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Angiotensin I-Converting Enzyme (ACE) Gene Polymorphism in Relation to Physical Performance, Cognition and Survival—A Follow-up Study of Elderly Danish Twins

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PURPOSE: Studies of younger individuals have suggested an association between ACE genotype and physical and cognitive performance. Using a longitudinal study of elderly twins we studied the association between ACE genotype and physical and cognitive functioning and survival in old age.
METHODS: Participants were 684 twins aged 73+ years from the 1997 and 1999 surveys of the Longitudinal Study of Aging Danish Twins. Cognitive skills were assessed by the MMSE, while physical abilities were determined through self-report in 1997 and through both self-report and measurement of performance in two physical tasks in 1999. Survival status was obtained through linkage with a national death register.
RESULTS: Neither physical nor cognitive performance was associated with ACE genotype at baseline in 1997, or at follow-up in 1999. For participants in both surveys longitudinal changes in these skills did not depend on ACE genotype. The relative risk of dying was increased in II compared with the DI and DD genotype with relative risks of 1.6 (95 percent confidence intervals 1.1–2.5) and 1.3 (0.8–2.1), respectively.
CONCLUSION: We found no substantial effects of ACE genotype on physical and cognitive performance, or rate of change among elderly. Persons with the D allele may have a lower mortality at older ages.
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KEY WORDS: Genetics, Epidemiology, Aging, Polymorphism (Genetics), Physical Fitness, Cognition, Survival, Twins.

INTRODUCTION

A polymorphism in the gene coding for Angiotensin I-Converting Enzyme (ACE) was identified in 1990 (1). The polymorphism is due to a 287 bp fragment in the ACE gene in chromosome 17. The fragment is present in the insertion (I) variant and absent in the deletion (D) variant, which results in the three genotypes: Homozygotes II and DD and heterozygotes DI. The genotype accounts for approximately half of the variance in the circulating ACE level and from the II to the DD genotype the presence of each D allele is associated with an additive effect on ACE activity (50% higher in the DD compared with the II genotype) (1). The cleavage of angiotensin-I by ACE produces the octapeptide angiotensin-II, which is a potent vasoconstrictor. The relationship between ACE genotypes, in particular DD, and the occurrence of cardiovascular and renal diseases has therefore been the focus of several studies in the past decade. The results from these association studies have not been consistent, and for ischemic heart disease publication bias has recently been shown to be a likely explanation for this discrepancy (2).

In the past few years the ACE gene polymorphism has also been associated with the outcome of physical exercise, especially endurance performance. Presence of the II genotype was associated with improved performance (3–6). However, the study subjects were mostly young healthy males from highly selected populations (e.g. elite athletes and military recruits) and the samples were small (3–6).

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Selected Abbreviations and Acronyms
ACE = Angiotensin I-Converting Enzyme
AD = Alzheimer's disease
LSADT = longitudinal study of aging Danish twins
MZ = monozygotic
ADL = activities of daily living
MMSE = mini mental state examination
DZ = dizygotic
SD = standard deviation
HR = hazard rates

Physical performance is important for younger people but even more so among the elderly where physical performance together with cognitive function determine whether life can be lived independently. Cognitive impairment and dementia have also been reported to be associated with ACE genotype, although recent studies have come to opposite conclusions regarding ACE genotype and risk for Alzheimer's disease (AD) (7, 8). An increased risk of AD was associated with the I allele in one study (7), but the D allele in another (8).

Survival to old age has also been suggested to be influenced by ACE genotype since a German study found an increased frequency of the DD genotype in octogenarians (9). This finding could not, however, be confirmed in two large studies of centenarians (10, 11). Studies of elderly twins have found evidence of substantial genetic influence on both physical (14) and cognitive functioning (15, 16) as well as a moderate genetic influence on life span (17). Twin studies have mostly been used for determining the relative contribution of genes and environment to the variation of a phenotype but less so for identifying specific genetic variants of importance. Based on the previous association studies and the fact that the renin-angiotensin system is involved in cardiovascular and renal homeostasis and that ACE activity and angiotensin receptors can be demonstrated in various peripheral tissues including skeletal muscle (12) and brain (13) it seems conceivable that the I/D polymorphism that is associated with the circulating ACE activity could be associated with physical and cognitive function and survival at older ages. We therefore found it relevant to investigate the possible relations of ACE genotype to physical and cognitive abilities in a large sample of older Danish twins who are being followed longitudinally. This twin cohort provided the evidence for a substantial genetic component to the phenotypes we study. Here we use the twin cohort as a longitudinal study of individuals, although we take advantage of and pay attention to the dependency between the two twins within a pair. Based on the previous literature, it could be hypothesised that the II ACE genotype is associated with better physical performance in the elderly. Previous studies were not consistent enough to allow us to make specific predictions about the relationship of ACE genotype to cognitive performance and survival. Due to the well-established association between the I/D genotype and the stepwise phenotypic expression of the ACE gene (1) it could further be hypothesized that any association with examined phenotypes would result in stepwise trends in the differences.

MATERIAL AND METHODS

Study Population

The population in this study was drawn from the 1997 and 1999 surveys of the longitudinal study of aging Danish twins (LSADT) which has been described in detail elsewhere (18). In brief, the LSADT began in 1995 and is an ongoing longitudinal study of twins born before 1929 and identified in The Danish Twin Registry. The Danish Twin Registry includes all twins born in Denmark between 1870 and 1910, and same-sex pairs born between 1911 and 1930. The LSADT participants are interviewed every second year in their homes by lay interviewers from the Danish National Institute of Social Research who have substantial experience in interviewing the elderly. The 1997 survey comprised 2172 individuals corresponding to a participation rate of 78.7 percent. We subsequently asked individuals from pairs where both twins participated in the interview study (n = 974) to allow a trained technician to visit them in their homes and draw a sample of blood. Blood was sampled from 689 individuals (Fig. 1) and ACE genotype was determined in 554. For 130 monozygotic (MZ) twins, the ACE genotype was determined for one twin in the pair and was then assigned to the co-twin. Genotyping failed due to technical problems in 5 cases. The study population from the 1997 survey therefore consisted of 684 individuals of whom 547 were reassessed in 1999 (Fig. 1).

As twin zygosity was determined through a self-report questionnaire, a method that has been shown to result in less than 5 percent misclassification (19), the number of misclassified MZ twins was very small.

Genotyping

The ACE genotyping was done according to Rigat et al (20). To avoid the earlier reported mistyping of ACE heterozygotes (ID genotypes misclassified as DD) (21, 22), all samples typed as DD were reamplified as described by Shanmugam et al (21) with another set of primers in the presence of a positive control (ID/II).

Physical and Cognitive Abilities

Physical ability was assessed through self-report in 1997, and through both self-report and the measurement of performance in two physical tasks in 1999. The questions re-

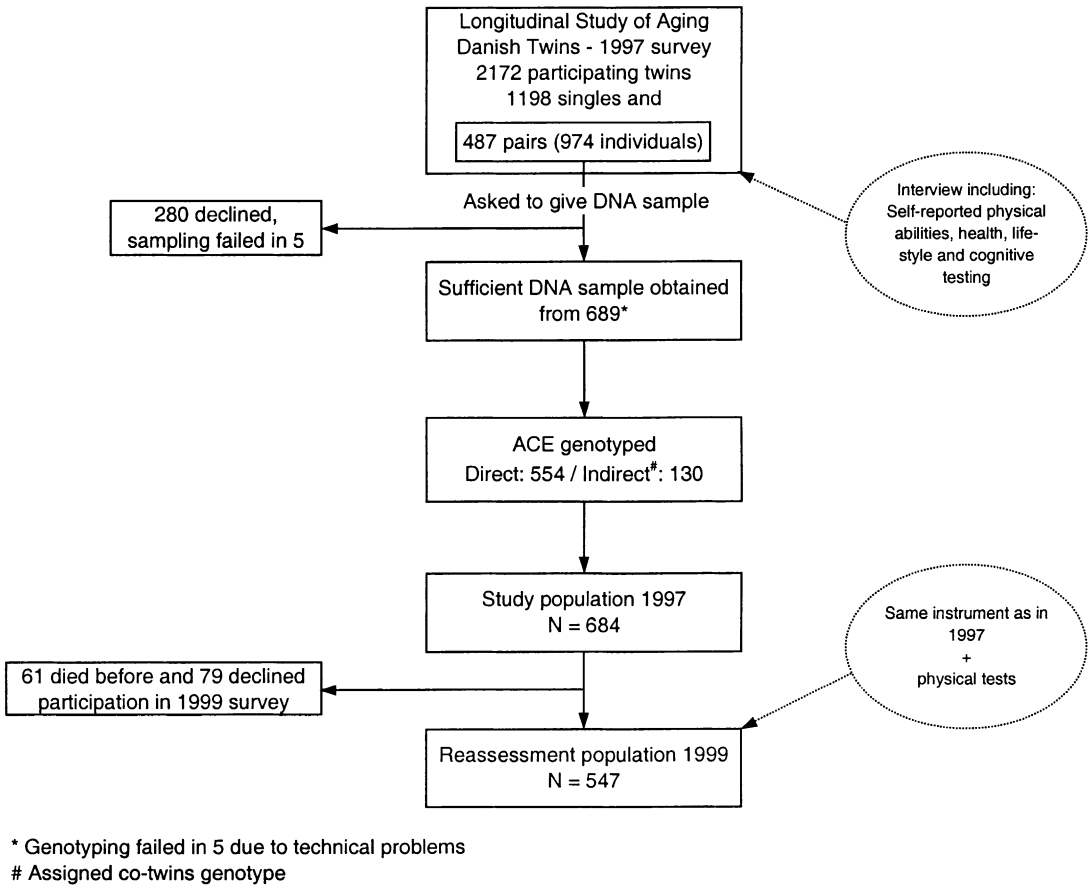


FIGURE 1. Flow chart of 684 ACE genotyped twins from the Longitudinal Study of Aging Danish Twins - the 1997 and 1999 surveys.

ferred to the ability on the day of the interview. Research has shown that physical abilities can be reliably and validly assessed through self-report (23). The self-reported physical abilities were determined from 26 items including items from Katz' index of activities of daily living (ADL) (24) as well as questions about demanding activities like running. This instrument has been validated in Denmark and shown to discriminate different levels of functional abilities among community dwelling elderly (25). All items were rated on a 4 to 1 scale with the response options ranging from "can do without fatigue" (4) to "cannot do" (1). To identify a quantitative subscale the items were factor analyzed in the total twin sample from the 1995 survey (14). This identified two factors where the first factor loaded highest on items dealing with ability to walk, run, climb stairs and carry weights and was interpreted to reflect a dimension of strength. The second factor loaded highest on items dealing with ability to wash, dress, and get in and out of bed and was interpreted to reflect a dimension of agility. Only the strength factor was used in this analysis due to little variability on the agility scale. The strength scores from the 1997 and 1999 surveys were calculated by taking the average response of the 11 items identified to be relevant for this score. The factor has previously been found highly reliable for functional abilities (26). In the 1999 survey three additional items dealing with endurance performance (self-reported walking, running and cycling distance) were included. A composite score was calculated taking the average response from these items.

In the 1999 survey the participants were also invited to perform two tests of physical abilities—maximum handgrip pressure and the repeated chair stand test. The grip strength was measured by a hand dynamometer (Smedley's dynamometer TTM, Tokyo). The maximum value of three measures with each hand was used in the analyses. In the repeated chair stand test the participants were asked to rise and sit five times from a chair as quickly as possible with their arms folded over their chest. The pulse was recorded immediately before and after the test. The test, which was timed, was stopped if five attempts were not successfully performed within 60 seconds.

The cognitive functioning of the participants was assessed using the mini mental state examination (MMSE), which was integrated in the interview.

Data Analyses

Allele frequencies were computed from the genotype frequencies and Hardy-Weinberg equilibrium was tested by a χ^2 test with one degree of freedom. We compared the three ACE-genotypes with regard to physical and cognitive abilities and other characteristics at baseline (1997 interview wave) and in 1999 at the second interview wave. Longitudinal changes in cognitive skills and physical abilities were examined for twins participating in both interview waves. Finally, we examined the influence of ACE-genotype on survival through linkage with mortality data for the entire cohort.

Continuous variables were compared using multivariate linear regression models and categorical data were compared using logistic regression models controlling for the age of the participants. To account for the non-independence of the observations on twins, twins from pairs where both participated (intact pairs) were analyzed as clusters of two in the multivariate models (27). Data were sex-stratified due to a tendency to a larger proportion of women among the DI and DD genotypes.

The participants were followed from the date of blood sampling and until emigration, death, or end of study period (January 1, 2001), whichever event came first. Information on emigration and death was retrieved from the Danish Central Population Register, which is continuously updated. We used the Kaplan-Meier method, and the influence of ACE genotype on survival was ascertained using the log-rank test. Subsequently, a Cox proportional-hazards regression analysis was undertaken to determine ACE genotype as an independent risk factor controlling for the effects of sex, age, cognitive function (MMSE score), and self-rated health. These parameters were included in the analysis because they were associated with ACE genotype and survival. Education, which also differed by ACE genotype, was omitted from the final model, as it did not contribute significantly in explaining survival. The proportionality assumption was confirmed with a log minus log survival function plot.

The physical and cognitive functioning and survival among individuals from intact dizygotic (DZ) twin pairs that were discordant for ACE genotype were finally compared using the Sign test.

RESULTS

Study Population

The population comprised 684 individuals (Fig. 1), 450 (65.8 percent) females and 234 (34.2 percent) males. The mean age was 78.2 with a standard deviation (SD) of 4.4 (females: 78.4 (4.6), males: 77.8 (4.0)). Sixteen (2.3 percent) participated in the interview through a proxy responder.

ACE Genotype

In all, 169 (24.7 percent) twins had the II genotype, 344 (50.3 percent) the DI, and 171 (25.0 percent) the DD genotype. The genotype frequencies in men and women, and in the age groups shown in Table 1, were in Hardy-Weinberg equilibrium ($p > 0.3$), and were highly comparable to proportions found in Danish populations in two previous studies (10, 28). The distribution of the ACE genotype in the MZ twins who were assigned to their co-twin's genotype did not differ from that of the other study subjects (results not shown).

Baseline Characteristics

Characteristics of the study population, which could potentially confound the association between ACE genotype and measures of physical and cognitive abilities and survival, are listed in Table 1. The distribution of most of these potential confounders between the ACE genotypes was highly comparable and the differences showed no stepwise trends across genotypes. However, the number with more than eight years of education was significantly higher in DD than in DI and II males, $p = 0.02$ (Table 1). In addition, the proportion with poor or very poor self-rated health was lower in ID than DD males, $p = 0.02$ (Table 1).

Physical Abilities

Self-reported data about physical abilities were obtained from 683 individuals. The median strength scores from the two surveys as well as their mean relative difference did not vary substantially by ACE genotype (Table 2). The composite endurance score of self-reported walking, running, and cycling from the 1999 survey did not differ by ACE genotype (Table 2). The maximum handgrip pressure was measured in 488 individuals with a mean-grip strength (SD) of 24.4 kg (8.6). Grip strength was highly dependent on sex, age, height and weight, but since height and weight were comparable in the three ACE genotypes (Table 1) this measure was analyzed age-adjusted and sex-stratified as other physical performance measures. Mean grip strength did not vary by ACE genotype (Table 2). The chair stand test was successfully completed by 426 individuals. The mean time (SD) used was 12.5 seconds (4.5) and the mean increase in pulse after five chair stands was 7.8 (4.8) heartbeats per minute. Both the time used to complete the test and the increase in pulse were highly comparable in the ACE genotypes (Table 2). The proportion of twins unable to perform the grip-strength and chair stand test did not vary by genotype (results not shown).

TABLE 1. Baseline characteristics of 684 twins participating in the longitudinal study of aging danish twins (LSADT) 1997 survey

	Females			Males		
ACE Genotypes	II	ID	DD	II	ID	DD
N (percent)	101 (59.8)	231 (67.2)	118 (69.0)	68 (40.2)	113 (32.8)	53 (31.0)
Age, mean ± SD	78.5 ± 4.6	78.5 ± 4.6	77.0 ± 4.6	76.8 ± 3.3	78.4 ± 4.3	77.9 ± 3.9
BMI, mean ± SD	24.5 ± 4.1	23.5 ± 3.8	23.4 ± 4.1	26.0 ± 3.3	25.2 ± 2.8	24.8 ± 3.3
Education, > 8 yrs[a]	14 (13.9)	44 (19.2)	28 (23.9)	9 (13.4)	19 (17.0)	18 (34.0)
Smokers, ever	57 (56.4)	121 (52.4)	56 (47.9)	56 (83.6)	91 (81.3)	42 (80.8)
Alcohol, > 10 units/week	8 (8.7)	29 (13.6)	16 (15.0)	24 (40.0)	39 (37.9)	18 (38.3)
Self-reported diseases[b]						
Diabetes	6 (5.9)	10 (4.3)	5 (4.2)	2 (2.9)	11 (9.7)	6 (11.3)
Hypertension	33 (32.7)	66 (28.6)	33 (28.0)	11 (16.2)	26 (23.2)	14 (26.4)
Other cardiovascular[c]	13 (12.9)	31 (13.4)	17 (14.4)	10 (14.7)	22 (19.5)	7 (13.2)
Stroke	3 (3.0)	12 (5.2)	5 (4.2)	7 (10.3)	5 (4.4)	6 (11.3)
Respiratory[d]	9 (8.9)	27 (11.7)	12 (10.2)	17 (25.0)	17 (15.0)	14 (26.4)
Poor/very poor self-rated health[e]	7 (7.1)	17 (7.5)	11 (9.3)	3 (4.8)	3 (2.8)	6 (11.3)

The figures are percentages within the respective ACE genotype in brackets if not otherwise stated.
No statistically significant differences among genotypes if not otherwise stated. Differences were tested with Logistic regression for categorical data and with multivariate linear regression for continuous data with the DD genotype as reference, controlling for age of the participants. Twins from intact pairs were analyzed as clusters of two in the multivariate models.
[a]Males, DI: p = 0.02, II: p = 0.02
[b]Participants were asked if a physician had ever told them that they suffered from any of the mentioned diseases.
[c]Angina, myocardial infarction or heart failure
[d]Chronic bronchitis or asthma
[e]Males, DI: p = 0.02, II: p = 0.25

Cognitive Abilities

The MMSE-test was completed by 674 persons with a median score of 27.0 (quartiles 24.0–28.0). The median test scores and the mean difference in scores between the two surveys were comparable in the three ACE genotypes (Table 3). Although not statistically significant the proportion of individuals with a score below 24 was approximately seven percent higher in participants with the II genotype of

TABLE 2. Physical abilities and ACE genotype

	Females			Males		
ACE genotype	II	ID	DD	II	ID	DD
Self reported physical abilities in 1997						
Median strength score (quartiles)	3.4 (2.5, 3.7)	3.5 (2.6, 3.7)	3.3 (2.5, 3.7)	3.5 (2.5, 3.7)	3.5 (3.2, 3.8)	3.5 (2.9, 3.7)
N	101	231	117	68	113	53
Self reported physical abilities in 1999[a]						
Median strength score (quartiles)	3.3 (2.5, 3.6)	3.4 (2.7, 3.5)	3.4 (2.5, 3.5)	3.5 (2.7, 3.6)	3.4 (2.6, 3.6)	3.5 (2.7, 3.7)
Mean endurance score (SD)[b]	4.7 (1.1)	4.7 (1.1)	4.8 (1.0)	4.2 (1.2)	4.4 (1.2)	4.4 (1.4)
N	73	173	89	54	91	42
Relative difference in self reported abilities 1997 to 1999						
Mean relative strength score difference (SD)	0.05 (0.2)	0.05 (0.2)	0.02 (0.2)	0.07 (0.2)	0.07 (0.2)	0.05 (0.2)
Measured physical performance in 1999						
Mean grip strength (SD), kg	20.1 (4.6)	19.6 (4.7)	19.5 (5.0)	34.2 (7.2)	32.3 (6.9)	31.7 (8.8)
N	65	161	86	51	85	40
Mean time to complete five chair stands (SD), seconds	12.1 (4.2)	12.9 (4.8)	12.9 (5.5)	12.4 (3.7)	11.7 (3.3)	12.4 (5.1)
Pulse increase after five chair stands (SD), bpm[c]	7.4 (4.6)	7.4 (4.4)	7.7 (4.7)	8.5 (4.6)	8.9 (5.9)	7.9 (4.7)
N	60	146	75	39	73	33

No statistically significant differences among genotypes. Differences were tested with multivariate linear regression for continuous data with the DD genotype as reference, controlling for age of the participants. Twins from intact pairs were analyzed as clusters of two in the multivariate models.
[a]Participants in 1999 follow-up were approximately 2 years younger at baseline than twins who only participated in 1997 survey (p < 0.001).
[b]Mean composite measure of walking, running, and cycling distance ± standard deviation.
[c]Beats per minute

TABLE 3. Mini Mental State Examination (MMSE) scores and ACE genotype

	Females			Males		
ACE genotype	II	DI	DD	II	DI	DD
Median MMSE score 1997 (quartiles)	26.0 (23.0, 28.0)	27.0 (24.0, 28.0)	27.0 (25.0, 29.0)	27.0 (23.0, 29.0)	27.0 (24.0, 29.0)	27.0 (25.0, 28.0)
Number with test score <24 (percent)	25 (25.3)	42 (18.4)	21 (17.9)	18 (27.3)	22 (19.8)	10 (18.9)
Median MMSE score 1999 (quartiles)[a]	26.0 (23.0, 28.0)	27.0 (24.0, 28.0)	26.5 (24.0, 29.0)	28.0 (25.0, 29.0)	27.0 (24.0, 28.5)	27.0 (24.0, 29.0)
Number with test score <24 (percent)	19 (26.4)	34 (19.5)	15 (16.7)	8 (15.4)	18 (20.2)	7 (17.1)
Mean relative MMSE score differences 1997 to 1999 (SD)	0.02 (0.1)	0.01 (0.1)	0.0 (0.1)	−0.01 (0.1)	0.02 (0.1)	0.04 (0.1)

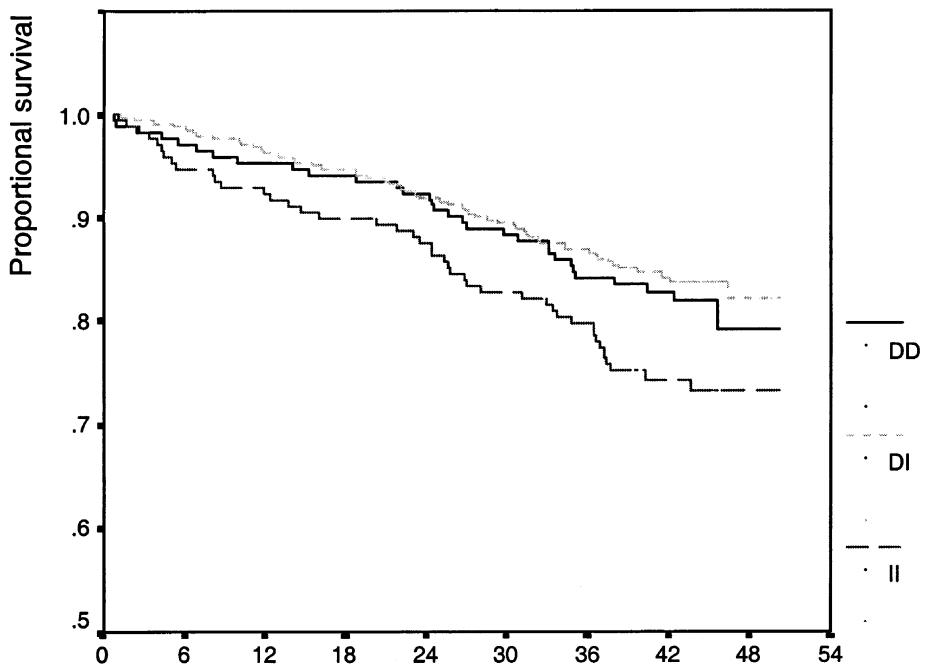
No statistically significant differences among genotypes. Differences were tested with Logistic regression for categorical data and with multivariate linear regression for continuous data with the DD genotype as reference, controlling for age of the participants. Twins from intact pairs were analyzed as clusters of two in the multivariate models.

[a]Participants in 1999 follow-up were approximately 2 years younger at baseline than their non-participating counter-parts ($p < 0.001$).

both sexes in the 1997 survey. The proportion not participating in cognitive testing did not vary by genotype (results not shown).

Survival

The mean follow-up time (SD) was 39.5 (10.3) months and none were lost to follow-up. During the follow-up period 130 participants died. The participants with the II genotype had marginally poorer survival, $p = 0.02$ (Fig. 2). Controlling for sex, age at baseline, self-rated health and MMSE score in a Cox regression analysis indicated that the II genotype may be an independent risk factor for death, the hazard rates (HR) (95 percent confidence intervals) for the II compared with the ID and DD genotype being 1.6 (1.1–2.5), and 1.3 (0.8–2.1) respectively. The survival was not signifi-



Persons at risk					
DD	171	163	156	144	14
DI	344	331	316	298	21
II	169	155	147	135	18

FIGURE 2. Survival curves of 684 ACE genotyped twins from the Longitudinal Study of Aging Danish Twins - the 1997 and 1999 surveys.

cantly different in DD and DI persons (Fig. 2). Using the D as the dominant allele resulted in hazard rates of 1.5 (1.0–2.2) for II compared with DI/DD persons.

Subgroup Analyses

Seventy-nine intact DZ twin pairs were discordant for ACE genotype. Physical and cognitive abilities as well as survival did not differ significantly between the individuals in these pairs (results not shown). Although statistics were not significant here, the proportion of self-reported diseases differed by genotype (Table 1). We therefore repeated the analyses restricted to those not suffering from any of the mentioned diseases but the results were virtually unaltered by this (results not shown).

DISCUSSION

In this study, we have focused on the possible association of the ACE genotypes with physical and cognitive performance and survival among the elderly. The study design provided both cross-sectional and longitudinal data. In our study, the ACE genotype was not associated with self-reported or measured physical performance or cognitive function. Having the D allele, however, improved chances of survival even after controlling for the effect of sex, age, cognitive function, and self-rated health. None of the analyses revealed any stepwise trends of the examined phenotypes with regard to ACE genotype.

The study population comprised twin pairs where both twins were alive at baseline, which could introduce selection bias. However, physical abilities in old twin pairs where both twins were alive have previously been shown only marginally better than in twins with a deceased cotwin (14). The instrument to determine physical performance in this study was self-report and measurements of upper and lower extremity function. This gives information from several functions each important for physical performance, none of which showed an association with ACE genotype. The assessment of physical abilities through self-report was done with a questionnaire that has been validated in a Danish population on several occasions. Further, the reliability of self-reported physical functioning in the elderly is reported to be high (23). Both physical performance measures (grip strength and repeated chair stands) have been used in other studies among the elderly and have been shown to discriminate different levels of physical functioning (29, 30). All the previous association studies comparing physical performance with ACE genotype have studied young healthy individuals. Two different types of studies have been used: intervention and association studies. Among male military recruits the intervention studies have found improved muscular function (3, 4) and whole body anaerobic response (31) after physical training in II persons exceeding that of the D allele persons. The association studies have determined ACE genotype prevalence in élite athletes compared with controls. Some have found increased prevalence of the II genotype in mountaineers who ascended beyond 7,000 m without supplementary oxygen (3) or in Olympic competitors (5, 6), whereas others found no difference in ACE genotype prevalence (32). All the intervention studies have as expected found comparable physical performance at baseline between different ACE genotypes since the range of physical abilities is narrow in young persons especially when using selected groups e.g. military recruits for the intervention. In old age, however, the variation of physical abilities is large, therefore differences in a cross-sectional study should occur if the ACE genotype was important for physical performance in this age group. Furthermore, ACE genotype was not associated with rate of change in self-reported physical abilities. The cause of the discrepancy between this and the previous studies is unknown. A possible explanation could be the highly selected populations used in the previous studies of ACE genotype and physical performance.

We found no association between ACE genotype and cognitive function with the cross-sectional and the longitudinal approach. The previous studies have focused on the relation between ACE genotype and dementia and have come to quite different conclusions. The risk of dementia (all types) or AD have thus been reported to be increased with the I allele (7), and the D allele, but confined to the age group 66 to 71 years (8), or to the male sex (33), and to have no association with ACE genotype (34, 35). We studied associations between ACE genotype and cognitive function on a continuous scale. Only one other cross-sectional study has examined the association between ACE genotype and MMSE score and failed as in the present study to show any relation between genotype and cognition (36).

The impact of ACE genotype on longevity is unknown. One study found a significantly larger proportion of DD's among octogenarians (9), whereas in a study of 9203 persons from the Copenhagen City heart study (28) and in two studies of centenarians (10, 11) the DD proportion was similar in the age groups compared. We studied mortality longitudinally and found an increased mortality among II's in old age. To our knowledge, only one longitudinal study has investigated survival in relation to ACE genotype in 61 patients with renovascular disease where the DD patients had a poorer survival than the ID patients (37). The small difference in the survival curves in the present study indicates that the ACE genotype does not have a major impact on survival and that the poorer II survival may reflect random variation.

In conclusion, we found no substantial effects of ACE genotype on physical and cognitive performance in neither the cross-sectional nor the follow-up study. Persons with

the D allele may have better survival chances than other persons have.

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