Angiotensin-Converting Enzyme Insertion/Deletion Genotype, Exercise, and Physical Decline

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Context Physical performance in response to exercise appears to be influenced by the angiotensin-converting enzyme (ACE) insertion (I)/deletion (D) genotype in young adults, but whether this relationship could help explain variation in older individuals’ response to exercise has not been well studied.

Objective To determine whether the ACE genotype interacts with significant physical activity to affect the incidence of mobility limitation in well-functioning older adults.

Design, Setting, and Participants The Health Aging and Body Composition (Health ABC) Cohort Study, conducted in the metropolitan areas of Memphis, Tenn, and Pittsburgh, Pa. A total of 3075 well-functioning community-dwelling adults aged 70 through 79 years were enrolled from 1997 to 1998 and had a mean of 4.1 years of follow-up.

Main Outcome Measure Incident mobility limitation defined as the report of difficulty walking a quarter of a mile (0.4 km) or walking up 10 steps on 2 consecutive semiannual interviews (n = 1204).

Results Physically active participants (those reporting expending ≥1000 kcal/wk in exercise, walking, and stair climbing) were less likely to develop mobility limitation regardless of genotype. However, activity level interacted significantly with the ACE genotype (P = 0.002). In the inactive group, the ACE genotype was not associated with limitation (P = 0.46). In the active group, those with the I I genotype were more likely to develop mobility limitation after adjusting for potential confounders compared with those with ID/DD genotypes (adjusted rate ratio, 1.45, 95% confidence interval, 1.08-1.94). The gene association was especially strong among participants reporting weightlifting. Exploration of possible physiological correlates revealed that among active participants, those with the II genotype had higher percentage of body fat (P = 0.02) and more intramuscular thigh fat (P = 0.02) but had similar quadriceps strength as those with ID/DD.

Conclusions Among older individuals who exercised, those with the ACE DD or ID genotypes were less likely to develop mobility limitation than those with the II genotype. Regardless of genotype, individuals who exercised were less likely to develop mobility limitation than those who did not exercise.

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is partly mediated through the maintenance of strength and physical endurance, and trials of both strength and aerobic interventions have shown benefit in improving function in older adults. Despite exercise's general benefit, individual responses to exercise vary. The basis for this is unclear, but there appears to be a strong genetic component. An insertion (I)/deletion (D) polymorphism in intron 16 of the angiotensin-converting enzyme (ACE) gene has been identified as a potential marker for the differential response to exercise. In the field of hypertension the D allele is associated with significantly higher serum ACE levels. In response to exercise, the D allele has been associated with increased muscle strength and power while the I allele has been associated with better muscular endurance although data are not entirely consistent.

Since both muscle strength and endurance are determinants of physical function in older adults, maintenance of physical function could be related to ACE I/D genotype. However, studies involving younger individuals suggest that a genotype effect would be seen primarily in response to high physical activity levels. Therefore, we examined the interrelationship between ACE I/D genotype, high levels of physical activity, and functional decline, defined as the incidence of mobility limitation, in the Health Aging and Body Composition (Health ABC) study.

**METHODS**

The Health ABC study is an ongoing prospective cohort study of incident mobility in 3075 well-functioning 70- to 79-year-olds from Memphis, Tenn, and Pittsburgh, Pa. Participants were recruited in 1997 and 1998 from a random sample of white and all of the black Medicare-eligible adults who lived in the 2 study areas. Race was self-identified. To be eligible, potential participants were required to report no difficulty in walking a quarter mile (0.4 km) or going up 10 steps without resting. Exclusion criteria included self-reported difficulties with activities of daily living, cognitive impairment, inability to communicate with the interviewer, intention of moving out of the vicinity in the next year, active treatment for cancer in the previous 3 years, or participation in a trial involving a lifestyle intervention. Of the 3075 baseline participants, 109 were excluded because they had either no genotype data (n=101) or no follow-up information (n=8), leaving 2966 individuals for analysis. Compared with nonexcluded participants, excluded participants were more likely to be black (52.3% vs 41.3%) and to be from Memphis (68% vs 50%) but did not significantly differ otherwise. The study was approved by institutional review boards at the University of Tennessee, Memphis, and the University of Pittsburgh, and written informed consent was obtained from all participants.

Participants were interviewed every 6 months to ascertain the incidence of persistent mobility limitation. Mobility limitation was defined as self-report of any difficulty either walking a quarter mile (0.4 km) or going up 10 steps without resting due to health or a physical problem on 2 consecutive interviews. This report includes incident cases ascertained through 4.1 years of follow-up. Follow-up at 4.1 years was more than 97% complete.

Physical activity over the previous 7 days was assessed by an interviewer-administered questionnaire. The time spent on gardening, heavy chores, light house work, grocery shopping, laundry, climbing stairs, walking for exercise, walking for other purposes, aerobics, weight or circuit training, high-intensity exercise activities, and moderate-intensity exercise activities was obtained in addition to information on the intensity level at which each activity was carried out. These data were used to derive an estimate of caloric expenditure for each activity.

Data from younger populations suggest that the ACE I/D genotype effect is most evident in the context of high-intensity exercise. However, the nature of the effect depends on the type of activity (ie, aerobic vs resistance). Therefore, we examined genotype-outcome relationships for 3 alternative categorizations of total physical activity—reported expenditure of at least 1000 kcal/wk from walking, stair climbing, and other exercise; high-intensity physical activity—reported expenditure of at least 400 kcal/wk in high-intensity exercise activities; and weight lifting—any weight lifting in the previous week.

The ACE I/D polymorphism in intron 16 of the ACE gene was determined using polymerase chain reaction (PCR) amplification with subsequent visualization of PCR products on 2% agarose gels by electrophoresis. The sequences of the sense and antisense primers were 5'-CTG-GAGGACACTCCTCCCCATCTTCT-3' and 5'-GATGTTGCCCATCACATTTCGTCAGA-3', respectively. The I allele is detected as a 490-base pair band, and the D allele is visualized as a 190-base pair band. The PCR products were visualized independently by 2 laboratory technicians who were blinded to activity and mobility status, and genotypes that were not scored identically by both technicians (<2%) were reanalyzed until agreement was reached.

Health habits, knee and foot pain for more than 30 days in the past year, and demographic information were collected by interview at baseline. Prevalent cardiovascular disease was based on self-report of endarterectomy, coronary artery bypass graft surgery, or myocardial infarction. Prevalent diabetes was based on either a self-report of diabetes or a fasting blood glucose greater than or equal to 126 mg/dL (7.0 mmol/L). Prevalent hypertension was defined by either self-reported hypertension in combination with antihypertensive medication use or by elevated blood pressure readings at the clinic visit (at least 90 mm Hg diastolic or 140 mm Hg systolic). Spirometry was performed according to American Thoracic Society guidelines. Participants with forced expiratory volume in 1 second less than 85% of expected or who reported a physi-
cian diagnosis of lung disease were classified as having reduced pulmonary function. Participants were asked to bring all prescription and over-the-counter medications and preparations used in the previous 2 weeks to the baseline clinic visit.

Height was measured using a wall-mounted stadiometer. Participants were weighed without shoes and in light clothing using a calibrated balance-beam scale. Body mass index was calculated as weight in kilograms divided by the square of height in meters. The cross-sectional areas of muscle and subcutaneous and intermuscular fat in both thighs was measured by computed tomography (at the Memphis site: Somatom Plus 4; Siemens, Erlangen, Germany, or PQ 2000S, Marconi Medical Systems; Cleveland, Ohio, and at the Pittsburgh site: 9800 Advantage; General Electric, Milwaukee, Wis) as described previously. Total body fat mass was assessed using fan beam dual-energy x-ray absorptiometry (QDR4500A, Hologic; Waltham, Mass; software version 8.21). The maximal and mean isokinetic strength of the knee extensors (Newton meters) was assessed by a Kin-Com 125 AP Dynamometer (Chattanooga, Tenn) at 60° per second.

We used the Pearson χ² test to determine whether the ACE (I/D) genotype distributions were consistent with expected proportions assuming Hardy-Weinberg equilibrium. The association between genotype and baseline characteristics was assessed using either χ² analysis (categorical outcomes) or analysis of variance (continuous outcomes). We used Cox proportional hazards regression models to estimate the relative hazard of mobility limitation based on ACE (I/D) genotype. The genotype-activity interaction was assessed by fitting terms for genotype modeled as the number of D alleles, total physical activity (yes, no), and the interaction between the two. In subsequent analyses, we combined the ID and DD genotypes because they did not differ significantly in their associations. Event times were defined as the number of days between the baseline clinic examination and the date of the first of 2 consecutive reports of mobility difficulty. Those not experiencing the end point were censored at the end of follow-up (4.1 years), death, or last contact. The proportional hazards assumption was assessed both by fitting interactions with time and by examining log (−log) survival plots. Once statistical evidence for a gene–physical activity interaction was found, we proceeded with analyses within strata of physical activity. We examined body composition and strength differences by genotype and physical activity level for evidence relating to which pathway(s) may be involved rather than adjusting for the multivariate models because these characteristics could be involved in the causal pathway. Overall, adjusted least square means were derived from a general linear model adjusting for age, site, race, sex, and a race-sex interaction. The proportional hazards assumption was consistent with Cox regression (categorical outcomes) and log rank (continuous outcomes). Analyses were conducted by S.B.K and E.M.L. using SAS version 8.2 (SAS Institute Inc, Cary, NC). Associations were considered to be statistically significant if the nominal P value was less than .05.

RESULTS
Overall, 33.6% of the Health ABC population were homozygous for the D allele, 19.2% were homozygous for the I allele, and 47.2% were heterozygous. The genotype distributions were consistent with Hardy-Weinberg proportions in blacks (DD, 428 [35.0%]; ID, 583 [47.6%]; II, 213 [17.4%]; P =.78), but not in whites (P =.04), due to fewer than expected heterozygotes at the Memphis site (DD, 290 [32.2%]; ID, 404 [44.9%]; II, 206 [22.9%]; P =.005). The genotype distribution among Pittsburgh whites was consistent with expected Hardy-Weinberg proportions (DD, 280 [33.2%]; ID, 412 [48.9%]; II, 150 [17.8%]; P = .29). Based on this observation, analyses were repeated excluding white participants from Memphis.

TABLE I presents baseline characteristics by genotype. No significant differences in the genotype frequencies were detected by sex, site, or race. The distribution of prevalent disease did not differ across genotype except for cardiovascular disease, which was more common than expected in the ACE (I/D) heterozygotes. The prevalence of ACE inhibitor use also did not differ across genotypes. Slightly less than a third (31.3%) of participants expended more than 1000 kcal/wk in any exercise activity (physically active), 8.7% expended more than 400 kcal/wk in high-intensity activities, and 7.6% reported weight lifting. Exercise frequency did not differ significantly by genotype.

During the 4.1 years of follow-up, 40.6% of Health ABC participants developed mobility limitation. Overall, the ACE (I/D) genotype was not associated with incident limitation (P =.40), with 39.9% of those with the DD, 40.0% of those with the ID, and 43.1% of those with the II genotypes developing mobility limitation. In contrast, total physical activity was strongly associated with a lower incidence of limitation: 27.9% of participants reporting expending more than 1000 kcal/wk of energy in walking, stair climbing, or other exercise developed limitation compared with 46.3% of less active participants. After adjusting for demographic characteristics, health habits, and prevalent health conditions at baseline, physically active participants experienced a 33% lower rate of incident limitation (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.57-0.76; P <.001).

The FIGURE shows the Kaplan-Meier survival plot of the onset of persistent mobility limitation by ACE (I/D) genotype and physical activity level. The ACE (I/D) genotype was not associated with the incidence of limitation among nonphysically active participants, but in those with high total physical activity, risk was graded by genotype, with the DD genotype having the lowest risk of limitation and the II genotype having the highest risk. Regardless of genotype, the physically active participants were at lower risk of mobility limitation than nonactive participants. Using proportional hazards modeling, the interaction between
ACE INSERTION/DELETION GENOTYPE AND MOBILITY

Genotype and physical activity status was statistically significant in both an unadjusted model (P = .002) and a model adjusting for age, sex, race, site, education, smoking status, alcohol use, knee pain, foot pain, diabetes, cardiovascular disease, reduced pulmonary function, and hypertension (P = .009). Although the Figure suggests a graded association between the number of D alleles and the outcome, the ID and DD genotypes were not statistically significantly different, and the genotypes had similar associations in adjusted models. Therefore, the ID and DD genotypes were combined.

Table 2 shows the rates of mobility limitation by alternative classifications of exercise. The rate of mobility limitation was not associated with genotype among those with lower total physical activity levels. In contrast, among participants with high levels of total physical activity, those having the II genotype developed limitation at a 45% higher rate (adjusted HR, 1.45; 95% CI, 1.08-1.94; P = .01) than those having the ID or DD genotype. Among individuals reporting an expenditure of more than 400 kcal/week of high-intensity exercise, those with the II genotype had an 87% higher incidence rate (unadjusted HR, 1.87; 95% CI 1.08-3.22). This difference was not statistically significant after adjusting for covariates although the precision of the finding is limited by the small number of older adults exercising at this level. The 7.6% of participants who reported that they weight lifted had an even stronger association by genotype (adjusted HR, 2.34; 95% CI 1.28-4.29; P = .006).

Among those with high levels of total physical activity, the association (II vs ID/DD genotypes) was similar between blacks and whites (adjusted HR, 1.56; 95% CI, 0.92-2.64 vs adjusted HR, 1.44; 95% CI, 1.00-2.06, respectively) and between men and women (adjusted HR, 1.58; 95% CI, 1.09-2.09, and adjusted HR, 1.33; 95% CI, 0.81-2.19, respectively). The association changed little after excluding those reporting ACE inhibitor use at baseline (adjusted HR, 1.41; 95% CI, 1.03-1.94). The association was also seen after excluding Memphis whites (adjusted HR, 1.67; 95% CI, 1.18-2.37).

To explore the physiological basis underlying the difference in the benefit of exercise between genotype groups, we determined whether body composition and muscle strength differed by genotype when stratified by total physical activity level (Table 3). Among the physically active participants, those with the II genotype had a slightly higher percentage of body fat (relative difference, 3%; P = .02) and more intermuscular thigh fat (relative difference, 12.5%; P = .02) than those with the ID/DD genotypes. Percent body fat was similar for those with ID (33.4%) and DD (33.5%). There was weak evidence for an association between the number of D alleles and levels of intermuscular thigh fat (DD, 9.50 cm²; ID, 10.24 cm²; II, 11.15 cm²). Those with the II genotype tended to have higher results on other adiposity measures, but these differences were not significant. Knee strength did not differ by geno-

Table 1. Baseline Characteristics by Angiotensin-Converting Enzyme Insertion/Deletion Genotypea

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACE Genotype</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DD (n = 998)</td>
<td>ID (n = 1399)</td>
</tr>
<tr>
<td>Demographics, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>526 (52.7)</td>
<td>696 (49.8)</td>
</tr>
<tr>
<td>Black</td>
<td>428 (42.9)</td>
<td>583 (41.7)</td>
</tr>
<tr>
<td>Residing in Memphis</td>
<td>497 (49.8)</td>
<td>722 (51.6)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>73.5 (2.8)</td>
<td>73.7 (2.9)</td>
</tr>
<tr>
<td>Cigarette smoking, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>103 (10.4)</td>
<td>141 (10.1)</td>
</tr>
<tr>
<td>Former</td>
<td>442 (44.4)</td>
<td>657 (47.0)</td>
</tr>
<tr>
<td>Never</td>
<td>450 (45.2)</td>
<td>599 (42.9)</td>
</tr>
<tr>
<td>Educational attainment, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;High school</td>
<td>254 (25.5)</td>
<td>353 (25.3)</td>
</tr>
<tr>
<td>High school</td>
<td>324 (32.5)</td>
<td>462 (33.1)</td>
</tr>
<tr>
<td>&gt;High school</td>
<td>419 (42.0)</td>
<td>579 (41.5)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.5 (4.9)</td>
<td>27.4 (4.7)</td>
</tr>
<tr>
<td>Health risks, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>182 (18.3)</td>
<td>269 (19.3)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>183 (18.8)</td>
<td>312 (22.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>607 (60.8)</td>
<td>857 (61.3)</td>
</tr>
<tr>
<td>Reduced pulmonary function</td>
<td>302 (30.3)</td>
<td>436 (31.2)</td>
</tr>
<tr>
<td>Knee pain</td>
<td>159 (15.9)</td>
<td>229 (16.4)</td>
</tr>
<tr>
<td>Foot pain</td>
<td>159 (15.9)</td>
<td>224 (16.0)</td>
</tr>
<tr>
<td>ACE inhibitor use</td>
<td>157 (15.8)</td>
<td>202 (14.5)</td>
</tr>
<tr>
<td>Physical activity, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High total physical activity†</td>
<td>323 (32.4)</td>
<td>425 (30.4)</td>
</tr>
<tr>
<td>High-intensity physical activity‡</td>
<td>96 (9.6)</td>
<td>122 (8.7)</td>
</tr>
<tr>
<td>Weight lifting in the previous week</td>
<td>76 (7.6)</td>
<td>110 (7.9)</td>
</tr>
<tr>
<td>Estimated energy expenditure in exercise, mean (SD), kcal/wk</td>
<td>488 (1204)</td>
<td>489 (1208)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index, which is calculated as weight in kilograms divided by the square of height in meters; D, deletion; I, insertion.

*Percentages may not sum to 100 due to rounding. Data were missing for the following variables: smoking status (n = 5), alcohol use (n = 11), educational attainment (n = 6), diabetes (n = 10), cardiovascular disease (n = 68), and ACE inhibitor use (n = 7).
†Weekly energy expenditure at least 1000 kcal during walking, stair climbing, and other exercise.
‡Weekly energy expenditure higher than 400 kcal during high-intensity exercise activities.

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type. Among the physically inactive participants neither knee extensor strength nor body composition differed significantly by genotype. Possibly due to small sample sizes, no significant differences were noted within the weight lifting or high-intensity exercising subgroups.

To assess the extent to which percentage of body fat and intermuscular thigh fat might affect the relationship between genotype and mobility limitation among the physically active participants, the adjusted models presented in Table 2 were refit adding terms for percent body fat and thigh intermuscular fat area. The rate ratio associated with the $\text{II}$ genotype decreased from 1.45 (95% CI, 1.08-1.94) to 1.20 (95% CI, 0.87-1.64). Among weight lifters, adjusting for both fat measures only minimally changed the genotype-mobility association (HR, 2.38; 95% CI, 1.19-4.79).

**COMMENT**

In this cohort of older well-functioning men and women, a high level of physical activity was associated with the preservation of physical function. Although physical activity was associated with less mobility limitation for all ACE $\text{I}^{\text{D}}$ genotypes, the improved risk benefit was significantly greater for those possessing the $\text{ID}$ or $\text{DD}$ genotypes compared with the $\text{II}$ genotype. The physiological basis for these findings is uncertain. However, among the physically active participants, the $\text{II}$ genotype was also associated with higher levels of total adiposity and intermuscular thigh fat.

Several correlates of physical function such as strength and speed of transfer and gait have been shown to be heri-

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**Figure.** Kaplan-Meier Curves of Mobility Limitation by Angiotensin-Converting Enzyme Genotype

[Graph showing Kaplan-Meier curves for mobility limitation by genotypes.]

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**Table 2. Rates of Incident Persistent Mobility Limitation by Angiotensin-Converting Enzyme Insertion/Deletion Genotype and Activity Category**

<table>
<thead>
<tr>
<th>Exercise Level and Genotype</th>
<th>No. of Participants</th>
<th>Incident Cases</th>
<th>Person-Years</th>
<th>Incidence Rate*</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>Unadjusted</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly energy expenditure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;1000$ kcal/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{DD/ID}$</td>
<td>1649</td>
<td>763</td>
<td>4675.7</td>
<td>16.3</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>$\text{II}$</td>
<td>395</td>
<td>183</td>
<td>1124.8</td>
<td>16.3</td>
<td>1.00 (0.85-1.17)</td>
<td>1.02</td>
<td>1.02 (0.87-1.21)</td>
</tr>
<tr>
<td>$\geq1000$ kcal/wk</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{DD/ID}$</td>
<td>748</td>
<td>195</td>
<td>2559.4</td>
<td>7.6</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>$\text{II}$</td>
<td>174</td>
<td>62</td>
<td>554.1</td>
<td>11.2</td>
<td>1.46 (1.10-1.94)</td>
<td>1.45</td>
<td>1.08-1.94</td>
</tr>
<tr>
<td>High-intensity exercise, $&gt;400$ kcal/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{DD/ID}$</td>
<td>218</td>
<td>54</td>
<td>750.0</td>
<td>7.2</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>$\text{II}$</td>
<td>41</td>
<td>17</td>
<td>123.9</td>
<td>13.7</td>
<td>1.87 (1.08-3.22)</td>
<td>1.50</td>
<td>0.77-2.92</td>
</tr>
<tr>
<td>Any weight lifting in the past week</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{DD/ID}$</td>
<td>186</td>
<td>44</td>
<td>634.3</td>
<td>6.9</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>$\text{II}$</td>
<td>38</td>
<td>17</td>
<td>114.1</td>
<td>14.9</td>
<td>2.11 (1.20-3.69)</td>
<td>2.34</td>
<td>1.28-4.29</td>
</tr>
</tbody>
</table>

Abbreviations: D, deletion; I, insertion.

*Per 100 person-years.
†Adjusted for age, race, sex, site, education, smoking status, alcohol use, knee pain, foot pain, diabetes, cardiovascular disease, reduced pulmonary function, and hypertension.
Table 3. Adjusted Mean Differences in Adiposity, Fat Distribution, and Leg Strength Between Participants With the II and ID/DD Angiotensin-Converting Genotypes by Level of Physical Activity

<table>
<thead>
<tr>
<th>Angiotensin-Converting Enzyme Genotype</th>
<th>Physically Active</th>
<th>Not Physically Active</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td></td>
<td>II (n = 174)</td>
<td>ID/DD (n = 748)</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>27.85 (0.35)</td>
<td>27.24 (0.17)</td>
</tr>
<tr>
<td></td>
<td>27.30 (0.23)</td>
<td>27.49 (0.11)</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>34.56 (0.42)</td>
<td>33.49 (0.21)</td>
</tr>
<tr>
<td></td>
<td>33.95 (0.28)</td>
<td>34.06 (0.14)</td>
</tr>
<tr>
<td>Thigh area measurements, cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area</td>
<td>217.61 (3.80)</td>
<td>211.83 (1.36)</td>
</tr>
<tr>
<td></td>
<td>210.04 (2.51)</td>
<td>210.88 (1.24)</td>
</tr>
<tr>
<td>Muscle</td>
<td>113.22 (1.38)</td>
<td>113.60 (0.68)</td>
</tr>
<tr>
<td></td>
<td>110.07 (0.91)</td>
<td>110.49 (0.45)</td>
</tr>
<tr>
<td>Subcutaneous fat</td>
<td>81.49 (2.75)</td>
<td>77.02 (1.36)</td>
</tr>
<tr>
<td></td>
<td>78.40 (1.82)</td>
<td>78.45 (0.90)</td>
</tr>
<tr>
<td>Intermuscular fat</td>
<td>11.15 (0.48)</td>
<td>9.91 (0.24)</td>
</tr>
<tr>
<td></td>
<td>10.51 (0.32)</td>
<td>10.43 (0.16)</td>
</tr>
<tr>
<td>Maximum knee extensor strength, Newton meter</td>
<td>108.02 (2.26)</td>
<td>109.61 (1.12)</td>
</tr>
<tr>
<td></td>
<td>102.79 (1.53)</td>
<td>104.65 (0.76)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; D, deletion I, insertion.
*Adjusted for age, race, sex, race-sex interaction and site.
†Body mass index is calculated as weight in kilograms divided by the square of height in meters.

Table, but evidence for the genetic influences on disability status is less clear. The ACE gene is an attractive candidate because data from younger populations indicate that the ID genotype can modulate the response to exercise training. ACE is a dipeptidyl carboxypeptidase that is both found in the circulation and as a membrane-bound protein on the surfaces of a wide variety of cell types in the body including skeletal muscle. Among its recognized functions are the conversion of angiotensin I to angiotensin II (fast twitch) muscle fibers. The D allele is associated with higher levels of ACE activity and, thus, greater conversion of angiotensin I to angiotensin II and the inactivation of bradykinin. The D allele is associated with higher levels of ACE activity and, thus, greater conversion of angiotensin I to angiotensin II and the inactivation of bradykinin. The D allele is associated with higher levels of ACE activity and, thus, greater conversion of angiotensin I to angiotensin II and the inactivation of bradykinin. The D allele is associated with higher levels of ACE activity and, thus, greater conversion of angiotensin I to angiotensin II and the inactivation of bradykinin. The D allele is associated with higher levels of ACE activity and, thus, greater conversion of angiotensin I to angiotensin II and the inactivation of bradykinin.

Frederiksen and colleagues examined the relationship between ACE (I/D) genotype and the maintenance of physical function over 2 years in a study of 547 older Danish twins. While those of the II and ID genotypes experienced slightly greater decline in self-reported physical function compared with those of the DD genotype, the difference was not statistically significant. However, the authors did not consider the possibility of an interaction between genotype and physical activity. In a post hoc analysis, the same group examined whether the ACE I/D genotype interacted with exercise across 4 trials of exercise interventions in older adults. The training effect did not differ by genotype. However, the sample size was modest and the exercise interventions included a combination of aerobic and strength components, which may have interacted differently with the ACE genotype.

Among those with high levels of total physical activity, ACE genotype was associated with differences in total adiposity and in intermuscular thigh fat cross-sectional area. Data from several studies show that adiposity is an independent predictor of both poor physical performance and poor physical function. Moreover, in the Health ABC Study, we have shown that intermuscular thigh fat is an independent predictor of both muscle weakness and poorer lower extremity physical performance independent of total adiposity and muscle area. Adding the fat measures to a multivariate model of the rate of limitation diminished the genotype effect among the physically active participants, consistent with a possible mediating role. The II genotype has been associated with elite performance in endurance events. Endurance trained athletes have markedly elevated levels of intramyocellular lipid and use this lipid as an energy substrate. It has not been determined whether the ACE I/D genotype is associated with the storage or utilization of intramyocellular lipid. However, while the propensity to store fat in muscle may be an advantage in elite endurance athletes, it is possible that in old age the accumulation of muscular fat is associated with insulin resistance and impaired muscle function. The association of the II genotype with increased adiposity among the physically active participants apparently contrasts with results from the Olivetti Prospective Heart Study showing that men with the DD genotype have a greater increase in body mass index over time compared with those of the II or ID genotypes.

This population was much younger than the Health ABC population and exercise was not considered, so it is difficult to know whether these findings conflict.

Since the II genotype is associated with lower ACE activity, one might predict...
that use of ACE inhibitors would mimic the observations seen herein. On the contrary, ACE inhibitor use has been associated with both increased lower extremity lean mass and better maintenance of walking speed compared with those using other antihypertensive drugs.35,36 and Carter et al.37 showed in a rat model of age-related disability that ACE inhibitor administration was associated with better maintenance of function and reduced fat accumulation. Kohlstedt et al.38 have shown that the endothelial cell-bound ACE functions as an "outside-in" signaling molecule. The signaling function is not activated by angiotensin I but is activated by both bradykinin and dynkinin is released by eccentric exercise and at least 1 signaling pathway is based on a large, biracial, well-functioning cohort, in which the richness of the measures available and the complete follow-up allows us to assess the role of many potential confounders and intermediary physiological pathways.

In summary, in the Health ABC cohort, more physical activity was associated with maintaining mobility function. Older adults possessing the ID or DD genotypes who exercised achieved more benefit in preserving mobility function than did those with the II genotype. However, the magnitude of the effect is not so strong as to imply that those possessing the II genotype do not benefit from exercise. Further study is required to confirm these associations and understand their physiologic basis.

### Author Contributions:
Dr. Kritchevsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kritchevsky, Pahor. Acquisition of data: Kritchevsky, Nicklas, Simonsick, Newman, Harel, Satterfield, Rubin, Pahor. Analysis and interpretation of data: Kritchevsky, Nicklas, Visser, Simonsick, Lange, Penninx, Goodpaster, Satterfield, Colbert, Pahor. Drafting of the manuscript: Kritchevsky, Nicklas, Pahor. Critical revision of the manuscript for important intellectual content: Kritchevsky, Nicklas, Visser, Simonsick, Newman, Harris, Lange, Penninx, Goodpaster, Satterfield, Colbert, Rubin. Statistical analysis: Kritchevsky, Lange. Obtained funding: Kritchevsky, Simonsick, Newman, Harris, Pahor. Administrative, technical, or material support: Visser, Simonsick, Newman, Harris, Goodpaster, Satterfield, Colbert, Rubin. Study supervision: Rubin, Pahor.

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### REFERENCES

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