Interactions of Apolipoprotein E Genotype and Dietary Fat Intake of Healthy Older Persons During Mid-Adult Life

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In a case control study of genetic and lifestyle risk factors for Alzheimer's disease (AD), we obtained recalled food consumption frequencies translated to nutrients and averaged over 2 age periods of adult life, 20 to 39 and 40 to 59 years. The proportion of controls with the apolipoprotein E ϵ4 (APOE ϵ4) genotype was significantly higher in the lowest tertile of fat consumption (36.3% of energy) compared with controls with ϵ4 in the highest tertile of fat intake (44.6% of energy). Healthy older persons with the ϵ4 allele who survived to be included in this study may be protected with lower dietary fat intake and other healthy behaviors. Diet-genotype interactions may have important influences on disorders of later life.

DIET-GENOTYPE interactions may have important influences on health with aging. Patterns of food consumption may be protective or may be risk factors for disease.[1,2] The apolipoprotein E ϵ4 allele (APOE ϵ4) is the most important genetic risk factor for Alzheimer's disease (AD) and cardiovascular diseases.[3-5]

Lifestyles, including dietary patterns during early and mid-adulthood, may influence the risk for AD and cardiovascular disease for those persons with the APOE ϵ4 allele. Notkola et al[6] concluded that high serum cholesterol early in life and the ϵ4 allele have synergistic effects in increasing AD risk in Finnish men. Variations in blood lipid responses to dietary fat interventions have been attributed to the presence of specific APOE genotypes.[7] High-fat diets may lead to greater lipid peroxidation and oxidative stress associated with the pathogenesis of AD and atherosclerosis.[8] The importance of gene-environmental interactions is suggested by the observation that many older persons with the APOE ϵ4 allele do not get AD and therefore may experience environmental influences that are protective. We conducted a case control study of adult lifetime risk factors for AD and report here the relationship between dietary fat intake during early and middle adult life and the APOE ϵ4 allele in healthy older controls.

SUBJECTS AND METHODS

The healthy controls in this case control study were friends or neighbors, 60 years of age or older, of AD cases enrolled in the Research Registry of the Alzheimer's Center of University Hospitals of Cleveland or members of organizations to which cases belonged. Cases and controls underwent the same medical and neurologic examinations and a comprehensive battery of neuropsychological tests. APOE genotype was determined using established polymerase chain reaction (PCR) procedures. All controls completed a Life History Questionnaire (LHQ) that included demographic, medical, educational, intellectual, smoking, occupational, recreational, and diet histories for 3 age periods: 20 to 39 years, 40 to 59 years, and 60+ years. The Institutional Review Board of The University Hospitals of Cleveland approved the study, and informed consent was obtained from each subject. A more complete description of the study has been previously reported.[9]

All subjects had cognitive performance in the normal range as defined by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery.[10,11] Subjects were excluded if they had histories of stroke, significant medical, surgical, or psychiatric illnesses, drug abuse, insulin-dependent diabetes, neurological conditions with the potential to affect cognition, cancer, or present or past alcoholism. APOE genotype was dichotomized as those having an APOE ϵ4 allele versus non-ϵ4 allele.

The dietary portion of the LHQ, adapted from the Block Health Habits and History Questionnaire, consists of a list of the 98 most frequently consumed foods as reported in national dietary surveys that contribute significantly to energy and nutrient intake in the United States.[12] Respondents indicated, for each age period, the frequency of consumption of each food per day, per week, per month, rarely, or never. A medium portion size was assumed for each food. Food frequencies were then translated into nutrients using software developed at the National Cancer Institute (Dietsys 3.6).[12] Dietary fat intake, expressed as percent of energy from fat and adjusted for energy intake,[13] was categorized in tertiles. χ^2 tests for independence were used to compare the proportions of individuals with the ϵ4 genotype in each tertile of fat intake.

RESULTS

Demographic characteristics of controls are shown in Table 1. Thirty percent of the ϵ4 group was male compared with 48.5% of the non-ϵ4 group. Fat intake has been standardized for gender, body size, and activity differences by adjusting for energy intake and expressed as percent of energy. Subjects were grouped according to high, medium, and low fat consumption and by genotype. Allele frequency for all controls was 12% with ϵ4 and 81.3% for those with ϵ3. Only 2.8% of subjects had the ϵ4/ϵ4 genotype. There was no difference between those with and without ϵ4 in their reported histories of heart disease, hypertension, or type 2 diabetes. All subjects were determined to be cognitively intact.

Dietary fat intakes during each age period are reported as percent of energy in tertiles for all controls in Table 2. The early and mid-adulthood age periods combined (20 to 59 years)

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Table 1. Demographic Characteristics of Controls

	ε4 (n = 46)	NO ε4 (n = 171)
Genotype (%)	21.2	78.8
Gender, male (%)	14 (30.4)	83 (48.5)
Year of birth, mean (SD)	1923 (6.0)	1922 (6.8)
Years of education, mean (SD)	15.7 (3.2)	15.5 (2.7)

are reported as the average percent of energy in tertiles for all controls by ϵ4 status and are shown in Fig 1. Fifty-two percent of the controls with the ϵ4 allele had fat intakes in the lowest tertile of fat intakes compared with only 17% of controls with ϵ4 in the highest tertile of fat intake ($P = .004$). Conversely, healthy controls without the APOE ϵ4 allele had fat intakes more evenly distributed among the tertiles.

DISCUSSION

Diet-genotype interactions have been reported with respect to health and chronic diseases.[2,14-16] Our results show remarkable differences by genotype in dietary fat consumption in healthy persons during early and mid adulthood. We found that healthy subjects with the ϵ4 allele consumed less fat in mid-adult life than those without the ϵ4 allele. This may be because of selective mortality and morbidity, as people with the ϵ4 allele and high-fat diet may be less likely to survive to be included in this study as healthy elderly.[17] It is also possible that homeostatic mechanisms regulating fat intake are influenced by APOE genotype. Lower fat consumption in healthy persons with the ϵ4 allele may be an indicator of food restriction, which has been shown to increase longevity and protect against disease in animals.[18]

Some important limitations must be considered in this study. In this investigation, we are relying on memory for the recall of past food patterns. There is an extensive literature on the ability to remember foods and their frequencies of consumption in the past.[19-22] These investigators indicate that recalls of diets in the distant past correlated well with past diet records and could be used to rank subjects into categories of food intake. Internal validation of this study shows a downward trend of fat consumption over time, which is consistent with dietary surveys conducted in the United States during the same age periods (Table 2).[23] We are reporting fat intakes in tertiles and recognize that there may be opportunity for misclassification; therefore, larger studies are needed to confirm these results.

Table 2. Median Percent of Energy From Fat in Each Tertile for all Controls by Age Period

Tertiles of % Energy From Fat	20 to 39 Years	40 to 59 Years	60+ Years
Low	37.2	35.0	25.9
Middle	41.8	39.8	33.9
High	46.0	44.0	39.8

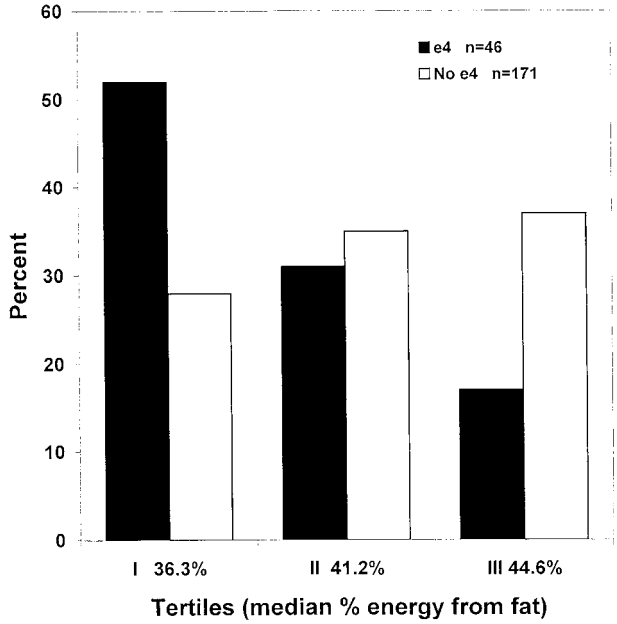

Fig 1. Proportions of controls with and without APOE ϵ4 genotype in each tertile of fat intake during mid-adult life, age 20 to 59 years ($P = .004$).

APOE ϵ4 genotype has been associated with cognitive decline with age.[24,25] However, other investigators have not shown this relationship in healthy older persons.[26-29] At the time of completion of the dietary frequency questionnaire, all controls in our study, regardless of ϵ4 status, were considered to be cognitively intact according to norms established for the CERAD test battery.[11]

Although the APOE ϵ4 genotype has been shown to be a risk factor for AD and for decline in cognitive ability, results in our study show a gene-diet relationship, which may protect cognitively intact persons with the ϵ4 allele.[28] The healthy older subjects who survived to be included in this study may be protected with lower fat higher-antioxidant dietary patterns along with other healthy behaviors. Controls with both ϵ4 genotype and higher fat dietary intakes may have other lifestyle practices that are protective. Larger studies will help to elucidate the complex relationships of genotype-diet interactions in the development of chronic disease.

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