- **Were the participants of this study healthy?**

These people were all above **70 years old** and had **mild cognitive impairment (1)**, that is, they had an increased risk for dementia. They were otherwise healthy. Half of them took a vitamin B treatment daily for a 2-year period to lower their homocysteine levels (vitamin B12 0.5 mg, folic acid 0.8 mg, vitamin B6 20 mg), half of them were taking a placebo (2).

- **What are the results of this study?**

By comparing the brain images of the placebo group and the B-vitamin group, we found that the B-vitamin treatment was effective in **slowing the loss of grey matter** (by up to 7-fold on average) in areas of the brain that "mattered", i.e. in the regions that are specifically affected by the Alzheimer's disease neurodegenerative process (3), such as the hippocampus, and which play a crucial role in the progression from mild cognitive impairment to Alzheimer's (4). These regions of the brain were also **related to the cognitive decline** in these participants.

We showed that this effect differed according to the homocysteine levels of the participants at the start of the study: participants with **lower levels of homocysteine** to start with (here, <11μmol/L) **did not benefit** from the vitamin B treatment, because they already have a slow loss of grey matter in the specific regions of the brain targeted by the Alzheimer's process.

On the other hand, the B-vitamin treatment was particularly effective in participants with **higher levels of homocysteine**: in the regions of the brain where we saw the benefit of the treatment, the participants with high homocysteine taking the placebo had **lost 5.2% of grey matter volume** in 2 years, whereas the participants with high homocysteine taking the B vitamins had **lost only 0.6%** (~90% reduction in grey matter loss in these specific brain areas). We also demonstrated that taking the B-vitamin treatment over the 2-year period had a similar beneficial effect on the brain to having a low level of homocysteine to start with.

- **Could B vitamins help prevent Alzheimer's disease progression?**

This is too early to say. What we have shown is that, in these elderly people at risk for dementia and with high levels of homocysteine, you can slow the grey matter loss in the areas of the brain that matter, and therefore slow their cognitive decline. However, we would need a **larger and longer trial** to determine the optimal threshold of homocysteine that would warrant vitamin B supplementation and, crucially, if this could therefore slow the progression of Alzheimer's.

Indeed, not all people with mild cognitive impairment progress to Alzheimer's. Large studies have shown that, within 5 years, only about 30% of them do. We would therefore need to follow **more participants** and possibly **for a longer period** to know whether they had mild cognitive impairment *due to Alzheimer's disease* and to be able to see a difference between the vitamin B group and the placebo group on the rate of conversion from mild cognitive impairment to Alzheimer's.

- **Other studies looking at the effect of B vitamins have not always demonstrated positive results, what is the difference here?**

Various factors possibly explain the discrepancies, such as different dosage, vitamin combination, duration of treatment and population treated (5, 6). For instance, in one study, participants already had Alzheimer's disease, so it might have been too late to slow the cognitive decline (7, 8). Another factor might be **the homocysteine levels of the participants** at the start of the study: for instance, two studies have shown that subjects with modestly raised homocysteine do experience a beneficial effect of B-vitamin treatment on cognitive decline (9, 10).

What makes our study unique, to the best of our knowledge, is that the participants were scanned at the beginning and at the end of the trial. For trials with the aim of slowing progression of cognitive decline, the usual design includes neuropsychological assessments. However, the scores on such tests can change from one day to another, or depend on the person rating the participant. In contrast, **structural neuroimaging provides a robust and unbiased way of assessing changes of a longer-term nature**, including the impact of the treatment.

The information obtained from the images allowed us to show, using a dedicated computational analysis, that there is a possible **causal pathway** starting with the B-vitamin treatment, leading to the lowering of homocysteine (mainly due to an increase of vitamin B12), followed by the slowing of loss of grey matter, and finally resulting in the slowing of cognitive decline.

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- **What is the supposed mechanism behind the effect of B vitamins?**

The short answer is that we don't know why the treatment (or having low levels of homocysteine to start with) is beneficial to these particular brain areas.

What we show is that B vitamins (and in our study particularly vitamin B12) lower homocysteine levels, and we also show that having high homocysteine levels increases your grey matter loss in these specific brain regions. So lowering homocysteine lowers grey matter loss. But why this should be true in these specific and relevant brain areas is unclear.

There is now more and more evidence for an impaired neuroregeneration in Alzheimer's, so it could be that lowering homocysteine might help **maintain adult neurogenesis** in the very regions targeted by Alzheimer's (11). Lowering homocysteine may also **lower the presence of neurofibrillary tangles** that are known to accumulate in these regions of the brain (12).

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- **How many people were involved in this trial with B vitamins?**

Originally, 223 participants were enrolled and completed this study. Not all of them were eligible to go into the MRI scanner, as contraindications include for instance claustrophobia, severe back ache, and presence of metallic implants, pacemaker and intraocular metallic foreign bodies. These contraindications tend to be more frequent in elderly people.

In the end, 180 participants, who volunteered and were eligible to go in the MRI scanner, could be scanned twice, 2 years apart. Amongst them, **156 participants** had scans that were of good enough quality for the sophisticated analyses we have done in this study. The scans were discarded from this study while not knowing (i.e., while being "blind" to) whether these participants were in the placebo or the B-vitamin arm of the trial.

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For more information on the B vitamins, in which food they can be found naturally, and the health risks from taking them in excess:

**B6:** http://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/
**Folate/folic acid/B9:** http://ods.od.nih.gov/factsheets/Folate-HealthProfessional/
**B12:** http://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/

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