The use of dietary supplements to improve health outcomes can be controversial, especially when scientific evidence is lacking. Folic acid, sometimes referred to as vitamin B9, is a good example of a dietary supplement that has been, and continues to be, studied for its health-related benefits. For example, folic acid has long been known to play an important role in neural-tube development in utero and as a consequence, high folic acid intake is indicated for women who are, or are planning to become, pregnant. For most adults in the US, adequate daily intake of fortified grains, citrus fruits, and leafy vegetables is sufficient to reach the current RDA of 5 micrograms per day. Some adults, such as those with folic-acid deficiency anemia, sickle-cell disease, or those who undergo dialysis may be advised by their physicians to supplement with a higher dose of folic acid. Recently, epidemiological studies have suggested that high doses of folic acid may also be beneficial for individuals with blood vessel dysfunction and/or cardiovascular disease; however, few studies have examined this potential effect in humans.

Even in the absence of diagnosed cardiovascular diseases, healthy older adults (>60 years) have reduced vascular function, which makes them more likely to suffer from adverse cardiovascular events such as heart attack and stroke. This vessel dysfunction is caused by a number of factors, one of which is a reduced production of nitric oxide. Nitric oxide, a gas produced inside the vessel wall, is a potent vasodilator and is essential for vascular health. However, as we age, our blood vessels produce less nitric oxide. One main research focus of the Cardiovascular and Thermoregulatory Laboratory in the Department of Kinesiology at Penn State is the identification of new intervention strategies to improve vascular health and function in older adults by increasing the ability of the vascular endothelium to produce nitric oxide. In a recent paper, Folic acid supplementation improves microvascular function in aged humans through nitric oxide-dependent mechanisms, published in the journal Clinical Science, we present new data suggesting that taking a high-dose folic acid supplement increases nitric oxide production in blood vessels of older adults.

To test the effects of folic acid, we conducted two sub-studies in the blood vessels of the skin of older subjects and compared their responses to those of healthy young subjects. In the first study, we locally perfused a metabolite of folic acid (5-methyltetrahydrofolate) into a small area of skin through a microdialysis membrane, and then tested the ability of the blood vessels to dilate in response to a localized heat stimulus. In the second study, subjects ingested 5 milligrams of folic acid or a placebo daily for 6 weeks in a double-blind, crossover study before undergoing a whole-body heating challenge to examine the integrated cardiovascular response to heat stress, which depends upon large increases in skin blood flow. Five milligrams, while still a safe dose, is 100 times the recommended daily intake for most adults in the US. In both studies, we found that folic acid improved the vasodilatory response compared to placebo treatment. We also found that this improvement was due to an increase in nitric oxide production following folic acid treatment.

Overall, these findings suggest that high-dose folic acid supplementation increases blood vessel function and general vascular health in older adults by increasing the production of nitric oxide and as such, folic
acid might be an efficacious intervention strategy to increase vascular health and prevent atherosclerotic disease as people get older.

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The full research article can be found online at [http://www.clinsci.org/content/129/2/159](http://www.clinsci.org/content/129/2/159).
Dr. Kenney is a member of the Aegis Shield Expert Panel.

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