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Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial

ASPREE Investigator Group[i]

Abstract

Cost-effective strategies to maintain healthy active lifestyle in aging populations are required to address the global burden of age-related diseases. ASPREE will examine whether the potential primary prevention benefits of low dose aspirin outweigh the risks in older healthy individuals. Our primary hypothesis is that daily oral 100 mg enteric-coated aspirin will extend a composite primary endpoint termed 'disability-free life' including onset of dementia, total mortality, or

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persistent disability in at least one of the Katz Activities of Daily Living in 19,000 healthy participants aged 65 years and above ('US minorities') and 70 years and above (non 'US minorities'). ASPREE is a double-blind, randomized, placebo-controlled trial of oral 100 mg enteric-coated acetyl salicylic acid (ASA) or matching placebo being conducted in Australian and US community settings on individuals free of dementia, disability and cardiovascular disease (CVD) events. Secondary endpoints are all-cause and cause specific mortality, fatal and non-fatal cardiovascular events, fatal and non-fatal cancer (excluding non-melanoma skin cancer), dementia, mild cognitive impairment, depression, physical disability, and clinically significant bleeding. To 20 September 2013 14383 participants have been recruited. Recruitment and study completion is anticipated in July 2014 and December 2018 respectively. In contrast to other aspirin trials that have largely focused on cardiovascular endpoints, ASPREE has a unique composite primary endpoint to better capture the overall risk and benefit of aspirin to extend healthy independent lifespan in older adults in the US and Australia.

Keywords

Aspirin; clinical trial; aging; dementia; disability; primary prevention

Introduction

There is evidence that aspirin may be effective in primary prevention against a broad spectrum of diseases prevalent in the aged such as myocardial infarction, stroke, cancer and possibly dementia, yet there has been no study focused on older persons [1-3]. Aspirin also has well documented potential for harm, mainly due to bleeding into the brain, gastrointestinal tract and elsewhere, which are also more prevalent in the elderly [4]. In some diseases, such as stroke, there is the potential for both harm and benefit [1, 5]. The population 65 years of age and older have rarely been the focus of most clinical trials and have been conspicuously absent in primary prevention studies of aspirin constituting only 12% of the primary prevention study population [6-11].

In contrast to other aspirin trials that have focused primarily on cardiovascular endpoints, ASPREE is examining whether the potential benefits of 100 mg daily aspirin for longevity and diseases associated with aging outweigh the risks associated with its use. ASPREE utilizes a unique composite primary endpoint with a trial design that examines the overall risk and benefit of aspirin in the elderly in promoting healthy independent lifespan. The secondary endpoints were selected based on the literature, raising hypotheses indicating potential benefits and/or harm associated with aspirin use.

The study was originally planned as a primary prevention cardiovascular disease (CVD) outcome study in the early 1990s to address the lack of aged participants in contemporary trials [6, 7, 12, 13]. The current iteration commenced in 2002 with the rationale still evident but expansion of the endpoints to include other prevalent diseases in the aged [8-11, 14, 15]. The combination of aspirin's off-patent status and low cost limited industry participation to providing trial drug and matching placebo. Funding was obtained from the Australian National Health and Medical Research Council (NHMRC) and the National Institute on Aging (NIA). Randomization commenced in March 2010.

Methods

Design Overview

ASPREE is a double-blind, randomized, placebo-controlled primary prevention trial with an average follow-up of 5 years, designed to assess whether daily active treatment of oral 100

mg enteric-coated aspirin will extend the duration of disability- and dementia-free life in healthy participants 65 years and older for the US minority groups of African Americans and Hispanics, with Caucasians and other minority groups 70 years and older. Participant visits occur at baseline (2 visits 1 month apart) and annually thereafter.

Setting and Participants

In Australia recruitment is carried out predominantly through general practice with general practitioners (GPs) as ASPREE co-investigators. GPs' clinical databases are searched by inclusion/exclusion criteria and a mailing list created. After GP review and approval patients are mailed a study invitation from the GP with a toll free telephone number. On calling the number, interested participants are screened again and suitable persons are invited to a baseline visit (week 0) at the GP's clinic. After an interim GP visit to discuss the study and check suitability again, participants return at week 4 for a randomization visit. In the US recruitment is community-based utilizing a range of methods such as clinic-based, mailing lists, media advertisements, pre-existing registries and electronic medical records. Select sites in the US are recruiting Caucasians with a special focus on enriching the group with minority groups (African Americans, Hispanics, Native Americans and others). African American and Hispanic groups have a lower age criterion due to a higher burden of disease and a survival disadvantage [16]. Minority recruitment has been challenging due to a lower number of minorities without previous cardiovascular events, disability or dementia, who are not taking aspirin, and a reluctance to cease aspirin if not clinically indicated. In addition, after an NIH moratorium on recruiting US Caucasians was enacted in 2011, there was increased hesitancy expressed by minorities regarding why ASPREE was only recruiting minorities. This at least in part is why the US recruitment is lower compared to Australia.

Inclusion criteria:

- Non-minority men and women 70 years of age and older;
- US minority (African American and Hispanic) 65 years of age and older;
- Willing and able to provide informed consent.

Exclusion criteria:

- A history of a diagnosed CVD event 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, or abdominal aortic aneurysm;
- A clinical diagnosis of atrial fibrillation;
- Serious illness likely to cause death within the next 5 years;
- A current or recurrent condition with a high risk of major bleeding;
- Anemia (hemoglobin <12 g/dl males, <11 g/dl females);
- An absolute contraindication or allergy to aspirin;
- Current participation in an ongoing clinical trial;
- Current use of aspirin for secondary prevention;
- Current continuous use of other antiplatelet drug or anticoagulant;
- A systolic blood pressure ≥180 mmHg and/or a diastolic blood pressure ≥105 mmHg;

- A history of dementia or a Modified Mini-Mental State Examination (3MS) score ≤ 77 [17];
- Severe difficulty or an inability to perform any one of the 6 Katz activities of daily living (ADLS) [18];
- Pill-taking compliance <80% during a 4-week placebo run-in phase.

People with current use of aspirin for reasons other than secondary prevention may enter the trial after agreeing to discontinue aspirin. Chronic use of non-steroidal anti-inflammatory drugs is not an exclusion criterion. During a 4 week run-in phase participants take placebo for compliance checking. Participants are instructed to take their study drug half an hour prior to any morning medication to minimize drug interactions.

Randomization and Interventions

Participants are remotely randomized via the ASPREE web portal according to a computer-generated randomization schedule, in a ratio of 1:1 to active or placebo therapy. Randomization is stratified for general practice in Australia, for regional site in the USA and for age (65-69 years, 70-79 years, 80 years+). Randomization is blocked within strata and utilising variable sized blocks of 2, 4, or 6.

Participants in the study are allocated to one of two treatments ASA 100 mg enteric-coated unscored white tablet [Bayer Schering Pharma (Germany)] or placebo enteric-coated unscored white tablet with identical appearance. A 100mg once daily dose was selected as this is the predominant international low dose aspirin regimen for primary prevention.

Study endpoints

The primary endpoint is the first occurrence of either death from any cause or incident dementia or persistent physical disability. This composite primary endpoint captures both the potential benefits (e.g. prevention of thrombotic events) and harms of aspirin (e.g. clinically significant bleeding events). It goes beyond counting these specific disease adverse events to their post event status, i.e. alive or dead, demented/disabled or not. Dementia will be diagnosed based on DSM-IV criteria [19]. Persistent physical disability will be defined as a self-report of ‘a lot of difficulty’ or ‘inability to perform independently’ any one of the 6 Katz basic ADLs (mobility, bathing, transferring, toileting, dressing, feeding) persisting for at least 6 months [18].

Secondary endpoints are all-cause mortality, fatal and non-fatal CVD events including coronary heart disease death, non-fatal MI, fatal and non-fatal stroke, hospitalization for heart failure, depression, fatal and non-fatal cancer (excluding non-melanoma skin cancer), dementia, mild cognitive impairment (MCI, assessed using 3MS [17] and other cognitive function measures), physical disability (Katz ADLs [18]) and clinically significant bleeding.

Study Measures and Visit Schedule

The ASPREE Measurement and Study Activity schedule is summarized in Table 1. Cognitive function is measured using a 30 minute cognitive battery that includes the Symbol-Digit Modalities Test (SDMT) [20], Hopkins Verbal Learning Test-Revised (HVLT-R) [21], and Controlled Oral Word Association Test (COWAT) [22]. Depression is measured using a self-reported questionnaire, the Center for Epidemiologic Studies–Depression (CES-D) assessment tool [23]. Cognitive function and depression scale are measured at baseline, annual visit 1, 3 and 5, and closeout visit.

Physical function is measured using the performance-based measures of gait speed and hand grip tests, self-reported Activities of Daily Living and Instrumental activities contained

within the LIFE questionnaire [24], and quality of life is measured using the Short Form 12 (SF-12) [25].

Laboratory measures include hemoglobin and urine albumin creatinine ratio. Hospitalization for reasons other than primary or secondary endpoints are also captured.

Adherence and Retention Strategies

Person-to-person calls occur at 3, 6 and 9 months between annual face-to-face visits for purposes of retention and to encourage compliance to treatment allocation. In addition, at the 6 month phone contact, information will be collected about new onset of serious adverse events or potential study endpoints.

Adherence to pill taking is checked by pill count at annual visit with participants returning unused pills and being issued with a new 400 pill container. Male and female participant containers are blue and pink spot labeled to avoid partners taking each other's pills. Each participant is contacted by telephone, initially if receipt of trial drug has not been registered (in Australia) or by 4 weeks after study medication is provided (in the US).

Multiple strategies are being employed to retain participants including:

- 3, 6 and 9 month research staff direct phone contact;
- Annual face-to-face visits;
- Contact details (including 2 non co-resident contacts) collected at baseline and updated at annual visits;
- Newsletters are sent to GP co-investigators and participants on a regular basis;
- In Australia, the study staff and GP co-investigator remain in contact;
- Crosschecking with morbidity and mortality registries;
- Data linkage through Medicare numbers will provide updated medical information and clinical events in both countries.
- In Australia, the research staff will be able to audit practice and hospital records in the event a participant is unable to be contacted.

Regardless of the decision to continue with the study medication, the participant will be asked to attend all scheduled follow-up visits as if they were maintaining full participation.

At each annual visit and 6 month telephone contact, the participant will be questioned as to the occurrence of any of the study endpoints over the previous 6 months. Notification of a potential study endpoint will trigger the collection of information for endpoint confirmation and adjudication. Confirmation of endpoints will be ascertained by collecting and forwarding information from medical records from the usual treating physician or practice–held medical record, medical records obtained by letter/fax/email contact with other treating specialist physicians or secondary/tertiary medical care centers.

Clinical Report Forms (CRFs) contain standardized questionnaires for the assessment of cognitive function, physical function and quality of life. Hospital records/discharge summaries, pathology reports, Australian Medicare and Pharmaceutical Benefits Scheme (PBS) records, death certification (US and Australian National Death Indexes) are routinely sourced for endpoint ascertainment.

Endpoint ascertainment

All primary, secondary and clinically significant bleeding events are adjudicated. An endpoint adjudication committee (EAC) consisting of US and Australian co-chairs and chairs from each of the endpoint adjudication subcommittees are adjudicating deaths. Other endpoint adjudications will occur in a relevant subcommittee (disability, dementia, stroke, cancer, cardiovascular, depression and clinically significant bleeding) of US and Australian experts. Adjudication is web-based. Two members adjudicate each event with discordant results going to a third member. Dementia is the exception with adjudication by consensus. Further detail of major safety and primary endpoint components follows.

Clinically significant bleeding endpoint ascertainment

An endpoint adjudication subcommittee (clinically significant bleeding) adjudicates all clinically significant bleeding events. They are defined as gastrointestinal hemorrhages or hemorrhages at other sites that required transfusion, hospitalization and or surgery or are fatal. This definition was chosen as other trial definitions were constrained by cardiovascular endpoints.

Dementia endpoint ascertainment

An endpoint adjudication subcommittee (dementia) is responsible for providing the assessment according to DSM-IV criteria [19]. An individual's 3MS score below 78, or fall over time by more than 10 points adjusted for age and level of education, triggers additional and uniformly applied cognitive and functional testing by research staff and the collection of ancillary data (laboratory tests and a CT or MRI) for endpoint ascertainment with additional cognitive tests including ADAS-Cog [26], Color Trails [27], the Lurian test of overlapping figures for visual agnosia [28], CAM [29] and ADCS-ADL with surrogate [30].

Disability Endpoint Ascertainment

For significant disability as a primary endpoint, the loss of one of the Katz ADLs will be defined as self or proxy report of having ‘a lot of difficulty with’ or ‘unable to perform’ one or more ADLs at the annual follow-up contact and then reassessed via a follow-up phone call repeating the same interview items at 6 months after the original report. For all deaths where disability data is missing in the year preceding death, we conduct a proxy interview to determine whether there was disability in the year prior to death and its approximate onset.

Statistical Analysis

The sample size calculation (including secondary endpoint power calculations) is described elsewhere [31] and was calculated on the basis of analysis with a univariate Cox proportional hazards regression model using Stata (Stata Statistical Software, Release 10, StataCorp, College Station, TX, 2007) [32]. The power calculation for the study uses the same method but is based on the assumptions given in Table 2. On the basis of these assumptions, 311 primary endpoint events in 1500 US minority participants and 3374 primary endpoint events in 17500 Australian and US White participants will yield 89% power to detect a 10% reduction (risk ratio of 0.90) in the primary endpoint in participants randomized to aspirin. Using the assumptions above, the overall primary endpoint rate in the Australian and US White placebo-group participants will be 47.7 per 1000 person years reducing to 42.9 per 1000 person years in the aspirin group, and the event rate in the US minority placebo-group participants will be 51.4 per 1000 person years reducing to 46.3 per 1000 person years in the aspirin group.

Stipulation of interim analysis has been left to the independent NIH-appointed Data Safety and Monitoring Board (DSMB). All primary and secondary outcomes will be in the form of

time-to-event data and rate ratios will be calculated using univariate Cox proportional hazards regression to directly compare event rates between treatment groups. In analyses of secondary endpoints, death due to causes other than those specified by the endpoint and loss to follow-up (see following) will be considered as censoring events. Given the large sample size, we anticipate randomization will adequately balance baseline characteristics of participants in the two treatment groups.

The primary and secondary endpoints will be analyzed according to intention-to-treat principles. No statistical adjustment will be made for the multiple secondary endpoints in the analysis but the reporting of all secondary endpoint analyses will make clear whether the primary endpoint was statistically significant [33] and will state the number of secondary endpoints proposed *a priori* in the study protocol [34].

In the survival analyses, the consideration of loss to follow-up as a censoring event equates to an assumption that data are missing at random given the participant's treatment group and the timing of their loss to follow-up. The adequacy of this assumption will be checked in sensitivity analyses that will include both a multiple imputation approach and adjustment for baseline covariates predictive of propensity for dropout [35].

Pre-specified sub-group analyses will utilize appropriate interaction terms in Cox proportional hazards regression models. The p-values for these interaction terms will be used to test for heterogeneity of treatment effect of aspirin between the sub-groups: males *versus* females, age below *versus* equal to or above study median, US *versus* Australia, ethnicity [Whites *versus* African-Americans *versus* Hispanics *versus* other (including Native Americans, Asians and Aboriginal Australians)], presence *versus* absence of a diagnosis of diabetes at baseline, and hypertensive *versus* non-hypertensive participants (defined as those who are on treatment for high blood pressure or those with blood pressure recorded above 140/90 mmHg at study entry), and current *versus* never or former smokers.

Trial Safety Issues

In the event of a clinical emergency the treating physician is instructed to assume that the participant is taking active therapy and manage accordingly. If the physician insists on unblinding then the code is broken by the nominated independent hospital pharmacy in each country. This procedure ensures that no one involved in the management or conduct of the study has access to the randomization code. Reasons for un-blinding are recorded and, if trial medication is ceased, then participants are encouraged to resume their assigned medication if possible after their immediate condition has resolved. The DSMB is also informed of any emergency code breaks in tabular form. The code is broken for an individual in the event where knowledge of the precise medication is essential for the clinical management. Blinding will be protected by this systematic approach. Adverse events (AEs) are obtained by self-report.

Ethics

This study is being conducted in accordance with the Declaration of Helsinki 1964 as revised in 2008, the NHMRC Guidelines on Human Experimentation, the federal patient privacy (HIPAA) law and ICH-GCP guidelines and the International Conference of Harmonisation Guidelines for Good Clinical Practice. We also follow the Code of Federal Regulations as it relates to areas of clinical research.

Governance

The ASPREE Steering Committee is responsible for the overall management and conduct of the trial including finalizing the protocol, approving the operational plan for the study, and

financial management of the trial. Since one of the principal goals of ASPREE is to evaluate the balance of benefits and risks of low dose aspirin, an important consideration for the DSMB will be all-cause mortality comparisons by study groups, in addition to the primary endpoint. Another important consideration is the possibility of event rates being lower than expected requiring an assessment of study futility. An interim analysis of the primary outcome will be performed at a time to be determined by the DSMB. The DSMB is presented with sequential monitoring statistics on comparison of mortality between study groups, i.e. sequential likelihood-ratio (LR) tests for consideration of early termination if LR test statistic value is >9.5 and value <0.055 [36].

Progress

To 20 September 2013 14383 (12492 Australian and 1891 US) participants have been recruited. Minority recruitment numbers are 1235 (10% of total) with 254 in Australia (2% of Australian participants) and 981 in the US (52% of US participants). Regular contact has been maintained with 98% of ASPREE participants (95% face-to-face and 3% follow-up through medical records or phone calls), with 1% participants unable to be contacted for 6 months or more and 0.4% withdrawing consent. The characteristics of the first 10000 participants are shown in Table 3.

Discussion

A large-scale clinical trial of aspirin in the aged is needed to capture risk and benefit in an aging population in whom life expectancy is truncated and multiple morbidity, polypharmacy, and disability are common. For example aspirin has well recognized protection against thromboembolic stroke but adverse risk for hemorrhagic stroke [1, 5]. It became obvious during the study development process that our primary endpoint needed to address these concerns and funder's requirements. The latter included adding participants with diabetes as current clinical guideline recommendations were not evidence-based for routine aspirin use in this age group, and the mandated inclusion of US minorities [37, 38]. Facilitation of US minority participation led to a differential age inclusion criterion, 65 years and older for US minorities due to a higher prevalence of exclusion criteria, a survival disadvantage and greater risk of other elements of the primary composite endpoint in minorities compared with non-minorities. A further refinement arising from the review process was support for a robust measure of the ability of an older person to live independently hence our current composite primary endpoint of death from any cause or incident dementia or persistent physical disability.

The benefit of study power, in our case 89%, is usually seen in terms of it providing a good chance of detecting (at $p < 0.05$) an aspirin effect at study completion even if that effect is somewhat smaller than the hazard ratio of 0.9 anticipated. An alternative view is that, if event rates are lower than anticipated, and if a hazard ratio of 0.9 were to be observed then we would still end up declaring statistical significance so long as we observed more than 1385 primary endpoint events.

ASPREE will also allow us to answer important secondary questions such as the efficacy of aspirin for cancer prevention by our use of a rigorous prospective placebo controlled design and the possibility of continuation of observations beyond the trial completion date, in the light of recent evidence [2].

Our pragmatic community-based trial also has restricted exclusion criteria, basically excluding those who have a current evidence-based indication for routine aspirin use or a contraindication for its use or already having either dementia or disability. We believe this will make the results readily generalizable.

Our transpacific US-Australian collaboration has been successful to date but has also taught us important lessons. The GP-based infrastructure has proved to be a significant advantage for Australian recruitment. Because the US has no equivalent 'universal' primary health care network, recruitment strategies have been largely limited to site-specific approaches. US minority recruitment has been tremendously challenging. There are logistical challenges of a 13-15 hour time zone difference to arrange regular teleconferences and face-to-face meetings, along with travel budget shortfalls for national and international meetings.

Conclusion

Healthy aging is a global public health goal with the proportion of the population reaching the age of 65 years and older dramatically increasing in most developed and developing countries. Cost-effective strategies to maintain healthy active life in these populations are required to address the global burden of age-related diseases. Daily low dose aspirin has the potential to be such a strategy as a simple, readily available, cost-effective intervention to extend healthy lifespan around the globe.

Acknowledgments

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Appendix A. General Practitioner Co-Investigators

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Table 1

ASPREE Measurement and Study Activity Schedule

(**X** indicates that all measures are carried out except where superscripts [a, b, c] indicate those tests that are the only ones performed at the designated time point). * Final annual visit will take place in years 3 to 7 depending on year of randomization. Only a small number of participants will have 3 or 7 years of follow up with an average of 5 years of follow up across the study. Final visit measurements will be the same as those indicated for year 5. * Final annual visit will take place in years 3 to 7 depending on year of randomization. Only a small number of participants will have 3 or 7 years of follow up with an average of 5 years of follow up across the study. Final visit measurements will be the same as those indicated for year 5.

Measurement/ Activity	Lifestyle Profile & Screening (Visit 1)	Randomization (Visit 2) 4 weeks	Each intervening 6-month phone contact	Follow-up					
				1 yr	2 yr	3 yr	4 yr	5 yr*	6 yr*
Review inclusion/	X	X							
Obtain informed consent	X								
Dispense study medication	X (Run-In)	X		X	X	X	X	X	X
Assess medication		X		X	X	X	X	X	X
Concomitant		X		X	X	X	X	X	X
Blood pressure & heart rate [a], height [b], weight [c]	X [a]	X [bc]		X [ac]	X [ac]	X [ac]	X [ac]	X [abc]	X [abc]
Demographics, family & personal history &	X			X	X	X	X	X	X
Laboratory testing: • Fasting blood: total cholesterol, HDL, LDL, triglyceride, glucose, creatinine & hemoglobin [a] • Urine:	X			X [a]	X [a]	X	X [a]	X	X
Quality of Life • SF-12		X		X	X	X	X	X	X
Assess cognitive function • 3MS [a] , SDMT [b] HVLT-R [b] & COWAT [b]	X [a]	X [b]		X		X		X	
Assess physical disability	X		X	X	X	X	X	X	X
Assess physical function		X			X		X	X	X
Assess depression • CES-D [a]	X [a]			X			X		X
Clinical event reporting		X		X	X	X	X	X	X

Measurement/ Activity	Lifestyle Profile & Screening (Visit 1)	Randomization (Visit 2) 4 weeks	Each intervening 6-month phone contact	Follow-up					
				1 yr	2 yr	3 yr	4 yr	5 yr*	6 yr*
• Questionnaire & medical									

Table 2
Assumptions used in power calculation for ASPREE primary endpoint

Effect of aspirin	The effect of aspirin is described by a hazard ratio of 0.90 in an intention-to-treat analysis. This assumes a slightly stronger underlying effect that will be weakened by cross-over of participants for reasons which include the development of a non-fatal, non-disabling cardiovascular or cerebrovascular event necessitating aspirin therapy or cessation (non-compliance) of aspirin therapy.
Treatment cross-over	We expect 5% per annum of placebo-group participants to initiate aspirin use (or *vice versa*).
Dementia rates	Annual dementia incidence rates of 3 per 1000 for the 65-69 years age group, 6/1000 (70-74 years), 11/1000 (75-79 years), 20/1000 (80-84 years), 37/1000 (85 years+) [39, 40] for Australian, US Hispanic and US White (non-Hispanic) participants. For US African Americans the rates are doubled [40, 41].
Disability rates	Annual disability (loss of one or more Katz ADLs) incidence rates 19.6/1000 (males, 70 years+), 26.5/1000 (females, 70 years+), 13.3/1000 (males, 65-69 years), 14.8/1000 (females, 65-69 years) where these incidence rates were observed in the subset of ASPREE-like participants in the Cardiovascular Health Study [41] which showed similar rates in US Whites and US minorities.
Mortality rates	Age-specific mortality rates in Australian and US. White (non-Hispanic) participants are based on the 2004 Australian population census [42]. Age-specific mortality rates in US African American and Hispanic participants are based on 2005 rates specific to each minority [43]. Mortality rates in ASPREE participants are assumed to be half the corresponding population age-specific rate.
Primary endpoint rate	To allow for the analysis to be time-to-first event, individual rates for death, ADL loss and dementia can be summed and the sum reduced by 10% to allow for the potential for different events to occur in the same individual [28].
Gender ratio	Participants will be 45% male and 55% female.
Age profile	The Australian participants will consist of 50%, 30%, 15%, 5% in age groups 70-74 years, 75-79 years, 80-84 years, 85 years and over, respectively and in US participants the age distribution will be 20%, 47%, 19%, 8%, 6% in the age groups 65-69 years, 70-74 years, 75-79 years, 80-84 years, 85 years and over, respectively.
Race	Participants will be recruited from the four categories Australian, White US, Hispanic, African-American according to the split: 84.2%, 7.9%, 2.6%, 5.3% respectively.
Follow-up time	The average at risk time will be 4.25 years per participant which allows for censoring due to the primary endpoint or non-completion of dementia screen or diagnosis, and non-completion of ADLs in persons alive at the end of follow-up.

Table 3

Baseline characteristics of the first 10,000 randomized ASPREE participants

Means and standard deviations unless otherwise specified. 3MS = Modified Mini-Mental State Examination [15].

Characteristics	All 10000		Australia 8460 (85)		US 1540 (15)	
N (%)	Men 4241 (42)	Women 5759 (58)	Men 3737 (44)	Women 4723 (56)	Men 504 (33)	Women 1036 (67)
Age (years)	75.3 (4.5)	75.6 (4.6)	75.5 (4.4)	75.8 (4.4)	73.9 (4.9)	74.7 (5.4)
Height (cm)	172.9 (6.7)	159.2 (6.5)	172.8 (6.6)	159.2 (6.2)	174.4 (7.3)	160.5 (7.3)
Weight (kg)	83.4 (13.0)	71.0 (13.9)	82.9 (12.6)	70.5 (13.6)	86.8 (15.5)	73.4 (15.2)
BMI (kg/m^2)	27.8 (3.9)	27.9 (5.2)	27.7 (3.8)	27.8 (5.1)	28.5 (4.6)	28.4 (5.5)
Blood pressure (mmHg)	141.6/78.8	138.7/77.9	142.4/79.0	139.7/78.3	135.8/77.4	133.7/76.1
SBP/DBP	2222 (52)	2560 (44)	2037 (55)	2221 (47)	185 (37)	339 (33)
SBP >140 N (%)	483 (11)	674 (12)	434 (12)	587 (12)	49 (10)	87 (8)
DBP> 90 N (%)	743 (18)	917 (16)	687 (18)	785 (17)	56 (11)	132 (13)
SBP>140						
DBP<80 N (%)						
Diabetes	400 (9)	416 (7)	331 (9)	300 (6)	69 (14)	116 (11)
N (%)						
Cognition 3MS scores	92.9 (4.8)	94.1 (4.5)	92.9 (4.7)	94.1 (4.4)	93.2 (5.3)	94.3 (4.9)