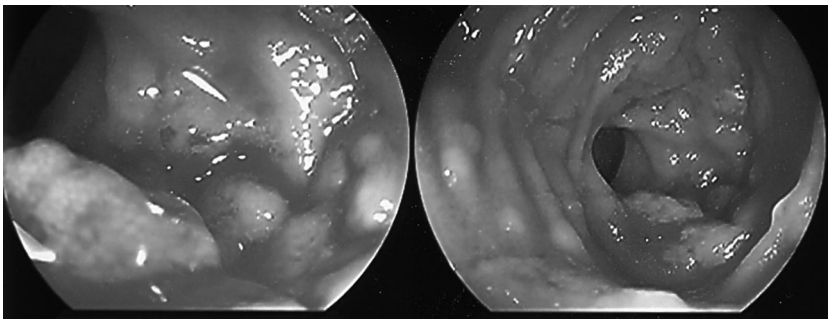

Endoscopic view of terminal ileum in child with attention-deficit-hyperactive disorder

Greatly enlarged lymphoid nodules in both fields of view.

and clinical features known to be related to the central nervous system (CNS), such as migraine,[2] infantile colic,[3] abdominal epilepsy,[4] allergic-tension-fatigue syndrome, and attention-deficit-hyperactivity disorder,[5] which have been related to food allergy, although the precise relation is still unclear. IgE-mediated food allergy is plainly not the only mechanism of tissue injury, and these specific disorders could involve other mechanisms.

A major investigative effort of our laboratories has been directed to the study of food allergy and the immunological involvement of the gut as a central focus for injury of other target organs (skin, lungs, and gastrointestinal tract). We have noted a striking appearance of ileal-lymphoid-nodular hyperplasia in patients with non-IgE-mediated food allergy who present with asthma, atopic dermatitis, and attention-deficit-hyperactivity disorder. We have also studied two patients with this hyperactive disorder who were allergic to various foods, and our findings obtained by colonoscopy of their terminal ileum, shown in the figure, match with those reported by Wakefield and co-workers.

In our study, ileal-lymphoid-nodular hyperplasia is the hallmark lesion of the gastrointestinal tract, which allows entry of antigens across the inflamed mucosa of the bowel as a result of the reactive inflammatory response in the adjacent lymphoid tissue of Peyer's patches in patients with non-IgE-mediated food allergy. We propose that similar mechanism(s) may be involved in the pathogenesis of the CNS dysfunction in the patients described by Wakefield and co-workers.[1]

Although Wakefield's study, which suggests a connection between the CNS and the gut in patients previously immunised with measles, mumps, and rubella vaccine, did not prove an association, it has stimulated further discussion and opened unanticipated lines of investigation concerning the role of ileal-lymphoid-nodular hyperplasia as a predictive marker of gastrointestinal inflammation responsible for immunologically mediated tissue injury in other target organs sites.

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1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351:** 637–41.
2 Egger G, Carter CM, Wilson J, Turner MW, Soothill JF. Is migraine food allergy? *Lancet* 1983 ii: 865–69.
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5 Egger G, Stolla A, McEven L. Controlled trial of hyposensitization in children with food induced hypercinetic syndrome. *Lancet* 1992; **339:** 1150–53.

Low-dose spiral computed tomography for lung-cancer screening

Sir—Shusuke Sone and colleagues (April 25, p 1242)[1] conclude that their study of mass screening for lung cancer, "clearly showed the superiority of low dose spiral CT [computed tomography] for detection of small peripheral lung cancers". This may be so but the results (and any future data from this study) tell us little about the effectiveness of low-dose CT as a screening procedure.

In evaluating screening tests, sensitivity and specificity need to be shown. In calculating these, we have assumed that all 223 patients undergoing further diagnostic work-up on the basis of the results of the low-dose CT had a positive test result. This includes patients with "non-cancerous but suspicious lesions", "lesions suspicious of lung cancer", and "indeterminate small nodules less than 3 cm". 19 had histologically and surgically confirmed lung cancer. This gives a provisional sensitivity of 95% (though this will fall as missed cancers become apparent between screening scans). The specificity is 95%. The positive predictive value is 8·5%, in this population. Thus, 204 of 223 patients underwent unnecessary, extensive, and often invasive investigation for lung cancer.

Until the false-negative rate and the outcome of treatment in screen-detected cancer are known, we can say little about the effectiveness of CT as a screening test. Sone et al propose comparing outcomes after 1 year, but this analysis is unlikely to advance knowledge greatly because the length of follow-up is so short and the allocation has not been random (the screened groups are volunteers). Only well designed, randomised, controlled trials can show whether low-dose CT is an effective screening procedure for lung cancer.

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1 Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with a mobile spiral computed tomograph scan. *Lancet* 1998; **351:** 1242–45.

Sir—Shusuke Sone and colleagues[1] report that spiral computed tomography (CT) was more accurate in mass screening for lung cancer, and led to early detection and an accurate diagnosis of lung cancer, and should be considered in the future health plans. They also claim that CT identified almost ten times as many cancers (0·48%) as standard mass screening (0·03–0·05%) in the same area. Clinically the positive predictive value (PPV) is more important than the cancer detection rate, and the PPV was only 8·5% (19 cancer cases from 223 with suspicious lesions, indeterminate nodules, and suspicion of lung cancer). 91·5% of patients referred for work-up by chest radiography and high resolution CT (some with trans-bronchial biopsy), proved not to have the disorder. A previous study, with chest radiography and sputum cytology found a greater PPV (19%)[2] and fewer false positives than Sone et al did.

Randomised trials at a population level and looking at survival or quality of life should be done before spiral CT screening is introduced. Widespread

implementation of unproven screening methods makes subsequent rigorous evaluation much more difficult—indeed, it may be impossible to correct the original mistake.

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1 Sone S, Takashima S, Feng L, et al. Mass screening for lung cancer with mobile computed tomography scanner. *Lancet* 1998; **351:** 1242–45.
2 Fontana RS, Sanderson DR, Taylor WF, et al. Early lung cancer detection. *Am Rev Respir Dis* 1984; **130:** 561–65.

Sir—Shusuke Sone and colleagues[1] attribute to the small sample size of smokers the fact that 0·52% of smokers versus 0·48% of non-smokers had cancers detected by spiral CT scanner. We calculate that this study had at least 95% power to detect even a 5-fold increased risk among smokers; since the risk among smokers is expected to be in the range 10–20-fold, this study should have certainly detected the difference, assuming there is no selection bias and that non-smokers are neither ex-smokers nor heavy passive smokers. The discrepancy between the similar frequency among smokers and non-smokers in this study and the fact that 95% of lung cancers normally diagnosed are in smokers, suggests that these subclinical cancers are not clinically relevant. Even the fact that only two of the 19 cancers found were squamous-cell cannot explain this equivalence of risk.

The incidence reported for non-smokers is too high. Let us conservatively assume that the findings of one in every 200 of non-smokers having a lung cancer is a 2-year incidence. The life-time (40 year) risk, would be 1 death from lung cancer in every 20 non-smokers; in the UK one in every 200 non-smokers dies from lung cancer.[2] This further suggests that most cancers detected by spiral CT are not clinically relevant.

The finding is very interesting, however, biologically. Perhaps lung cancer (especially adenocarcinoma) is similar to breast and prostate cancer—ie, normal lung harbours multiple subclinical cancers, many of which will never surface in life. This might mean that the critical inhibition of angiogenesis goes on continuously in all of us and is more important in homoeostasis than previously supposed.[3]

**Jayant S Vaidya, Michael Baum*

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1 Sone S, Takashima S, Feng L, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998; **351:** 1242–45.
2 Wald NJ, Hackshaw A. Cigarette smoking: an epidemiological overview. *Br Med Bull* 1996; **52:** 3–11.
3 Folkman J. New prospectives in angiogenesis research. *Eur J Cancer* 1996; **32A:** 2534–39.

Author's reply

Sir—Sarah Conolly and her colleagues and Yasuharu Tokuda argue that our study of spiral CT reveals little about the method's effectiveness as a screening procedure. It is argued that the follow-up is too short and the lack of randomisation is noted. We are conducting this Nagano project on lung-cancer screening with a mobile spiral CT scanner in a 5-year programme to investigate the medical applications of satellite communications, from 1995 to 1999, and we cannot, unfortunately, extend the follow-up. Although the follow-up will be too short to reveal the outcome for patients treated in the project we will be able to establish the radiological diagnoses for almost all those receiving CT screening.

To improve outcome in lung cancer we must detect and treat it much earlier—eg, Sagawa et al[1] reported 5-year-survival rate of 83% for patients with lung cancer measuring 2 cm or less and no lymph-node metastasis. Because most of the cancers found by CT alone were smaller than 2 cm with no lymph-node metastasis, yet showed no evidence in the chest radiograph, we would expect a better outcome than for those found in the chest radiograph.

We are now accumulating data on sensitivity and specificity; however, there is a question about how to define the presence of lung cancer before interpretations can be classed as false negative or false positive. There seems to be no consensus, from a clinical standpoint, about size of tumour;[1] 3 mm or 5 mm may be the clinically significant threshold because lung cancers less than 3 mm are very difficult to detect even on conventional CT and nodules less than 5 mm are difficult to establish radiographically or by biopsy-based histology. 5 mm seems an appropriate threshold and we allocated a case to false negative when a tumour of 5 mm or more was missed in the CT image—but other professionals may hold different opinions. We cannot pursue high specificity when interpreting screening CT images because that will increase missed cancers. We must maintain a high sensitivity while at the same time avoiding cursory interpretation of screening CT images, to keep the numbers needing further work-up exams within a reasonable range.

The X-ray dose used in the CT screening is relevant here. The low exposure dose means that the image quality reveals lung nodules but is inadequate for a precise differential diagnosis. We prefer a low dose in screening symptomless individuals, reserving higher-dose diagnostic examinations for those with suspicious or indeterminate nodules. In other words, the role of CT screening is to check the presence or absence of a lung nodule not to test for lung cancer. Therefore we do not feel it appropriate to talk of specificity for CT screening in detecting lung cancers (rather than lung nodules). By the way, our diagnostic work-up is not as expensive or invasive as your correspondents imply. We do further CT scans without contrast and rarely recommend bronchoscopy. Nor were all the work-ups on non-cancer patients unnecessary; some patients had non-cancer lung lesions that demanded medical consultation or treatment.

Jayant Vaidya and Michael Baum argue that the incidence of lung cancer (mainly adenocarcinoma) among non-smokers was too high and they suspect that most cancers detected by spiral CT are not clinically relevant. I agree that more needs to be known about the growth characteristics of this type of cancer if we are to manage patients on a sound scientific basis. In the meantime, however, we should look for early (preclinical) cancer and treat it;[2] most patients with lung cancer die because of delay in diagnosis, and we do not yet know how to discriminate the preclinical but life-threatening cancer from indolent one. The prevalence rate of CT-screening-detected cancer was nearly 5 per 1000 screened (males 10 cases in 2115 screenees, females, 11 in 1852). The age and sex-adjusted expected cancer incidence in the screened population was 4·57 (male 3·85, female 0·72) for 3967 screenees based on the data in the Cancer Registry of Japan. This means that we have detected nearly 4·6 times as many cancer patients as expected (2·6 times in males, 15·7 in females). I suspect that our high detection rate was due to the inclusion of lung cancers missed by the general health survey of the previous year, and adenocarcinoma of the lung in the female may lie undetected by conventional chest radiography for over 15 years on average.

Shusuke Sone

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1 Sagawa M, Saito Y, Takahashi S, et al. Clinical and prognostic assessment of patients with resected small peripheral lung cancer lesions. *Cancer* 1990; **66:** 2653–57.
2 Noguchi M, Morikawa A, Kawasakii M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995; **75:** 2844–52.

Angina pectoris caused by microvascular spasm

Sir—Masahiro Mohri and colleagues' (April 18, p 1165)[1] suggestion that angina pectoris may be caused by coronary microvascular spasm deserves some comment. We believe that the proposal of microvascular coronary spasm as a clinically relevant pathogenetic mechanism of angina should be accompanied not only by more stringent diagnostic criteria, but also by a more careful clinical and electrocardiographic (ECG) characterisation of affected patients.[2]

In Mohri's report, patients without evidence of occlusive or subocclusive epicardial artery spasm were grouped according to the presence or absence of anginal pain and ECG changes during intracoronary acetylcholine infusion: one group of 29 patients with microvascular spasm and another of 25 patients with atypical chest pain. Such distinction, made a posteriori on the basis of test results, is incorrect. Anginal pain should be classified as typical or atypical on the basis of clinical features, independently of ECG, angiographic, and coronary sinus findings.

The possibility that myocardial ischaemia can be caused by microvascular coronary constriction is not at issue; previous studies showed that intense microvascular constriction can cause massive ischaemia after neuropeptide γ infusion in human beings[3] and after endothelin infusion in dogs.[4]

A key question in the interpretation of Mohri's results is the normal range of the response of coronary arteries to increasing doses of intracoronary acetylcholine. In Mohri and co-workers' study, the angiographic response to acetylcholine in the 29 patients with microvascular spasm was similar to that of the 25 patients with atypical chest pain, although lactate production was detected in the coronary sinus of nine of 11 patients in the first group, but in none of the ten patients in the second group. In a previous study in a series of patients with normal coronary arteries and atypical chest pain, we observed that low doses of acetylcholine caused coronary dilation, whereas higher doses caused constriction of the same segments, and a further increase of the dose caused diffuse microvascular constriction with severe ischaemia, chest pain, ST segment changes, and impairment of left-ventricular function.[5] Therefore, the distinction between patients with microvascular spasm and those with atypical chest pain proposed by Mohri may be arbitrary, and their results may be simply related to differences in the individual coronary smooth muscle dose-response to intracoronary acetylcholine and, possibly, in pain sensitivity among patients.[2]

There is limited information in their study about the relation between the features of chest pain and ECG changes observed during acetylcholine infusion and those developed by patients during their daily life, which makes it difficult to understand the actual clinical relevance of their observations. Thus, although the evidence for the occurrence of microvascular constriction as a cause of myocardial ischaemia seems fairly established, its prevalence and clinical correlates remain elusive.

**Attilio Maseri, Gaetano A Lanza*
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1 Mohri M, Koyanagi M, Egashira K, et al. Angina pectoris caused by coronary microvascular spasm. *Lancet* 1998; **351:** 1165–69.
2 Maseri A. Ischaemic heart disease. A rational basis for clinical practise and clinical research. London: Churchill Livingstone, 1995: 507–32.
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5 Newman CM, Maseri A, Hackett DR, El-Tamimi HM, Davies CJ. Response of angiographically normal and atherosclerotic left anterior descending coronary arteries to acetylcholine. *Am J Cardiol* 1990; **66:** 1070–76.

Author's reply

Sir—As Attilio Maseri and Gaetano Lanza state, we grouped our patients on the basis of the results of acetylcholine testing a posteriori. However, two points should be noted. First, our aim was to find evidence for a possible contribution of coronary microvascular spasm to the pathogenesis of angina. Thus, there were two subgroups: patients with and those without chest pain and ECG changes during acetylcholine testing.

Our results suggest that the patients who developed chest pain and ECG changes had myocardial ischaemia as evidenced by production of myocardial lactate, whereas patients without chest pain or ECG changes had no myocardial ischaemia. These results indicate that microvascular spasm may be the cause of angina in a subgroup of patients with microvascular angina.

Atypical chest pain was a diagnosis given to a group of 25 patients who had no coronary artery disease, no epicardial spasm, no chest pain or no ECG changes during acetylcholine infusion. The type of chest pain in patients with microvascular angina (including those caused by microvascular spasm) is generally atypical compared with effort angina.[1]

We found that the clinical features of angina and ECG changes in patients with microvascular spasm did not differ greatly from those in patients with spasm of epicardial coronary arteries, so that the diagnosis requires coronary angiography to exclude epicardial coronary artery spasm.

We disagree with Maseri and Lanza's comments on the clinical relevance of our findings. As described in our report, in 25 of 29 patients acetycholine induced chest symptoms that were similar to the patients' previous ones. Furthermore, in seven of nine patients it reproduced ischaemic ECG changes that had been documented during spontaneous attacks.

It should be noted that 100 μg acetylcholine is about 10^{-4} mol/L if left-coronary blood flow is assumed to be 150 mL/min. This dose is 10–100 times lower than that adopted in the Newman study.[2] Acetylcholine infusion at 100 μg is widely used to induce epicardial coronary spasm. The sensitivity and the specificity of this test in diagnosis of epicardial spasm are greater than 90%. We do not know how specific this testing is in diagnosing microvascular spasm, but some of our patients with microvascular angina developed myocardial ischaemia at the lower dose of 5–30 μg, or even spontaneously without acetylcholine. Such high sensitivity for coronary small vessels to constrict to a small dose of acetylcholine may be termed as spasm and the cause of microvascular angina, as we already discussed in our report.

We believe that our study offers evidence that coronary microvascular spasm does cause myocardial ischaemia and is clinically relevant to patients' symptoms in a subgroup of patients with chest pain and normal

coronary arteriograms. The prevalence of coronary microvascular spasm is not known, as Maseri and Lanza correctly point out.

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1 Kaski JC, Rosano GMC, Nuhoyannopoulos P, Collins P, Maseri A, Pool-Wilson P. Cardiac syndrome X: clinical characteristics and left ventricular function: a long-term follow-up study. *J Am Coll Cardiol* 1995; **25:** 807–14.

2 Newman CM, Maseri A, Hackett DR, El-Tamimi HM, Davies GJ. Response of angiographically normal and atherosclerotic left anterior descending coronary arteries to acetylcholine. *Am J Cardiol* 1990; **66:** 1070–76.

HSV-1 and risk of Alzheimer's disease

Sir—We were surprised that Beffert and colleagues (May 2, p 1330)[1] conclude that their results contrast with ours.[2] In fact the values in their table show exactly the same trend as ours did: a higher apoE-ϵ4 allele frequency for the herpes simplex virus 1 (HSV-1)-positive patients with Alzheimer's disease (AD) than for those who were HSV-1-negative, or the HSV-1-positive or HSV-1 negative non-Alzheimer's although their data, unlike ours do not reach statistical significance. Possibly the non-significance relates to their low number of controls and, as they suggest, to the difference in prevalence of apoE ϵ4 between the two AD populations. (We have recently examined brain specimens from further AD patients and age-matched HSV-1 negative, non-Alzheimer controls, and have obtained apoE-ϵ4 allele frequencies for all groups that are wholly consistent with our earlier values.[3]) Equally surprisingly, Beffert and colleagues make two more deductions that are prefaced by "in contrast to the results of Itzhaki et al". These statements seem to be based on a misreading of our report since their deductions are exactly those that we make in our results and discussion sections, respectively: that HSV-1 alone is not an independent risk factor for AD and that other apoE-ϵ4 allele carriers are not more susceptible to HSV-1 infection than non-carriers.

Thus Beffert and colleagues' data and deductions add useful support to our findings and conclusions, just as their previous findings (of which we were unaware), in which they detected HSV-1 in a high proportion of elderly normal and AD brains,[4] broadly substantiated our earlier study on that topic.[5] We fully agree with their comment about the need for investigation of larger numbers, although we emphasise that the search for virus at low levels by PCR requires great care and numerous checks for the absence of artifacts[2,3,5]

*Ruth F Itzhaki, Woan-Ru Lin, Gordon K Wilcock, Brian Faragher

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1 Beffert U, Bertrand P, Champagne D, et al. HSV-1 in brain and risk of Alzheimer's disease. *Lancet* 1998; **351:** 1330–31.

2 Itzhaki RF, Lin W-R, Shang D, et al. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet* 1997; **349:** 241–44.

3 Lin W-R, Graham J, MacGowan SM, et al. Alzheimer's disease, herpes virus in brain, apolipoprotein E4 and herpes labialis. *Alzheimer's Rep* 1998; **1:** 173–78.

4 Bertrand P, Guillaume D, Hellauer K, et al. Distribution of herpes simplex virus type 1 DNA in selected areas of normal and Alzheimer's disease brains: a PCR study. *Neurodegeneration* 1993; **2:** 201–08.

5 Jamieson G, Maitland NJ, Wilcock GK, et al. Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. *J Med Virol* 1991; **33:** 224–27.

Authors' reply

Sir—Although a trend may be indicated by our initial data linking the combination of HSV-1 and the ϵ4 allele of apolipoprotein E (apoE) to Alzheimer's disease (AD), we concluded that by contrast with Itzhaki and colleagues[1] synergism between both markers was not indicated. Because of the low numbers of controls in our study, we may not have had sufficient statistical power to reject the null hypothesis of Itzhaki and colleagues. To be able to make a further contribution to the question of synergy, we pooled our data with those of Itabashi and co-workers.[2] Despite ethnic differences between the populations it was reasonable to pool the two studies since statistical analysis showed no significant differences between the marker distribution within cases and controls.

We recalculated odds ratios (OR) for the event of having either the ϵ4 allele of apoE or HSV-1, or both, compared with having neither marker (table) and compared the results with those of Itzhaki et al.[1] From these results we can conclude that: (1) HSV-1 infection alone is not a risk factor for AD (OR=0·8, NS); (2) the ϵ4 allele of apoE is a risk factor for AD (OR 6·1; 95% CI 1·6–23); and (3) in combination, apoE ϵ4 and HSV-1 confer no greater risk for AD than apoE ϵ4 alone (6·2; 2·3–17). Itzhaki and colleagues, however, showed a low OR for apoE ϵ4 (1·8) and a very high OR for the combination of apoE ϵ4 and HSV-1 (25). Their results yield a synergy factor of 31 compared with 1·3 from our pooled data.

The reasons for such discrepancies between the two studies are beyond our understanding, but an important point to consider when doing population studies with very small sample sizes is errors due to potential sampling bias. For example, it is now well established that the apoE-ϵ4 allele frequency is increased 2–3-fold within a large AD sample compared with a large control sample. In their study, Itzhaki and co-workers found a 10-fold difference (0·045 *vs* 0·43) of the apoE-ϵ4 allele frequency between their cases and controls, probably because of an unknown sampling bias. Therefore, results from studies with low case numbers might not be reproducible by others but represent important findings for further analysis. Furthermore, we are undertaking a more detailed analysis of these same patients with respect to brain region to establish whether a particular area may be more susceptible to HSV-1 in AD patients with the apoE-ϵ4 genotype.[3]

*Uwe Beffert, Philippe Bertrand, Danielle Champagne, Serge Gauthier, *Judes Poirier

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1 Itzhaki RF, Lin W-R, Shang D, Wilcock G, Faragher B, Jamieson G. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet* 1997; **349:** 241–44.

2 Itabashi S, Arai H, Matsui T, Higuchi S, Sasaki H. Herpes simplex virus and risk of Alzheimer's disease. *Lancet* 1997; **349:** 1102.

3 Beffert U, Bertrand P, Champagne D, et al. Herpes simplex virus type 1 in brain, apolipoprotein E genotype and Alzheimer's disease. *McGill J Med* (in press).

ApoE ϵ4/HSV-1	Controls	Alzheimer's disease	Odds ratio	95% CI
−ve/−ve	24 (14)	29 (8)	Reference	. .
−ve/+ve	23 (26)	23 (7)	0·8 (0·5)	ns (ns)
+ve/−ve	3 (2)	22 (2)	6·1* (1·8)	1·6–23 (1·4–2·1)
+ve/+ve	6 (2)	45 (29)	6·2† (25)	2·3–17 (5·5–116)

*p<0·01, †p<0·001 (χ^2 Yates' corrected), NS=not signfiicant. Numbers in parentheses=Itzakhi's results.

Odds ratios for controls and Alzheimer's disease according to HSV-1 status