Common alleles of the apolipoprotein-E gene (APOE) are associated with different risks of ischemic heart disease, Alzheimer’s disease, and other chronic conditions in European populations. Also, the APOE allele frequencies vary widely among European countries. We estimated the proportion of differences in mortality and differences in life span that are attributable to differences in APOE allele frequencies in Europe. Mortality rates by age, sex, and APOE genotype for six countries (Denmark, Finland, France, Italy, the Netherlands, and Sweden) were used to standardize mortality rates to the allele frequencies in Italy. Differences in APOE allele frequencies explain 12%–17% of the variation among these countries in mortality in people older than 65 years and 1%–2% of the variation in life span in those older than 65 years. Differences by genotype in mortality in people older than 15 years account for about 3.5% of the genetic contribution to the variation in life span in Denmark.

Researchers have examined a number of alleles for possible association with all-cause mortality in humans (1). Of these, the most thoroughly studied are the three common alleles of the gene for apolipoprotein-E (APOE): e2, e3, and e4. These alleles differ by single nucleic acids at positions 112 and 158. APOE e4 has arginine at both sites, e3 has cysteine at 112, and e2 has cysteine at both sites. Numerous other variants of the APOE gene have been identified, but they have not been studied as extensively (2–4).

APOE is the only gene that has been clearly demonstrated to meet the three criteria for genes that have population level impact on mortality (5). First, the simple substitutions that differentiate the three alleles are associated with substantial variation in the risk of two common causes of death in populations of European origin: ischemic heart disease and Alzheimer’s disease (6–9). There is also evidence that the APOE genotype might be associated with stroke mortality (10) and possibly several other causes of morbidity and mortality (11–13). Second, the three alleles are relatively common. In most populations, at least 50% of the population has two copies of the e3 allele (e3/3 genotype) and at least 20% carry at least one copy of the e4 allele (e2/4, e3/4, or e4/4). The e2 allele appears to be absent in some populations living in arctic regions but, in most populations, at least 5% carry one or two copies (e2/2, e2/3, or e2/4) (14). Third, the frequency of the e4 allele varies substantially across populations. Several reviews have demonstrated the wide range of estimates (14,15), but there are data on APOE allele frequencies for approximately 200 populations worldwide.

Despite the large number of studies on differences in mortality by APOE genotype, there has not been a systematic study of the role APOE plays in explaining differences in all-cause mortality across countries.

Methods

By combining estimates of mortality by genotype for one country with the genotype frequencies for a second country (direct standardization), we can estimate how much the mortality rates in the two countries would differ if they had the same genotype frequencies (16). Applying the same genotype frequencies to the genotype-specific mortality for a number of countries allows us to estimate the proportion of the variation in mortality rates that is attributable to APOE genotype frequencies.

This analysis is based on previous research that provides estimates of mortality rates specific for age, sex, and APOE genotype for seven populations: Denmark, Finland, France, Italy, the Netherlands, Sweden, and American whites (17). Two types of data were combined to estimate the parameters of the model. First are cohort studies that provide estimates of mortality by genotype. The original research used data from three cohort studies (18–20). The parameter estimates have been updated using new data from two recent studies of American whites (21,22) and one study from Finland (23). When combined, these six studies include data on almost 6000 individuals (approximately 1500 aged older than 85 years) for an average of 5.6 years of observation each.

The second type of data comes from cross-sectional studies of populations that provide evidence of changes in APOE genotype frequencies at the older ages. These studies often show declines in the e4 allele frequency at the oldest ages due to excess mortality. The original research included data from eight studies of APOE genotype frequencies at the older ages (18,20,24–29) and five other studies that only provide data for younger ages in comparable populations (26,30–33). The updated parameter estimates are based on additional data from the baseline surveys from the two American cohort studies (21,22) plus two studies from the...
Netherlands (34,35). These studies include a combined total of more than 3000 individuals younger than 65 years, approximately 2000 aged 65–84, and more than 4000 aged 85 and older.

The data show no evidence of differences in the relative risks between northern and southern Europe or between males and females (17). The relative risks were assumed to increase between ages 20 and 60 in proportion to the percentage of deaths to ischemic heart disease at each age in the U.S. in 1990. In this analysis, the rare e2/2 genotype was combined with the e2/3 and the e2/4 is combined with the e3/3, giving four main genotypes.

RESULTS

The updated analysis suggests that, in populations of European heritage, the e3/4 genotype has a mortality rate at age 65–69 years that is 1.40 times that of the e3/3 genotype. The e2/3 genotype has a mortality rate 0.81 times that of the e3/3. These estimates suggest slightly larger variation in mortality by genotype than the original analysis. The relative risks converge toward 1.0, so that by age 100 there are virtually no differences by genotype (17). This is consistent with the idea that APOE is not a ‘‘longevity gene’’ specifically related to survival at the very oldest ages. Rather, it is a ‘‘frailty gene’’ that affects mortality at all adult ages (24).

Figure 1 presents APOE allele frequencies for young adults in six European countries: Denmark, Finland, France, Italy, the Netherlands, and Sweden. These countries were chosen because they are the European countries included in the estimation of the parameter estimates. Allele frequencies are rarely available for nationally representative samples; however, the differences within countries are small compared to the large differences between countries. The estimates used here were selected to reflect the national average. The e4 allele frequencies follow a frequently noted North–South gradient (28,40). The e4 frequencies in Sweden and Finland are among the highest in the world; the value in Italy is among the lowest. There is no clear geographic pattern for the e2 allele. The highest value, 9.5%, is found in Sweden with the lowest value, 3.9%, in neighboring Finland.

Mortality Differences Among Countries

APOE probably has little or no effect on mortality under age 40 and may not reach its full effect until age 60 when ischemic heart disease becomes the dominant cause of death. Therefore, it is useful to focus on measures of adult mortality.

Figure 2 shows all-cause mortality rates in the six European countries for men aged 65–69 years born in 1925–1929 (41). Figure 2 also shows what these rates would be if these countries had the same APOE genotype frequencies at age 65 as does Italy. Italy is a useful standard because it has the lowest e4 frequency but average mortality rates. Standardizing the genotype frequencies does not explain the large mortality difference between Sweden and Denmark. However, it does reduce the difference between France and Denmark by 16% and the difference between Italy and Finland by 48%. Overall, standardization reduces the variance in the mortality rate for men aged 65–69 years by 13%.

For women, the range of mortality rates at ages 65–69 is much larger because of exceptionally high mortality among women in Denmark. Differences in APOE genotype frequencies explain 12% of the variation among these countries in all-cause mortality at ages 65–69.

At ages 85–89, those born in 1915–1919 have a lower e4 allele frequency than those aged 65–69 who were born 20 years later. For example, among Dutch men, the e3/4 frequency is 13.9% at ages 85–89 compared with 21.5% at ages 65–69. There are two reasons for this. First, the e4 frequency declines with age because of the excess mortality among e4 carriers. Second, those born in 1915–1919 experienced higher mortality at all ages, and, therefore,
a more rapid decline in the e4 frequency with age. Despite this, standardizing for differences in genotype frequencies reduces the variation in all-cause mortality at ages 85–89 among the six countries by 23% among men and 25% among women. These percentages are larger than those for people aged 65–69 because the absolute differences in mortality between genotypes increase between these ages.

We now examine differences in national life expectancy for a given year. Combining genotype-specific mortality rates for each age group from different birth years produces a life table for each genotype that applies to approximately 1995. This leads to estimates of what the life expectancy would be if the genotype-specific mortality rates of the mid-1990s remained constant.

Figure 3 shows the life expectancy at age 65 for men in the six European countries. The values range from 14.3 years in Denmark to 16.0 years in France. Standardizing each country to the APOE genotype frequencies in Italy reduces the variation in life expectancy at age 65 for men by 16%. The proportion for women is 17%. For life expectancy at age 20, the proportions of variance explained are 9% for men and 14% for women.

Differences in Life Span Among Individuals

It is also possible to examine the effect of APOE on the variation in life span (age at death) among individuals in the same country. Figure 4 shows the estimated distribution of ages at death over age 15 for individuals of both sexes with the e2/3 and e3/4 genotypes born in Denmark in 1895–1899. The curve for the e2/3 genotype reaches a maximum at age 83. The peak for the e3/4 genotype occurs 6 years earlier at age 77. This reflects the differences in life expectancy at age 15 (the mean age at death for survivors to 15) by genotype: 58.7 years for e2/3 and 54.6 for e3/4.

Table 1 shows that 0.9% of the variation in age at death among survivors to age 15 in this Danish cohort is explained by differences in mortality among APOE genotypes. If we examine only deaths among survivors to age 65, the percentage increases to 1.8%. The comparable figures for Italy, which has the lowest e4 allele frequency, are lower (0.3% and 1.1%).

This result can be compared with the estimate from Danish twins that approximately 25% of the variation in mortality over age 15 is attributable to genetics (42). Therefore, approximately 3.5% of the variability attributable to genetics is accounted for by differences among APOE genotypes.

Studies of variability among individuals have much lower proportions of variance explained than do comparisons of populations. These percentages can be put into perspective by comparing them to the proportion of the variance in life span explained by sex. Table 1 shows that in Denmark, APOE explains the same proportion of variation in life span after age 15 as sex (0.9%). APOE explains a smaller proportion than sex for deaths over 65 (1.8% and 3.5%). In France, there are larger differences by sex and smaller effects of APOE, so that at age 65, sex explains about 4.5 times as much as APOE. Overall, the explanatory power of the APOE genotype in European populations is less than that of sex, but the effects are comparable in magnitude.

**DISCUSSION**

This is the first time that differences in a gene have been shown to explain a substantial fraction of the variance in mortality across large populations. Although the differences in APOE allele frequencies and the relationship between APOE genotype and mortality are both well known, they have not previously been combined to examine the implications for populations.

We find that differences in APOE genotype frequencies explain 12%–17% of the variation in various measures of mortality over age 65. These results are, of course, dependent on the sample of populations used in the analysis. Therefore, it is difficult to find comparable estimates for other risk factors. However, these percentages are probably comparable to the proportions of variance explained by more traditional risk factors such as diet, smoking, and differences in health care services.
African Americans despite similar APOE allele frequencies Alzheimer’s disease is much lower in Nigerians than in European populations. For example the incidence of Alzheimer’s disease is far too little evidence on the effects of other variants or might be due to other variations in the APOE gene. There are far too little evidence on the effects of other variants or on their frequency in different European populations to speculate on the full effect beyond that explained by the three most studied e2, e3, and e4 alleles. A full analysis incorporating many more of the APOE variants might find a larger or smaller total effect.

It is also too early to extrapolate these results to non-European populations. For example, it is tempting to hypothesize that APOE might explain some of the differences in mortality between Asian Americans (who generally have a low e4 frequency), Americans of European descent, and African Americans (who have a higher e4 frequency). However, it is not clear that there are differences in mortality by APOE genotype in non-European populations (21,22). In other populations, interactions between APOE and other genes or between APOE and environment might alter the relationships between genotype and disease found in European populations. For example the incidence of Alzheimer’s disease is much lower in Nigerians than in African Americans despite similar APOE allele frequencies in the two populations (43).

### Table 1. Estimates of the Proportion of Variance Among Individuals in Life Span After Ages 15 and 65 Attributable to Differences in Mortality by APOE Genotype and by Sex, for Six European Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Age 15 APOE</th>
<th>Age 15 Sex</th>
<th>Age 65 APOE</th>
<th>Age 65 Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>0.9%</td>
<td>0.9%</td>
<td>1.8%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Finland</td>
<td>0.6%</td>
<td>3.3%</td>
<td>1.6%</td>
<td>4.7%</td>
</tr>
<tr>
<td>France</td>
<td>0.3%</td>
<td>9.1%</td>
<td>1.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Italy</td>
<td>0.3%</td>
<td>1.1%</td>
<td>1.1%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.9%</td>
<td>2.4%</td>
<td>1.5%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.7%</td>
<td>0.9%</td>
<td>2.2%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

*Note: APOE = apolipoprotein-E.*

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