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PROTOCOL PAPER

ASPREE-D: Aspirin for the prevention of depression in the elderly

Michael Berk,[1,2,3,4] R. L. Woods,[2] M. R. Nelson,[5] R. C. Shah,[6] C. M. Reid,[2,7] E. Storey,[8] S. M. Fitzgerald,[2] J. E. Lockery,[2] R. Wolfe,[2] M. Mohebbi,[1] A. M. Murray,[9] B. Kirpach,[9] R. Grimm[9] and J. J. McNeil[2], on behalf of the ASPREE investigators

[1]*Deakin University, School of Medicine, IMPACT Strategic Research Centre, Barwon Health, Geelong, Victoria, Australia*
[2]*School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia*
[3]*Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia*
[4]*Orygen Youth Health Research Centre, Parkville, Victoria, Australia*
[5]*Menzies Institute for Medical Research, University of Tasmania, Tasmania, Australia*
[6]*Department of Family Medicine and the Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, USA*
[7]*School of Public Health, Curtin University, Perth, Western Australia, Australia*
[8]*Central Clinical School, Monash University, Victoria, Australia*
[9]*Berman Center for Outcomes & Clinical Research, Hennepin County Medical Center, Minneapolis, Minnesota, USA*

ABSTRACT

Background: Not only is depression associated with increased inflammation but inflammation is a risk factor for the genesis of depression. Many of the environmental risk factors for depression are transduced through inflammatory signaling. Anti-inflammatory agents show promise for the management of depression in preclinical, epidemiological, and early clinical studies. This opens the door to the potential for anti-inflammatory agents to treat and prevent depression. There are no evidence-based pharmacotherapies for depression prevention.

Method: ASPREE-D, aspirin in the prevention of depression in the elderly, is a sub study of ASPREE, which explores the potential of aspirin to prevent a range of inflammation related disorders in the elderly. With a sample size of 19,114, and a duration of 5 years, this placebo controlled study will be one of the largest randomized controlled trials in psychiatry and will provide definitive evidence on the ability of aspirin to prevent depression.

Results: This paper presents the rationale for the study and presents a summary of the study design.

Conclusions: ASPREE-D may not only define novel therapy but will provide mechanistic proof of concept of the role of inflammation in depression.

Key words: immunology, antidepressants, biomarkers, aspirin, inflammation, risk, prevention, depression

Introduction

The 2013 Global Burden of Disease study ranks major depression as a principal contributor to disease burden. In almost every other area of health, preventative strategies have made a major difference to disease incidence, whether it be vaccination for infectious disease, smoking control and lung cancer, clean water and diarrheal diseases, or risk factor modification and cardiovascular disease. In stark contrast to the somatic medical field, psychiatry is almost entirely lacking in evidence-based prevention strategies. Preventive interventions in psychiatry mainly consist of adapted cognitive behavior type therapy given to individuals with early or emerging symptoms (Cuijpers *et al.*, 2008). Notably, there are no evidence-based preventative pharmacotherapies for psychiatric disorders.

Current evidence suggests a possible etiological role for inflammation in the genesis and pathophysiology of depression. Increased mean plasma levels of the inflammatory blood biomarkers, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and C reactive protein (CRP) are found in patients with clinical depression including the

Correspondence should be addressed to: Michael Berk, IMPACT Strategic Research Centre, School of Medicine, Deakin University, 75 Pigdon's Road, Waurn Ponds, Geelong, Victoria 3216, Australia. Phone: +61 3 42153330. Email: mikebe@barwonhealth.org.au. Received 25 Feb 2016; revision requested 22 Mar 2016; revised version received 22 Mar 2016; accepted 14 Apr 2016. First published online 31 May 2016.

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elderly (Pasco *et al.*, 2010b). The possible link between inflammation and depression raises the question of whether the association is causal, and if so, whether pharmacological suppression of inflammation is effective in preventing depression.

ASPREE (ASPirin in Reducing Events in the Elderly) is a National Institute on Aging (NIA) and NHMRC supported 5 year randomized controlled trial (RCT) of aspirin (100 mg daily) or placebo in 19,000 healthy, older adults. Depression is a secondary endpoint of the ASPREE principal trial and this sub-study focuses further on depression, aiming to study the impact of low-dose aspirin on the incidence of this condition and to determine whether the relationship between inflammation and depression is likely to be causal (2013). ASPREE-D is both one of the first trials to explore preventative pharmacotherapy for psychiatric disorders, and will be one of the largest RCTs ever in psychiatry, with a sample size amply powered to detect the predicted incidence. In addition to examining the efficacy of aspirin in reducing depression in the elderly, ASPREE-D will measure biomarkers from blood samples collected from ASPREE participants to confirm or refute whether inflammatory biomarkers are risk biomarkers for depression genesis.

Aim

The primary aim of this sub-study (ASPREE-D) is to determine if use of low-dose aspirin reduces the risk of depression in healthy individuals aged 65 years or older.

Primary hypothesis

Low dose aspirin will reduce the risk of depression, defined as a Centre for Epidemiologic Studies Depression Scale (CES-D)-10 item scale score of 8 or above, at any post randomization time-point.

Secondary hypotheses

1. Higher levels of inflammatory biomarkers [TNF-α, IL-6, or CRP] in plasma are associated with the risk of depression.
2. 100 mg aspirin suppresses inflammation as measured through the above plasma biomarkers.
3. The degree of suppression of inflammatory markers is predictive of the effect of aspirin on risk of depression.
4. Low-dose aspirin improves quality of life, assessed using the Quality of life Short Form–12 (SF-12), in healthy individuals over 65 years of age at least in part by reducing depression.
5. Treatment with low-dose aspirin compared with placebo-treatment in those with pre-existing depression (high CES-D at baseline) will reduce the severity of depression.

Background

Major depressive disorder and the elderly

Major Depressive Disorder (MDD) is common across the lifespan. Prevalence estimates of depression (MDD, minor depression, and dysthymic disorder) in the elderly range from 10–15% (Alexopoulos, 2005). Where individuals were examined for a depressive episode at ages 70, 75, 79, 81, 83, and 85 years, the prevalence of depression increased from 5.6% at age 70 to 13.0% at age 85, indicating a significant burden of incident episodes across this age span (Palsson *et al.*, 2001). Depression in the elderly is associated with a wide range of adverse outcomes, including increased mortality, increased dementia, and substantial psychosocial disability (Ancill and Holliday, 1990). With the rapid increase in the aged population in developed countries, the societal impact of depression will increase, hence the importance of identifying approaches to reduce its impact.

Major depressive disorder and inflammation

While inflammation is a common accompaniment of depression, a fundamental question is whether inflammation contributes to the severity or genesis of depressive symptoms or is a by-product of depression. The most consistently elevated inflammatory markers in patients with MDD confirmed by meta-analysis (Liu *et al.*, 2012) are CRP, IL-6, and TNFα. In addition, elevation of markers of cell mediated immune activation such as IL-1-beta (IL-1β), serum soluble IL-2 receptor and interferon-γ have been identified in several studies (Maes *et al.*, 2012b). Exogenous cytokine administration induces depression in volunteers and is arguably the best human model of depression (Maes *et al.*, 2012a). Depression occurs at a substantially higher rate in patients with inflammatory disorders such as multiple sclerosis, psoriasis, rheumatoid arthritis, and inflammatory bowel disease (Krishnadas and Cavanagh, 2012).

Elevated cytokines such as TNFα are found in both blood and brains of people with depression who commit suicide (Dean *et al.*, 2010). Pro-inflammatory cytokines such as CRP, IL-6, TNFα, and IL-10 affect serotonergic and other MDD-related transmitter systems, and modulate synaptic plasticity, which is similarly disrupted in MDD (Krishnadas and Cavanagh, 2012). Inflammatory cytokines can potentiate excitotoxic damage produced through NMDA receptor activation and reduce neurogenesis (Moylan *et al.*, 2013).

Levels of inflammatory biomarkers in plasma increase with age (Jenny *et al.*, 2012). Elevated levels of inflammatory biomarkers including CRP,

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IL-6, and TNF-α may ante-date the onset of depression in the elderly. Inflammatory markers, especially IL-1β and IL-6, are reduced with antidepressant treatment (Hiles *et al.*, 2012). These findings provide support for the use of immune interventions that directly address this aspect of the pathophysiology of depression (Maes *et al.*, 2012b).

Aspirin and depression

Mechanisms

Aspirin is a non-steroidal anti-inflammatory drug that is an irreversible inhibitor of cyclooxygenase-1 (COX-1) and COX-2. It stimulates endogenous production of anti-inflammatory regulatory "braking signals", including lipoxins, which dampen the inflammatory response and reduce levels of inflammatory biomarkers, including CRP, TNFα, and IL–6, but not negative immunoregulatory cytokines, such as IL-4 and IL-10.

Aspirin may reduce inflammatory changes in the brain given that COX-1 is found in microglia where it presumably has a role in modulating neuro-inflammation (Berk *et al.*, 2013). Aspirin has a specific antithrombotic and thrombolytic action through inhibition of COX-1 in platelets, which may reduce the incidence of micro-vessel changes and ischemic stroke (Berk *et al.*, 2013). Since aspirin reduces the incidence of vascular events, including stroke, this decrease in cerebrovascular burden could potentially contribute to reduce the risk of depression. An exploratory hypothesis that will be tested in ASPREE-D is whether aspirin use reduces depressive episodes associated with cerebrovascular and cardiovascular events. Because of the particular contribution of vascular disease to depression in the elderly, it seems reasonable to assume that aspirin may also play a therapeutic role through anti-thrombotic pathways.

Aspirin and the suppression of inflammation

Aspirin's action in reducing inflammatory biomarkers has been inconsistently demonstrated. In a randomized crossover trial of 40 patients with chronic stable angina, MCSF, IL-6, and CRP were all reduced after 6 weeks of 300 mg aspirin compared to placebo (Ikonomidis *et al.*, 1999). In 121 patients with metabolic syndrome randomized to aspirin for 2 weeks, aspirin 100 mg/day and 300 mg/day significantly decreased blood levels of high sensitivity (hs)-CRP and thromboxane B2 compared to baseline (Gao *et al.*, 2009). Both hs-CRP and TNF-α were significantly decreased by 100 mg aspirin daily at 7 and 30 days in a randomized trial of 115 patients with non-ST-segment elevation acute coronary syndrome (Chen *et al.*, 2006). In the 16,297 adults $\geq$45 years old from the REGARDS cohort, the combined use of aspirin and statins was associated with synergistically lowered CRP concentrations, especially among participants taking aspirin for >5 years (Fisher *et al.*, 2008). Another five trials in clinical cohorts did not demonstrate a reduction in inflammatory markers, although most comprised small sample sizes and were therefore potentially subject to a type 2 error. On the basis of this data it appears that aspirin in the dose employed in ASPREE may have a modest but variable effect on suppressing biomarkers of inflammation.

Preclinical data in depression

There is a preclinical evidence base, with salient findings including that combined treatment of fluoxetine and aspirin reversed an animal model of depression more rapidly than fluoxetine alone (Brunello *et al.*, 2006). In addition, aspirin treatment significantly improved depressive-like behaviors in a rat model of resistant depression (Wang *et al.*, 2011).

Epidemiological and clinical data

There is limited clinical evidence to support a role of aspirin in modulating mood disorders. In one study, patients receiving aspirin at the time of coronary angiography were less likely to have depressive symptoms. In a large European record linkage study, patients on lithium for bipolar disorder who were concurrently receiving low-dose aspirin were substantially less likely to have new medication events, the index of mood instability in the study. Almeida showed that aspirin reduced the risk for depression, although this effect was only evident in those with baseline elevated risk biomarkers, particularly plasma homocysteine levels. However, a study of 5,556 older men showed no association between current aspirin use and depression, although men who discontinued aspirin had a greater odds ratio for depression than those not using aspirin (Almeida *et al.*, 2010).

Epidemiological data suggests that aspirin exposure is associated with a reduced risk of *de-novo* depression. In a nested case control study within the Geelong Osteoporosis Study, an age-stratified community sample of 1,494 women randomly selected from electoral rolls that was followed up over a period of 10 years. One hundred and four women had been exposed to aspirin; median duration of exposure was 7.0 years (IQR 2.1–10.0). Exposure to aspirin was associated with a

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trend towards an age-adjusted reduction in risk for de-novo MDD, with an OR of 0.18 (95%CI 0.02–1.39, $p = 0.1$). Exposure to aspirin was documented for 1 of 22 depression cases and 103 of 323 controls (5% vs. 32%, $p = 0.007$) (Pasco *et al.*, 2010a). The relationship between aspirin exposure and depression risk has also been examined in men in the same study. Among 139 exposed and 803 non-exposed men followed for 5 years, aspirin was associated with an OR of 0.18 (0.07–0.44 $p = 0.00$; unpublished data) for less depression. Although observational data alone does not provide strong evidence of efficacy it provides a rationale for a definitive assessment in a randomized placebo-controlled trial.

There is also clinical trial evidence suggesting possible beneficial effects of aspirin when given concurrently with antidepressant medication in depression. In an observational study of 70 patients with depression, administration of aspirin together with fluoxetine conferred a greater reduction in biochemical markers of oxidative stress compared with fluoxetine alone. In another study, there appeared to be an accelerated antidepressant response to antidepressants with adjuvant aspirin (Mendlewicz *et al.*, 2006). A number of anti-inflammatory agents as diverse as celecoxib, pioglitazone, and infliximab have also shown promising efficacy in depression (Maes *et al.*, 2012b). In aggregate, this evidence is not of sufficient strength to warrant change in clinical practice, but is supportive of the role of this study.

ASPREE study design

Overview of the ASPREE principal trial

ASPREE is a multi-center, randomized, double-blinded, placebo-controlled trial of daily 100 mg enteric-coated aspirin in 19,114 healthy community dwelling older adults in Australia and the USA. Age eligibility is 65 years and over (African Americans and Hispanics in the USA) and all others aged 70 years and over. The aim of ASPREE is to determine whether 100 mg aspirin daily extends disability-free and dementia-free survival in the elderly, and is a primary prevention study. The trial is conducted according to the requirements of the Australian National Statement on Ethical Conduct in Human Research (Australian Government, NHMRC, 2007) and the Australian Code for the Responsible Conduct of Research and has been approved by institutional review boards at all sites, adhering to the ethical principles mandated by the 2008 Declaration of Helsinki and encompasses the protocol items recommended by the International Conference on Harmonisation Good Clinical Practice E6 guidance. The protocol was developed in accordance with Standard Protocol Items Recommendations for Intervention Trials (SPIRIT) 2013 guidelines, and will be reported using CONSORT guidelines and registered on ClinicalTrials.gov Identifier: NCT01038583.

The ASPREE study methods have been described in detail elsewhere (ASPREE Investigator Group, 2013). In brief, the majority of ASPREE participants have been recruited through partnerships with general practitioner co-investigators. A minority has been recruited directly from the community.

Inclusion criteria include men and women who are able to give informed consent and able to attend a study visit. Exclusion criteria include a past history of cardiovascular event or established cardiovascular disease (including stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery reperfusion procedures and bypass grafting, abdominal aortic aneurysm, cardiac failure), atrial fibrillation, dementia or score of <78 on Modified Mini-Mental State (3MS) examination, disability as defined by severe difficulty or inability to perform anyone of the Katz activities of daily living (ADLs) at the time of randomization, a condition with a high current or recurrent risk of bleeding, anemia, a condition likely to cause death within 5 years, current use of other antiplatelet or antithrombotic medication, current use of aspirin for secondary prevention, and uncontrolled hypertension.

Randomization of study drug follows a block randomization procedure and is stratified by site and age (65–79 and >80 years). Participants were randomized to receive either 100 mg of enteric coated aspirin or an enteric coated placebo, which were identical in appearance, in a ratio of 1:1, with study participants, investigators and general practitioner co-investigators blinded to allocation.

The ASPREE study began in 2010, completed recruitment in December 2014 (16,703 in Australia and 2,411 in the USA) and will conclude in 2017/2018.

The primary ASPREE endpoint is a composite of death or dementia (adjudicated according to the DSM-IV criteria) or persistent loss of the same Katz ADL. Pre-specified secondary endpoints include death, cardiovascular and cerebrovascular disease, cancer, cognitive impairment, depression, physical disability, and clinically significant bleeding. All clinical and safety endpoints, especially bleeding, are adjudicated by independent endpoint adjudication committees who are provided with de-identified clinical information about the event.

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Study design of ASPREE-D (depression)

ASPREE-D is a sub-study of the ASPREE principal clinical trial, and has been approved by the ASPREE International Steering Committee. The primary outcome variable will be a diagnosis of an episode of MDD defined as CES-D-10 item scale score of 8 or above. As some participants may have a CES-D score of 8+ at baseline or a past history of depression, the study aims to look at both incident and recurrent depression. The CES-D self-completed questionnaire rates the severity of depressive symptoms in general populations. Use of self-rated scales obviates inter-rater variability issues in multi-site studies. It has been extensively validated across different cultural groups and the elderly (Dozeman *et al.*, 2011). It identifies depression in the elderly with or without cognitive impairment and has a single factor structure. Using the Structured Clinical Interview for DSM-IV as the reference, the sensitivity and specificity of the CES-D was 82% and 83% respectively (Ghubash *et al.*, 2000) in one study, 74% and 87% respectively for current major depression or dysthymia in a second study (Tuunainen *et al.*, 2001).

The CES-D was administered initially at baseline and at each odd year of follow-up (1, 3, 5, or 7 years). Upon receipt of further funding we more recently have added CES-D assessments to the intervening even years (2, 4, and 6 years). Hence in ASPREE-D, participants will be measured for depression annually until the end of their participation in the study. The Quality of life Short Form–12 (SF-12) is a secondary outcome measure of ASPREE-D. It is a 12-item self-rated generic tool to assess functional health and well-being, with physical component summary (PCS) and mental component summary (MCS) scores.

Baseline bloods are already collected on the majority of Australian ASPREE participants through the ASPREE Healthy Ageing Biobank, approximately 8,500 prior to starting trial medication, with approximately 6,800 of these contributing a follow-up year three sample and approximately 5,000 of these still on randomized study medication. We plan to measure biomarkers at baseline and at 3 years follow up in this sub-sample of 5,000 participants. Inflammatory biomarkers to be measured in the sub-sample of cases and controls include hs-CRP, IL-6, and TNF-α, based on recent meta-analyses highlighting these as the key biomarkers of depression risk (Hiles *et al.*, 2012).

For the primary hypothesis, the target ASPREE sample size was 19,000. To assess power for testing the primary hypothesis that aspirin will reduce the risk of depression over the 5 years of the study, we assume based on the extant literature that the risk of depression at any time point in the placebo group is 10%. We assume a correlation of 0.6 between baseline and follow up measurements of depression with a compound symmetry correlation pattern. With a 5% significance level, and assuming a 5% drop out rate per year over 5 years, we have 90% power to detect an odds ratio of 0.9 when comparing depression risk in the aspirin group to the placebo group.

For secondary hypothesis 1, using simulation techniques, the smallest detectable effect size for continuous biomarker levels, based on 90% power in multivariate logistic regression models for each biomarker fitted to data from 2,500 in the aspirin group and 2,500 controls, is an odds-ratio of 1.05 for each μg/ml unit increase of CRP level, 1.1 for each ng/ml unit increase of TNF-α level and 1.003 for each pg/ml unit increase of IL-6 level. For secondary hypothesis 2, the study will have 90% power to detect 0.5 μg/ml (SD = 3) difference in CRP, 0.3 ng/ml (SD = 2) difference in TNF-α and 6 pg/ml (SD = 40) difference in IL-6. For secondary hypothesis 3, we use the assumed 0.9 reduction in the odds of depression due to aspirin (from the primary hypothesis) and additionally assume a 1.3 fold increase in odds of depression associated with a "high" biomarker change based on a dichotomization of biomarker change scores into "high"/"low". Based on these assumptions the study has 90% power to detect an odds-ratio of 0.5 for the interaction effect of aspirin/placebo group allocation and low/high biomarker change. Power will be greater for analysis of this interaction with biomarker change on a continuum. All these calculations for secondary hypotheses are based on two-sided 0.01 type I error to allow for multiple comparisons.

All randomized ASPREE participants will have their CES-D outcome for each time point included in a logistic regression model that includes the covariate treatment group (with odds ratios estimated using generalized estimating equations with an exchangeable working correlation matrix to take account of the repeated measures for each participant). The primary outcome will be analyzed according to intention-to-treat principles. A pre-specified sub-group analysis will be performed by lifetime history of depression at baseline inclusive of a baseline CES-D of 8+, in order to look at aspirin's effect on recurrent as well as *de novo* depression. A secondary analysis will be conducted in which participants' CES-D outcomes will be removed from analysis from the time that they experience a life-limiting illness, specifically stroke, CVD, cancer (excluding non-melanoma

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skin cancer), or dementia. If necessary, a secondary set of analyses will be performed to adjust for any baseline characteristics that are found to be imbalanced between groups to the extent of a 0.25 standard deviation difference in means (quantitative measures) or an odds ratio of 1.5 (binary measures).

All analyses of secondary hypotheses related to inflammatory biomarker levels will be based on the nested case control study. Logistic regression will be used to compare baseline biomarker levels between cases and controls to address secondary hypothesis 1. Secondary hypothesis 2 will be analyzed by comparing the change in biomarkers from baseline to 3 years post randomization between the aspirin and placebo groups using analysis of covariance to adjust for baseline biomarker levels. For secondary hypothesis 3, logistic regression for the outcome depression (case/control status) will include treatment group, biomarker level at baseline, and baseline to year three change in biomarker as predictors. The model will include an interaction effect between treatment group and change in biomarker level to test the hypothesis. A second analysis will be undertaken with biomarker change dichotomized to enhance clinical interpretation. All of the analyses for each secondary hypothesis will adjust for the baseline characteristics, age, sex, comorbidity, concomitant medication, and lifetime history of depression. For hypothesis 4, that low-dose aspirin improves quality of life, assessed using the Quality of life Short Form–12 (SF-12), in healthy individuals over 65 years of age at least in part by reducing depression, we will undertake mediation analyses of aspirin's effect on QoL including the effects of CES-D. Finally, for hypothesis 5, that treatment with low-dose aspirin in those with baseline depression (high CES-D at baseline) will reduce the severity of depression compared with placebo-treatment, we will test whether mean CES-D-10 scores in subsequent years will be lower in those treated with aspirin compared with placebo in those with pre-existing depression using linear mixed models repeated measures.

Intention-to-treat analyses and dealing with missing outcome data

In additional secondary analyses, missing baseline and follow-up outcome data will be estimated through multiple imputation based on missing not at random assumption. Analyses based on imputed data will be reported as part of the sensitivity analyses using four-point framework that has been proposed to deal with this issue.

Summary

Depression produces the second-highest burden of illness worldwide. This reflects both the direct treatment costs of this disorder, and its broader impacts on other medical treatments, hospital outpatient medical care, and increased requirements for institutional care. Despite the available standard depression treatments, a large proportion of the patients with depression do not achieve remission of depressive symptoms (typically $\sim$ 30%) and most patients with depression experience a chronic illness course with multiple relapses over time. In this context, it needs to be stressed that in most branches of medicine, the greatest successes have been in prevention, and psychiatry to date has largely lacked a preventive agenda or a preventive evidence base.

ASPREE-D provides an opportunity to comprehensively establish whether an anti-inflammatory and antithrombotic agent – aspirin – can prevent the development of depression in the elderly. Large-scale prevention studies in psychiatry are rare. This study will be the first large-scale study of a preventative pharmacotherapy for depression. The size of the proposed study will likely give a definitive answer to the research hypotheses being proposed. Given the overall prevalence of MDD in this population, even a very small reduction in the incidence of depression will have a long-standing and substantive impact, at a population level and for the cost of medical care. This study may have an immediate and direct translational impact in establishing the role for aspirin in the prevention of depression in the elderly and exploring its relationship to quality of life, aided by the very low cost of the intervention. This study also will serve as a proof of concept confirmation of the inflammatory theory of depression, and establish the role of anti-inflammatory agents in both the primary and secondary prevention of depression, as well as in symptom reduction. This is likely to support the exploration of other treatment approaches targeting these pathways in both the prevention and treatment of depression, both in the elderly and in younger age groups.

Lastly, the numerator of benefit has to be balanced against the denominator of risk. For any preventive intervention rolled out across a community, the greater the number of disorders that may benefit, the greater the viability of the intervention. The use of aspirin in this age group as a preventative agent will thus be influenced by its broader efficacy and safety impact on a range of disorders that are major outcomes of the principal ASPREE study, including cardiovascular, cerebrovascular disease, and cancer. Similarly, a

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trial of this size is unique in psychiatry and only possible embedded in an existing RCT. Given that shared risk pathways such as diet, smoking and physical activity contribute to the non-communicable disorders, and appear to contribute to inflammation, this trial is an exemplar of an integrated approach to prevention (O'Neil *et al.* 2015).

Conflicts of interest

MB has received Grant/Research Support from Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier, and Woolworths, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and served as a consultant to Astra Zeneca, Bioadvantex, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck, and Servier. RCS receives research support from Eli Lilly & Co., Inc., Genentech, Inc., Merck & Co., Inc., H. Lundbeck A/S,Navidea Biopharmaceuticals, and Takeda Development Center Americas, Inc., and Toyama Chemical Co., Ltd., as a Site PI or a Site Subinvestigator. MRN has participated in trials that have received funding from SmithKline Beecham, AstraZeneca, Bayer, Sanofi-Aventis, Merck Sharpe and Dohme, Pfizer, Servier Laboratories and Bristol-Myers Squibb, has served on advisory boards for Sanofi-aventis, Novartis, Schering-Plough Solvay Pharmaceuticals and AMGEN, has prepared educational material for Servier Laboratories, AstraZeneca Bristol-Myers Squibb and MediMark and has received conference and travel support from Bayer HealthCare AG, Merck Sharpe and Dohme, Novartis and Sanofi-aventis.

Description of authors' roles

All authors contributed to study design and manuscript preparation.

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References

Alexopoulos, G. S. (2005). Depression in the elderly. *Lancet*, 365, 1961–1970.

Almeida, O. P., Alfonso, H., Jamrozik, K., Hankey, G. J. and Flicker, L. (2010). Aspirin use, depression, and cognitive impairment in later life: the health in men study. *Journal of the American Geriatrics Society*, 58, 990–992.

Ancill, R. J. and Holliday, S. G. (1990). Treatment of depression in the elderly: a Canadian view. *Prog Neuropsychopharmacol Biol Psychiatry*, 14, 655–661.

ASPREE Investigator Group (2013). Study design of ASPirin in reducing events in the elderly (ASPREE): a randomized, controlled trial. *Contemporary Clinical Trials*, 36, 555–564.

Australian Government, NHMRC. (2007). National Statement on Ethical Conduct in Human Research (2007) - Updated May 2015. Available at: https://www.nhmrc.gov.au/guidelines-publications/e72.

Berk, M. *et al.* (2013). Aspirin: a review of its neurobiological properties and therapeutic potential for mental illness. *BMC Medicine*, 11, 74.

Brunello, N. *et al.* (2006). Acetylsalicylic acid accelerates the antidepressant effect of fluoxetine in the chronic escape deficit model of depression. *International Clinical Psychopharmacology*, 21, 219–225.

Chen, Y. G. *et al.* (2006). Effect of aspirin plus clopidogrel on inflammatory markers in patients with non-ST-segment elevation acute coronary syndrome. *Chinese Medical Journal (Engl)*, 119, 32–36.

Cuijpers, P., van Straten, A., Smit, F., Mihalopoulos, C. and Beekman, A. (2008). Preventing the onset of depressive disorders: a meta-analytic review of psychological interventions. *American Journal of Psychiatry*, 165, 1272–1280.

https://doi.org/10.1017/S104161021600079X Published online by Cambridge University Press

Dean, B., Tawadros, N., Scarr, E. and Gibbons, A. S. (2010). Regionally-specific changes in levels of tumour necrosis factor in the dorsolateral prefrontal cortex obtained postmortem from subjects with major depressive disorder. *Journal of Affective Disorders*, 120, 245–248.

Dozeman, E., van Schaik, D. J., van Marwijk, H. W., Stek, M. L., van der Horst, H. E. and Beekman, A. T. (2011). The center for epidemiological studies depression scale (CES-D) is an adequate screening instrument for depressive and anxiety disorders in a very old population living in residential homes. *International Journal of Geriatric Psychiatry*, 26, 239–246.

Fisher, M., Cushman, M., Knappertz, V. and Howard, G. (2008). An assessment of the joint associations of aspirin and statin use with C-reactive protein concentration. *American Heart Journal*, 156, 106–111.

Gao, X. R. *et al.* (2009). Efficacy of different doses of aspirin in decreasing blood levels of inflammatory markers in patients with cardiovascular metabolic syndrome. *Journal of Pharmacy and Pharmacology*, 61, 1505–1510.

Ghubash, R., Daradkeh, T. K., Al Naseri, K. S., Al Bloushi, N. B. and Al Daheri, A. M. (2000). The performance of the center for epidemiologic study depression scale (CES-D) in an Arab female community. *International Journal of Social Psychiatry*, 46, 241–249.

Hiles, S. A., Baker, A. L., de Malmanche, T. and Attia, J. (2012). A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. *Brain Behavior and Immunity*, 26, 1180–1188.

Ikonomidis, I., Andreotti, F., Economou, E., Stefanadis, C., Toutouzas, P. and Nihoyannopoulos, P. (1999). Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation*, 100, 793–798.

Jenny, N. S. *et al.* (2012). Long-term assessment of inflammation and healthy aging in late life: the cardiovascular health study all stars. *The Journals of Gerontology, Series A Biological Sciences and Medical Sciences*, 67, 970–976.

Krishnadas, R. and Cavanagh, J. (2012). Depression: an inflammatory illness? *Journal of Neurology, Neurosurgery & Psychiatry*, 83, 495–502.

Liu, Y., Ho, R. C. and Mak, A. (2012). Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. *Journal of Affective Disorders*, 139, 230–239.

Maes, M. *et al.* (2012a). Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Medicine*, 10, 66.

Maes, M., Fisar, Z., Medina, M., Scapagnini, G., Nowak, G. and Berk, M. (2012b). New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates–Nrf2 activators and GSK-3 inhibitors. *Inflammopharmacology*, 20, 127–150.

Mendlewicz, J., Kriwin, P., Oswald, P., Souery, D., Alboni, S. and Brunello, N. (2006). Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. *International Clinical Psychopharmacology*, 21, 227–231.

Moylan, S., Maes, M., Wray, N. R. and Berk, M. (2013). The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Molecular Psychiatry*, 18, 595–606.

O'Neil, A. *et al.* (2015) A shared framework for the common mental disorders and non-communicable disease: key considerations for disease prevention and control. *BMC Psychiatry*. 5, 15.

Palsson, S. P., Ostling, S. and Skoog, I. (2001). The incidence of first-onset depression in a population followed from the age of 70 to 85. *Psychological Medicine*, 31, 1159–1168.

Pasco, J. A. *et al.* (2010a). Clinical implications of the cytokine hypothesis of depression: the association between use of statins and aspirin and the risk of major depression. *Psychotherapy and Psychosomatics*, 79, 323–325.

Pasco, J. A. *et al.* (2010b). Association of high-sensitivity C-reactive protein with de novo major depression. *British Journal of Psychiatry*, 197, 372–377.

Tuunainen, A., Langer, R. D., Klauber, M. R. and Kripke, D. F. (2001). Short version of the CES-D (Burnam screen) for depression in reference to the structured psychiatric interview. *Psychiatry Research*, 103, 261–270.

Wang, Y., Yang, F., Liu, Y. F., Gao, F. and Jiang, W. (2011). Acetylsalicylic acid as an augmentation agent in fluoxetine treatment resistant depressive rats. *Neuroscience Letters*, 499, 74–79.

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