


Catechol-O-Methyltransferase Genotype, Frailty, and Gait Speed in a Biracial Cohort of Older Adults

Shannon Mance, MPH, BSN, RN,*  Andrea Rosso, MPH, PhD,* Joshua Bis, PhD,†
Stephanie Studenski, MD, MPH,‡ Nico Bohnen, MD, PhD,§ and Caterina Rosano, MD, MPH*

OBJECTIVE: To examine whether the association between dopamine-related genotype and gait speed differs according to frailty status or race.

DESIGN: Cross-sectional population-based study (Cardiovascular Health Study).

SETTING: Multicenter study, four U.S. sites.

PARTICIPANTS: Volunteer community-dwelling adults aged 65 years and older, without evidence of Parkinson's disease (N = 3,744; 71 years; 82% White; 39% male).

MEASUREMENTS: Gait speed (usual pace; m/s), physical frailty (Fried definition), and genetic polymorphism of catechol-O-methyltransferase (*COMT*; rs4680), an enzyme regulating tonic brain dopamine levels, were assessed. Interaction of *COMT* by frailty and by race predicting gait speed were tested, and, if significant, analyses were stratified. Multivariable regression models of *COMT* predicting gait speed were adjusted for demographics and locomotor risk factors. Sensitivity analyses were repeated, stratified by clinical cutoffs of gait speed (0.6 and 1.0 m/s) instead of frailty status.

RESULTS: The interaction of *COMT* by frailty and *COMT* by race were $P = .02$ and $P = .01$, respectively. Compared with Met/Met (higher dopaminergic signaling), the Val/Val group (lower dopaminergic signaling) walked marginally more slowly in the full cohort (0.87 vs 0.89 m/s; $P = .2$). Gait speed differences were significant for frail (n = 220; 0.55 vs 0.63 m/s; $P = .03$), but not for prefrail (n = 1,691; 0.81 vs 0.81 m/s; $P = .9$) or nonfrail (n = 1,833; 0.98 vs

0.97 m/s; $P = .7$); results were similar in fully adjusted models. Among frail, associations were similar for Whites and Blacks, with statistical significance for Whites only. Associations stratified by clinical cutoffs of gait speed were not significant.

CONCLUSION: The association of dopamine-related genotype with gait speed is stronger among adults with frailty compared with those without frailty. The potential effects of dopaminergic signaling on preserving physical function in biracial cohorts of frail adults should be further examined. *J Am Geriatr Soc* 69:357-364, 2021.

Keywords: frailty; genetics; dopamine; gait speed

INTRODUCTION

Slower gait is a common and disabling condition in older age, increasing falls' risk, reducing independence, and accelerating conversion to dementia and disability.¹ Although age-related changes in peripheral nervous and musculoskeletal systems are well-known contributors of gait slowing,² recent evidence suggests an important role for the central nervous system,³⁻⁶ and in particular for dopaminergic signaling.⁶⁻⁹

The Val(158)Met polymorphism of catechol-o-methyltransferase (*COMT*) regulates tonic release of dopamine in the prefrontal cortex with changes in phasic dopamine in subcortical regions.¹⁰ The Met/Met genotype yields the highest dopamine levels, followed by the heterozygous genotype Val/Met, with the lowest levels among Val/Val carriers. Given the importance of dopamine on control of gait functions, it would be expected that those with Met/Met genotype would have faster gait compared with those with the Val/Val genotype. In work done by us¹¹⁻¹⁴ and others,^{15,16} the association between the *COMT* genotype and gait speed in older adults without other neurological diseases is of variable strength, with some studies

From the *Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania; †Cardiovascular Health Research Unit, University of Washington, Seattle, Washington; ‡Geriatric Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; and the §Departments of Radiology & Neurology, University of Michigan School of Medicine & Ann Arbor VA, Ann Arbor, Michigan.

Address correspondence to Caterina Rosano, MD, MPH, 130 DeSoto St, 5139 Public Health, Pittsburgh, PA 15261. E-mail: rosanoc@edc.pitt.edu

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reporting positive associations for the heterozygous genotype, but not for Met/Met. This discrepancy suggests other factors influence the relationship between *COMT* genotype and gait speed, with some people being more vulnerable than others to the effects of *COMT* polymorphism on gait speed.

Frailty, a common condition of older age,¹⁷ could be one such factor. Frailty is considered a state of “decreased resistance to stressors and increased vulnerability to adverse outcomes.”^{18,19} Recent studies suggest a frailty-related heightened vulnerability to stressors acting on the central nervous system. For example, individuals with frailty appear more vulnerable to amyloid accumulation, with cognitive impairment manifesting for lower burden of neuropathology.²⁰ A role for frailty-related vulnerability has also been suggested for Parkinson’s disease and depression.^{21,22}

We propose the *COMT* polymorphism, specifically the Val/Val genotype predisposing to lower dopamine, may act as a risk factor for gait slowing, especially among those with frailty. Our primary hypothesis is that the association between *COMT* polymorphism and gait speed differs by frailty status, with associations stronger for those with frailty compared with those without frailty. Our secondary hypothesis is that race may also modify these associations, due to its relation to both frailty²⁴ and *COMT* genotype.²³ Given the high prevalence of frailty in older age, especially among Blacks,²⁴ and the serious clinical implications of slow gait, understanding the contributors of gait slowing among at-risk older adults is important.

METHODS

Participants and Sampling

The Cardiovascular Health Study (CHS) is a prospective population-based cohort study of adults older than 65 years, sampled randomly within age strata using Medicare eligibility lists from Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania.²⁵ After enrolling 5,201 participants in 1989 to 1990, an additional 687 Black participants were recruited using identical methods in 1992 to 1993.²⁶ Eligibility criteria included: being in the designated sampling frame or living in the same household as someone who was sampled; older than 65 years at the time of examination; noninstitutionalized; expected to remain in the area for the next 3 years; and able to give informed consent without a proxy.²⁵ Of the eligible persons contacted, 57% enrolled in the study.²⁷

Data Collection

Baseline characteristics obtained from telephone contact and in-person examinations²⁸ included a brief physical examination, cognitive function measures, electrocardiograms, respiratory measures, and blood samples.²⁵ Participants were followed up by annual clinic visits and semiannual telephone contacts through the year 1999.²⁵ For this analysis, baseline measurements were used. DNA was collected from blood samples from most participants, and thousands of single-nucleotide polymorphisms (SNPs) for candidate gene regions have been genotyped.

Analytic Sample

Of 5,888 CHS participants, 4,043 had complete data for *COMT* gene and walk time. From these participants, we excluded those with: missing data on frailty ($n = 291$) or on medications for Parkinson’s disease ($n = 5$); and participants having Parkinson’s disease at baseline ($n = 2$) or taking a Parkinson’s disease medication ($n = 1$). Selection criteria for data collection did not differ by race status. Figure 1 provides details.

Measurements

Blood samples were drawn from participants at their baseline examination. Genotyping was performed at the General Clinical Research Center’s Phenotyping/Genotyping Laboratory at Cedars-Sinai for participants who consented to genetic testing and had DNA available using the Illumina 370CNV BeadChip system (for European ancestry participants, in 2007) or the Illumina HumanOmni1-Quad_v1 BeadChip system (for Black participants, in 2010). All Black participants were genotyped; European ancestry participants were excluded from the genome-wide association study sample if they had coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke, or transient ischemic attack. Beyond laboratory genotyping failures, participants were excluded if they had a call rate of 95% or less or if their genotype was discordant with known sex or prior genotyping (to identify possible sample swaps). After quality control, genotyping was successful for 3,268 European ancestry and 823 African American participants. Genome-wide genotyping contributed SNPs of the *COMT* Val158Met (rs4680). The following exclusions were applied to identify a final set of 306,655 autosomal SNPs: call rate of less than 97%, Hardy-Weinberg Equilibrium $P < 10^{-5}$, more than two duplicate errors or mendelian inconsistencies (for reference Centre d’Etude du Polymorphisme (CEPH) trios), heterozygote frequency = 0, and SNP not found in HapMap. These SNPs served as the basis for imputation to the Haplotype Reference Consortium (r1.1 2016) panel, which was performed on the University of Michigan’s imputation server. The two primary races identified in the CHS cohort, White and Black, tend to have different frequencies of the *COMT* genotype²³; as such, interactions by race were tested and models were repeated stratified by race.

Participants were grouped as frail based on the Fried physical frailty phenotype¹⁸ if they had more than three of the following: dominant hand grip strength (lowest 20% at baseline), self-reported exhaustion, self-reported unintentional weight loss of 10 pounds or greater in 1 year, gait speed (slowest 20% at baseline), and physical activity (lowest quintile). Those with one to two signs were classified as intermediate frail, and those with none were classified as nonfrail.

Gait speed (m/s) was measured while walking a 15-foot course at a usual pace starting from standing still. Grip strength was measured three times on dominant and nondominant hands, and the average was computed. The Minnesota Leisure Time Activities and Paffenbarger questionnaires assessed physical activity (kcal).^{29,30} Exhaustion and unintentional weight change were by self-report.

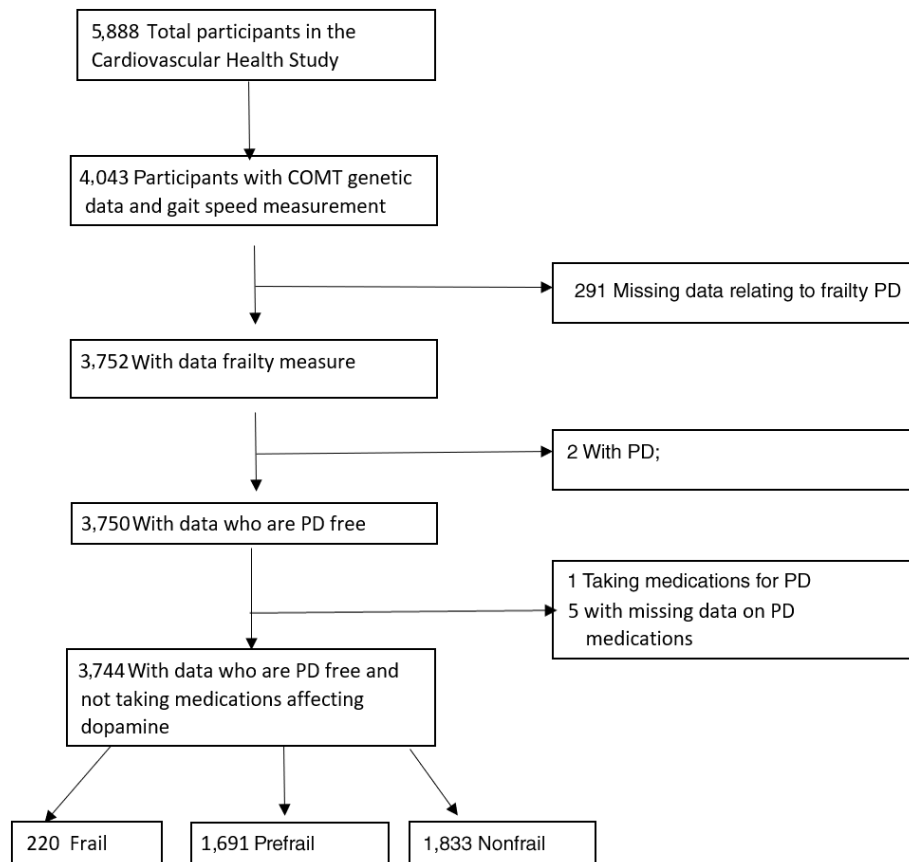


Figure 1. Flowchart illustrating the participants included in the analysis. COMT, catechol-O-methyltransferase; PD, Parkinson's disease.

In addition to age, sex, and race, other baseline variables were: education (converted from year reached in school to high school diploma, general equivalency diploma, or higher education vs not finishing high school); body mass index (BMI) (height and weight); ankle-arm index (supine blood pressures from the right arm and both ankles); depression (Center for Epidemiologic Studies Depression Scale)³¹; and cognitive function (Mini-Mental State Examination)³², with scores >27 classified as normal).³³ Presence of vision problems, diabetes mellitus, arthritis, chronic lung disease, and cerebrovascular and cardiovascular diseases were self-reported measures with adjudication by clinicians after consultation of medical history and medications.

Analysis

Mean and standard deviation or median and interquartile range were computed for continuous variables, depending on normality of the distribution. Differences in frailty status, gait speed, and population characteristics by *COMT* genotypes were tested using two-sample *t*-tests (or Mann-Whitney *U* tests in case of skewed distribution) and Pearson chi-square (or Fisher exact values for $N > 5$) as appropriate (Table 1). Similar approaches were used to compare population characteristics by frailty status (Supplementary Table S1). Each variable's correlation with gait speed was

computed for the full cohort and stratified by frailty status using Pearson for continuous variables and Spearman for categorical variables (Supplementary Table S2).

Multivariable linear regression analyses tested the association of *COMT* genotype (with Met/Met as the reference group) with gait speed, with interaction terms by race and frailty status in separate models. Models were adjusted for demographics first and then for variables that were bivariately associated with the *COMT* genotype at $P < .05$. Additional potential covariates were considered for adjustment if they were significantly associated with gait speed at $P < .05$. Associations of *COMT* with frailty were also tested in logistic regression models; odds ratios are reported for *COMT* predicting being frail versus prefrail, as well as predicting frail versus nonfrail, and prefrail versus nonfrail. Given the association between frailty and gait speed (slow gait is also one of the Fried criteria to classify frailty), it is possible that a variation of the association between *COMT* and gait speed by frailty status could be driven by differences in gait speed in each frail group; in other words, the association could be strongest among frail due to gait being slowest in this group, not because of frailty being a status that heightens vulnerability to stressors. To address this possibility, sensitivity analyses modeled *COMT* predicting gait speed in groups stratified by gait speed, using clinically meaningful cutoffs¹ of less than 0.6 m/s ($n = 384$), 0.6 to 1.0 m/s ($n = 2,565$), and greater than 1.0 m/s ($n = 838$).

Table 1. Baseline Characteristics Stratified by COMT Genotype

Variable	Val/Val (n = 1,053)	Val/Met (n = 1,818)	Met/Met (n = 873)	P values for Val/Val vs Val/Met	P values for Val/Met vs Met/Met	P values for Val/Val vs Met/Met
Frailty measures						
Frail (severe vs moderate or none), present	77 (7.3)	107 (5.9)	36 (4.1)	.13	.056	.003
Gait speed, mean (SD), m/s	0.87 (0.22)	0.88 (0.21)	0.89 (0.2)	.55	.10	.051 ^a
Grip strength, (mean (SD), kg	28.8 (10.9)	28.2 (10.2)	28.1 (9.9)	.21	.81	.20 ^a
Physical activity, median (IQR), total kcal	893.8 (1,702.5)	1,215 (1,950)	1,207 (2,155.5)	<.001	.38	<.001 ^b
Exhaustion, present	312 (29.6)	573 (31.5)	273 (31.3)	.29	.89	.44
Unintentional weight loss ≥10 lbs, present	111 (10.5)	210 (11.6)	80 (9.2)	.49	.09	.32
Demographics						
Age, median (IQR), y	71 (8)	71 (7)	71 (8)	.36	.82	.57 ^b
Sex, male	423 (40.2)	716 (39.4)	325 (37.2)	.68	.28	.19
Race, Black	326 (31)	278 (15.3)	81 (9.3)	<.001	<.001	<.001
Education ≥high school	740(70.3)	1,335 (73.4)	635 (72.7)	.08	.74	.24
Health-related factors						
BMI, mean (SD), kg/m ²	27 (4.7)	26.6 (4.7)	26.5 (4.7)	.02	.71	.02 ^a
Ankle-arm index, mean (SD), %	1.1 (0.2)	1.1 (0.2)	1.1 (0.1)	.40	.90	.53 ^a
Depression score (CES-D), median (IQR)	3 (5)	3 (5)	3 (5)	.52	.87	.69 ^b
Impaired vision, present	53 (5)	105 (6)	46 (5)	.41	.68	.75
Arthritis, present	517 (49)	905 (50)	442 (51)	.79	.61	.49
Diabetes mellitus, present	124 (12)	181 (10)	72 (8)	.13	.16	.01
Chronic lung disease, present	4 (0)	4 (0)	1 (0)	.19	.22	.09 ^c
Cerebrovascular disease, present	28 (3)	28 (2)	10 (1)	.04	.42	.02
Cardiovascular disease, present	156 (15)	177 (10)	86 (10)	<.001	.93	.001
Normal cognitive function, present	790 (75)	1,471(82)	705(81)	<.001	.78	0.003

Note: Data are given as number (percentage), unless otherwise specified. *P* values are from chi-square test, unless otherwise specified. Prevalence: rounded to nearest decimal point.

Normal cognitive function based on assessment with 30-point Mini-Mental State Examination (≥27).

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; COMT, catechol-O-methyltransferase; IQR, interquartile range; SD, standard deviation.

^aTwo-sample *t*-test.

^bMann-Whitney *U* test.

^cFisher exact test.

RESULTS

Genotype distributions were consistent with Hardy-Weinberg equilibrium in the full sample ($P = .10$) as well as in the Black ($P = .06$) and White ($P = .69$) participants' races. In the full cohort, 7% of those with Val/Val genotype (indicating lower dopamine) also had frailty (Table 1); gait speed differences between Val/Val and Met/Met were marginally significant (Table 1). Compared with Val/Met and Met/Met, Val/Val were more likely to be Black and to have lower physical activity, higher BMI, and a higher proportion having diabetes mellitus, cerebrovascular disease, cardiovascular disease, and abnormal cognitive functioning (all $P < .05$; Table 1). Differences in age, sex, or education were not statistically significant (Table 1).

As expected, the frail group had a worse profile on all variables examined, compared with the nonfrail or prefrail group (Supplementary Table S1). The unadjusted mean gait speed for the frail group was about 30% slower, compared with those in the prefrail or nonfrail group. In the total

cohort, the factors predicting slower gait were consistent with what we and others have previously shown: older age, female sex, lower education, lower grip strength, and generally worse health (Supplementary Table S2). Results were similar in the frail group, but less strong in the prefrail or nonfrail groups; all variables except weight loss, chronic lung disease, and cerebrovascular disease were significantly correlated with gait speed at $P < .05$ and in the expected direction (Supplementary Table S2).

In multivariable logistic regression models predicting frailty, the association between COMT and frailty became not significant after adjustment for demographics ($P > .23$).

In multivariable linear regression models of COMT predicting gait speed, the association of COMT with gait speed significantly differed by frailty status (interaction between COMT and frailty $P = .03$) and by race (interaction between COMT and race $P = .02$). The three-way interaction of COMT by frailty and by race was not significant ($P > .1$).

Table 2. Multivariable Linear Regression of Genotype Predicting Average Gait Speed (m/s), for the Full Cohort and Stratified by Frailty Status

Variable	All cohort (n = 3,744)		Frailty (n = 220)		Moderate frailty (n = 1,691)		No frailty (n = 1,833)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Val/Val	-.031 (-.03 to .006) <i>P</i> = .19	-.030 (-.03 to .007) <i>P</i> = .23	-.201 (-.13 to -.01) <i>P</i> = .03	-.198 (-.13 to -.01) <i>P</i> = .03	.001 (-.03 to .03) <i>P</i> = .99	-.002 (-.03 to .03) <i>P</i> = .94	.012 (-.02 to .03) <i>P</i> = .71	.013 (-.02 to .03) <i>P</i> = .68
Val/Met	-.027 (-.03 to .004) <i>P</i> = .14	-.028 (-.03 to .003) <i>P</i> = .23	-.079 (-.09 to .03) <i>P</i> = .31	-.068 (-.09 to .03) <i>P</i> = .35	.007 (-.21 to .03) <i>P</i> = .81	.004 (-.22 to .03) <i>P</i> = .88	-.035 (-.31 to .006) <i>P</i> = .18	-.037 (-.31 to .005) <i>P</i> = .16

Note: Data are given as standardized β coefficient (95% confidence interval); referent group = Met/Met. Model 1: adjusted for age, sex, education, and race. Model 2: further adjusted for variables bivariately associated with catechol-O-methyltransferase genotype: body mass index, diabetes mellitus, cerebrovascular diseases, cardiovascular diseases, and cognitive status. Bold text indicates statistically significant results ($P < .05$).

In models stratified by frailty status (Table 2), the association of COMT with gait speed was significant among those with frailty, but not for prefrail ($P > .81$) or nonfrail ($P > .2$). Among frail participants, Met homozygotes walked approximately 13% faster compared with those with Val homozygous status, with a between-group difference of about 0.10 m/s (Table 2). Results were similar after further adjustment for factors associated with gait speed, specifically depression and vision (Supplementary Table S2).

In models stratified by race (Table 3), gait speed differences between Val/Val and Met/Met were statistically significant in Whites but not in Blacks, albeit similar in size in both groups; standardized β values were between .05 and .06, corresponding to about 0.01 m/s or 1% difference between Val/Val and Met/Met. Among frail participants, gait speed differences between Val/Val and Met/Met were much larger than in the full group; these differences were statistically significant for White, but not for Black participants, albeit similar in size; standardized β values were between .17 and .24, corresponding to about 0.07 m/s or a 10% difference between Val/Val and Met/Met, for both White and Black participants. Mean differences in gait speed by frailty and by frailty and race are illustrated in Figure 2.

In sensitivity analyses stratified by clinical cutoffs of gait speed instead of frailty status, the associations of COMT with gait speed were not significant for any of the groups (data not shown).

DISCUSSION

In this study of community-dwelling older adults, frailty status and race modified the associations of COMT polymorphism, an indicator for dopaminergic signaling, with gait speed. Associations were significant among adults with frailty, but not for prefrail or nonfrail; and for Whites but not Blacks. Results were robust to adjustment for health-related factors and known locomotor risk factors; sensitivity analysis indicates results are not driven by extreme gait slowing among frail.

If confirmed in other studies, our results may have implications for future lines of inquiry. First, our findings contribute to the emerging conceptualization of gait slowing due to poorer dopaminergic signaling, especially among adults with the frailty phenotype. Second, our findings support the notion that frailty may increase vulnerability to stressors; specifically, frail adults may be more vulnerable to the effects of lower dopaminergic signaling on gait

Table 3. Multivariable Linear Regression of Genotype Predicting Average Gait Speed (m/s), Stratified by Race for the Full Cohort and Among Frail Subgroup

Variable	White, all cohort (n = 3,059)		Black, all cohort (n = 685)		White, frail (n = 177)		Black, frail (n = 87)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Val/Val	-.06 (-.04 to -.003) <i>P</i> = .02	-.05 (-.04 to -.003) <i>P</i> = .02	-.06 (-.02 to .09) <i>P</i> = .17	-.06 (-.02 to .09) <i>P</i> = .17	-.23 (-.14 to -.006) <i>P</i> = .03	-.24 (-.14 to -.004) <i>P</i> = .04	-.18 (-.20 to .05) <i>P</i> = .23	-.17 (-.20 to .06) <i>P</i> = .26
Val/Met	-.03 (-.03 to .004) <i>P</i> = .13	-.03 (-.03 to .003) <i>P</i> = .11	-.005 (-.05 to .06) <i>P</i> = .91	-.000 (-.05 to .05) <i>P</i> = .99	-.04 (-.08 to .05) <i>P</i> = .68	-.03 (-.08 to .06) <i>P</i> = .75	-.14 (-.18 to .06) <i>P</i> = .32	-.11 (-.17 to .07) <i>P</i> = .41

Note: Data are given as standardized β coefficient (95% confidence interval); referent group = Met/Met Model 1: adjusted for age, sex, education, and race. Model 2: further adjusted for variables bivariately associated with catechol-O-methyltransferase genotype: body mass index, diabetes mellitus, cerebrovascular diseases, cardiovascular diseases, and cognitive status. Bold text indicates statistically significant results ($P < .05$).

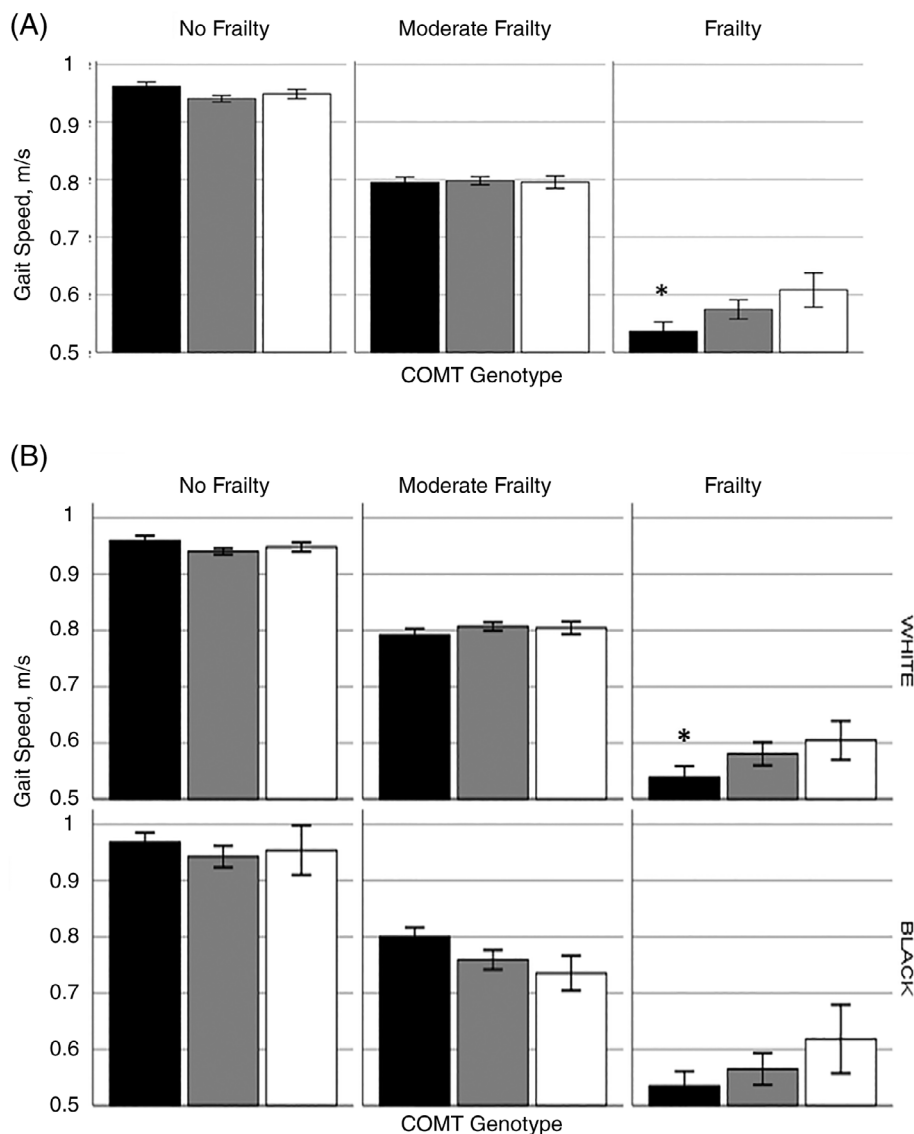


Figure 2. Means and standard errors of gait speed stratified by frailty (A) and by frailty and race (B). Black, Val/Val; gray, Val/Met; white, Met/Met. Asterisks: significantly different from Met/Met at $P < .05$. COMT, catechol-O-methyltransferase.

slowing. Although our analyses were not designed to identify the reasons of this heightened vulnerability, a few explanations could be discussed. Emerging evidence suggests subclinical neurovascular changes, including small vessel disease, and/or neurodegenerative processes, such as Lewy body disorders, are common among frail adults³⁶; these processes are known to reduce brain reserve and lower tolerance to stressors.²⁰ In these participants, a prodromal neurodegenerative profile underlying frailty might have lowered the symptomatic threshold of dopaminergic levels needed to cause slow gait. Another explanation is that frailty itself is due to lower dopaminergic signaling. Lower dopamine can impair signaling and functioning of sensorimotor, reward, and executive control networks,^{10,21} which, in turn, can lead to slower gait as well as to other signs of frailty: weaker muscle strength, exhaustion, reduced movement (physical activity), and appetite (thus weight loss). If this were the case, individuals with both frailty and the COMT Val/Val genotype would have the

lowest levels of dopamine; our findings that this group also had slow gait would further support the relevance of dopamine in gait control. Unfortunately, neurobiological studies of frailty are sparse; although frailty and Parkinson's disease co-occur, the overlap between dopaminergic signaling and frailty has not been tested directly. In our study, only 7% of those with Val/Val had frailty, and the association between COMT and frailty was not significant after adjustment for demographics. Neurobiological studies of frailty using neuromolecular and neuroimaging methods should assess whether the frailty phenotype reflects lower dopaminergic signaling and/or is a marker of failed compensatory processes.

Associations of COMT with gait speed among the non-frail and intermediate groups were not statistically significant. This could be due to a lack of variation in gait speed in these subgroups; there are differences in the distribution of gait speed values across groups, with larger variations among frail compared with nonfrail or intermediate frail,

with standard errors comparatively narrow in the nonfrail cohort. Indeed, in sensitivity analyses stratified by gait speed cutoffs yielding smaller ranges of gait speed in each group, associations of *COMT* with gait speed were not significant.

Our findings potentially explain the discrepancies in other studies that did not account for frailty. Our results of an association between *COMT* and gait speed differ from a previous cross-sectional study on *COMT* and gait speed, where Val/Met was the fastest genotype and Val/Val and Met/Met did not have significant differences in speed when compared with each other.¹⁶ This could be due to our stratification by frailty status, but also that the study's total cohort had a mean age about 7 years older than our total cohort, hence having a relatively larger prevalence of frailty. Our results of a lack of association for the nonfrail group are consistent with a recent cross-sectional study.¹²

Our results should be interpreted cautiously. A major limitation is that we assessed the effects of one gene on gait speed. A recent genome-wide meta-analysis, which included the CHS cohort, found SNPs relating to 69 genes with suggestive associations with gait speed but found insignificant results for the *COMT* polymorphism.³⁵ Our analysis indicates that a well-characterized candidate gene may have a more pronounced prominent influence on frail adults due to their increased vulnerability to stressors; studying other genes in this population may be valuable. Such studies should account for other causes of gait slowing in older age,³⁴ as a single or even multiple gene polymorphism is unlikely to completely explain the variance of gait speed among adults who also have complex multisystem impairments of varying severity. A simultaneous study of the dopaminergic and multisystem contribution to slowing gait among frail adults can help better understand its causes and help design multimodal interventions to ameliorate gait slowing.

COMT is important for the metabolism of norepinephrine and epinephrine, in addition to dopamine; thus, it cannot be excluded that these effects may be due to other catecholamines.³⁷ Other limitations of this study include the cross-sectional design. Differential effects of *COMT* genotypes on gait slowing over time have been shown, indicating that a single cross-section may not adequately demonstrate the relationship between gait speed and the *COMT* genotype. Further studies on *COMT* and gait speed specifically in frail populations using longitudinal designs may be helpful. Another limitation was the small sample size of our population, especially when separated by frailty and by race. Although the regression coefficients were similar in both races, associations did not reach statistical significance among Blacks. It is also possible that the influence of *COMT* on gait speed among Blacks was confounded (e.g., reduced) by the higher burden of cardiovascular diseases compared with Whites. The influence of residual confounding and whether associations are significant among Blacks should be examined in larger samples.

CONCLUSIONS

This study suggests a robust relationship between *COMT* polymorphism and gait speed in older adults with frailty. Our findings may inform studies of the dopaminergic contribution to gait slowing and frailty. If our results are

confirmed in future studies, *COMT* genotyping may be used for risk stratification and to better understand the causes of gait slowing.

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Author Contributions: Caterina Rosano conceived of the presented idea and further developed it alongside Shannon Mance. Shannon Mance developed and ran analyses and wrote the manuscript with support and guidance from Caterina Rosano. Andrea Rosso, Nico Bohnen, Joshua Bis, and Stephanie Studenski suggested additional analyses, provided feedback, and helped shape the manuscript.

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REFERENCES

1. Studenski S. Gait speed reveals clues to lifelong health. *JAMA Netw Open*. 2019;2(10):e1913112. <https://doi.org/10.1001/jamanetworkopen.2019.13112>.
2. Alexander NB. Gait disorders in older adults. *J Am Geriatr Soc*. 1996;44(4):434-451. <https://doi.org/10.1111/j.1532-5415.1996.tb06417.x>.
3. Holtzer R, Epstein N, Mahoney JR, Izzetoglu M, Blumen HM. Neuroimaging of mobility in aging: a targeted review. *J Gerontol A Biol Sci Med Sci*. 2014;69(11):1375-1388. <https://doi.org/10.1093/gerona/glu052>.
4. Tian Q, Chastan N, Bair W-N, Resnick SM, Ferrucci L, Studenski SA. The brain map of gait variability in aging, cognitive impairment and dementia—a systematic review. *Neurosci Biobehav Rev*. 2017;74:149-162. <https://doi.org/10.1016/j.neubiorev.2017.01.020>.
5. Wennberg AMV, Savica R, Mielke MM. Association between various brain pathologies and gait disturbance. *Dement Geriatr Cogn Disord*. 2017;43(3-4):128-143. <https://doi.org/10.1159/000456541>.
6. Seidler RD, Bernard JA, Burutolu TB, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev*. 2010;34(5):721-733. <https://doi.org/10.1016/j.neubiorev.2009.10.005>.
7. Rosano C, Metti AL, Rosso AL, Studenski S, Bohnen NI. Influence of striatal dopamine, cerebral small vessel disease, and other risk factors on age-related parkinsonian motor signs. *J Gerontol A Biol Sci Med Sci*. 2020;75(4):696-701. <https://doi.org/10.1093/gerona/glz161>.

8. Buchman AS, Shulman JM, Nag S, et al. Nigral pathology and parkinsonian signs in elders without Parkinson disease. *Ann Neurol.* 2012;71(2):258-266. <https://doi.org/10.1002/ana.22588>.
9. Chu Y, Buchman AS, Olanow CW, Kordower JH. Do subjects with minimal motor features have prodromal Parkinson disease? *Ann Neurol.* 2018;83(3):562-574. <https://doi.org/10.1002/ana.25179>.
10. Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology.* 2004;29(11):1943-1961. <https://doi.org/10.1038/sj.npp.1300542>.
11. Metti AL. COMT genotype and gait speed changes over ten years in older adults. *J Am Geriatr Soc.* 2017;65(9):2016-2022.
12. Metti AL, Rosano C, Boudreau R, et al. Catechol-O-methyltransferase genotype and gait speed changes over 10 years in older adults. *J Am Geriatr Soc.* 2017;65(9):2016-2022. <https://doi.org/10.1111/jgs.14980>.
13. Rosso AL, Bohnen NI, Launer LJ, Aizenstein HJ, Yaffe K, Rosano C. Vascular and dopaminergic contributors to mild parkinsonian signs in older adults. *Neurology.* 2018;90(3):e223-e229. <https://doi.org/10.1212/WNL.0000000000004842>.
14. Rosso AL, Metti AL, Glynn NW, et al. Dopamine-related genotypes and physical activity change during an intervention: the lifestyle interventions and independence for elders study. *J Am Geriatr Soc.* 2018;66(6):1172-1179. <https://doi.org/10.1111/jgs.15369>.
15. Hupfeld KE, Vaillancourt DE, Seidler RD. Genetic markers of dopaminergic transmission predict performance for older males but not females. *Neurobiol Aging.* 2018;66:180.e11-180.e21. <https://doi.org/10.1016/j.neurobiolaging.2018.02.005>.
16. Holtzer R, Ozelius L, Xue X, Wang T, Lipton RB, Verghese J. Differential effects of COMT on gait and executive control in aging. *Neurobiol Aging.* 2010;31(3):523-531. <https://doi.org/10.1016/j.neurobiolaging.2008.05.011>.
17. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc.* 2012;60(8):1487-1492. <https://doi.org/10.1111/j.1532-5415.2012.04054.x>.
18. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-M156. <https://doi.org/10.1093/gerona/56.3.m146>.
19. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet.* 2013;381(9868):752-762. [https://doi.org/10.1016/S0140-6736\(12\)62167-9](https://doi.org/10.1016/S0140-6736(12)62167-9).
20. Wallace LMK, Theou O, Godin J, Andrew MK, Bennett DA, Rockwood K. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. *Lancet Neurol.* 2019;18(2):177-184. [https://doi.org/10.1016/S1474-4422\(18\)30371-5](https://doi.org/10.1016/S1474-4422(18)30371-5).
21. Brown PJ, Rutherford BR, Yaffe K, et al. The depressed frail phenotype: the clinical manifestation of increased biological aging. *Am J Geriatr Psychiatry.* 2016;24(11):1084-1094. <https://doi.org/10.1016/j.jagp.2016.06.005>.
22. Vaughan L, Corbin AL, Goveas JS. Depression and frailty in later life: a systematic review. *Clin Interv Aging.* 2015;10:1947-1958. <https://doi.org/10.2147/CIA.S69632>.
23. Palmatier MA, Kang AM, Kidd KK. Global variation in the frequencies of functionally different catechol-O-methyltransferase alleles. *Biol Psychiatry.* 1999;46(4):557-567. [https://doi.org/10.1016/s0006-3223\(99\)00098-0](https://doi.org/10.1016/s0006-3223(99)00098-0).
24. Hirsch C. The association of race with frailty: the cardiovascular health study. *Ann Epidemiol.* 2006;16(7):545-553.
25. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol.* 1991;1(3):263-276. [https://doi.org/10.1016/1047-2797\(91\)90005-W](https://doi.org/10.1016/1047-2797(91)90005-W).
26. Podewils LJ, Guallar E, Kuller LH, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *Am J Epidemiol.* 2005;161(7):639-651. <https://doi.org/10.1093/aje/kwi092>.
27. Schellenbaum GD. Survival associated with two sets of diagnostic criteria for congestive heart failure. *Am J Epidemiol.* 2004;160(7):628-635.
28. Study component schedules: baseline (1989/90) through year 4 (1991/92). CHS Coordinating Center, University of Washington. <https://chs-nhlbi.org/schedule/schbt04>. Published 2001. Accessed September 2, 2019.
29. Paffenbarger RS, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol.* 1978;108(3):161-175. <https://doi.org/10.1093/oxfordjournals.aje.a112608>.
30. Taylor HL. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis.* 1978;31:741-755.
31. Orme J. Factorial and indiscriminate validity of the center for epidemiologic studies depression (CES-D) scale. *J Clin Psychol.* 1986;42:28-33.
32. Folstein MF. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.
33. O'Bryant SE. Detecting dementia with the mini-mental state examination (MMSE) in highly educated individuals. *Arch Neurol.* 2008;65(7):963-967.
34. Rosso AL, Studenski SA, Chen WG, et al. Aging, the central nervous system, and mobility. *J Gerontol A Biol Sci Med Sci.* 2013;68(11):1379-1386. <https://doi.org/10.1093/gerona/glt089>.
35. Ben-Avraham D, Karasik D, Verghese J, et al. The complex genetics of gait speed: genome-wide meta-analysis approach. *Aging (Albany, NY).* 2017;9(1):209-246. <https://doi.org/10.18632/aging.101151>.
36. Rosa G, Giannotti C, Martella L, et al. Brain aging, cardiovascular diseases, mixed dementia, and frailty in the oldest old: from brain phenotype to clinical expression. *J Alzheimers Dis.* 2020;75(4):1083-1103. <https://doi.org/10.3233/JAD-191075>.
37. Ben-Itzhak R, Giladi N, Gruendlinger L, Hausdorff JM. Can methylphenidate reduce fall risk in community-living older adults? a double-blind, single-dose cross-over study. *J Am Geriatr Soc.* 2008;56(4):695-700. <https://doi.org/10.1111/j.1532-5415.2007.01623>.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: Baseline Characteristics of Participants in the Full Cohort and Stratified by Frailty Status

Supplementary Table S2: Correlations of Population Characteristics with Gait Speed, for the Full Cohort and Stratified by Frailty Status