Influence of Dietary Patterns on Stroke Risk in China

To the Editor:

I read with interest the study of dietary influence on stroke risk in women reported by the Nurses’ Health Study group.1 The authors concluded their article by saying that “because dietary pattern may vary in different populations, our results need to be verified in other populations.” I wish to confirm that similar risk associations have been observed in China, just as in the case of coronary artery disease.2

Zhou3 reported in 2002 that the dramatic increase in mortality in coronary artery disease in China could be attributed to the observed changes from a traditional Chinese diet to a Western diet,4 such as a 5-fold increase in consumption of red meats, eggs, and oils between 1978 and 19925 and a decrease in fruit and vegetable intake during the same period.6 This correlation holds true for stroke in China (B.F. Zhou, personal communication, September 12, 2004).

Zhou presented further confirmatory data from the International Study on Macronutrients and Blood Pressure (INTERMAP) in a Chinese medical journal.5 The INTERMAP included participants from China, Japan, the United Kingdom, and the United States in the late 1990s.6 According to Zhou,5 hypercholesterolemia (≥5.17 mmol/L) was detected in one third of the Chinese participants, in whom the incidence of coronary artery disease and stroke was 10%. Zhou5 contrasted this escalating trend in China with the declining trend in Japan (from a stroke mortality of 385 per 100 000 males and 225 per 100 000 females in 1970 to 79 per 100 000 males and 41 per 100 000 females in 1990s) as a result of control of the dietary risk factors in Japan.

That a Western dietary pattern, characterized by high intake of red and processed meats and high-fat dairy products and desserts and reflected by an elevated plasma cholesterol level, is associated with an increased risk of ischemic stroke1 is also evidenced by findings reported recently from China of different subtypes of stroke in China.7 The Collaborative Study Group of China Multicenter Study of Cardiovascular Epidemiology7 found a great variance in the proportion of stroke subtypes among different populations with the same ethnic backgrounds and within the same country. High plasma cholesterol and body mass index increased the risk of ischemic stroke.7 In China, plasma cholesterol is higher in urban than in rural populations and higher in northern than in southern populations, thus explaining a higher proportion of ischemic stroke in urban and northern populations than in rural and southern populations.7

There is a price that developing countries must pay for modernization; however, let the price the Chinese pay not exceed the benefits derived from modernization. Can we achieve a utopian stage in the 21st century in which the modern Chinese retain their ancestral low rates of cardiovascular disease while adapting the positive aspects of a modern Western lifestyle?8

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Correlation of Systemic Inflammatory Response With Infarct Volume in Acute Ischemic Stroke Patients

To the Editor:

In the September 2004 issue of Stroke, Audebert and colleagues1 commented on a study conducted by our group “in a small number of acute stroke patients.”2 Contrary to the authors’ assertion that “[T]here are no reports so far on the association between lesion size and elevated CRP in the acute phase of ischemic stroke,” the relationship between C-reactive protein (CRP) and both infarct volume and clinical outcome in this study was subsequently reported in January 2004.3 In fact, despite the smaller size of our study, a notable difference between the studies is that whereas Audebert et al suggest the correlations with CRP are quite weak,1 our own data indicated rather higher correlations across a range of measures, although they were not as high as for interleukin-6, which is a more direct measure of tissue inflammation. A possible explanation lies in the measurements of CRP used in the German study. Their lower cutoff for CRP was 0.5 mg/dL, which does not approach the normal range, and our own data suggest they may have used a cutoff value of 0.4 mg/dL for approximately half the data points. That this is the case is supported by the data in Figure 2, in which the error, or range, for day 1 CRP is indicated as a negative value, which is clearly not possible. Their large range of ties at 0.4 mg/dL could then result in spuriously low correlations in the analyses.

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**Response:**

We thank Dr Emsley for his critical comment on our article. In fact, their analysis of January 2004 resulted in a relationship between infarct volume and C-reactive protein (CRP) in the acute phase of ischemic stroke. However, it was published just at the time when our paper was submitted the first time to *Stroke*. We agree that the relatively weak correlation between CRP and lesion size on the first day after admission may be caused by the lower cutoff level of CRP (0.5 mg/dL) in our study. This cutoff was introduced for clinical use to exclude nontherapeutic elevations of CRP. The reduced sensitivity in lower CRP ranges is less relevant in the subsequent days, when CRP increases, especially in patients with large infarcts. However, the peak plasma CRP levels (measurements within 5 to 7 days) as used in the publication of Emsley et al are a different method and cannot be compared directly to our results with particular correlations for each day.

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**Letters to the Editor 229**

**Insular Lesions and Hyperglycemia in Acute Stroke Revisited**

To the Editor:

I have read with interest the article by Allport et al reporting that insular cortical ischemia was associated with poststroke hyperglycemia. Previous studies have associated insular lesions with ECG abnormalities and have suggested a relation to cerebrogenic sudden death, possibly through the generation of fatal cardiac arrhythmias. It has further been hypothesized that this might come about either in an indirect manner by activation of the sympathicoadrenal system or by direct effects. Laterality of insular effects in humans has further been demonstrated. As increasing sympathicoadrenal tone causes hyperglycemia, the finding of higher blood glucose in patients with insular lesions may support this mechanism.

We investigated s-cortisol levels in the light of insular lesions in 172 patients with acute stroke within 6 hours of admission, 42 of whom had unilateral insular lesions. In univariate analysis, we found that cortisol levels related significantly to insular damage, especially right insular damage. However, in multivariate analysis also including stroke severity on admission and early infarction signs on initial CT scan, this was no longer the case.

On reading the article of Allport et al, I further tried to reproduce their findings concerning blood glucose and insular lesions in our 179 patients in whom blood glucose was measured on admission within 6 hours of stroke onset. Mean blood glucose in patients with insular lesions was 6.6 mmol/L in comparison to 6.4 mmol/L in patients with no insular lesions (*P* = 0.317). In patients with right insular lesions, mean blood glucose was 7.0 mmol/L in comparison to 6.4 mmol/L in patients with left or no insular lesions (*P* = 0.564).

These findings support the idea of insular damage causing its effects in a direct manner rather than in an indirect manner by sympathicoadrenal activation.

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**Response:**

We thank Dr Christensen for his interest in our study. Dr Christensen suggests that the cardiac effects of insular cortical (IC) infarction result from elevated sympathetic stimulation of the heart and not elevated sympatho-adrenal activity. The IC does indeed contain chronotropic sites, but these are anatomically so closely related to more general sympathetic efferent regions that selective damage in ischemic stroke seems unlikely. Furthermore, IC sympatho-adrenal and cardiac responses appear to share the same subcortical relaxes, which have been shown in animals to include the lateral hypothalamic area and ventrolateral medulla. Experimental IC ischemia has been shown to result in increases in extracardiac sympathetic nerve activity and epinephrine levels. It is therefore our hypothesis that cardiac perturbations after IC stroke are part of a more generalized sympathetic stress response, which ultimately culminates in hyperglycemia.

Nonetheless, Dr Christensen has reported a lack of elevation in acute glucose levels in his large cohort of acute ischemic stroke patients with IC involvement. We believe that this discordance between our 2 studies can be explained by 2 factors. The first is the difference in imaging techniques. Although we certainly agree that early ischemic changes can be readily appreciated with CT, even within 6 hours, the full extent of acute bioenergetic compromise is best visualized with diffusion-weighted imaging. The second factor is recognition that the posterior IC is an autonomic efferent region, whereas the anterior IC functions as visceral sensory cortex. For this reason, we analyzed our patients with respect to diffusion-weighted imaging changes in the anterior or posterior IC and indeed found elevated glucose levels only in the latter group. Dr Christensen’s cohort most certainly contains patients with isolated anterior IC involvement, as occurs in superior divisional middle cerebral artery infarction, in whom we would not expect to see autonomic changes that included glucose elevation.


**NINDS Reanalysis Committee’s Reanalysis of the NINDS Trial**

To the Editor:

In their Special Report, the authors stated, “there was no evidence that the imbalance in the distribution of baseline National Institutes of Health Stroke Scale (NIHSS) (stroke severity) between the treatment groups had either a statistically or clinically significant effect on the trial’s results.”

First, note that the imbalance only existed in the 91- to 180-minute arm of the trial, and the National Institute of Neurological Disorders and Stroke (NINDS) Reanalysis Committee did not specifically address the issue as to whether the imbalance affected the correct interpretation of the results of the 91- to 180-minute arm. In their original report, the NINDS Study Group Investigators reported the favorable stroke outcome results for the 91- to 180-minute arm of the trial as follows: absolute risk difference, 20%; OR, 2.4; RR, 1.8 (for a modified Rankin Scale 0,1 stroke outcome result). The 20% absolute risk difference, 20%; OR, 2.4; RR, 1.8 (for a modified Rankin Scale 0,1 stroke outcome result).

Second, note that the imbalance only existed in the 91- to 180-minute arm of the trial, and the National Institute of Neurological Disorders and Stroke (NINDS) Reanalysis Committee did not specifically address the issue as to whether the imbalance affected the correct interpretation of the results of the 91- to 180-minute arm. In their original report, the NINDS Study Group Investigators reported the favorable stroke outcome results for the 91- to 180-minute arm of the trial as follows: absolute risk difference, 20%; OR, 2.4; RR, 1.8 (for a modified Rankin Scale 0,1 stroke outcome result). The 20% absolute risk difference, 20%; OR, 2.4; RR, 1.8 (for a modified Rankin Scale 0,1 stroke outcome result).

I suggest that the NINDS Reanalysis Committee did not uncover the extent to which the imbalance in baseline stroke severity affected the correct interpretation of the NINDS trial’s results, because they only approached the problem from one perspective. In a critique of the NINDS Reanalysis Committee’s Special Report, I have demonstrated how varying the absolute number of very mild stroke (baseline NIHSS, 0 to 5) and very severe stroke (baseline NIHSS >20) patients between the tPA and placebo groups significantly affects the final estimated RD values.

I believe that the stroke research community has not fully appreciated how stroke severity heterogeneity imbalances can affect the accurate interpretation of a tPA-for-stroke randomized control trial’s results, and I think that this problematic issue should be more thoroughly investigated and debated.

**Response:**

Dr Mann correctly points out, and in our article we acknowledge, that there was an imbalance in baseline stroke severity favoring the tissue plasminogen activator (tPA) group for patients randomized between 91 and 180 minutes after stroke in the National Institute of Neurological Disorders and Stroke (NINDS) tPA for acute ischemic stroke treatment trial. As indicated on page 2421 in our article, and detailed on page 53 in our report, using a wide variety of standard accepted statistical adjustment approaches, we found neither a clinically nor a statistically significant effect of this imbalance on the tPA–placebo comparison. Furthermore, subgroup analyses need to be interpreted cautiously, with the burden of proof resting on making the case that the treatment effect is different between subgroups. For example, it is good practice to estimate or test for a treatment by subgroup interaction. If this is not compelling, as was the case in our analysis, then concluding there are subgroup differences must rest on strong supporting evidence from other studies. Although no statistical analysis can definitively rule out subgroup differences, passionate belief in a personal perspective will not change the biology. As stated by Brookes et al, subgroup analyses must be interpreted very cautiously because the erroneous identification of differential subgroup effects may lead to inappropriate provision, or withholding, of treatment. Additional data from an adequately powered new study are needed to assess possible subgroup effects. Until an adequately powered assessment of the effect of tPA in the 91- to 180-minute group stratified by baseline stroke severity is performed, we have no basis to believe that tPA is not equally effective among acute ischemic stroke patients with different baseline stroke severity treated at any time with intravenous tPA within 3 hours of stroke onset.

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Early Recurrent Stroke or Neurological Deterioration?

To the Editor:
The article by Coull and Rothwell calls for a standard definition of recurrent stroke. They suggest the definition “any stroke ≥24 hours after the incident event excluding early deterioration not caused by a stroke” as they emphasize the importance of using a definition that does not miss early recurrences. I heartily agree with the authors about the need of such definition. However, I do not think that their suggestion meets with what we need from the definition.

- It is not clear if it is any stroke ≥24 hours after the onset of the incident event or ≥24 hours after neurological stability.
- The new neurological deficit should be in my view be quantified by a stroke scale.
- Neurological deterioration/stroke in progression must be separated from stroke recurrence in a way that makes both biological and clinical sense.

Studies on neurological deterioration have described this phenomenon with different time frames, some up to 7 days. The causes of neurological deterioration are not well defined, but the clinical course has been linked to radiological findings including large infarcts, mass effect, and hemorrhagic infarction. However, the classic interpretation that neurological deterioration is caused by continuous thrombosis in the same vascular territory still stands, even though it has not actually been demonstrated.

A practical approach to this problem could be a distinction based on time from stroke onset. A reasonable distinction could be 72 hours because at this time brain swelling as well as secondary hemorrhage in infarctions based on late reperfusion is most likely to have occurred.

In my experience, it is probably not possible to make a watertight distinction between neurological deterioration and recurrent stroke, which calls for some caution in working with this field.

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Response:
I am grateful to Christensen for these comments. However, I do not agree that 72 hours should be required before a “recurrent stroke” can be said to have occurred. There is a very high risk of recurrent stroke during the first 72 hours after an initial stroke.

Such strokes might well be preventable and it is essential that they are not excluded from risk estimates in epidemiological studies or from outcome events in randomized controlled trials.

I agree with Christensen that neurological deterioration caused by complications resulting from the initial stroke pathology should be excluded. I said in the discussion of our article, “it is, of course, important that progression of the initial stroke, hemorrhagic transformation of infarction, systemic disturbances, or edema and mass effect resulting in fluctuations in cerebral perfusion, are not misclassified as recurrent strokes.” However, the distinction between deterioration caused by such processes and that caused by a further episode of embolism or thrombosis should be left to clinical judgment rather than being based on an arbitrary time period. Moreover, it should be noted that early recurrence is most common after minor ischemic stroke, in which hemorrhagic transformation, edema, mass effect, and systemic disturbances are least likely.

A consensus is clearly needed before a standard definition of recurrent stroke can be determined. The aim of our article was simply to point out the problems inherent in the use of the current standard epidemiological definitions, which exclude events within either 21 or 30 days of the incident stroke, irrespective of the severity of the presenting event. I illustrated the differences in risk obtained using the definition: any recurrent stroke occurring >24 hours after the onset of the incident stroke, irrespective of vascular territory, that is considered to be a new episode of embolism or thrombosis rather than a deterioration caused by hemorrhagic transformation of infarction, systemic disturbances, or edema and mass effect resulting from the initial stroke. Similar definitions have been used previously.

I also disagree with Christensen’s view that the definition should be based on a change in a particular stroke scale. This is unlikely to improve reliability and would introduce potential artifacts caused by intra-observer and inter-observer variability in administering such scales.

I did not address the important issue of recurrent strokes within the first 24 hours after a transient ischemic attack because epidemiological studies frequently have insufficient detail to determine the course of events reliably in the acute phase. However, this is an issue that also needs to addressed given the high frequency of such events and the potential for prevention by emergency intervention.

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Systemic Inflammatory Response Depends on Initial Stroke Severity but Is Attenuated by Successful Thrombolysis

To the Editor:

We read with interest the article by Audebert et al1 concerning inflammatory response in patients with acute ischemic stroke. The authors describe an association between inflammatory parameters and stroke severity, as well as stroke volume measured by cranial computed tomography (CCT) and magnetic resonance imaging. Moreover, they analyzed in more detail the subgroup of patients receiving thrombolysis and found that the inflammatory markers were significantly lower in patients with improvement after recombinant tissue plasminogen activator treatment.

This is an additional important study concerning inflammation in acute stroke and supports other investigations analyzing C-reactive protein (CRP) in acute ischemic stroke.2–5 The largest study up to now was recently published by Di Napoli et al6 and could demonstrate that elevated levels of CRP were related to the risk of new cardiovascular events.

In general, the findings of the recent study corroborate our results concerning the prognostic relevance of early serial CRP measurements in 127 patients with acute ischemic stroke.5 In our study, the first CRP measurement was performed within 12 hours after symptom onset (mean, 5.0 hours). The second CRP measurement was performed within 24 hours after symptom onset (mean, 19.6 hours). The third was performed 24 hours after the second measurement (mean, 43.1 hours). We also determined the lesion volume on diffusion-weighted imaging (DWI) in a subgroup of 43 patients in which the DWI was performed within 12 hours after symptom onset. However, we only observed a significant association between the third CRP value and the DWI lesion size. In contrast, Audebert et al1 described a significant association between inflammatory response and lesion size already for the first CRP measurement regarding all included patients. These differences might be explained by the use of different imaging techniques: DWI within 12 hours after symptom onset in our investigation and CCT or T2-weighted magnetic resonance imaging in the study by Audebert et al,1 as well as the later CRP determination (first CRP within 24 hours after symptom onset). Furthermore, one possible limitation of the study is the fact that follow-up imaging is not performed in every patient and that the lesion volume measured with early CCT might be underestimated. In our opinion, it would be helpful to know in which proportion of patients only a CCT was performed and how long the time interval between symptom onset, imaging, and the first CRP measurement was. In our opinion, the main novel finding of Audebert et al1 was the observation of significant lower CRP values during follow-up in patients who improve after thrombolysis.

Response:

We thank Dr Sander for her very interesting comment. She reported a positive correlation of C-reactive protein (CRP) with infarct size in diffusion-weighted (DWI) magnetic resonance imaging in a substudy of 43 patients. This correlation was only seen in the third CRP measurement after >24 hours. This observation fits our findings, but in the analysis of Winbeck et al CRP levels before 12 hours and between 12 and 24 hours were not associated with larger lesion volume. This is in contrast to our results in which the first CRP measurement (mean, 6.8 hours after onset) already had a positive correlation (P<0.05).

A direct comparison of the analyses is difficult for different reasons. The image analysis in Winbeck et al was performed with early DWI scans within 12 hours of onset. It is known that DWI signals are partially reversible. However, volume measurements in computed tomography scans, as mainly used in our sample, can differ in the same patients because of the infarct edema.

The statistical methods were different. In the study of Winbeck et al, the CRP values were dichotomized into 2 groups (< or ≥0.86 mg/dL), whereas in our analysis the Spearman correlation coefficient was used for all values.

The sample of Winbeck et al was smaller, but the analysis was performed prospectively, whereas our study had a retrospective design. The most important message of our study was that in acute stroke, inflammation parameters increase independently of infectious complications, but this inflammatory response can be stopped by successful thrombolysis.

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Telephone Assessment of Stroke Outcome Is Reliable

To the Editor:

The modified Rankin Scale (mRS) and Barthel Index (BI) are often used to evaluate long-term outcome in stroke studies.1–3 However, there are several potential problems with their use. An investigator’s knowledge of the clinical data may bias scoring of the scales, and direct patient contact for outcome assessment months after the stroke is not always feasible. Telephone interviews can simplify study design and potentially avoid investigator bias. Telephone interviews have been used prospectively in stroke studies to evaluate clinical outcome, functioning and disability after stroke, cognitive status, stroke-free status, and cognitive function in community outpatient.4–6 Newcoman et al conducted a study to validate assessment of the mRS over the telephone by nonphysician interviewers using a structured interview. They found that inter-rater reliability was excellent between physician observers in the clinic but less so between each
of 2 clinical observers and the telephone interviewer (κ=0.38 [95% CI, 0.21 to 0.55] and κ=0.3 [95% CI, 0.13 to 0.47]). The agreement was higher for patients with Rankin scores at either end of the scale (mRS=0 or ≥4). The reliability of the commonly used scales to detect the cut-off points in the BI and the mRS when not interviewing the patient face-to-face is unknown.6

The objective of this pilot study was to test the hypothesis that mRS and BI scores obtained over the phone by an experienced research nurse correlate with scores taken during the clinical evaluation. We scored the BI and mRS of 33 consecutive stroke patients who returned for follow-up visit 2 to 3 months after the index stroke. Subsequently, an experienced research nurse blind to all previous clinical and radiological data scored the scales via phone interview. We compared median scores obtained by the 2 scorers with the Wilcoxon Rank test. To evaluate the correlation between in-person and phone scores, we dichotomized the scores using cut-off points commonly used in stroke trials (mRS ≤1, mRS ≤2, and BI ≥95) and calculated unadjusted κ values. We also used unadjusted κ values to evaluate the agreement between observers based on tissue plasminogen activator (tPA) treatment status. The mean (SD) time to scoring in person and on the phone was 85 (28) and 150 (58) days, respectively. The median mRS was 1 for in-person scoring and 0 over the phone (P=0.03). The difference may be attributable to the time elapsed between interviews. The median BI score by both scorers was 100. The table details the agreement between observers. When outcomes were dichotomized, there was substantial agreement between the clinical and phone scores for all outcomes regardless of tPA treatment status.

Our findings suggest that an experienced blinded rater can reliably score commonly used stroke outcome measures over the phone. This has implications for the design of stroke studies. A central rater may reduce bias and the inter-rater variability and may be preferable in large clinical trials, particularly those that involve multiple institutions. Validation in a larger sample is under way.

| Agreement Between In-Person and Phone Scoring (Unadjusted κ [95% CI]) |
|-----------------|-----------------|-----------------|
| Outcome         | Overall Sample  | Treated With tPA | Not Treated With tPA |
| mRS≤1           | 0.78 (0.54 to 1) | 0.79 (0.40 to 1) | 0.77 (0.47 to 1)     |
| mRS≤2           | 0.74 (0.47 to 1) | 0.79 (0.40 to 1) | 0.70 (0.30 to 1)     |
| BI≥95           | 0.82 (0.58 to 1) | 0.79 (0.40 to 1) | 0.83 (0.51 to 1)     |

Correlation of Systemic Inflammatory Response With Infarct Volume in Acute Ischemic Stroke Patients
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