Sir—Your contributors' and others'1,2 observation of an association between late-onset Alzheimer's disease and apoE-ε4 allele on chromosome 19 raises several questions about the distribution of apoE alleles in aged populations. In early studies the frequency of apoE-ε4 allele was shown to be lower in octogenarians than in young adults.3 Because the ε4 allele is a well-known risk factor of atherosclerosis, this was interpreted as meaning that subjects carrying the ε4 allele would die at a younger age from CHD. In fact, the estimation of the apoE allele frequencies in elderly population samples is confounded by the association of ε4 allele with degenerative cerebral disease. Since the rate of dementia is higher in individuals living in institutions than those not in institutions, the reported decrease of ε4 allele frequency may only reflect a selection bias of healthy elderly and exclusion of demented elderly subjects, mainly institutionalised.

An estimate of the ε4 allele in a Caucasian sample of octogenarians can be calculated from published data. If the frequency of the ε4 allele is estimated at 30% in late-onset Alzheimer's disease—range 25%3 to 40% (Saunders et al, Sept 18, p 710, and ref 1)—and at 9% in non-demented healthy subjects,2 and the prevalence of dementia is 30%, in individuals over age 80,4 then the estimate of the ε4 allele frequency in octogenarians is 15.3%—range 14–18%. This estimate is different from the published data in octogenarians.

Selection of appropriate elderly control samples is critical for the accurate determination of lod scores and odds ratios of the diseases under study.5 For instance in a linkage analysis, Borgaonkar et al (Sept 4, p 625) used a genetic model where the frequencies of apoE alleles were taken from a large control sample of unrelated white subjects of Westphalia with a mean age of 37 (12) years.6 The misspecification of apoE allele frequencies in the lod score calculation of Borgaonkar's study results in an underestimation of the association.

We conclude that apoE allele frequencies need to be assessed in random samples of representative elderly populations, to calculate with precision the risk of Alzheimer's disease and chronic disease associated with apoE polymorphism.

Philippe Amouyel, Thierry Broussolle, Jean-Charles Fruchart, Jean Dallongeville
Service d'Épidémiologie et de Santé Publique, INSERM U 325, Institut Pasteur de Lille, Lille, France

Sir—Several reports from your contributors and others1,2 have shown that late-onset Alzheimer's disease is associated with the ε4 allele of apoE; the apoE gene on chromosome 19 has three common alleles (ε2, ε3, and ε4), which encode three major apoE isoforms. To further evaluate the involvement of ApoE isoforms in Alzheimer's disease, we examined the ApoE phenotypes in 93 unrelated French patients of both sexes by polymerase chain reaction (PCR), and compared the findings with those of 498 healthy blood donors from Paris,4 identified by isoelectric focusing.

Genomic DNA was prepared from peripheral blood leukocytes from the patients. Amplification of DNA by PCR and restriction isotyping of the polymorphic ApoE gene sequence was done by a method adapted from Wenham et al.6 Our patients were diagnosed as sporadic cases of probable Alzheimer's disease; all these patients (mean age of onset > 60 years) are classified as late-onset (with an average age of 68.9 [8.3]). ApoE ε2, ε3, and ε4 allele frequency estimates in our patients were 8%, 46%, and 45%; and in controls 8%, 80%, and 12%, respectively. The frequencies of ε4 allele in patients with Alzheimer's disease were significantly higher than those in controls (0.45 [0.07] vs. 0.12 [0.02]).

Each allele frequency was compared with that of the corresponding Hardy-Weinberg (HW) theoretical distribution; our Alzheimer's group is not in HW equilibrium (x2 test, p < 0.001), because of heterozygous E3, E4 excess. In our sample 77%-4% of patients have at least one ε4 allele. Odds ratio for allele frequencies in patients and controls were calculated assuming the control population was in HW equilibrium; in our study the odds ratio is 11.82 (6.96 - 20.01), (x2 = 83.51, 1 df). These data corroborate the statement that ε4 genotype may be a very important susceptibility factor in the aetiopathology of sporadic late-onset Alzheimer's disease (Poirier et al, Sept 18, p 697).

We thank Prof Allen Roses for sharing unpublished information from his group's ApoE studies.

G Lucotte, F David
Regional Centre of Neurogenetics, Neurology Department, Robert Debré Hospital 61092 Reims, France

S Visvikis, B Leinninger-Müller, G Siest
Centre de Preventive Medicine, Laboratory of Clinical Biology, Vandoeuvre-Les-Nancy, France

M C Babron
Unit of Epidemiological Genetics, Château de Longchamp, Paris, France

R Couderc
Laboratory of Biochemistry, Tenon Hospital, Paris, France


Sir—Your correspondents' and others' work from the USA, Canada, and Japan has shown an increased frequency of the ApoE4 allele in patients with Alzheimer's disease. We have investigated 42 patients satisfying NINCDS-ADRDA criteria for probable and possible AD,7 7 patients with frontal