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TABLE OF CONTENTS

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What We Know, Think We Know, or Are Starting to Know

We know that stroke is the second leading cause of mortality globally, and comes with a significant additional public health burden given that nearly half of stroke survivors are chronically disabled [1]. The two broad types of stroke - ischaemic stroke and haemorrhagic stroke - differ in their underlying cause. Ischaemic stroke is primarily caused by interrupted blood supply to the brain, which may be caused by underlying atherosclerosis, while haemorrhagic occurs due to ruptured blood vessels. Haemorrhagic stroke prevalence of 9% in high-income countries, although this can very by region, and a majority of stroke mortality globally is attributable to ischaemic stroke [2].

The primary risk factor for stroke is age, however, the relationship with modifiable risk factors is strong and the INTERSTROKE collaboration analysis across 32 countries identified a number of risk factors, including high cholesterol, hypertension, current smoking, alcohol intake, stress, lack of activity, and poor diet [3]. Thus, the relationship with age is one of increasing duration of exposure to these risk factors, a factor which characterises disease with long-latency periods*.

*Geek Box: Latency Periods

The 'latency period' of a disease is the period during which it is developing, without any overt signs or symptoms, prior to diagnosis. For example, while heart attacks increase in prevalence from age 50 onwards, we know that the process of atherosclerosis can begin to develop in teenage years. This process adds up to a cumulative burden over time, manifesting as a disease after up to 40-years of an exposure [in this case, and exposure to LDL-cholesterol mediated by genetic, dietary, and other lifestyle factors]. All chronic lifestyle diseases - heart disease, diabetes, stroke, etc. - are diseases characterised by long-latency periods. This is critically important to how we study diet-disease relationships. Nutrition science emerged during a period when the conditions facing public health - rickets, beri-beri, pellagra, goitre - were conditions defined by single-nutrient deficiency states, and characterised by short-latency periods: symptoms onset rapidly in deficiency, and resolved rapidly once deficiency was addressed, and nutritional adequacy restored. However, modern nutritional epidemiology is faced with a logistical problem of trying to determine relationships between diseases with long latency periods and populations in which the exposure of interest – food – is a continuous, daily, exposure. In this respect, long-term prospective cohort studies are an under-appreciated – and misunderstood – tool with which to examined long-term diet-disease relationships. Capturing the relationship between dietary exposures earlier in life, and disease onset later in life, has been the defining challenge for nutritional epidemiology, and the primary reason for the development of food-frequency questionnaires, which may capture a picture of past dietary history, to be related to disease outcomes years later during the follow-up period of the study.

While diet is clearly a factor in the overall risk factor equation for stroke, the relationship between dietary patterns and stroke has been more ambiguous than one might think. For example, the Japanese have traditionally been characterised by significantly lower rates of heart disease than Western countries, which has often been attributed to their very low saturated animal fat, high oily fish polyunsaturated fat intake. However, historically the Japanese have had very high rates of stroke, which was related to very high levels of sodium (soy sauce, etc.) in the diet [(4)]. In fact, of the various risk factors listed above, the INTERSTROKE study suggests that hypertension is the most significant risk factor for all strokes [(3)]. Many food groups are under-researched with regard to stroke, and the present study aimed to investigate the association with major foods and stroke across a number of European cohorts.

The Study

The European Prospective Investigation into Cancer and Nutrition [EPIC] Study, is a large scale prospective cohort study with cohorts recruited across nine countries; the UK, Netherlands, Denmark, Germany, Norway, Sweden, Spain, Greece, and Italy.

The present study included 418,329 men and women through 22 centres in the included countries, who were recruited between 1992 and 2000.

Dietary assessment was conducted at baseline, which was country-specific, with each dietary assessment having been validated in that specific population as part of the EPIC methodology. Food-frequency questionnaires [FFQ] were primarily utilised. To calibrate the accuracy of the FFQ, a random sample of 8% of the overall cohort across all centres completed a computerised 24-hour diet recall which was compared to the FFQ completed by the same people in the sample.

Primary outcome measures where ischaemic and haemorrhagic stroke, which included both fatal and non-fatal incidence. All analyses were adjusted for age, smoking and number of cigarettes per day, alcohol intake, history of diabetes, hypertension, and elevated cholesterol, employment status, education level, physical activity, body mass index, and total energy intake. Results were calculated as hazard ratios [HR], and presented with 95% confidence intervals*.

*Geek Box: Confidence Intervals

You may want to read the 'Results' section again having read this, but let's break down how to use confidence intervals to your advantage when interpreting research, especially epidemiological research. Results are expressed according to the risk estimator that the investigators have used; relative risk ['RR', hazard ratios 'HR'], or odds ratios ['OR'], which depends on the type of analysis undertaken. Because all of these calculations are against a reference group, the reference is 1.0; anything above 1.0 is a positive association, or increased risk/odds, while anything below 1.0 is an inverse association, or reduced risk/odds. For example, HR 1.23 means the hazard ratio is a 23% [i.e., 23, after the decimal] increase in risk. Conversely, HR 0.82 means an 18% reduction in risk [i.e., 100-82 = 18]. Now, this is generally the part of the result that people hone in on, but a more refined approach is to look at the certainty, or confidence, that the result would fall within a certain range 95% of the time. Enter 'confidence intervals', which have also been described as the 'coverage probability'. This is the probability that the interval expressed includes or covers the true effect size. For example, let's say the HR is 1.23 [a 23% increase], and the confidence interval for that result is 1.17-1.39; this shows that the entire interval is in a positive association range, and is significant. This indicates that the minimum increase in risk is 17% [1.17], and the maximum increase is 39% [1.39]. The HR may indicate a 23% increase in risk, but the true effect could be anywhere from 17% to 39%. This type of result warrants attention, because the true effect would still be positive. The inverse is true for reduced risk; if you read [HR 0.82, 95% CI 0.76-0.93], you can see that while there was an 18% reduction in risk, the maximum reduction was 24% [0.76] and the minimum reduction was 7% [0.93]. This is also significant, as the true effect would be within an internal of reduced risk. However, where a CI straddles 1.0, and is very wide, this result is practically meaningless, as we cannot deduce where the true effect would lie; such results are statistically insignificant. For example, HR 1.04, 95% CI 0.89-1.15 tells us nothing of meaning in inferring the risk associated with the exposure of interest. Start to focus more on confidence intervals in interpreting findings, they provide a more refined assessment of the result than the risk ratio alone.

Results: The mean follow-up period was 12.7-years, in which 4281 cases of ischaemic stroke and 1430 cases of haemorrhagic stroke occurred. Participants who suffered stroke were on average 7-years older for men, and 10-years older for women, at time of recruitment. Stroke incidence was related to heavy smoking [<20/d], lower education, higher unemployment rates, and history of hypertension and diabetes.

In relation to ischaemic stroke, the following associations with reduced risk were observed:

- Per 200g higher fruit and vegetable (combined) intake: 13% lower risk [HR 0.87; 95% CI 0.82-0.93]
- Per 10g/d higher fibre: 23% lower risk [HR 0.77, 95% CI 0.69-0.86]
- Per 200g higher milk intake: 5% lower risk [HR 0.95, 95 CI 0.91-0.99]
- Per 100g higher yogurt intake: 9% lower risk [HR 0.91, 95 CI 0.85-0.97]
- Per 30g higher cheese intake: 12% lower risk [HR 0.88, 95 CI 0.81-0.97]

Red meat was associated with increased risk in the basic adjusted model: per 50g/d higher intake, a 14% increase in risk [HR 1.14, 95 CI 1.02-1.27]. However, after adjusting for fibre intake, the strength of the association for red meat was attenuated, and no significant associations with red meat were observed when adjusting for fibre, vegetable, fruit, milk, yogurt, and cheese intake [0.93, 95% CI 0.76, 1.13].

In relation to haemorrhagic stroke, the only significant association was observed for egg intake: a 25% increase in risk per 20g/d intake [HR 1.25, 95% CI 1.09-1.43]. This result was the same in both the basic adjustment model, and the model adjusted for different foods. No significant associations were noted in relation to any other foods and risk for haemorrhagic stroke.

Analysis of the relationship between foods associated with stroke, and hypertension and blood lipid levels, found that the foods associated with reduced risk correlated with lower blood pressure and cholesterol, while foods associated with increased risk correlated with higher blood pressure and cholesterol.

The Critical Breakdown

Pros: The large number of participants in the cohort reduces the possibility for measurement error in dietary assessment to influence results. The added calibration of the FFQ allowed for the investigators to have stronger comparability between different centres across the cohort, while correcting for measurement error inherent in dietary assessment methods. Each dietary assessment was country-specific, and validated in that population. Overall, the dietary assessment methodology in the EPIC cohort is robust. Finally, the follow-up period was of sufficient duration to observe an effect of longer-term exposure.

Cons: The relatively lower numbers of haemorrhagic stroke, 1,430 cases from 7,378 total stroke case [19.3%], and the low overall egg consumption in the entire cohort, gives rise to the possibility that the association with eggs may result from type-1 error, or a 'false positive'. As with all observational research, the default caveat of the findings being associative, rather than demonstrating causality, applies.

Key Characteristic

The broad range of dietary intake across a range of different European countries is a strength of the dietary assessment methodology, for which EPIC was designed to address.

This is because one of the challenges for measuring diet in populations is that variance in nutrition intake tends to be narrow. For example, it would be rare to go from consuming 5,000kcal one day to 800kcal the next, and general day-to-day intake of nutrients may vary, but within a narrow range; salt intake could range from 1,300mg-2,700mg, for example.

Detecting a relationship between exposures with narrow ranges of intake, in populations with relative homogenous dietary patterns, using epidemiological tools [like FFQ] which contain inherent measurement error, is difficult. Trying to hear a specific signal in a lot of noise.

To overcome this, two factors are needed; huge numbers in a cohort, and a sufficient contrast in dietary intake. The contrast in dietary intake is best achieved by having people within the cohort at extreme ends of intake for a nutrient; for example, if we want to compare saturated fat, having a subgroup in the cohort consuming 6-9% [like a Mediterranean diet], and another subgroup consuming >18%. This then provides a sufficient contrast to detect an effect.

By incorporating participants across different European countries, EPIC contained a cohort with different ranges of intake of different foods and nutrients, which combined with the large cohort numbers, provided a more robust dietary assessment to detect relationships with associated outcomes.

Interesting Finding

Perhaps the most interesting finding in this study was that the relationship between red meat and stroke was not longer evidence after adjusting for fibre, and dairy foods.

A number of factors may mediate this relationship. The first is to say that overall, meat consumption in the EPIC cohort is low; the highest quintile of red meat was 67.8g per day; in contrast, when stratifying meat intake and adverse health outcomes, the most pronounced risk is observed in American cohorts, who have higher levels of intake (5).

One of the factors which may influence the relationship with dairy is calcium, which has an under-appreciated role in reducing blood pressure (6). In addition, the dairy sources found to be protective in this study were unrefined - milk, yogurt, and cheese - and these foods are known to have different effects on blood cholesterol levels to other saturated animal fats, exerting an overall positive influence on blood cholesterol (7). Dietary fibre has consistently been associated with reduced risk of stroke (8). Ultimately, the lower levels of meat in the EPIC cohort, and the mediating effect of fibre and dairy foods, suggests that the total dietary pattern, and absolute overall intake of foods, is more relevant than isolated foods themselves in this pan-European cohort.

Relevance

This is a highly well-conducted work of nutritional epidemiology, with robust dietary assessment methods. Although the finding with regard to eggs will generate controversy and headlines, I would advise caution in interpreting this finding having regard to the wider literature. A combined analysis of 4 studies comparing high [increment of one egg per day] vs. low egg intake found a 25% reduction in risk for hemorrhagic stroke [RR 0.75, 95% CI 0.57 to 0.99]. As stated in the 'Cons' above, the potential for the finding in this study to be a false-positive cannot be ruled out.

The reduced risk with milk, yogurt, and cheese adds to a body of literature suggesting that these particularly dairy foods are protective against cardiometabolic disease, including stroke. The finding has been shown elsewhere, with a 9% reduction in stroke noted in a recent study from dairy intake (9).

The foods associated with reduced risk in this study are consistent with dietary pattern interventions, like the Dietary Approaches to Stop Hypertension [DASH] Diet, which has been consistently shown to reduce high blood pressure (10,11). Given hypertension is established as a leading risk factor for stroke, dietary factors influencing blood pressure may be important for stroke risk, which is supported by the fact that in the current study, foods associated with reduced risk correlated with lower blood pressure levels.

Application to Practice

The overall main risk factor for stroke is age, however, the modifiable factors may better characterise the relationship as diet/lifestyle>risk factors>age; i.e., age as a risk reflects exposure to those risk factors. Of those risk factors, hypertension appears to be the strongest, and from a dietary perspective, the most modifiable. Interventions like DASH may be an appropriate dietary pattern for people at risk of stroke, particularly with elevated blood pressure. Encouragement of such a dietary pattern, however, rich in fibre, vegetables, fruit, and dairy - is arguably prudent in everyone.

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