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Research Letter

THE DISTRIBUTION OF APOLIPOPROTEIN E GENOTYPE OVER THE ADULT LIFESPAN AND IN RELATION TO COUNTRY OF BIRTH

Apolipoprotein E (ApoE) is encoded by the codominant alleles ε2, ε3, and ε4, resulting in 6 bi-allelic genotypes (1–4). The corresponding protein isoforms differ in their lipoprotein receptor affinity, antioxidant activity, and inflammation modulatory properties (1, 5–8). *APOE* ε4 carriership is associated with an increased risk of atherosclerosis and dementia (9). Approximately 65%–75% of patients with Alzheimer's disease carry the ε4 allele (9–11). Several studies in which the relative proportion of *APOE* alleles over the lifespan were examined showed stable ε4 frequencies at midlife and a decrease after a certain turning point. The age for this turning point differed between studies (10, 12–15). Furthermore, the *APOE* allele distribution seems to depend on ethnicity and varied with latitude (15–22), with higher ε4 frequencies being more common close to the equator and in the northern polar region (16, 17, 19, 21, 22). This might introduce confounding in gene-association studies. Therefore, the aim of the present Swedish population-based study was to consider *APOE* allele distribution in relation to age and country of birth.

METHODS

The study included persons who were 25–99 years of age from 4 different population-based studies in Gothenburg, Sweden (23–26). Both people living in private households and those living in residential care were included. The Swedish Ethics Committees for Medical Research approved the studies. *APOE* status was available for 4,579 persons (2,742 women and 1,837 men). Country of birth was self-reported. A total of 4,210 subjects came from countries of northern latitude (≥55°N), hereafter referred to as Nordic countries. Nordic countries comprised Scandinavia (Sweden, Norway, and Denmark), Finland, and the Baltic States. *APOE* allele frequencies were calculated for each participant. Age at examination was analyzed in categories of 10 years starting at age 30 years (with an additional category of 25–29 years) to investigate the possibility of a nonlinear relationship between allele frequencies and age. The countries of origin were grouped into 5 regions with decreasing average latitude, ranging from Nordic countries to the Middle East and Northern Africa. Subjects born outside these regions or for whom information was missing were excluded from the subanalyses ($n = 123$). Ordinal logistic regression was used to assess the association of age, sex, or region of birth with the percentage of each *APOE* allele independent of the 2 other alleles. Proportional odds assumptions were tested for each model ($P > 0.3$ for all results). Binary logistic regressions were used to examine the associations between age categories and genotype frequencies. Analyses were performed using SAS, version 9.3 (SAS Institute Inc., Cary, North Carolina), and Matlab, version 7 (R2011a, MathWorks, Inc., Natick, Massachusetts). The significance level was set at 0.05 (2-sided tests).

RESULTS

In the whole sample with all ethnicities combined, the *APOE* allele frequencies were constant across age categories except in the oldest age group (90–99 years), in which lower ε4 (−5.9%; $P < 0.0001$) and higher ε3 (+4.3%; $P = 0.002$) and ε2 (+1.6%; $P = 0.08$) frequencies were found compared with overall average allele frequencies (Web Table 1, available at http://aje.oxfordjournals.org/). There was no difference in allele frequencies between the sexes. The characteristics of the participants are given in Web Table 2.

In all samples combining all ages, the ε4 frequency increased with latitude, whereas ε3 frequency decreased and ε2 frequency was stable (Figure 1A). The ε4 frequency was lower among non-Nordic immigrants than in Nordic-born subjects, with an opposite trend for ε3 (Figure 1B).The numbers of non-Nordic participants in the 2 oldest age groups were insufficient to allow examination of allele frequencies.

DISCUSSION

We found that the relative *APOE* allele frequencies stayed constant over a large age interval (25–90 years), and the results were replicated separately in participants born in both Nordic and non-Nordic countries (25–80 years). The ε4 frequency was lower in participants who were older than 90 years of age, which is a high age turning point. This result was only observed in the Nordic population because there were insufficient numbers of non-Nordic participants in the highest age groups, and it is possibly related to death from dementia or cardiovascular disease. Our finding is in line with the theory that there is an increased genetic influence with age (27, 28), with several factors contributing to longevity. In contrast to our study, McKay et al. (14) reported a continuous decrease in ε4 prevalence after 60 years of age. Participants in that study were controls from a study of age-related macular degeneration, which is an *APOE*-related disease (29–32). Controls from studies of *APOE*-related diseases might display an altered age-specific prevalence of ε4, with fewer participants having dementia compared with population controls. In our elderly, dementia was neither an exclusion nor selection criterion, suggesting higher representativeness. Our study emphasizes the importance of being aware of selection bias in descriptive studies when excluding prevalent diseases. In association studies, the same exclusion criteria for cases and controls should be applied. In our study,

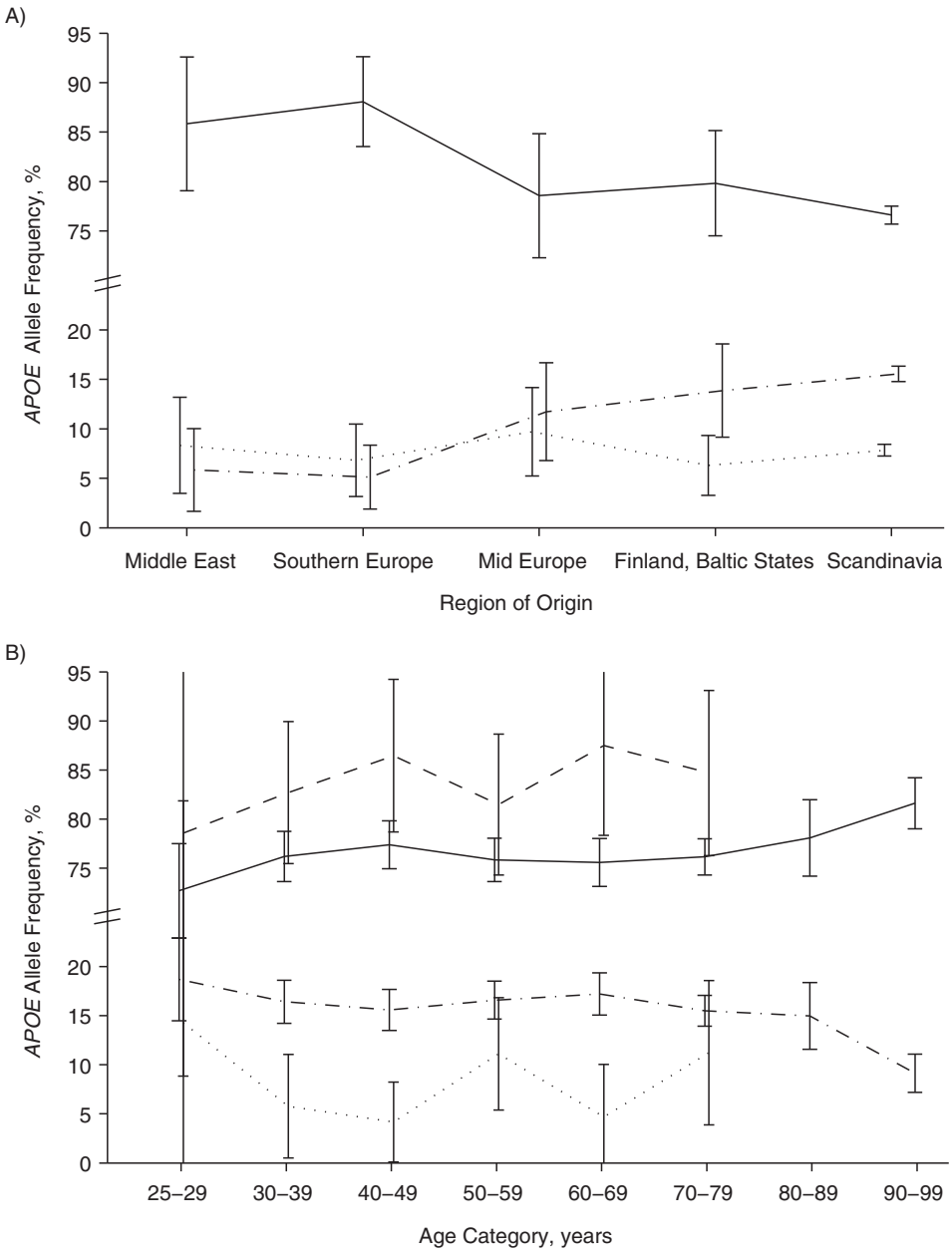

Figure 1. Frequencies of apolipoprotein E (*APOE*) alleles by region of origin (A) and age (B) in 4 population-based studies, Gothenburg, Sweden (1996–2009). A) Frequencies of the ε4 (dashed-dotted line), ε3 (solid line), and ε2 (dotted line) alleles by region of birth with increasing latitude from left to right: Middle East, including North Africa (30°N); Southern Europe (40°N); Mid Europe (50°N); Finland and the Baltic States (60°N); and Scandinavia (Sweden, Norway, and Denmark; 60°N). B) ε3 allele frequencies for subjects of Nordic (solid line) and non-Nordic (dashed line) origin and the ε4 allele frequencies for subjects of Nordic (dashed-dotted line) and non-Nordic (dotted line) origin. Nordic countries included Scandinavia, Finland, and the Baltic States ($n = 4,210$). Non-Nordic countries included Mid and Southern Europe, the Middle East, and North Africa ($n = 246$). Bars, 95% confidence intervals.

we showed stable allele frequencies up to age 80 years when stratified by ethnicity and not explicitly excluding subjects with dementia. In previous studies, ethnicity has not been considered when examining US citizens of European descent (14, 15). Because the number of non-Nordic participants was small, our data have to be interpreted cautiously. However, our findings underscore the fact that population studies in Western countries contain participants with different ethnic backgrounds because of globalization. To further decrease bias, it has become more important for descriptive studies to study allele frequency by age and for association studies to consider ethnicity.

Paralleling previous studies, we found higher ε4 frequencies in subjects who lived at higher latitudes (17, 22, 33). Nevertheless, higher dementia prevalence in the Northern European countries was not demonstrated (34). In different populations, ε4 may exert differential influence on dementia, as shown in the Nigerian-Ibadan study that found high ε4 frequencies and low dementia prevalence (35). In the relationship between hypercholesterolemia and dementia risk, ε4 may be an intermediate factor, suggesting that lifestyle factors leading to longevity in Sweden might attenuate the negative influences of ε4.

The strength of the present study is the large age interval (25–99 years) and the inclusion of persons regardless of comorbid conditions. A limitation was the low overall participation rate and the small numbers of non-Nordic participants. Further, the representativeness of the non-Nordic participants of their countries of origin is unclear. However, our allele frequencies were similar to those from previous studies (17, 22, 33). The low overall participation rate was mainly determined by the youngest participants (25, 26, 36), who had relatively stable *APOE* allele frequencies. In the older age groups, the participation rate was higher. Equal mortality between participants and nonparticipants among elderly subjects suggests similar *APOE* allele distribution (36).

In conclusion, in genetic epidemiologic studies, it is important to consider ethnicity and selection bias resulting from exclusion of prevalent diseases. Similar evaluations in other independent populations are required to fully understand the impact of ethnicity and age in epidemiologic studies regarding the *APOE* allele.

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