Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Aspirin (low-dose) and NSAIDs

Evidence Summary

Limited benefit in dementia, but strong evidence for primary prevention of cardiovascular disease, cancer, and overall mortality.

Neuroprotective Benefit: Aspirin does not consistently associate with less risk in epidemiology and it has failed in trials for dementia, but it has anti-inflammatory and cardioprotective properties.

Aging and related health concerns: Mild but consistent benefit for primary prevention of overall mortality, myocardial infarction, and cancer incidence based on substantial trial and epidemiology literature.

Safety: Increased risk of bleeds but likely reduced risk of cardiovascular disease and cancer consistently seen in randomized and observational studies.

What is it? Aspirin is ASA (acetylsalicylic acid), a salicylate type of NSAID. NSAIDs are Non-Steroidal Anti-Inflammatory Drugs, sometimes referred to as NSAIMs, that reduce pain, fever and inflammation. While traditional NSAIDs act by transiently inhibiting both COX-1 and COX-2, aspirin irreversibly inactivates COX-1 and COX-2, with much stronger inhibition of COX-1 (1). This inhibition reduces the production of prostaglandins and thromboxane. The irreversible suppression of thromboxane A2 in platelets is responsible for aspirin's inhibition of platelet aggregation (i.e. clotting).

Neuroprotective Benefit: Aspirin does not consistently associate with less risk in epidemiology and it has failed in trials for dementia, but it has anti-inflammatory and cardioprotective properties.
Types of evidence:

- 1 Cochrane meta-analysis of 3 RCTs
- 2 meta-analyses of observational studies plus 7 subsequent cohort studies

The available randomized trial data show no benefit for dementia from low-dose aspirin. In patients with dementia, aspirin does not slow disease progression based on 3 open-label clinical trials totaling 1745 patients, treated with 50-150 mg/day for 6 months to 3 years (2). Trials on other NSAIDs also failed to show efficacy (see NSAIDs (non-Aspirin) report).

The epidemiology on aspirin and dementia prevention is mixed, as it is for the other NSAIDs. A 2004 meta-analysis of 5 cohort and 3 case-control studies reported no significant association with Alzheimer's risk (Risk ratio (RR): 0.87, 95% CI 0.70 to 1.07, p=0.79) (3) but a 2008 meta-analysis of 6 cohorts reported a reduced risk (adjusted Hazard ratio (aHR): 0.78, 95% CI 0.66 to 0.92) (4). Subsequent large prospective studies have reported either no effect (5-8), increased risk (9, 10), or reduced risk (11) on various measures of cognitive health, dementia risk, or dementia pathology.

There are several possible reasons that could explain the conflicting results. The epidemiology may have varying degrees of residual confounding and bias; or, the protective effect is real but dependent on being given at the right time to the right people, such as long-term treatment in *APOE4* carriers. Some studies suggest that NSAIDs may accelerate neurodegenerative disease in non-*E4* carriers and/or in people with low inflammatory baseline levels and/or in people at later stages of cognitive decline (i.e. close to a dementia diagnosis).

Low-dose aspirin has cardiovascular benefits that other NSAIDs lack that could theoretically lead to a decreased risk of vascular dementia in particular. In people with previous cardiovascular adverse

events, low-dose aspirin can substantially reduce the risk of subsequent myocardial infarction, stroke, and vascular death (12), which may in turn protect from cognitive decline. At least one observational study has reported less cognitive decline in previous stroke patients who use secondary prevention strategies like aspirin (13). However, in patients without existing cardiovascular disease, low-dose aspirin may not protect against stroke, although 20% less risk of non-fatal myocardial infarction has been reported (14). In epidemiology, aspirin has not appeared to protect against vascular dementia (8, 15) or slow its progression(16), although residual confounding would be very hard to control.

APOE4 interactions: NSAIDs overall have been suggested to interact with *E4* status, with NSAID use protecting *E4* carriers but harming non-carriers (See NSAIDs (non-Aspirin) report).

Aging and related health concerns: Mild but consistent benefit for primary prevention of overall mortality, myocardial infarction, and cancer incidence based on substantial trial and epidemiology literature.

Types of evidence:

- Large meta-analyses on RCTs in patients with and without existing cardiovascular disease
- Cancer – 5 meta-analyses
- 1 lifespan study in mice; 2 lifespan studies in *C. elegans*; 1 cell culture study

Aging biology and mortality: For people without current cardiovascular disease or cancer, low-dose (75 mg daily) aspirin is estimated to slightly reduce mortality risks (RR: 0.94, 95% CI 0.88 to 1.00), with reduced risk of cancer and myocardial infarction although no effect on stroke risk. In mice, aspirin increased median survival but not maximum lifespan in males but not females in the Interventions Testing Program of the National Institute on Aging (17) and, in *C. elegans*, aspirin has increased lifespan either through the DAF-16/FOXO and AMPK pathways (18) or protection from oxidative stress (19). One cell culture study also reported that aspirin protects against cell senescence induced by high glucose levels (20), but otherwise there is no strong evidence that it slows or reverses biological indicators of aging.

Cardiovascular disease prevention: In people with diagnosed cardiovascular disease or prior stroke, aspirin is clinically recommended to reduce the risk of myocardial infarction, stroke, and cardiovascular-related death (12). For other patient populations, clinical guidelines are somewhat mixed in terms of balancing the potential benefit from cardiovascular disease and the risks of bleeding. Low-dose aspirin will likely reduce the risk of myocardial infarction but not stroke in people who don't already have

cardiovascular disease (14). A nonsignificant trend for increased risk of hemorrhagic stroke has been seen in primary prevention trials. Aspirin may not reduce cardiovascular risk in patients who are also taking anti-coagulants like warfarin, due to clinical studies showing no added benefit.

Cancer primary prevention: The use of low-dose aspirin for 4+ years seems to protect against many though not all forms of cancer, based on both observational and randomized studies (21). A 2012 meta-analysis of 6 RCTs of low-dose daily use for primary prevention (n of 35,535) reported that low-dose aspirin used for 3+ years reduced the risk of cancer (OR: 0.76, 95% CI 0.66 to 0.88 for women; OR: 0.75, 05% CI 0.59 to 0.94 for men). When the meta-analysis included any dose of daily aspirin, 5+ years of use also reduced cancer deaths (OR: 0.63, 95% CI 0.49 to 0.82), with fewer non-vascular deaths overall (22). Higher doses and longer durations may confer greater protection against colorectal cancer (23) and pancreatic cancer (24). For breast cancer, the use of aspirin after diagnosis, but not before, was associated with reduced risk of death and relapse/metastasis (25).

Safety: Increased risk of bleeds but likely reduced risk of cardiovascular disease and cancer consistently seen in randomized and observational studies.

- *Bleeding* – Aspirin raises the risk of bleeding. Most of these bleeds occur in the gastrointestinal tract but bleeds can occur in the brain as well. Randomized trials may underestimate these risks due to the shorter time-frame and the highly selective participants of clinical trials. In one study of over 186,000 Italians, low-dose aspirin was associated with higher rates of hemorrhagic events after 5.7 years (RR: 1.55, CI 1.48 to 1.63), with 20 more major bleeding events per 10,000 treated patients. Interestingly, this risk was not seen in patients with diabetes (26). The risk of bleeding appears to be similar between low doses around 75 mg/d and higher doses around 325 mg/d (27). The risk of gastrointestinal bleeding increases in elderly people and is twice as high in men than women (28). It is also higher in patients with a history of ulcer disease or GERD/dyspepsia symptoms. The risk may also be increased by the concurrent use of drugs like corticosteroids, anticoagulants, antiplatelet therapies, SSRIs, and calcium- channel blockers (29). Gastrointestinal bleeding risk or ulcer risk from aspirin may be somewhat decreased by proton pump inhibitors or misoprostol but probably not H2 receptor antagonists (UpToDate). Aspirin that is enteric-coated or buffered is probably no safer than plain aspirin for GI bleeds (30).

- *Cardiovascular and overall mortality risks:* In contrast to regular-dose traditional NSAIDs, which are associated with higher cardiovascular risks and increased overall mortality risks, low-dose aspirin associates with lower risks (see Aging section above).

- *Sensitivity:* Some people have an aspirin sensitivity and cannot tolerate the drug, with possible resulting respiratory tract disease or urticarial/angioedema.

Dosing and Sources:

Doses between 75-325 mg/day are sufficient to achieve the potential cardiovascular benefits of aspirin (27). Within this range, lower doses still increase the risks of gastrointestinal bleeds (27). Higher doses of aspirin have sometimes been better linked to a reduced risk of cancer but low-dose aspirin still appeared to reduce risk in several meta-analyses (see cancer discussion in Aging section).

Future research:

- ASPREE is a clinical trial underway in 19,000 healthy people between 65-70 years of age in Australia and the USA. It is comparing 100 mg/d of enteric-coated aspirin versus placebo for five years, looking at total mortality, persistent disability, dementia onset, as well as all-cause and cause-specific mortality, fatal and non-fatal cancer, fatal and non-fatal cardiovascular disease, dementia, MCI, depression, physical disability, and bleeding, with a sub-study in 600 subjects tracking how changes in biomarkers like MRI or retinal vascular imaging correlate with cognitive function (31, 32)

- Ongoing studies are testing if subpopulations of people are more likely to benefit from NSAID treatment, such as baseline inflammatory state by Sid O'Bryant's group. The long-term effects of NSAIDs may also depend on *APOE4* status or on mid-life vs late-life treatment. Most longitudinal cohorts will lack sufficient power to address these questions but perhaps could be pooled.

- Clinical studies are testing other strategies to reduce systemic inflammation. Etanercept, a TNF alpha inhibitor, may have slowed cognitive decline in a small recent Alzheimer's trial (AlzForum). An additional etanercept trial funded by the EU (below) is scheduled to begin soon.

- The EU has recently invested in a large collaborative project on neuroinflammation called INMiND – Imaging Neuroinflammation in Neurodegenerative Diseases. Key components: a

clinical trial on etanercept in MCI patients, the development of imaging tools to measure neuroinflammation, and differentiating good vs bad microglial phenotypes (33).

Search process:

PubMed

- Aspirin plus (separately searched) cognitive, dementia, Alzheimer, vascular dementia, stroke-related dementia, mortality, lifespan
- ASA, cognitive
- ASA, delirium
- Nsaids, cognitive
- NSAIDs, Alzheimer
- low-dose ibuprofen, mortality
- cellular senescence, NSAID, cox
- prostacyclin, thromboxane, lifespan
- prostacyclin, thromboxane, filtered for meta-analyses & systematic reviews
- cox, telomere
- nsaid, telomere
- dyspepsia, NSAID
- TNFalpha, ibuprofen
- TNFalpha NSAIDs
- Cytokines NSAIDs
- PPIs, NSAID (google search)
- Aspirin & cognitive or dementia or Alzheimer or mortality

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