

# Dietary Anti-Oxidant Capacity, Dietary Inflammation Index, and the Risk of Stroke in a Large Prospective Cohort Study.

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## Research

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# Abstract

## Background

Whilst the Western and Mediterranean/prudent diets have long been associated with the risk of stroke, it is less clear if increased inflammation and reduction of oxidations are their respective mechanisms. This study aimed to understand the associations between the dietary inflammatory index (DII), and total anti-oxidant capacity of the diet (TAC), with regards to stroke risk.

## Methods

The study population included 71,460 women free of cardiovascular disease at baseline from the E3N cohort, who completed a diet history questionnaire which was used to estimate the dietary pattern scores. Scores were considered grouped as quintiles and as splines in order to determine the dose-response shape. Hazard ratios (HRs) and 95% confidence intervals (95% CI) for hypertension were estimated with multivariate Cox models with age as the time scale, and adjusted for potential confounding factors. After Bonferroni correction, a p-value of 0.013 was considered significant.

## Results

Over 14.5 years of follow-up, 414 cases of incident stroke were identified. The Western, and Prudent dietary patterns were both highly associated with the risk of stroke (Western  $HR_{Q1Q4} = 1.85$  [1.27: 2.69], p-trend = 0.002, Prudent  $HR_{Q1Q4} = 0.59$  [0.44: 0.78], p-trend < 0.001), as was TAC from non-coffee sources ( $HR_{Q1Q4} = 0.47$  [0.33: 0.68], p-trend < 0.001). All three showed a clear dose-response, and the associations with the Western and Prudent scores were consistent in sensitivity analysis. Weaker evidence was observed for DII ( $HR_{Q1Q4} = 1.33$  [1.01: 1.78], p-trend = 0.03), which did not show a clear dose-response. TAC from coffee was not associated with the risk of stroke.

## Conclusion

These results suggest that diets high in anti-oxidants are associated with a reduced risk of stroke, but that inflammation from the diet does not play as large a part in the risk of stroke. Factors other than inflammation may be driving associations with stroke and western diet.

## Introduction

Stroke is the second leading cause of mortality and disability, in the world. In 2016, it was estimated that stroke account for 5.5 million deaths and 116.4 million global disability-adjusted life-years worldwide<sup>1</sup>. During most of the lifespan, men and women have a similar age-specific stroke rate, and up to 20 % of women will have a stroke during their lifetime, typically suffer poorer outcomes than males, with a 1.25 times higher risk of fatal stroke<sup>2</sup>. Whilst metabolic risks (hypertension, BMI, type-2 diabetes) are the main drivers of stroke<sup>3,4</sup>, numerous lifestyles related risk-factors have been identified, such as body-weight<sup>5</sup>,

physical activity<sup>6,7</sup> and diet<sup>8,9</sup>. Since diet is easily modifiable, it presents as an easy target for interventions. Multiple randomised controlled trials and prospective studies have shown that a traditional Prudent diet, high in fruit, vegetables and healthy fats is protective against various forms of cardiovascular disease<sup>10-12</sup>, and that the typical western diet, higher in processed food, cholesterol and saturated fats leads also to an increased likelihood of these diseases<sup>13-15</sup>.

While there are many postulated mechanisms through which Western and Prudent dietary patterns might act; inflammation and oxidative stress are likely the most relevant pathways. The dietary inflammatory index (DII)<sup>16</sup>, and the total anti-oxidant capacity (TAC)<sup>17,18</sup> of the diet have been developed in order to analyse the inflammatory and anti-oxidising aspects of a diet. Previous studies have identified that the DII is positively associated with inflammatory markers<sup>19</sup>, hypertension<sup>20,21</sup>, and cardiovascular disease<sup>22</sup>. Conversely, the TAC has been associated with lower rates of hypertension<sup>23</sup>, and cardiovascular disease.

In this article, we aimed to investigate and compare the associations of these dietary scores with stroke in the E3N cohort of French women, and to determine the shape of any dose-responses.

## Methods

### Study cohort

The E3N is a French prospective cohort started in 1990 comprising 98,995 women aged 40–65 years at baseline and insured by the MGEN, a health insurance plan for employees of the French education system and their families. The cohort received ethical approval from the French National Commission for Computerized Data and Individual Freedom (ClinicalTrials.gov identifier: NCT03285230), and all participants in the study signed an informed consent form. Participants returned mailed questionnaires on lifestyle information and disease occurrence every 2 to 3 years. The average response rate at each questionnaire cycle was 83 %, and the total loss to follow-up was 3%.

We considered women who completed a diet history questionnaire at baseline (n = 74,522) and then excluded women with unrealistic BMI and calorie consumption (1st and 99th percentiles of the distribution in the population, n = 2964) and finally those with stroke (n = 70) before or at the 1993 questionnaire. The final study population included 71,460 women.

### Estimation of dietary patterns

In 1993 dietary data was collected using a two-part questionnaire detailing consumption of 208 food items during the year prior to the questionnaire, which has been shown to be reproducible and valid to classify study subjects according to their food and nutrient intake over a one-year period<sup>24</sup>. Women were asked to answer questions about quantities and frequencies of consumption of food groups. Eleven possible responses were available, never or less than once a month; 1 to 3 times a month, and 1 to 7 times a week. A photo booklet was added to help estimate portion sizes. From this questionnaire and using a detailed food composition table, mean daily intakes of energy (excluding energy from alcohol),

alcohol, and nutrients were estimated. We used this data to estimate two *a-priori* patterns (the TAC and DII), and two *posteriori* patterns (Western and Prudent).

## Western and Prudent patterns

The western and Prudent patterns were derived using factor analysis, as has been previously described<sup>25</sup>. Estimation of these patterns used 56 food items from the dietary questionnaire were considered, and those with a factor loading value greater than 0.4 were retained for identification of the diet patterns.

These patterns share many traits with those observed in other cohorts<sup>26</sup>, and traditional diets<sup>27</sup>. For example, the Prudent pattern can be considered 'healthy' and is characterised by high intakes of fruits, vegetables, grains, and lower quantities of processed foods, meat and poultry. The Western pattern can be considered 'unhealthy' and is characterised by high intakes of processed foods, eggs, dairy, cakes, and refined grains.

## Total anti-oxidant capacity

Dietary TAC was estimated using an Italian database<sup>17,18</sup> which used the TRAP (Total Radical-trapping Antioxidant Parameter) assay to estimate the TAC of foods based on the transfer of hydrogen to stabilize a free radical<sup>28</sup>. For each food item in the diet history questionnaire, we identified an equivalent food in the TAC database. TRAP from coffee represented 75% of overall dietary TRAP, 6% for fruit, 5% for wine, 5% for tea, 4% for vegetables, 3% for chocolate, and 3% for other sources.

Antioxidant supplement intake was assessed through the 1995, 2000, 2002, and 2005 questionnaires. Participants were asked about their intakes of different vitamins and minerals, including vitamin E, vitamin C, and beta-carotene if consumed at least three times per week.

Because of the dominant proportion of coffee, and because of doubts about the proportion of polyphenols from coffee to be absorbed and play an actual systemic role, we decided to present in the main text analysis on non-coffee TRAP, and included coffee TRAP analysis in the supplementary materials. Previously we have observed that for TAC excluding coffee, major sources of anti-oxidants were fruit, red wine, tea, vegetables, and dark chocolate<sup>23</sup>.

## Dietary Inflammatory Index

The adapted dietary inflammatory index proposed by Woudenberg et al<sup>29</sup> was used in combination with the updated dietary components weights by Shivappa et al<sup>16</sup>. This DII has been proposed on the basis of nutritional rationale. First, the inflammatory weights of dietary components are multiplied by the standardised energy adjusted intake, which acts to reduce between-person variation. Second, the intake of all components are standardised by subtracting the mean intake of the population (in this case E3N, n = 74,522) from the individual's intake, and then divided by the standard deviation of the intake from the population. Finally, the inflammatory effects of energy and total fat were not calculated separately, as they were considered to be equivalent to the sum of the inflammatory effects of all energy-providing

macronutrients, and all separate fatty acids, respectively. Similarly, as ethanol was used in the estimation of the DII, we did not consider separately the inflammatory effect from specific alcoholic beverages. A total of 32 of the 35 possible dietary components were used for DII calculation<sup>20</sup> based on the food frequency questionnaire. A positive DII score is representative of a pro-inflammatory diet, and negative values of an anti-inflammatory diet.

Previously we have observed that the DII is positively associated with intakes of various unhealthy foods including added sugars, white bread, dairy based desserts, fried potatoes, fast foods such as burgers, pâtés, and sausages. Inverse associations were observed with intakes of vegetables, fibre, and fresh fruit.

## **Ascertainment of stroke cases**

Incident stroke was self-reported at each questionnaire by the study participants. Following the identification of a self-reported event, both the participant and the general practitioner of the study participant were contacted in order to acquire additional information and documentation (hospital discharge reports, medical imaging reports, reports of other ancillary exams conducted in relation with the event) needed to validate and characterize the event. Causes of death were obtained from the French National Service on Causes of Death, and strokes were identified according to ICD-9/10 codes, available until December 2010. Fatal stroke were considered if the primary cause of death reported on the death certificate was stroke. Non-fatal strokes were validated by certified stroke neurologists working in the group. We classified incident stroke cases as ischaemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage, and stroke of unknown type if information was insufficient to derive the stroke type. Specific details of the validation process are presented in the supplementary material. For analysis, we considered all stroke as the primary outcome, and then ischaemic stroke and haemorrhagic stroke (intracerebral and subarachnoid together, due to low case numbers) separately. A separate analysis assessed intracerebral and subarachnoid separately, and is presented with the sensitivity analysis.

## **Assessment of potential confounding factors**

Since BMI can be affected by diet, we assessed BMI at 1992 in order to separate it from the dietary measurement, and reduce the risk of bias. Self-reported height and weight from the questionnaire were used to calculate body mass index (BMI), defined as weight (kg) divided by squared height (m<sup>2</sup>). In the cohort, self-reported anthropometry has proven reliable in a validation study<sup>30</sup>. We assessed total physical activity with a questionnaire in 1993 that included questions on weekly hours spent walking, cycling, and performing light and heavy household chores, or recreational activities and sports (e.g., swimming and tennis) considering the winter and summer seasons. It included questions on the time spent walking (to work, shopping, and leisure time), cycling (to work, shopping, and leisure time), housework, and sports activities (such as racket sports, or swimming). Each activity was assigned a Metabolic equivalents (METs) value based on values from the Compendium of Physical Activities<sup>31</sup>.

Family history of cardiovascular disease (yes/no), diabetes (yes/no), education (no high school diploma, high school diploma), and smoking (ever smoker, current smoker, or never smoker) were based on self-reports. Hypertension was based on self-report, which was cross-referenced against reimbursement for anti-hypertensive medications with 82 % agreement for those reporting hypertension in 2008<sup>32</sup>. Diabetes was based on self-reports, which were later validated using a specific questionnaire<sup>33</sup>. Dyslipidaemia was based on self-reported high-cholesterol requiring treatment.

## Statistical analysis

Each of the dietary scores was split into quartiles depending on the population distribution. These quartiles were then considered as exposures in a cox proportional hazard model with age as the timescale considering the lowest group as the reference, were used to assess the risk of incident stroke, including subtypes (ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage). Time at entry was the age at the beginning of follow-up (1993), exit time was the age when participants were diagnosed with stroke, died (dates of death were obtained from the participants' medical insurance records), were lost to follow-up, or were censored at the end of the follow-up period (the age at receipt of the eighth questionnaire), whichever occurred first. P-values for trends were calculated using the quintile median value as a quasi-continuous variable in the model. Models were initially adjusted for calorie intake with age as the timeline (age-adjusted), then on alcohol intake (g/day), caffeine intake (g/day), hypertension at baseline (yes/no), dyslipidaemia at baseline (yes/no), diabetes at baseline (yes/no) smoking status (current/ex/never), family history of cardiovascular disease (yes/no), education level (high-school/no high-school), total physical activity, and BMI (continuous).

Spline regression<sup>34</sup>, which fits low-order polynomials between fixed equidistant points known as 'knots' in order to smooth the variable, was used to assess the shape of the association between diet scores, and the risk of stroke. The spline term was included as a variable in a Cox model. The splines were then plotted, showing the relationship between the hazard ratio for stroke, and the diet score value.

The proportional hazards assumption was assessed graphically, by plotting the Schoenfeld residuals. An adjusted p-value of  $p = 0.013$  was used for statistical significance after a simple Bonferroni correction, i.e. dividing the p-value of 0.05 by four. As a sensitivity analysis, cases occurring within 2 years, and then 5 years were excluded from analyses. A secondary sensitivity analysis excluded fatal strokes.

Tabulated data is presented as percentage, mean (standard deviation (sd)) or median (inter quartile range (iqr), the difference between the 75th and 25th quantile).

## Results

### Baseline trends and basic results

Over an average follow-up of 14.5 years per person, 414 cases of stroke were identified and validated at a rate of 0.4 / 1000 person-years, including 225 non-fatal ischemic events, 74 non-fatal intracerebral haemorrhage events, 32 non-fatal subarachnoid haemorrhage events, and 112 fatal stroke events. The

mean age at stroke was 64.2 years. Compared to cases, non-cases were slightly younger at baseline, had a lower BMI, reported more physical activity, were more educated, and were less likely to report hypertension or dyslipidaemia at baseline. Cases had a higher western diet score, a lower prudent diet score, a higher DII, and lower intake of antioxidants (i.e. a lower TAC) at baseline, and reported higher consumption of coffee and alcohol (Table 1).

Table 1  
Cohort characteristics at baseline.

Characteristic (mean (sd) or %)	Whole cohort (n = 71,460)	Cases (n = 414)	Non cases (n = 71,046)
Age (years)	52.9 (6.7)	55.2 (6.8)	52.9 (6.7)
BMI (kg / m <sup>2</sup> )	22.7 (2.9)	23.4 (3.1)	22.7 (2.9)
Physical activity (METs-h / week)	55.0 (30.2)	45.9 (29.5)	55.0 (30.2)
Smoking (smoking/X/never) (%)	13.8 / 33.0 / 53.7	11.3 / 32.5 / 56.2	13.4 / 33.1 / 53.5
Education (University or higher) (%)	35.9	23.2	36.0
Family history of cardiovascular disease (%)	34.7	30.0	34.7
Prevalent hypertension (%)	36.8	48.9	36.7
Prevalent diabetes (%)	1.1	0.7	1.1
Prevalent dyslipidaemia (%)	7.2	10.1	7.2
Dietary variables			
Calories (kcal)	2078 (712)	2071 (715)	2078 (712)
Alcohol (g / day)	6.9 (15.0)	8.7 (15.0)	6.9 (15.0)
Caffeine (mg / day)	174 (177)	187 (161)	174 (177)
Western	-0.13 (1.20)	-0.09 (1.30)	-0.13 (1.20)
Prudent	-0.12 (1.22)	-0.30 (1.11)	-0.12 (1.22)
TAC (non-coffee) (mmol / day)	4.5 (3.0)	4.1 (2.7)	4.5 (3.0)
TAC (coffee) (mmol / day)	12.9 (18.5)	14.7 (15.7)	12.8 (18.5)
DII	0.4 (4.6)	0.75 (4.44)	0.4 (4.6)

Negative correlations were observed between DII and the prudent score ( $r = -0.79$ ), and TAC ( $r = -0.23$ ). Positive associations were observed between DII and the western score ( $r = 0.20$ ). The prudent score correlated with TAC from coffee ( $r = 0.31$ ). Correlations are presented as a heatmap in sup. Figure 1.

## Western diet

The Western diet showed a strong positive association with the risk of stroke after adjustment for potential confounders ( $HR_{Q1Q4} = 1.85 [1.27: 2.69]$ ,  $p\text{-trend} = 0.002$ , Table 2). When considering spline-based models, a strong positive dose-response relationship was observed (Fig. 1 a). Result were consistent when considering ischaemic stroke ( $HR_{Q1Q4} = 2.38 [1.46: 3.88]$ ,  $p\text{-trend} = < 0.001$ ), but were not significant when considering haemorrhagic stroke ( $HR_{Q1Q4} = 1.24 [0.69: 2.24]$ ,  $p\text{-trend} = 0.65$ ).

Table 2

Associations between dietary scores and incident stroke. Hazard ratio [95 % confidence interval].

	Q1	Q2	Q3	Q4	p-trend
Western	ref	1.30 [0.98: 1.73]	1.37 [1.01: 1.87]	2.21 [1.56: 3.12]	< 0.001
Adjusted Western	ref	1.23 [0.92: 2.64]	1,25 [0.91: 2.72]	1.85 [1.27: 2.69]	0.002
Prudent	ref	0.79 [0.61: 1.03]	0.71 [0.54: 0.92]	0.58 [0.43: 0.77]	< 0.001
Adjusted Prudent	ref	0.82 [0.63: 1.05]	0.73 [0.56: 0.95]	0.59 [0.44: 0.78]	< 0.001
TAC (non-coffee)	ref	0.93 [0.72: 1.20]	0.69 [0.52: 0.91]	0.58 [0.43: 0.78]	< 0.001
Adjusted TAC (non-coffee)	ref	0.91 [0.71: 1.18]	0.65 [0.49: 0.86]	0.47 [0.33: 0.68]	< 0.001
DII	ref	1.07 [0.81: 1.43]	1.20 [0.91: 1.58]	1.32 [1.00: 1.74]	0.03
Adjusted DII	ref	1,08 [0.81: 1.44]	1.22 [0.92: 1.61]	1.33 [1.01: 1.78]	0.03
Initially adjusted with age as the time line and for calorie intake. Risk-factor adjusted as hypertension at baseline (yes/no), dyslipidaemia at baseline (yes/no), diabetes at baseline (yes/no), smoking status (current/ex/never), family history of cardiovascular disease (yes/no), education level (high-school/no high-school), total physical activity, and BMI (continuous).					

## Prudent diet

The Prudent diet was inversely associated with the risk of stroke after adjustment for potential confounders ( $HR_{Q1Q4} = 0.59 [0.44: 0.78]$ ,  $p\text{-trend} < 0.001$ , Table 2). When considering spline-based models, a strong negative dose-response relationship was observed (Fig. 1b). Result were consistent when considering both ischaemic stroke ( $HR_{Q1Q4} = 0.60 [0.41: 0.87]$ ,  $p\text{-trend} = < 0.01$ ), and haemorrhagic stroke ( $HR_{Q1Q4} = 0.60 [0.39: 0.95]$ ,  $p\text{-trend} = 0.04$ ).

## TAC

In unadjusted and adjusted models, non-coffee TAC was inversely associated with the risk of stroke ( $HR_{Q1Q4} = 0.47 [0.33: 0.68]$ ,  $p\text{-trend} < 0.001$ , Table 2). When considering the TAC from coffee, mutually adjusted for non-coffee TAC, and caffeine intake, TAC from coffee was borderline associated with the risk

of stroke ( $HR_{Q1Q4} = 2.11$  (0.98: 2.76),  $p$ -trend = 0.07, sup. table 1). When considering spline-based models, a modest negative dose-response relationship was observed between the risk of stroke and non-coffee TAC (Fig. 1c). Results were consistent when considering both ischaemic stroke ( $HR_{Q1Q4} = 0.46$  [0.29: 0.73],  $p$ -trend = < 0.001), and haemorrhagic stroke ( $HR_{Q1Q4} = 0.49$  [0.29: 0.84],  $p$ -trend < 0.01).

## Dietary inflammatory index

The DII was risk of stroke after adjustment for potential confounders, but this association was not statistically significant after Bonferroni correction ( $HR_{Q1Q4} = 1.33$  [1.01: 1.78],  $p$ -trend = 0.03, Table 2). When considering spline-based models, no deviation from the null was observed for a positive DII, and a weak association was observed with a negative DII (anti-inflammatory diet), when compared to a score of zero (Fig. 1d). Results were consistent but borderline when considering haemorrhagic stroke ( $HR_{Q1Q4} = 1.57$  [0.99: 2.47],  $p$ -trend 0.04), but not when considering ischaemic stroke ( $HR_{Q1Q4} = 1.19$  [0.83: 1.70],  $p$ -trend = 0.34).

## Sensitivity analysis

Associations were consistent for the Western score when excluding cases occurring after two (remaining cases = 397) and five years (remaining cases = 338) (two years:  $HR_{Q1Q4} = 1.90$  [1.30: 2.77], five years:  $HR_{Q1Q4} = 2.10$  [1.39: 1.71]), as well as for the Prudent score (two years:  $HR_{Q1Q4} = 0.59$  [0.45: 0.85], five years:  $HR_{Q1Q4} = 0.58$  [0.42: 0.79]). Associations were similar for TAC (two years:  $HR_{Q1Q4} = 0.46$  [0.32: 0.66], five years:  $HR_{Q1Q4} = 0.44$  [0.29: 0.65]) and DII (two years:  $HR_{Q1Q4} = 1.35$  [1.01: 1.81], five years:  $HR_{Q1Q4} = 1.33$  [0.97: 1.81]).

When considering only non-fatal cases, results were comparable for the western score ( $HR_{Q1Q4} = 2.65$  [1.70: 4.14]), and the prudent score ( $HR_{Q1Q4} = 0.52$  [0.37: 0.73]), TAC score ( $HR_{Q1Q4} = 0.44$  [0.30: 0.67]), and were significant for DII ( $HR_{Q1Q4} = 1.41$  [1.02: 1.96]).

Considering subarachnoid haemorrhage and intracranial haemorrhage separately gave large confidence intervals, and non-significant results for all dietary patterns assessed (data not tabulated).

## Discussion

In this large prospective study, the strongest associations between diet and stroke risk were observed for the Western and Prudent patterns. The Western, Prudent patterns, and a high content of anti-oxidants in the diet all showed consistent associations after adjustment for confounding factors. The prudent and TAC showed high positive correlation, and a similar magnitude of negative association with stroke. When considering splines, the Western, Prudent and TAC showed dose responses which agreed with the quintile-based models.

Many studies have shown that a traditional, or prudent diet, is associated with lower rates of chronic and non-communicable diseases. The traditional Mediterranean diet is perhaps the best known diet

associated with lower rates of chronic disease, and is defined by high consumptions of olive oil, nuts, fruit and vegetables, similar to the Prudent pattern identified in the E3N cohort. Recently, a large American study identified inverse associations between an alternate Mediterranean diet and a healthy plant diet, with cardiovascular disease (including stroke) and mortality<sup>35</sup>. In this study of E3N women, the prudent diet score showed positive correlations with TAC, and negative correlations with DII, suggesting that it is both rich in anti-oxidants, and anti-inflammatory, which may explain the strong observations. Anti-oxidants are associated with lower rates of high blood-pressure<sup>23</sup>, a main risk factor for stroke. Dietary TAC has been previously inversely associated with stroke<sup>36,37</sup>, and other diseases such as coronary disease<sup>38</sup>, cancer<sup>28,39</sup>, and mortality<sup>40</sup>. In this population, a diet high in anti-oxidants was associated with a 29 % lower risk of stroke than a diet low in anti-oxidants, a similar magnitude to the prudent diet score. TAC has also been associated with outcome after stroke<sup>41</sup>. A systematic review<sup>42</sup> of cross-sectional and prospective studies concluded that intakes of carotenoids (an anti-oxidant common in yellow and red fruits and vegetables) are associated with a reduced risk of stroke, but that the mechanism was yet to be determined. Interestingly, TAC from coffee was not associated with the risk of stroke in this population. It is possible that this is due to residual confounding from other lifestyle factors associated with coffee consumption in the French population, such as smoking. Previously, coffee-TAC also showed null associations with hypertension in this cohort. Other prospective studies and meta-analyses have identified weak protective associations between coffee and stroke.

Western dietary patterns have been linked to higher risk of chronic and non-communicable diseases in many other studies. Consistent associations have been observed between western diets and stroke, coronary disease, and cardio-metabolic risk factors. The strong observations presented in this work add to the plethora of studies that support the idea that a western diet, with a high consumption of processed foods, and refined carbohydrates, is positively associated with stroke risk and should be considered a major risk-factor. The western diet is recognised as being highly inflammatory, and is associated with increased levels of inflammatory markers in human studies<sup>26,43</sup>. Similarly, the DII has been shown to be associated increased concentrations of inflammatory markers<sup>19</sup>, and show positive associations with a number of diseases such as stroke, coronary disease and CVD mortality<sup>22,44</sup>, hypertension<sup>20,23</sup>, and cancer<sup>45,46</sup>. Only weak associations were observed between DII and stroke in our study of E3N women. Previously, we have observed only weak associations between DII and hypertension in this cohort<sup>20</sup>, suggesting a pro-inflammatory diet may not be a strong stroke risk-factor in this population.

## Mechanisms

Ischaemic stroke is a heterogeneous entity for which one of the leading mechanisms is atherosclerosis of the arteries supplying blood to the brain, which can cause reduced lumen diameter, and eventually becoming blocked by thrombus. Reactive oxygen species (ROS) are implicated in the atherogenic pathway, and can cause the oxidation of low-density lipoprotein in the vascular wall. All cardiovascular risk-factors including dyslipidaemia, hypertension and diabetes are known to increase ROS production. Vascular cells contain various anti-oxidising enzymes in order to reduce the oxidative burden, but a diet

rich in anti-oxidant molecules could independently reduce the availability of ROS through free radical scavenging<sup>47</sup>, and their negative effects. Flavonoids (a type of anti-oxidant) in particular have been shown to have blood pressure lowering effects, and can improve endothelial function<sup>48</sup>. Oxidative stress is also potentially implicated in the high-morbidity and mortality rate attributed to haemorrhagic stroke. For example iron deposited after haemorrhagic stroke can lead to the production of free radicals and oxidative stress, leading to nerve damage in the brain<sup>49</sup>. A diet high in anti-oxidants may enhance the antioxidant defence capacity following haemorrhagic stroke, and studies in animals have suggested that pre-treatment with certain antioxidants may reduce neurological deficit after haemorrhagic stroke<sup>50</sup>. Similarly, oxidative stress may be implicated another leading cause of stroke, cerebral small vessel disease<sup>51</sup>, and a diet high in anti-oxidants may reduce the risk of its development.

Chronic inflammation is a feature of aging, and is implemented in the route leading to ischaemic stroke through atherosclerosis and endothelial damage. Pro-inflammatory mediators can cause endothelial cells lining the blood vessels to adhere to white blood cells, eventually leading to the formation of plaques through the migration of smooth muscle cells from the media to the intima layer of the blood vessel<sup>52,53</sup>. It has been demonstrated that certain foods, such as saturated fats<sup>54,55</sup>, can increase the presence of inflammatory markers and endotoxins in the blood. Oxidised LDL can also trigger vascular inflammation<sup>56</sup>, leading to a cascading effect. If a diet with a high inflammatory potential was to raise levels of inflammatory mediators, this could potentially increase the rate of atherogenesis and lead to an increased risk of stroke. Local brain inflammation also increases following both ischaemic and haemorrhagic stroke<sup>57</sup>, which can last for weeks following the stroke, and can lead to secondary damage of the brain. It is unclear if a diet leading to a high level of chronic inflammation may exacerbate this, or if a diet with a high anti-inflammatory potential may reduce the risk of secondary damage.

## Strengths and Limitations

The main strengths of this study are the large cohort, long follow-up, detailed dietary assessment, and the use of only validated stroke cases according to a standardized procedure by trained stroke physicians. The main limitation is a relatively small number of stroke cases. The E3N cohort is at relatively low risk of diseases such as stroke, and other studies in low risk populations have also reported low incidence rates<sup>58</sup>. Moreover, as the ascertainment of incident stroke events is initially based self-reporting in questionnaires, we cannot exclude that minor strokes that have not led to a hospitalization may have been underreported, which may explain the relatively high proportion of fatal strokes. Data on fatal strokes was also available for a slightly longer period, until December 2010, which explains partly the relatively high fatal stroke incidence. Dietary data was self-reported, and could be subject to recall error, or bias. Since the study is observational, it cannot claim causality. One limitation with regards to considering dietary scores is that they cannot be used to give specific dietary advice, and are difficult to consider as a well-defined exposure. There is a possibility that the results are due to unmeasurable confounding, but this would be unlikely to explain the strong associations observed.

One potential reason for the slightly stronger associations from the prudent and western pattern could be that they are developed using data specific to the cohort (post-priori), whereas the DII and TAC are scored depending on specific food items (a-priori). For the TAC, we chose values based on an Italian database, as opposed to a Norwegian database, assuming that the Italian diet would be closer to the French. For DII, we made use of the majority of the foods used to calculate the score; however a small number had to be omitted as they were not present in our questionnaire. A-priori scores may benefit from corrections or calibrations depending on variations on the regional diet.

## **Conclusion**

In conclusion, we observed strong positive associations between a Western dietary score, and the risk of stroke, and strong inverse associations with a traditional Prudent score, high in vegetables and fruit. Evidence also supported that high consumption of foods rich in anti-oxidants could reduce stroke risk. The DII showed weaker associations with stroke risk. These results reinforce the evidence that adopting healthy diets may reduce stroke risk.

## **Declarations**

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### **Contributions of Authors:**

CJM - designed research, conducted research, analysed data, wrote paper

ALM – conducted research, analysed data

NL – conducted research, analysed data

SS – designed research, collected data

SD – designed research, collected data

GS - designed research

MCBR - primary responsibility for final content

All authors read and approved the final manuscript.

### **Availability of data**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request to qualified researchers.

### **Competing interests**

The authors declare that they have no competing interests.

### **Ethics approval and consent to participate**

The cohort received ethical approval from the French National Commission for Computerized Data and Individual Freedom (Commission Nationale Informatique et Libertés), and all participants in the study signed an informed consent.

### **Consent for publication**

Not applicable.

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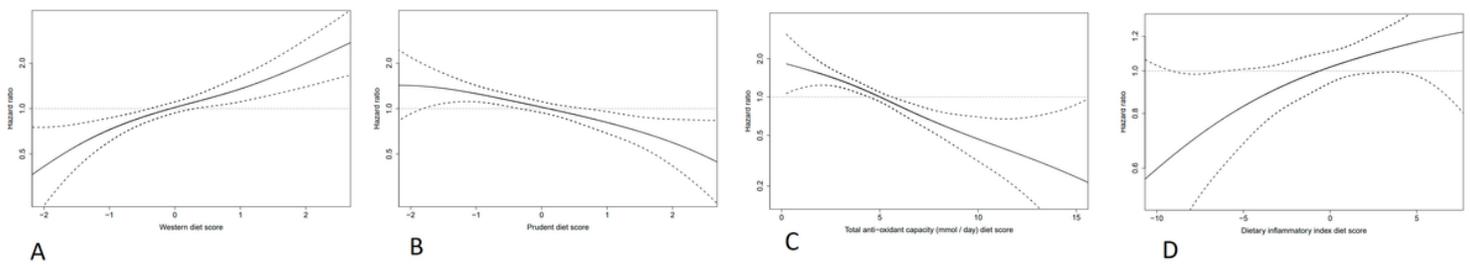
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## Figures



**Figure 1**

Spline models showing the dose response from the Western (a), Prudent (b), TAC (c) and DII (d) scores.

(a) Western (b) Prudent (c) TAC (d) DII

## Supplementary Files

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