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Regular Aspirin Use Does Not Reduce Risk of Cognitive Decline

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To the editor

Regular aspirin use is routinely recommended for protection against cerebrovascular and cardiovascular events. Although cerebrovascular pathology contributes importantly to risk of dementia, it is not well-established whether aspirin use attenuates this risk. Our previous work has demonstrated that transient ischemic attack (TIA) or report of stroke-like symptoms are associated with increased risk of cognitive impairment in cross-sectional analyses¹ and with incident cognitive decline during longitudinal follow-up² in the Reasons for Geographical and Racial Differences in Stroke (REGARDS) study³.

Our objective was to determine whether regular aspirin use protects against incident cognitive decline in REGARDS. The REGARDS study has enrolled 30,239 participants for whom extensive demographic and health data were collected. Several cognitive assessments have occurred during longitudinal follow-up of the cohort. A measure of global cognitive status, the Six-item Screener (SIS) has been administered annually since 2003. Additional cognitive measures were subsequently added to the protocol for consistency with the 5-minute neuropsychological battery recommended by the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) Harmonization Standards.⁴ These tasks, administered every 2 years, evaluate memory (Word List Learning—WLL and Word List Recall—WLR) and executive function (Animal Fluency Test—AFT and Letter Fluency—LF)..

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Longitudinal SIS data were available for 23,915 participants who were cognitively normal at baseline (SIS > 4): 38% black, 43% female, mean age 64 years (SD=9.2) at enrollment, with an average follow-up of 5.9 years. Analyses of the SIS data indicate that those who did not use aspirin regularly have a higher likelihood of incident impairment on the SIS (SIS < 5 on most recent assessment) in univariate models (OR: 1.11, 95% CI: 1.09, 1.13). However, after adjustment for demographic factors, the association between regular aspirin use and incident impairment on the SIS is no longer significant (OR 0.99, 95% CI 0.89, 1.09). Additional inclusion of Framingham Stroke Risk total scores or individual factors did not change this finding.

For separate analyses of cognitive change on the WLL, WLR, AFT and LF measures, difference scores were calculated based on each participant's first and last assessments on each measure, adjusted for initial score values. There were 12,231 participants with longitudinal WLL data: 35% black, 56% female, mean age 64 (SD=8.4), with an average follow-up of 3.6 years. In ANCOVA models the association between aspirin use and change in WLL score was significant before (Model 1), but not after adjustment for demographics (Model 2), or risk factors (Models 3 & 4). Analysis of the WLR data produced similar findings. To understand the reduction of association between aspirin use and change in WLL and WLR scores due to demographic factors, we studied the impact of adding each demographic variable individually and found that age is the dominant factor responsible for the effect attenuation. Similar results were obtained for AFT and LF (see Table).

The protective effects of aspirin for heart disease and as a secondary preventive treatment for stroke are well-documented. Many epidemiologic studies have identified stroke and heart disease as independent risk factors for cognitive decline or dementia. It would stand to reason that daily aspirin use could reduce the risk of cognitive decline through reduction of cardiac and cerebrovascular disease, and that this effect should be larger in people having higher risk of stroke. Previous small studies⁵ have reported a protective effect, and this was seemingly confirmed in data from the Canadian Health Study⁶ and the Baltimore Longitudinal Study of Aging⁷.

Other longitudinal cohorts have not replicated these findings. The Women's Health Study found no association between aspirin use and cognitive performance over 9.6 years of follow-up.⁸ Analysis of data from 3,229 participants in the Cardiovascular Health Study over age 65 reported no protective effect for aspirin.⁹ A 5-year RCT of low-dose aspirin, the Aspirin for Asymptomatic Atherosclerosis trial, reported no association between cognitive decline and aspirin use.¹⁰

We examined cognitive change in REGARDS along two dimensions: memory and executive function. We also were able to capture clinically relevant incident impairment in global cognitive status. Given the large sample, REGARDS is sufficiently powered to detect even small associations, should they exist. However, in this large national sample of black and white adults, we saw no relationship between daily aspirin use and cognitive change over 2 to 6 years of follow-up after controlling for the impact of age.

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Dr. Wadley receives grant funding from Genzyme Corporation, receives research support from NIH,, served as an invited speaker for the Alzheimer's Association Research Roundtable, and serves on the editorial boards of Current Gerontology and Geriatrics Research and Journal of Aging Science.

Dr. Unverzagt has served as a consultant to Piramal Life Sciences, Eli Lilly and Company, and UCB Biosciences; serves as an editorial board member for Neuropsychology, and Journal of the International Neuropsychological Society; receives research support from NIH and Posit Science Inc; holds stock in Eli Lilly, Inc; and provides medico-legal reviews.

Dr. Kissela is a consultant for Allergan, has been paid to adjudicate clinical trial events for AbbVie and Reata, and receives research support from NIH.

Dr. Kleindorfer serves as a consultant for Genentech, and receives research support from the NIH and the CDC.

Dr. G. Howard receives research support from NIH, and is on study advisory boards for Cerevast and PhotoThera.

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Table

Multivariable results for cognitive change scores by aspirin use.

	Model 1	Model 2	Model 3	Model 4
WLL (n = 12,231)				
Aspirin users	−0.099	−0.44	−1.12	−0.32
Non-aspirin users	0.418	−0.35	−1.21	−0.32
p-value	<0.0001	0.23	0.34	0.97
WLR (n = 11,722)				
Aspirin users	0.0096	−0.13	−0.39	−0.087
Non-aspirin users	0.27	−0.064	−0.41	−0.050
p-value	<0.0001	0.043	0.62	0.27
Letter F Fluency (n = 5,126)				
Aspirin users	−0.4962	−0.8868	−1.092	−0.8766
Non-aspirin users	−0.3092	−0.7691	−1.067	−0.7400
p-value	0.053	0.22	0.84	0.18
Animal Fluency (n = 8,366)				
Aspirin users	−1.01	−1.37	−1.47	−1.36
Non-aspirin users	−0.65	−1.22	−1.33	−1.22
p-value	<0.0001	0.086	0.21	0.13

Model 1: adjusted for baseline score

Model 2: adjusted for first assessment, demographics (age, sex, race, education, income, region—stroke belt vs non-stroke belt)

Model 3: adjusted for first assessment, demographics, and Framingham Stroke Risk Profile factors considered individually (age, systolic blood pressure, antihypertensive medication, diabetes, current smoker, history of cardiovascular disease, atrial fibrillation, left ventricular hypertrophy)

Model 4: adjusted for first assessment, demographics, Framingham Stroke Risk Profile total score