Should we be taking B vitamins to prevent age-related macular degeneration? Not yet, but worth doing more research1,2

Jennifer Evans

Wouldn’t it be great if we could prevent the development of age-related macular degeneration (AMD)? This has recently been identified as one of the key research questions that people affected by AMD, and their clinicians, would like answered (1). AMD is important because it causes significant visual impairment—with all the loss of independence that entails—and occurs commonly in older life. We are all living longer, and so many more of us may be affected by AMD. At the moment, we don’t have very effective treatments for the disease, although treatments are improving all the time and we can now reverse some of the damage done by new blood vessels growing in the back of the eye (which is associated with this condition).

There has been a long-standing interest in the role of diet and AMD. This is because AMD is associated with aging and historically has been linked with the “antioxidant hypothesis” of aging (2). Despite a couple of decades of research, there is no good evidence as yet that antioxidant vitamin supplements prevent the development of AMD (3). We only have good-quality data on β-carotene and vitamin E, which show that taking these as supplements does not reduce the risk of AMD. There is more encouraging evidence on the role of antioxidant vitamins in slowing down progression for people with the disease (4), largely from the Age-Related Eye Disease Study trials (5). The role of other vitamins has not been studied so extensively. In this issue of the Journal, there is a report on the association between homocysteine, folate (vitamin B-9), and vitamin B-12 and the incidence of AMD over 10 y in people taking part in the Blue Mountains Eye Study in Australia (6). This study found that increased concentrations of serum total homocysteine were associated with ~30% increased odds of developing AMD over 10 y and increased concentrations of serum vitamin B-12 were associated with ~30% reduced odds of developing AMD. Serum folate was less strongly associated, with an approximate reduced odds of 10% for development of AMD. People with folate or vitamin B-12 deficiency at baseline were approximately twice as likely to get AMD. Associations with dietary intake were less consistent.

Observational studies have shown that increased concentrations of homocysteine (an amino acid involved in methionine metabolism) are associated with the development of cardiovascular disease (7). AMD is associated with the development of lipid-rich deposits under the retinal pigment epithelium, known as drusen, and later stages of the disease involve the blood vessels. Another long-standing theory has been that the development of AMD is analogous to the development of cardiovascular disease and therefore risk factors for cardiovascular disease are a good place to start when looking at causes of this disease. This approach for studying the epidemiology of AMD by analogy has resulted in some success: the association between smoking and AMD is relatively well established (8). However, the homocysteine story may be a little less clear cut. Although supplementation with B vitamins reduces the concentration of homocysteine in the blood, it does not apparently reduce the risk of cardiovascular disease, at least as measured in randomized controlled trials of supplementation with B vitamins (9).

So how likely is it that the reported association between homocysteine, vitamin B intake, and AMD is causal? The advantage of the current study is that it is prospective—concentrations of vitamin B and homocysteine were measured before AMD developed—and a reasonable number of people were followed up for a long time. Over 10 y, as expected, there was a fair amount of attrition, and there is the possibility of selection bias with loss to follow-up, if the association between these factors and AMD differed for some reason in those individuals who were not followed up. And of course the real difficulty with observational epidemiology, uncontrolled confounding: people who have vitamin-rich diets, or take vitamin supplements, differ in many ways from those who don’t. Some of these differences may be associated with the risk of developing AMD. Although the current study controlled for some potential confounders, as for all observational epidemiologic studies, it is difficult to be sure that the resulting association is not explained by confounding by another, unknown, factor. The observed association is not very strong, with ORs in the region of 1.5 and all <3, which means they could possibly be explained by bias or uncontrolled confounding. However, a weak association may still be causal, and overall the study was largely coherent in the direction of effects observed.

Before drawing conclusions on causality, ideally we would observe these associations consistently in a number of studies.

1 From the International Centre for Eye Health, London School of Hygiene and Tropical Medicine, London, United Kingdom.
2 Address correspondence to J Evans, International Centre for Eye Health, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, United Kingdom. E-mail: jennifer.evans@lshtm.ac.uk.

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There are a number of relatively small cross-sectional or case-control studies reporting higher concentrations of serum total homocysteine in people affected by AMD compared with controls; however, this has not been consistently reported. Of note is the Women’s Antioxidant and Folic Acid Cardiovascular Study, which found that supplementation with vitamins B-6, B-9, and B-12 resulted in a 40% reduction in the risk of developing AMD over an average of 7 y of follow-up (10). A particular difficulty with interpreting a body of evidence is assessing the effects of publication and selective outcome reporting bias. There is reasonably good empirical evidence for randomized controlled trials (where this evidence is easier to study because trials are registered and have a protocol) that these biases can be a problem (11). It is likely to be even more of a problem for observational epidemiology. How much it applies in this context is not clear. The authors of the current study have quite rightly concluded that “replication in other large cohort studies [is] clearly needed,” and hopefully both positive and negative findings will be reported.

In conclusion, this is an interesting, biologically plausible hypothesis that needs further study. Given the experience from cardiovascular disease, where promising results from observational studies of homocysteine and vitamin B supplementation have failed, as yet, to be translated into useful public health interventions, it would be good to be cautious at this stage about making recommendations to the general public.

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REFERENCES