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Effect of Aspirin vs Placebo on the Prevention of Depression in Older People
A Randomized Clinical Trial

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IMPORTANCE Depression is associated with increased inflammation, which may precede its onset, especially in older people. Some preclinical data suggest potential antidepressant effects of aspirin, supported by limited observational data suggesting lower rates of depression in individuals treated with aspirin. There currently appears to be no evidence-based pharmacotherapies for the primary prevention of depression.

OBJECTIVE To determine whether low-dose aspirin (100 mg) reduces the risk of depression in healthy older adults.

DESIGN, SETTING, AND PARTICIPANTS This double-blinded, placebo-controlled randomized clinical trial was a substudy of the Aspirin in Reducing Events in the Elderly (ASPREE) trial, which examined if aspirin increased healthy life span, defined as survival free of dementia and disability. The prespecified secondary outcome was depression. Individuals of all races/ethnicities older than 70 years in Australia, as well as white individuals older than 70 years and black and Hispanic individuals older than 65 years in the United States, were included.

INTERVENTIONS Participants were randomized to aspirin (100 mg daily) or placebo, with a median (interquartile range) follow-up of 4.7 (3.5-5.6) years.

MAIN OUTCOMES AND MEASURES The primary outcome was a proxy measure of major depressive disorder defined as a score of 8 or more on the Center for Epidemiologic Studies Depression 10-item (CES-D-10) scale.

RESULTS Of the 19 114 participants enrolled in the trial, 9525 received aspirin and 9589 received a placebo. The mean (SD) age was 75.2 (4.0) years in the aspirin group and 75.1 (4.5) years in the placebo group; 9531 (56.4%) were women. Participants' demographics and clinical characteristics at baseline were similar between groups. A total of 79 886 annual CES-D-10 measurements were taken, with a mean of 4.2 measurements per participant. There were no significant differences at annual visits in the proportions of CES-D-10 scores of 8 or more between the aspirin and placebo groups. The incidence rate of new CES-D-10 scores of 8 or more was 70.4 events per 1000 person-years in the aspirin group and 69.1 in the placebo group (hazard ratio, 1.02 [95% CI, 0.96-1.08]; $P = .54$).

CONCLUSIONS AND RELEVANCE Low-dose aspirin did not prevent depression in this large-scale study of otherwise healthy older adults.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01038583

Supplemental content

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Preventive approaches for many noncommunicable disorders from cancer to cardiovascular disease have had major influence on incidence, morbidity, and mortality. Psychiatry, in contrast, lacks an evidence base for population-wide prevention strategies. Existing effective preventive strategies for depression largely use psychotherapeutic, cognitive behavioral-type therapies for people with early-stage or emerging symptoms.[1] There are no evidence-based primary preventive pharmacotherapies for depression.

Support for a possible role of inflammation in depression include the association between inflammatory disorders and higher rates of depression, the propensity of proinflammatory cytokines and interferon administered to volunteers to induce depressive symptoms, and higher levels of the inflammatory blood biomarkers tumor necrosis factor α, interleukin-6 (IL-6), and C-reactive protein in depression, including in late-life depression.[2,3] After antidepressant treatment for depression, IL-4, IL-6, and IL-10 cytokine levels were reduced when symptoms were reduced.[4] Higher levels of cytokines and acute-phase markers, such as C-reactive protein, appear to precede the onset of de novo depression.[5] These associations raise the question as to whether depression could be prevented by suppressing inflammation. Indeed, preclinical, pharmacoepidemiologic, and pilot clinical trial data suggest that aspirin, with its anti-inflammatory properties, may have clinical potential.[6]

The Aspirin for the Prevention of Depression (ASPREE-D) trial[7] is a substudy of the Aspirin in Reducing Events in the Elderly (ASPREE) trial. The parent study was a 5-year randomized clinical trial jointly supported by the National Institute on Aging and the Australian National Health and Medical Research Council comparing the effects of aspirin (100 mg daily) and placebo in 19 114 healthy older adults on survival free of dementia or physical disability.[8,9] The primary aim of ASPREE-D was to determine if the use of low-dose aspirin reduces the risk of depression in healthy individuals 70 years or older (or 65 years or older among racial/ethnic minorities in the US), as assessed using the Center for Epidemiologic Studies Depression Scale 10-item (CES-D-10) scores.[9] The secondary aims were to determine its effect on mental health quality of life, as indexed by the 12-item Short Form Health Survey (SF-12) mental component summary scores, and assess the time to a first CES-D-10 score of 8 or more, as well as incidence of hospitalization for depression. The primary hypothesis was that low-dose aspirin would reduce the risk of depression, defined as a CES-D-10 score of 8 or more, at any postrandomization point.

Key Points

Question Does low-dose aspirin reduce the risk of depression in healthy older adults?

Findings In this randomized clinical trial of 19 114 older adults in Australia and the United States, those taking low-dose aspirin (100 mg daily) did not have a lower rate of prevalent depression compared with those taking a placebo, per measurements taken at any of the postrandomization annual visits.

Meaning In this study, low-dose aspirin did not prevent depression in healthy older adults.

Methods

The ASPREE trial was a multicenter, double-blinded, placebo-controlled, primary-prevention randomized clinical trial of daily usage of 100 mg of enteric-coated aspirin among older adults who were relatively healthy and community dwelling in Australia and the US and were 70 years and older (or 65 years or older, if African American or Hispanic and dwelling in the US). The trial was conducted according to the Australian National Statement on Ethical Conduct in Human Research,[10] the Australian Code for the Responsible Conduct of Research,[11] the 2008 Declaration of Helsinki,[12] and the International Conference on Harmonization of Good Clinical Practice E6[13] and was approved by institutional review boards at all sites. The protocol was developed in accordance with Standard Protocol Items Recommendations for Intervention Trials (SPIRIT) 2013 guidelines,[14] reported using the Consolidated Standards of Reporting Trials (CONSORT) guidelines and according to the International Conference on Harmonization E9 Statistical Principles for Clinical Trials,[15,16] and registered on ClinicalTrials.gov (identifier NCT01038583).

Both ASPREE and ASPREE-D study methods are published in detail elsewhere (protocol in Supplement 1).[7,9] In Australia, recruitment largely took place in primary care settings. General practitioners provided a list of participants who were potentially eligible, and they were sent letters of invitation. When participants contacted the ASPREE Coordinating Center, screening questions were asked, and further screening was conducted at 2 baseline study visits. In between the study visits, the general practitioners assessed participants' health and those considered sufficiently healthy for a primary prevention trial of low-dose aspirin were deemed eligible for the study. Researchers in the US identified participants using clinic-based mailing lists, electronic medical records, and advertisements. Men and women were included in the study if they were willing and able to give informed consent and were eligible for randomization. Key exclusion criteria were a history of a diagnosed 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, and cardiac failure); atrial fibrillation; dementia or a score of less than 78 on the Modified Mini-Mental State Examination; substantial physical disability, defined by severe difficulty or inability to perform any of the 6 Katz activities of daily living at baseline; 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; or uncontrolled hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥105 mm Hg).

Randomization of the study drug followed a block randomization procedure and was stratified by site and age (65-79 vs >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. Study participants, investigators, and general practitioner coinvestigators were blinded to treatment allocation.

The ASPREE study began in March 2010, completed recruitment in December 2014, and was concluded in June 2017 because of a National Institutes of Health determination of futility regarding the primary end point. The primary ASPREE end point was a composite of death or dementia (adjudicated according to the *DSM-IV* criteria) or persistent loss of the same Katz basic activity of daily living. All clinical and safety end points were adjudicated by independent end point adjudication committees who were provided with deidentified clinical information about the event.

The principal outcome variable of ASPREE-D was a proxy measure of major depressive disorder, defined as a CES-D-10 score of 8 or more. Because some participants may have had a CES-D-10 score of 8 or more at baseline or a history of depression, this primary outcome pooled both incident and recurrent depression. The CES-D-10 is a validated self-rated questionnaire with a single factor structure[17] that indexes depressive symptom severity in community populations.[18,19] When compared with a formal psychiatric diagnosis of late-life depression, the scale has been shown to have a sensitivity of 97% and a specificity of 84%.[20] Against a formal *DSM-IV* diagnosis, the sensitivity and specificity of the CES-D-10 were 82% and 83%, respectively.[21]

The CES-D-10 was initially administered at baseline and at years 1, 3, 5, and 7. On receipt of further funding (National Health and Medical Research Council identifier GNT1081901), we added CES-D-10 assessments to years 2, 4, and 6. Participants were thus assessed for depression annually until the end of their participation in the study. The number of participants who reached the CES-D-10 threshold at any annual follow-up was a secondary outcome measure of ASPREE and a primary outcome of ASPREE-D. The SF-12 was administered annually. The mental component summary score was a secondary outcome measure of ASPREE-D.

The target ASPREE sample size was 19 000. To assess power for the ASPREE-D primary hypothesis, we extrapolated from the extant literature[22] that the risk of prevalent depression at any time in the placebo group would be 10%. We anticipated a 5% annual dropout rate and a within-participant correlation of 0.60 between baseline and follow-up measurements of depression, using a compound symmetry matrix. Based on these assumptions, we had 90% power to detect the specified difference in depression risk (ie, an odds ratio [OR] of 0.90 at annual follow-up) between the aspirin and placebo group at a 5% significance level.[7]

Statistical Analyses

Primary analyses were undertaken by 3 authors (M.M., J.E.L., and R.W.) on an intent-to-treat basis, including all participants as randomized regardless of treatment received. Details of the predefined statistical analyses plan for ASPREE have been published elsewhere.[8] The primary effectiveness analysis compared the aspirin and the placebo groups with regard to changes in the prevalence ratio of CES-D-10 scores of 8 or more from baseline to annual follow-up visits. Treatment effects for the repeated binary CES-D-10 outcomes were determined via a population mean model using the generalized estimating equation (GEE) approach with logit link function. The GEE model accounted for within-individual repeated measures using an exchangeable working correlation matrix, and a robust sandwich variance estimator was used. The model contained the fixed effect of intervention allocation and nominal values of measurement points (annual visits) as the main effects, and a 2-way interaction between intervention allocation and annual visit. The 2-way interaction estimates the effect of aspirin across the annual visits in this setting. Ratios of ORs and 95% CIs from the 2-way interaction parameters were reported to compare the aspirin group with placebo at each annual visit follow-up with respect to baseline. The global test of the interaction term was then used to test the primary hypothesis of differential between-group (ie, aspirin vs placebo) change in the proportions of CES-D-10 scores of 8 or more. Similar analytical approaches were used for exploratory analyses based on higher cutoffs of CES-D-10 scores at 10 or more and 12 or more, given data that biological therapies, such as antidepressants, may have greater efficacy in individuals with more severe depression.[23]

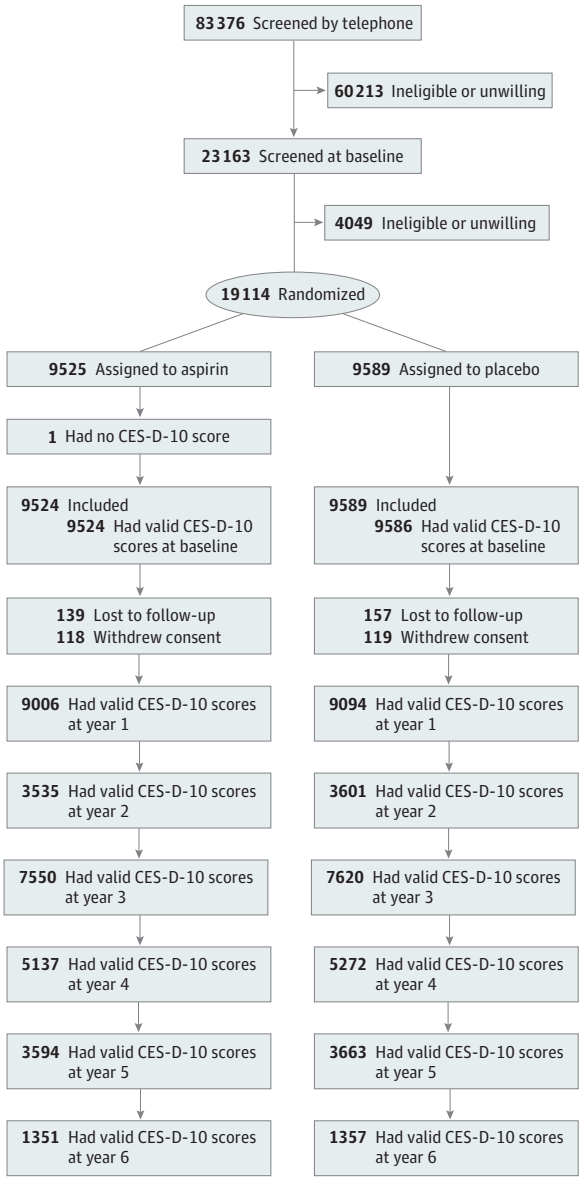
The GEE models, assuming Gaussian distribution with identity link function, were used for analyzing the SF-12 mental component. The GEE models accounted for within-individual repeated measures using an unstructured working correlation matrix. The SF-12 models used the same fixed-effect parameter structure as the CES-D-10 binary outcome models, and for SF-12, the 2-way interaction of intervention allocation and follow-up time estimated the intervention effect as between-group differential change from baseline scores at each annual visit follow-up. The coefficients from the 2-way interactions were reported as aspirin effects at each follow-up annual visit, with 95% CIs. In addition, the Cohen *d* effect size for between-group differential change was reported. Cox proportional-hazards models were used in participants with CES-D-10 scores less than 8 at baseline to compare incidence rate of CES-D-10 scores of 8 or more at annual follow-ups between the aspirin and placebo groups. Hazard ratios and 95% CIs were reported.

Logistic regression was used for comparing overall proportion of hospitalization at follow-up periods attributable to depression in the aspirin and placebo groups. All tests of treatment effects were conducted using an α level of .05. For the primary outcome, *P* values were not presented for the annual follow-up comparisons, and only the overall χ^2 test for the interaction was reported. Confidence intervals and *P* values were not adjusted for multiple comparisons in secondary outcomes. All analyses were performed using Stata version 15 (StataCorp).

Results

A total of 19 114 participants (16 703 in Australia and 2411 in the US) were recruited from March 2010 to December 2014 and randomized to receive aspirin or placebo (9525 participants to the

Figure 1. Consolidated Standards of Reporting Trials Diagram for the Aspirin for the Prevention of Depression Trial



CES-D-10 indicates Center for Epidemiologic Studies Depression 10-item scale.

aspirin group and 9589 to the placebo group) (**Figure 1**). The demographic and clinical characteristics of the participants at baseline according to the CES-D-10 cutoff in both groups were similar (**Table 1**). The mean (SD) age of the participants was 75.2 (4.60) years in the aspirin group and 75.1 (4.5) years in the placebo group, and 9531 (56.4%) of the participants were women. Regarding background, 16 007 participants (93.5%) were white, and 16 463 (95.6%) spoke English at home. Details of the baseline characteristics of the cohort are published elsewhere.[24]

The mean (SD) CES-D-10 score at baseline was 3.2 (3.3) in both groups. There were 1879 participants with a baseline CES-D-10 score of 8 or more, with 925 (9.7%) in the aspirin group and 954 (9.9%) in the placebo group. A total of 1666 participants (50.2% in the aspirin group) reported a history of depression (ie, having ever been diagnosed or treated by a physician for depression), of whom 202 (24.1%) had CES-D-10 scores of 8 or more at baseline taking aspirin and 206 (24.9%) taking placebo. Subgroup analysis of these participants showed no significant difference in the prevalence of depressive symptoms at annual follow-ups (follow-up year by treatment group interaction: χ^2_6, 3.75; P = .71). Further exploration showed no specific pattern in baseline adjusted depressive symptoms ratios at annual follow-ups (OR range, 0.92-1.67). Antidepressant use was not statistically different between treatment groups at baseline or across annual follow-ups.

Adherence to treatment was measured, and 11 281 of 17 868 participants (63.1%) were still taking study medication after the median 4.7 years of follow-up. The participants in each group taking the study medication in the final year numbered 5512 of 8869 (62.1%) for aspirin and 5769 of 8999 (64.1%) for placebo. When calculated as a proportion of time in the study, participants in the aspirin arm took the study medication for a mean (SD) of 73% (35%) of their time in the study; this was a mean (SD) of 75% (34%) in the placebo arm. These rates are consistent with other pragmatic primary prevention trials.

Principal End Point of ASPREE-D (CES-D)

Of 19 114 randomized participants, 1 participant had no CES-D-10 measurement and 19 113 participants had a baseline and at least 1 valid follow-up CES-D-10 measurement. In total, 79 886 CES-D-10 participant measurements were reported across the study period, with a mean of 4.2 measurements per participant.

Table 2 shows the number of participants with CES-D-10 scores of 8 or more in aspirin and placebo groups at baseline and follow-up annual visits. The prevalence of depressive symptoms was higher at annual visits than baseline in both groups (Table 2), with the proportion of participants with CES-D-10 scores of 8 or more increasing to almost double at the end of follow-up. However, the changes from baseline were not significantly different between aspirin and placebo groups.

Secondary End Points of ASPREE-D

SF-12 Mental Scores

A total of 90 980 SF-12 measurements from 19 111 participants were taken over the study period (**Table 3**). The mean (SD) mental component summary scores at baseline were 55.8 (7.1) and 55.6 (7.2) in the aspirin and placebo groups, respectively. Between-group differential changes (aspirin vs placebo) from baseline ranged from 0.0 to 0.3 points in favor of the placebo group; however, the differences were very small (Cohen d ≤0.10). No significant differences were observed between aspirin and placebo groups in differential changes from baseline of the SF-12 mental component summary score (χ^2_6, 9.61; P = .14).

Hospitalization Attributable to Depression

A total of 58 participants were hospitalized for depression during the study period, of whom 33 (0.35%) were in the aspirin group and 25 (0.26%) were in the placebo group. There was

Table 1. Demographic Characteristics of Participants, Stratified by Center for Epidemiologic Studies Depression 10-Item Scale (CES-D-10) Score of 8 or More at Baseline

	Patients, No. (%)			
	Aspirin group (n = 9524)[a]		Placebo group (n = 9586)[a]	
Demographic categories	CES-D-10 < 8	CES-D-10 ≥ 8	CES-D-10 < 8	CES-D-10 ≥ 8
Total	8599 (90.3)	925 (9.7)	8632 (90.0)	954 (10.0)
Age, mean (SD), y	75.1 (4.6)	75.3 (4.8)	75.1 (4.5)	75.1 (4.6)
Weight, mean (SD), kg	76.9 (15.0)	77.6 (16.6)	77.1 (14.7)	76.6 (15.8)
BMI, mean (SD)	28.0 (4.7)	28.8 (5.5)	28.0 (4.6)	28.6 (5.3)
Female	4778 (55.6)	595 (64.3)	4753 (55.1)	653 (68.5)
Country				
Australia	7526 (87.5)	795 (86.0)	7578 (87.8)	800 (83.9)
United States	1073 (12.5)	130 (14.0)	1054 (12.2)	154 (16.1)
Living status				
At home alone	2710 (31.5)	387 (41.8)	2739 (31.7)	414 (43.4)
At home with family, friends, or a spouse	5858 (68.1)	529 (57.2)	5856 (67.8)	534 (56.0)
In a residential home[b]	31 (0.4)	9 (1.0)	37 (0.5)	6 (0.6)
Hispanic/Latino ethnicity	215 (2.5)	25 (2.7)	209 (2.4)	39 (4.1)
Race				
White	7992 (94.0)	832 (90.6)	8015 (93.8)	855 (90.7)
Black/African American	391 (4.6)	66 (7.2)	387 (4.5)	65 (6.9)
Other	124 (1.4)	20 (2.2)	143 (1.7)	23 (2.4)
English-speaking	8189 (95.2)	885 (95.7)	8274 (95.9)	912 (95.6)
Born overseas	1928 (22.4)	215 (23.2)	1937 (22.4)	195 (20.4)
Education >12 y	4744 (55.2)	473 (51.2)	4737 (54.9)	523 (54.8)
Smoking status				
Current	298 (3.5)	54 (5.8)	326 (3.8)	56 (5.9)
Former	3519 (40.9)	389 (42.1)	3522 (40.8)	367 (38.4)
Never	4782 (55.6)	482 (52.1)	4784 (55.4)	531 (55.7)
Alcohol drinking				
Current	6644 (77.3)	664 (71.8)	6629 (76.8)	701 (73.5)
Former	488 (5.7)	78 (8.4)	493 (5.7)	77 (8.1)
Never	1467 (17.0)	183 (19.8)	1510 (17.5)	176 (18.4)
Depression history[c]				
Unsure	48 (1.6)	8 (1.8)	41 (1.4)	12 (2.8)
No	2356 (77.5)	238 (53.1)	2385 (78.2)	216 (49.8)
Yes	635 (20.9)	202 (45.1)	623 (20.4)	206 (47.4)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] One CES-D-10 score was missing in the aspirin group, and 3 were missing in the placebo group at baseline.

[b] Supervised care or assisted living.

[c] The question about a history of depression were only asked after June 2013 (n = 6970 participants).

no statistically significant difference in the between-group comparison of hospitalization proportions (OR, 1.33 [95% CI, 0.79-2.24]).

Incidence Rate of CES-D-10 Scores of 8 or More

A total of 2350 participants in the aspirin group (70.4 events per 1000 person-years) and 2314 in the placebo group (69.1 events per 1000 person-years) reached the end point of a CES-D-10 score of 8 or more for the first time at an annual follow-up. The between-group difference was not significant (hazard ratio, 1.02 [95% CI, 0.96-1.08]; $P = .54$) (**Figure 2**).

Exploratory End Point of ASPREE-D

CES-D-10 Scores of 10 or More and 12 or More

In a sensitivity analysis, a similar pattern of only small differences between the aspirin and placebo groups was observed for those with more severe depression using both CES-D-10 score cutoffs of 10 or more and 12 or more, as was seen for the cutoff score of 8 or more (eTable in Supplement 2). None of these were statistically significant.

Discussion

The results of ASPREE-D failed to support the primary hypothesis of this study that individuals taking low-dose aspirin would have a lower rate of prevalent depression compared with those taking placebo, with depression defined in this large pragmatic trial as a CES-D-10 score of 8 or more at any postrandomization annual visit. Given the large sample size, the prolonged observation window, and the rigor of the primary ASPREE study in ascertaining end points and maintaining follow-up, this suggests that low-dose aspirin is unlikely to be effective in preventing depression in a healthy older cohort. It

Table 2. Comparison of Prevalent Scores of 8 or More on the Center for Epidemiologic Studies Depression 10-Item Scale at Follow-up in Aspirin and Placebo Groups[a]

Year	Patients, No.	Aspirin group, No. (%)	Placebo group, No. (%)	Odds ratio[b] (95% CI)
Baseline	19 110	925 (9.7)	954 (9.9)	NA
1	18 100	1454 (16.1)	1424 (15.7)	1.06 (0.96-1.18)
2	7132	566 (16.0)	539 (15.0)	1.09 (0.94-1.24)
3	15 170	1316 (17.4)	1307 (17.1)	1.06 (0.95-1.17)
4	10 409	868 (16.9)	903 (17.1)	1.04 (0.92-1.17)
5	7257	663 (18.5)	675 (18.4)	1.05 (0.92-1.19)
6	2708	257 (19.0)	245 (18.1)	1.13 (0.94-1.34)

Abbreviation: NA, not applicable.

[a] *P* value and (test statistic) for intervention by follow-up (annual visit) interaction test: χ^2_6, 2.68; *P* = .85.

[b] Odds ratio comparing aspirin with placebo at follow-up annual visit, divided by the odds ratio comparing the 2 groups at baseline.

Table 3. Twelve-Item Short-Form Health Survey Mental Component Summary Scores Comparison in Aspirin and Placebo Groups

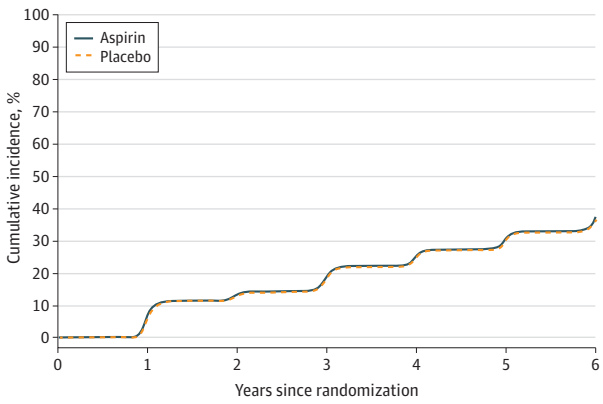
		Mental component score			
		Mean (SD)			
Year	Patients, No.	Aspirin group	Placebo group	Differential change[a] (95% CI)[b]	Effect size (Cohen *d*)
Baseline	19 106	55.8 (7.1)	55.6 (7.2)	NA	NA
1	18 088	55.5 (7.4)	55.6 (7.1)	-0.3 (-0.5 to 0.0)	-0.03
2	17 350	55.7 (7.3)	55.6 (7.4)	0.0 (-0.2 to 0.2)	0.00
3	15 112	55.6 (7.5)	55.6 (7.3)	-0.1 (-0.4 to 0.1)	-0.01
4	11 413	55.6 (7.5)	55.7 (7.4)	-0.2 (-0.5 to 0.0)	-0.02
5	7209	55.2 (7.5)	55.4 (7.5)	-0.3 (-0.7 to 0.0)	-0.04
6	7209	55.5 (7.6)	55.4 (7.2)	-0.2 (-0.7 to 0.2)	-0.07

Abbreviation: NA, not applicable.

[a] Differential change from baseline at follow-ups (aspirin vs placebo) was estimated from a 2-way interaction of intervention allocation and follow-up annual visit from a generalized estimating equation model; the references were the baseline measurement and the placebo group.

[b] *P* value and test statistic for intervention by follow-up annual visit interaction test: χ^2_6, 9.61; *P* = .14.

Figure 2. Cumulative Incidence of Incident Depression



An episode of major depressive disorder was defined as Center for Epidemiologic Studies Depression 10-item scale score of 8 or more. Shown is the cumulative incidence of incident depression (ie, first episodes of depression among those in whom it was not present at baseline) observed during the trial.

also adds to the null findings for aspirin in cardiovascular events,[25] disability-free survival,[26] and all-cause mortality[27] in the ASPREE parent study.

The association of depression with elevated markers of inflammation has spurred the initiation of multiple preclinical,[28-30] epidemiological,[31-34] and clinical[35,36] studies of aspirin and other anti-inflammatory therapies, such as celecoxib. A meta-analysis of observational data supports the efficacy of celecoxib in depression.[37] Aspirin is a nonsteroidal anti-inflammatory agent that acts as an irreversible inhibitor of both cyclooxygenase-1 and cyclooxygenase-2. It promotes production of anti-inflammatory moieties, such as lipoxins, which may lower levels of inflammatory biomarkers, including C-reactive protein, tumor necrosis factor α, and IL-6, and reduce biomarkers of oxidative damage.[6]

Aspirin was associated with increased sucrose preference and reduced immobility in the forced swim test, as well as decreased cortisol levels and increased brain serotonin levels in an interferon model of depression in Sprague Dawley rats, suggesting both clinical model efficacy and influences on salient pathways.[38] Several pharmacoepidemiology studies suggest that people taking aspirin may have a lower risk for depression,[33,34,39,40] notwithstanding some conflicting data that have failed to show a benefit of aspirin.[41,42] Early clinical trials of aspirin in mood disorders have also generated promising but preliminary signals of efficacy. Adjunctive aspirin together with sertraline was superior to sertraline alone in participants with major depressive disorder. Additionally, in two 2 × 2 designs of minocycline and aspirin and *N*-acetylcysteine and aspirin, both combination strategies seemed more effective than the placebo combinations.[31,43,44] However, treatment and prevention studies of definitive methodological quality are necessary to confirm these preliminary findings.

The major successes in morbidity of other noncommunicable disorders have arguably been in prevention, not treatment. Unlike the declining rates of disability resulting from, for example, cardiovascular disease,[45] the burden of disability from depression has not declined and may even be increasing.[46] The identification of inflammatory biomarkers associated with depression risk suggests that strategies targeting these may be a plausible therapeutic and preventive approach. Because these inflammatory markers are shared between a myriad of common noncommunicable medical disorders, treatment affecting these pathways may provide compound benefits across several common mental and medical conditions.[47] This argues for a shared approach to tackle noncommunicable disorders,[48] a

key philosophical premise of ASPREE. However, the many off-target outcomes of aspirin use,[49] particularly those associated with bleeding,[25] might challenge the widespread indication of aspirin for primary prevention in an older population that is otherwise healthy. Accordingly, the significant increased risk of bleeding events documented in the ASPREE study was not matched by benefit in terms of reduced depression risk.

Strengths of the study include its large sample size, extensive characterization of the participants, the extensive length of the follow-up period, the participation of healthy older people across 2 continents, and the simplicity of the design. In this complex multi-end point study, structured diagnostic interviews were not feasible. The CES-D-10 score, despite being designed as a screening tool, is validated for use in such studies, correlates well with structured interview, and obviates interrater variability issues in multisite studies.

Limitations

The fact that the ASPREE cohort had higher baseline quality of life than is noted in other population-based studies of older adults probably suggests biased recruitment in favor of individuals who are healthy, a reflection of this primary prevention study's exclusion criteria. Therefore, some demographic features may have differed from the broader population (such as lower rates of smoking), which may compromise assay sensitivity and the generalizability of our findings.[50] Nevertheless, there were high CES-D-10 scores at baseline across the cohort, despite the selection of an older population that was relatively healthy. These data are thus not necessarily translatable to people with substantial medical comorbidities or younger populations. Annual assessments may miss intercurrent changes in mood.

The dosage of aspirin is an area of uncertainty. The literature is unclear on the question of whether low-dose aspirin is able to lower inflammatory cytokines to a meaningful extent.[51-53] A successful treatment study of aspirin in schizophrenia used a dose of 1 g daily.[54] This negative trial therefore should not necessarily inhibit future studies that, for example, include younger cohorts at earlier illness stages, use higher doses, stratify for baseline biomarkers, or examine groups at high risk and explore indicated or secondary prevention. Stratification according to baseline biomarkers might clarify groups that could benefit from such therapies; future studies in this regard are planned. Future studies should also consider the balance between potential benefits vs harms of low-dose aspirin for primary prevention—especially in light of the significant increased bleeding risk described in ASPREE and other cohorts, including in younger individuals.[55,56]

Conclusions

In summary, this study failed to confirm any potential benefit of low-dose aspirin in reducing the risk of depression in this relatively healthy older population. This lack of efficacy is compounded by a clear increase in the risk of bleeding events documented in previous reports from this study.[24] The findings do not support the hypothesis that low-dose aspirin can prevent late-life depression.

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