
Hemoglobin, g/dL	Mean, SD	14.2	1.2	14.2	1.2
Fasting glucose, mg/dL; n=18,769	Mean, SD	98.7	18.8	98.8	19.2
HDL, mg/dL; n=18,670	Mean, SD	61.4	18.4	61.5	18.4
Total cholesterol, mg/dL; n=18,921	Mean, SD	202.5	38.3	202.8	38.1
Serum/plasma creatinine, mg/dL; n=18,655	Mean, SD	0.9	0.2	0.9	0.2
SBP, mmHg: ≥160	n, %	1171	12.3	1136	11.8
	Mean, SD	139.2	16.5	139.2	16.5
DBP, mmHg: ≥90	n, %	1147	12.0	1057	11.0
	Mean, SD	77.3	10.0	77.2	9.9
Heart rate, bpm	Mean, SD	70.6	10.6	70.9	10.8
Chronic Kidney Disease*; N=18,695	n, %	2456	26.4	2464	26.3
Concomitant medication use	n, %	8310	87.2	8329	86.9
Statin use†	n, %	3244	34.1	3226	33.6
Polypharmacy: use 5+ medications	n, %	2604	27.3	2484	25.9
Depression, CES-D-10 score: 8+	n, %	925	9.7	954	10.0
	Mean, SD	3.2	3.3	3.2	3.3
3MS	Mean, SD	93.4	4.7	93.5	4.6
HVLT-R delayed recall	Mean, SD	7.7	2.8	7.7	2.8

COWAT	Mean, SD	12.1	4.6	12.1	4.6
SDMT	Mean, SD	36.7	10.1	36.8	10.3
Gait time to walk 3m, seconds	Mean, SD	3.1	0.9	3.2	1.0
Grip strength of dominant hand, Kg; n=18,835	Mean, SD	26.8	10.0	27	10.0
Some difficulty with 1 flight of stairs	n, %	1402	14.8	1369	14.3
SF12 MCS: below the median, <57	n, %	4286	45.0	4381	45.7
	Mean, SD	55.8	7.1	55.6	7.2
SF12 PCS: below the median, <50	n, %	4686	49.2	4667	48.7
	Mean, SD	48.3	8.7	48.4	8.8
Multimorbidity‡					
No conditions	n, %	799	8.4	772	8.0
1 to 2 conditions	n, %	6836	71.8	6874	71.7
3 or 4 conditions	n, %	1890	19.8	1943	20.3

Comparison of baseline characteristics according to not prespecified subgroups in the aspirin and placebo groups. Participant numbers are more than 19,000 unless otherwise stated. For details of acronyms, abbreviations or further definitions, see Supplementary Table S2 of study measures. All variables satisfied p>0.05 and had differences of less than 0.25 SD (if means compared) or odds ratios between 0.67 and 1.5 (if proportions compared) meaning that the prespecified reason to adjust the primary analyses was not satisfied.

The following conversions may be used: hemoglobin from g/dL to g/L multiply by 10; glucose from mg/dL to mmol/L multiply by 0.05551, cholesterol (and HDL) from mg/dL to mmol/L, multiply by 0.0259; creatinine from mg/dL to μmol/L multiply by 88.42.

Body Mass Index (BMI) categories <20, 20-24.9, 25-29.9, 30+ kg/m^2 are described in the Statistical Analysis Plan [10] and closely match the WHO definitions of underweight, normal weight, overweight and obese.

*Chronic kidney disease (CKD) defined as eGFR < 60 ml/min/1.73m^2 or 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 mellitus, dyslipidemia and CKD

Table S4: Annual Visit Completion By Trial Group

	Aspirin		Placebo	
Visit type	Visits completed	% completed*	Visits completed	% completed*
Year 1	9392	99%	9449	99%
Year 2	9254	99%	9316	99%
Year 3	8063	98%	8128	98%
Year 4	6092	98%	6151	98%
Year 5	3847	96%	3897	97%
Year 6	1372	92%	1366	93%
TOTAL	**38020**	**98%**	**38307**	**98%**

Visits were considered completed if in person, by phone or medical records only. * Percent completed is number of visits conducted as a proportion of visits due (not listed) - visits were considered due if the participant was not deceased or withdrawn altogether on the due date (anniversary of study entry) of that visit year. Year 7 has not been included since the numbers of people completing this year are very low (97 people were living and not withdrawn at the end of their 7th year of follow-up; 49 in the aspirin arm and 48 in the placebo arm).

Table S5: Participant Follow-up Status By Trial Group

	Aspirin		Placebo	
	Total completed	**% completed of those due**	**Total completed**	**% completed of those due**
Randomized	9,525		9,589	
Attending annual in-person visits	7769	81.6%	7907	82.5%
Attending annual visits by phone	308	3.2%	316	3.3%
Annual visits via medical records only (MRO)	1000	10.5%	910	9.5%
Visit not completed*	448	4.7%	456	4.8%

Visits are those completed in the 12 month window prior to study medication cessation in June 2017. The numbers of visits, whether in person, by phone or Medical Records Only (MRO) include participants who died after a visit was conducted, but prior to June 2017. *'Visit not completed' includes those who had withdrawn or were lost to follow up or were deceased before the visit could be conducted.

Table S6: Medication Adherence and Pill Count By Trial group

	Aspirin	Placebo
Number of participants	9,525	9,589
Number of pills consumed	10,962,411	11,336,214
% compliance	72.9%	74.3%
During the final year of the study, participants taking any study medication (%)	62.1%	64.1%
During the final year of the study, participants taking >80% of study pills as a proportion of participants taking any study medication (%)	86.8%	87.5%

'During the final year of the study' refers to any annual visit from July 2016 – June 2017.

Table S7: Adherence to Study Drug and Open Label Use of Aspirin by Trial Group

	Aspirin (N=9,525)			Placebo (N=9,589)		
Visit	Eligible* N	On study drug† N (%)	On open label aspirin‡ N (%)	Eligible* N	On study drug† N (%)	On open label aspirin‡ N (%)
Baseline	9525	9447 (99.2%)		9589	9505 (99.6%)	
Year 1	9467	7872 (83.2%)	94 (1.0%)	9534	8071 (84.7%)	127 (1.3%)
Year 2	9364	7056 (75.4%)	283 (3.0%)	9420	7321 (77.7%)	317 (3.4%)
Year 3	8227	5695 (69.2%)	274 (3.3%)	8304	5928 (71.4%)	286 (3.4%)
Year 4	6226	3976 (63.9%)	265 (4.3%)	6290	4152 (66.0%)	250 (4.0%)
Year 5	3987	2235 (56.1%)	169 (4.2%)	4033	2342 (58.1%)	171 (4.2%)
Year 6	1485	729 (49.1%)	137 (9.2%)	1456	735 (50.5%)	118 (8.1%)

* Eligible is defined as all participants not withdrawn or deceased who reached the end of each follow-up year prior to the end of the study

† Participants 'on study drug' are those who took any study medication throughout that year

‡ May include short term aspirin

Year 7 has not been included since the numbers of people completing the year were very low with 97 people living and not withdrawn at the end of their 7th year of follow-up (49 in the aspirin arm and 48 in the placebo arm) and 45% and 42%, respectively, still taking study medication.

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