- **Who are the participants of this study?**

We investigated the brain scans of roughly **40,000 UK Biobank volunteers**. These participants were **aged between 44 and 83 years old**. They can be described as overall quite healthy, and healthier than the general population, with only a very small minority (a few dozen) who received a diagnosis of dementia before their scans.

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

Our study investigated **the impact that genetic and modifiable risk factors have on parts of the brain that are particularly fragile**.

We have **previously demonstrated the existence of a 'weak spot' in the brain**, a specific network of higher-order brain regions that not only develop slowly during adolescence, but also show early degeneration in old age. Importantly, this brain network also defines regions of heightened vulnerability to schizophrenia and Alzheimer's disease[1].

We have now found that, of all common modifiable risk factors for dementia, the most harmful to this weak spot are **diabetes, traffic-related pollution, and alcohol consumption**.

For the genetic risk factors, we have **discovered seven changes in the genome** that impact on this vulnerable brain network, and that are very relevant. We know for instance that some of them are **related to Alzheimer's disease and Parkinson's disease, to an increased risk of cardiovascular deaths, and to schizophrenia**. Two of these seven mutations were entirely novel however, in a relatively unexplored region of the genome, and that codes for a still enigmatic blood group called XG.

- **What makes it different from other brain imaging studies of aging in the brain?**

This study is different for three main reasons.

First, we have **considered all the modifiable risk factors for dementia at once**. We started off with 161, distributed across 15 categories of the most common risk factors for dementia: blood pressure, cholesterol, diabetes, weight, alcohol consumption, smoking, depressive mood, inflammation, pollution, hearing, sleep, socialisation, diet, physical activity, and education. We ended up with the 12 most detrimental risk factors, and ranked them. The three that emerged as the most harmful were diabetes ('diabetes diagnosed by doctor'), air pollution that is specifically related to traffic and combustion engines ('nitrogen dioxide in 2005'), and alcohol ('alcohol intake frequency').

Second, for the genetic risk factors, we have also **investigated the X chromosome**, which is typically left out for most genome-wide association studies. This revealed our strongest genetic finding in a very peculiar region known to be shared by both sex chromosomes.

Third, we have **focused our investigation on these very vulnerable brain regions**, the weak spot of the brain, over and above all the other parts of the brain. In other words, these findings are entirely specific to these fragile parts of the brain, which are in turn related to schizophrenia and Alzheimer's, and degenerate earlier in old age.

- **Why look at both genetic and modifiable risk factors?**

These **provide complementary types of information**: while genetic factors are non-modifiable in nature, they can reveal mechanisms behind accelerated aging or increased vulnerability to disease; meanwhile, modifiable risk factors can be *potentially* (an important qualifier!) changed throughout life to prevent or delay the onset of disease, and curb the aging process.

- **Why consider all the modifiable risk factors altogether?**

We wanted to look at the complete picture, as seeing only part of it can be misleading. Indeed, it is easy to grasp that many modifiable risk factors might share some information: consider exercise and sleep for instance. Is it truly exercise that has a beneficial impact on our brains, or could it be that it makes us sleep better, and that is turn what is the most protective? Or is it because we also tend to socialise when we go out to exercise, and socialisation is what keeps our brains engaged and thus protected?

Similarly, as we age, we naturally get more at risk of increased blood pressure and cholesterol levels, so what are these risks, regardless of our age?

That is why we considered all these modifiable risk factors together: this makes it possible to **look at the complete picture**, and **reveal the *relative* impact each one of them has on the fragile brain regions**, over and above the others, and above the natural effects of age.

- **Does this mean diabetes, pollution and alcohol are the worst for our brains, and for our dementia risk in general?**

We cannot say from our study: what we now know is that, for these specific parts of the brain that are very fragile, degenerate earlier, and are associated with Alzheimer's and schizophrenia, these three modifiable risk factors – diabetes, air pollution and alcohol – are indeed the single most harmful. It is followed by sleep, weight, smoking and blood pressure.

Of course, this is dependent on the way these factors are captured in UK Biobank, and these results need to be replicated in other very large datasets containing information on all these modifiable risk factors.

While diabetes and alcohol have long been associated with an increased risk of dementia, outdoor air pollution, and in particular traffic-related, has only emerged very recently as one key player in dementia[2,3], an aggravating factor when we know that outdoor air pollution

already contributes to the death of over 4M people a year from heart disease, chronic obstructive pulmonary disease, cancer or pneumonia[4]. Our work **adds to the fast-growing evidence for the harmful role that traffic-related pollution has on the brain**. This should help inform further government and local policies that try to improve air quality through traffic regulations and cleaner transport.

- **Are these findings causal?**

It is difficult to say. In the case of genetic risk factors, we might be more confident that the mutations we unearthed are causal, but this would need to be tested formally. What we investigated further, however, is the genetic mutation associated with both Alzheimer's disease and the vulnerable brain network. We have asked whether these brain regions 'mediate' the effects of the genetic change and Alzheimer's disease, in other words, if the change in the genome leads to Alzheimer's disease by impacting on these fragile brain regions. The answer is yes.

Another intriguing element is that one of the novel genetic mutations we have discovered on the X chromosome is linked with early life and socioeconomic factors, such as the number of siblings the UK Biobank participants have, whether they were breastfed as a baby, or if their mother smoked around birth. These remarkable findings will need further investigation, to examine if these in general are due to the genetic variations present in one of the parents of the volunteers rather than the volunteers themselves. These changes in the genome of the parent may in turn modulate the effect of early life environment of the participants; this is the so-called 'nature of nurture'[5].

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