

## Background Q&A

**\*\* Lancet embargo: 23.30 UK time on Thursday 4 April 2019 \*\***

### **“Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China”**

#### **What does this study show?**

Drinking alcohol increases blood pressure and increases stroke risk in approximate proportion to the amount drunk. Four drinks a day would increase the risk of having a stroke by about one-third, with no protective effects of light or moderate drinking.

#### **What was already known about alcohol and stroke, or alcohol and heart attack?**

Although people who have one or two drinks of alcohol a day have a somewhat lower risk of stroke and heart attack than people who don't drink, there had previously been no agreement whether this was because moderate drinking was slightly protective, or whether it was because non-drinkers had other underlying health problems (eg, being former drinkers who had stopped because of illness).

#### **Why do a study in China?**

In East Asia, there are common genetic variants that greatly reduce alcohol tolerability, because they cause an extremely unpleasant flushing reaction after drinking. Although these genetic variants greatly reduce the amount people drink, they are unrelated to other lifestyle factors such as smoking. Therefore, they can be used to study whether alcohol itself actually affects disease risks.

This technique is often called Mendelian Randomisation – it is a useful tool to help assess whether a particular risk factor (in this case, alcohol) causes a particular disease, when sufficiently large, long-term randomised trials are impracticable, either because of cost or because it would be difficult to maintain sufficiently good compliance with the random allocation to abstain or drink moderately.

#### **What were the main results?**

Among men, these genetic variants caused a 50-fold difference in average alcohol intake, from near zero to about four units (drinks) per day, mostly spirits. The genetic variants that decreased alcohol intake also decreased blood pressure and stroke risk. From this evidence, the authors conclude that alcohol increases the risk of having a stroke by about one-third for every four additional drinks per day, with no protective effects of light or moderate drinking.

#### **What about women?**

Few women in China drink alcohol (less than 2% of women in the study drank in most weeks, and when they did drink they consumed less than men), and the genetic variants that cause alcohol intolerance had little effect on blood pressure or stroke risk. This helps confirm that the effects of these genetic variants on stroke risk were caused by alcohol, not by some other mechanism.

#### **What about heart attacks?**

The findings for heart attack were less clear-cut, and more evidence is still being collected. In the analysis, there were about 10,000 strokes but only 2,000 heart attacks among men with genetic measurements. It will take a few more years to get reliable answers about heart disease, but because strokes are so common in China the stroke results are already based on large enough numbers to be reliable.

#### **What sort of strokes were affected?**

In China, more years of life are lost to stroke than to any other disease. This study shows that, among Chinese men, alcohol is a cause of 8% of all strokes from a blood clot in the brain and 16% of all strokes from bleeding into the brain.

#### **How were study participants recruited?**

The China Kadoorie Biobank (CKB) is a prospective study of 500,000 men and women, recruited from ten rural and urban areas of China during 2004-2008. They were asked about their lifestyle (including smoking and drinking) and medical history, blood pressure and weight were measured, a blood sample was collected and stored for future genetic and other analyses, and they are being followed up to see what diseases they develop. So far, they have been followed for about ten years.

**How are participants followed up?**

Participants are followed by linkage to the nationwide health insurance system and to local death registries, giving information on all diseases recorded in hospital and on all deaths. Hospital records of stroke or heart attack were checked by study doctors to ensure the information was correct.

**What genetic variants were measured?**

In the body, alcohol gets metabolised in two steps. First, an enzyme called ADH oxidises it to acetaldehyde, which can cause considerable discomfort until an enzyme called ALDH de-toxifies it. The study measured two genetic variants that alter these steps, one in the gene for ADH and another in the gene for ALDH.

Both of these genetic variants affect alcohol tolerability and substantially reduce the amount of alcohol people choose to drink. The first is called rs1229984, and the second is called rs671 (and causes the severe "East Asian flushing reaction").

**Is such a study of alcohol genetics possible only in East Asian populations?**

The more important of the two genetic variants (rs671) is found only in people with some East Asian ancestry, most of whom live in China, Japan or Korea.

**How many people were in this study?**

So far, 160,000 of the 500,000 CKB participants have had measurements of the two genetic variants that strongly affect alcohol tolerability, but in a few years much more detailed genetic measurements will become available on all 500,000.

**Why is alcohol use so low among women in China?**

Both smoking and drinking are uncommon among women in China, mainly for cultural reasons.

**Is there a difference between different types of alcoholic drink?**

Most of the alcohol consumed was spirits, as is normal in China, and other types of drink could not be assessed. However, alcohol itself is the same in all drinks, and the analyses were based on the number of grams of alcohol.

**Are the results affected by smoking?**

Smoking is a major cause of death in Chinese men, but it cannot affect the study findings as the genetic factors that strongly influenced alcohol consumption did not influence smoking.

**Are the study findings relevant to populations outside China?**

The purpose of the study was not to assess the effects of particular genotypes in China, but to assess causal effects of alcohol intake that would be of general relevance in any population.

**Will this study affect policies on alcohol use?**

Our aim is not to set policy, but to provide reliable evidence.

**How are the study participants protected?**

The CKB was approved by ethics committees in the UK and in China, all participants provided written informed consent, and all participant information remains confidential.

**Who conducted this study?**

This study was conducted jointly by the University of Oxford, Peking University and the Chinese Academy of Medical Sciences.

**Who funded this study?**

This study was funded by the Wellcome Trust, Medical Research Council, British Heart Foundation, Cancer Research UK, GlaxoSmithKline, Chinese Ministry of Science and Technology, Kadoorie Charitable Foundation of Hong Kong, and National Natural Science Foundation of China. The funders were not involved in the study design or analysis.