

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

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**F**UNCTIONAL LIMITATION IS AN intermediate state on a trajectory from health to physical disability.<sup>1</sup> Mobility limitation (ie, difficulty walking and climbing steps) is of particular interest because it is common, is strongly related to major health outcomes, and may represent a stage in the disablement process amenable to intervention. Approximately 34% of the US population 70 years and older report walking limitations, ie, difficulty walking a quarter mile (0.4 km). Those reporting such difficulty are at nearly 4 times the risk of nursing home placement and 3 times the risk of death over 2 years compared with those reporting no difficulty.<sup>2</sup>

In older adults, a strong inverse association between physical activity and functional decline has been observed consistently.<sup>3-8</sup> The benefit of activity

**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  $\geq 1000$  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 ( $P=.002$ ). In the inactive group, the ACE genotype was not associated with limitation ( $P=.46$ ). In the active group, those with the *II* 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 ( $P=.02$ ) and more intermuscular thigh fat ( $P=.02$ ) 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.

JAMA. 2005;294:691-698

www.jama.com

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is partly mediated through the maintenance of strength and physical endurance,<sup>9</sup> and trials of both strength and aerobic interventions have shown benefit in improving function in older adults.<sup>9-13</sup> Despite exercise's general benefit, individual responses to exercise vary.<sup>14</sup> The basis for this is unclear, but there appears to be a strong genetic component.<sup>15-17</sup> 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.<sup>18</sup> In the field of hypertension the *D* allele is associated with significantly higher serum *ACE* levels.<sup>19</sup> 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.<sup>20-25</sup>

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.<sup>26</sup>

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).<sup>18</sup> 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<sup>27,28</sup>; 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-GAGACCACTCCCATCCTTTCT-3' AND 5'-GATGTGGCCATCACATTC-GTCAGA-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 re-analyzed 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).<sup>29</sup> 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).<sup>30</sup> Spirometry was performed according to American Thoracic Society guidelines.<sup>31</sup> 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.<sup>32</sup> 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 (Chatanooga, Tenn) at 60° per second.

We used the Pearson  $\chi^2$  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  $\chi^2$  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.<sup>25,33</sup> Adjusted least square means were derived from a general linear model adjusting for age, site, race, sex, and a race-sex interaction. 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 1 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

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 mod-

els. 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 cm<sup>2</sup>; *ID*, 10.24 cm<sup>2</sup>; *II*, 11.15 cm<sup>2</sup>). 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 Genotype\*

Characteristic	ACE Genotype			P Value
	<i>DD</i> (n = 998)	<i>ID</i> (n = 1399)	<i>II</i> (n = 569)	
Demographics, No. (%)				
Women	526 (52.7)	696 (49.8)	305 (53.6)	.19
Black	428 (42.9)	583 (41.7)	213 (37.4)	.10
Residing in Memphis	497 (49.8)	722 (51.6)	273 (48.0)	.32
Age, mean (SD), y	73.5 (2.8)	73.7 (2.9)	73.6 (2.8)	.35
Cigarette smoking, No. (%)				
Current	103 (10.4)	141 (10.1)	62 (10.9)	.74
Former	442 (44.4)	657 (47.0)	263 (46.2)	
Never	450 (45.2)	599 (42.9)	244 (42.9)	
Alcohol use, No. (%)				
Nondrinkers	495 (49.8)	705 (50.5)	283 (49.9)	.51
0-1 Drink/d	433 (43.6)	585 (41.9)	238 (42.0)	
>1 Drink/d	65 (6.6)	106 (7.6)	46 (8.1)	
Educational attainment, No. (%)				
<High school	254 (25.5)	353 (25.3)	130 (22.8)	.73
High school	324 (32.5)	462 (33.1)	187 (32.9)	
>High school	419 (42.0)	579 (41.5)	252 (44.3)	
BMI, mean (SD)	27.5 (4.9)	27.4 (4.7)	27.4 (4.9)	.78
Health risks, No. (%)				
Diabetes	182 (18.3)	269 (19.3)	106 (18.8)	.81
Cardiovascular disease	183 (18.8)	312 (22.8)	108 (19.5)	.04
Hypertension	607 (60.8)	857 (61.3)	342 (60.1)	.89
Reduced pulmonary function	302 (30.3)	436 (31.2)	173 (30.4)	.88
Knee pain	159 (15.9)	229 (16.4)	92 (16.2)	.96
Foot pain	159 (15.9)	224 (16.0)	103 (18.1)	.47
ACE inhibitor use	157 (15.8)	202 (14.5)	89 (15.7)	.63
Physical activity, No. (%)				
High total physical activity†	323 (32.4)	425 (30.4)	174 (30.6)	.56
High-intensity physical activity‡	96 (9.6)	122 (8.7)	41 (7.2)	.27
Weight lifting in the previous week	76 (7.6)	110 (7.9)	38 (6.7)	.67
Estimated energy expenditure in exercise, mean (SD), kcal/wk	488 (1204)	489 (1208)	455 (1469)	.85

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 = 69), 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.

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 *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

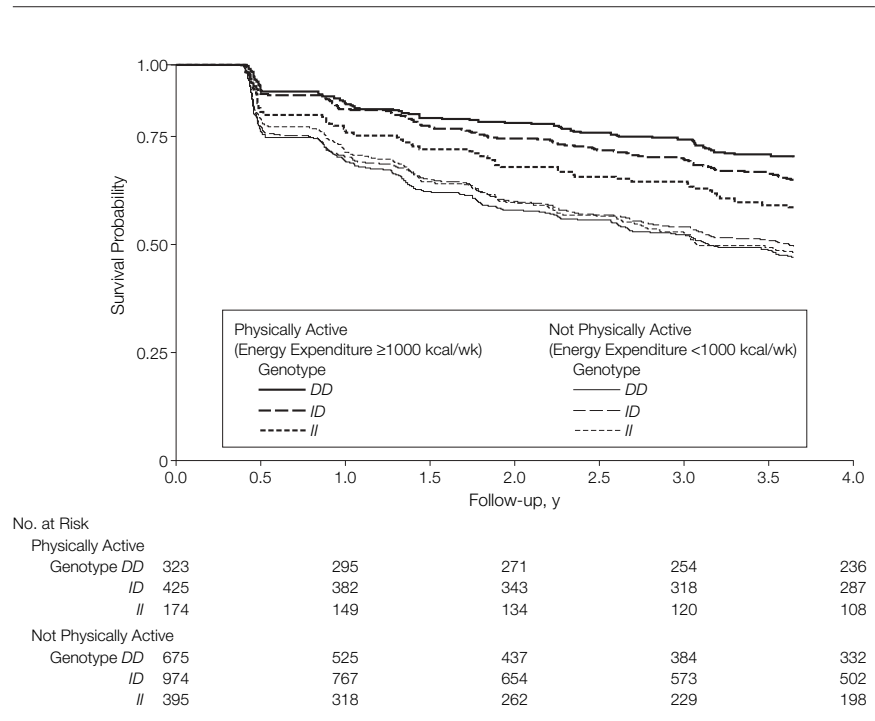
In this cohort of older well-functioning men and women, a high level of physical activity was associated with the preservation of physical function. Although physical activity was associated with less mobility limitation for all ACE *I/D* genotypes, the improved risk benefit was significantly greater for those possessing the *ID* or *DD* geno-

types compared with the *II* genotype. The physiological basis for these findings is uncertain. However, among the physically active participants, the *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-

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



The probability of remaining free from persistent mobility limitation by angiotensin-converting enzyme (insertion [*I*]/deletion [*D*]) genotype and high total physical activity level (< vs ≥1000 kcal/wk expended in exercise).  $P=.002$  when comparing genotype × activity interaction,  $P=.002$  when comparing genotype among physically active individuals, and  $P=.46$  when comparing genotype among nonphysically active individuals.

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

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

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

	Angiotensin-Converting Enzyme Genotype					
	Physically Active			Not Physically Active		
	Mean (SE)		<i>II-ID/DD</i> Difference (95% CI)*	Mean (SE)		<i>II-ID/DD</i> Difference (95% CI)*
	<i>II</i> (n = 174)	<i>ID/DD</i> (n = 748)		<i>II</i> (n = 395)	<i>ID/DD</i> Mean (SE) (n = 1649)	
Body mass index†	27.85 (0.35)	27.24 (0.17)	0.61 (−0.15 to 1.37)	27.30 (0.23)	27.49 (0.11)	−0.19 (−0.70 to 0.31)
Percent body fat	34.56 (0.42)	33.49 (0.21)	1.07 (0.16 to 1.98)	33.95 (0.28)	34.06 (0.14)	−0.11 (−0.71 to 0.50)
High area measurements, cm <sup>2</sup>						
Area	217.61 (3.80)	211.83 (1.88)	5.78 (−2.46 to 14.01)	210.04 (2.51)	210.88 (1.24)	−0.84 (−6.31 to 4.62)
Muscle	113.22 (1.38)	113.60 (0.68)	−0.38 (−3.36 to 2.61)	110.07 (0.91)	110.49 (0.45)	−0.42 (−2.40 to 1.56)
Subcutaneous fat	81.49 (2.75)	77.02 (1.36)	4.47 (−1.49 to 10.42)	78.40 (1.82)	78.45 (0.90)	−0.05 (−4.00 to 3.91)
Intermuscular fat	11.15 (0.48)	9.91 (0.24)	1.24 (0.19 to 2.28)	10.51 (0.32)	10.43 (0.16)	0.08 (−0.62 to 0.77)
Maximum knee extensor strength, Newton meter	108.02 (2.26)	109.61 (1.12)	−1.59 (−6.49 to 3.31)	102.79 (1.53)	104.65 (0.76)	−1.86 (−5.19 to 1.47)

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.<sup>34</sup> The *ACE* gene is an attractive candidate because data from younger populations indicate that the *I/D* genotype can modulate the response to exercise training.<sup>24,25</sup> *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.<sup>35,36</sup> Among its recognized functions are the 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.<sup>37</sup> Angiotensin II augments overload-induced hypertrophy of skeletal muscle.<sup>38</sup> The *D* allele is also associated with a higher proportion of type II (fast twitch) muscle fibers.<sup>39</sup> The percentage of type II fibers, which declines with age, is important to the generation of muscle power.<sup>40</sup> In older adults, findings suggest that muscle power is a pivotal predictor of physical function.<sup>41,42</sup> Muscle power was not assessed in Health ABC, but we did not observe a difference in quadriceps strength across genotypes.

Frederiksen and colleagues<sup>43</sup> 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.<sup>44</sup> 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.<sup>45-47</sup> 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.<sup>32,48</sup> 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.<sup>23,49</sup> Endurance trained athletes have markedly elevated levels of intramyocellular lipid and use this lipid as an energy substrate.<sup>50</sup> 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.<sup>32,51,52</sup> The association of the *II* genotype with increased adiposity among the physically active participants apparently contrasts with results from the Olivetti Prospective Heart Study<sup>33</sup> 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,<sup>53,54</sup> and Carter et al.<sup>55</sup> 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.<sup>56</sup> 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 ACE inhibitors, and the activation of this pathway increases ACE synthesis. Bradykinin is released by eccentric exercise and by high-intensity muscular contraction, and at least I signaling pathway activated by ACE in the endothelial cell is also activated in skeletal muscle in response to eccentric exercise.<sup>57-59</sup> Whether the *D* allele leads to stronger postexercise intracellular signaling consistent with the chronic activation of the pathways caused by ACE inhibition use will require future research.

The current study has several limitations and strengths. Self-report is an imprecise method for quantifying physical activity, due both to the nature of recall itself and normal variation in activity levels over time. Nevertheless, these errors are not likely to be related to genotype and so would be expected to lead to conservative effect estimates. The genotype was not in Hardy-Weinberg equilibrium in one subgroup (Memphis whites). It is unlikely that this is the result of a genotyping problem because all genotyping was done at the same time with samples intermixed by site and race and without knowledge of participant's race or site. In any event, the association between genotype and limitation persists in the physically active after removing this subpopulation from the analysis. Although we report an interaction with the ACE *I/D* genotype, this variant is not part of a coding region of the ACE gene. So, although it is a strong correlate of

ACE activity in diverse populations, it is not thought to be a functional variant.<sup>19,60,61</sup> Thus, it is possible that there may be a genetic marker that is associated more strongly with mobility limitation. Similarly, we cannot exclude the possibility that some or all of the association is due to population stratification, which was not assessed in this study.<sup>62</sup> On the other hand, this study 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 physiological 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.

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**Administrative, technical, or material support:** Visser, Simonsick, Newman, Harris, Goodpaster, Satterfield, Rubin.

**Study supervision:** Rubin, Pahor.

**Financial Disclosures:** None reported.

**Funding/Support:** This work was supported by the following contracts and grants from the National Institute on Aging: NO1-AG-6-2101, NO1-AG-6-2103, and NO1-AG-6-2106; R01 AG-18702; Claude D. Pepper Older Americans Independence Center P30 AG-021332.

**Role of the Sponsor:** The National Institute on Aging designed the Health ABC study and supervised its conduct. It also participated in the collection and analysis of the data and approved the manuscript.

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