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Catechol-O-Methyltransferase Genotype, Frailty, and Gait Speed in a biracial cohort of older adults

Short running title: COMT Genotype, Frailty and Gait Speed

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ABSTRACT (Word count: 276)

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 Multi-center study, 4 US sites.

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

MEASUREMENTS: Gait speed (usual pace, m/sec), 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 cut-offs of gait speed (0.6 and 1.0m/sec) instead of frailty status.

RESULTS. The interaction of *COMT* by frailty and *COMT* by race were p=0.02 and p=0.01, respectively. Compared to 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/sec, p=0.2). Gait speed differences were significant for frail (n=220, 0.55 vs 0.63 m/sec, p=0.03), but not for pre-frail (n=1691, 0.81 vs 0.81 m/sec, p=0.9), or non-frail (n=1833, 0.98 vs 0.97 m/sec, p=0.7); 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 cut-offs of gait speed were not significant.

CONCLUSION. The association of dopamine-related genotype with gait speed is stronger among adults with frailty compared to those without. The potential effects of dopaminergic signaling on preserving physical function in biracial cohorts of frail adults should be further examined.

Keywords: Frailty, genetics, dopamine, gait speed

(Manuscript word count: 2930)

(3 Tables, 2 Figures, 2 Supplementary Tables)

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].
While 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 to
those with the Val/Val genotype. In work done by us,[11–14] and others,[15,16] the association
between the *COMT* genotype and gait speed in older adults without other neurological
diseases are of variable strength, with some studies 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] Very 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 as compared to those without frailty. Our secondary hypothesis is that race may also modify these associations, due to its relation to both frailty[24] 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 very important.

Methods

Participants and sampling

The Cardiovascular Health Study (CHS) is a prospective population-based cohort study of adults > 65, 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 1989-1990, an additional 687 Black participants were recruited using identical methods in 1992-1993.[26] Eligibility criteria included: being in the designated sampling frame or living in the same household as someone who was sampled; >65 years at the time of examination; non-institutionalized; expected to remain in the area for the next three years; and able to give informed consent without a proxy.[25] Fifty seven percent of the eligible persons contacted enrolled in the study.[27]

Data collection

Baseline characteristics obtained from phone contact and in–person examinations[28] included a brief physical examination, cognitive function measures, electrocardiograms, respiratory measures, and blood samples.[25] Participants were followed by annual clinic visits and semi-annual phone 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 5888 CHS participants, 4043 participants had complete data for *COMT* gene and walk time. From these we excluded those with: missing data on frailty (n=291) or on medications for Parkinson's disease (n=5); participants having Parkinson's disease at baseline (n=2) or taking a Parkinson medication (n=1). Selection criteria for data collection did not differ by race status. See Figure 1 for 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 GWAS study sample is 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<=95% 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 < 97%, HWE P < 10-5, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, 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* genotype;[23] 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 phenotype[18] if they had >3 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 one-year, gait speed (slowest 20% at baseline), and physical activity (lowest quintile). Those with 1-2 signs were classified as intermediate frail and those with none were non-frail.

Gait speed (m/sec) 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 non-dominant hands, and the average computed. The Minnesota Leisure Time Activities and Paffenbarger questionnaires assessed physical activity (kcals).[29,30] Exhaustion and unintentional weight change were by self-report.

In addition to age, sex and race, other baseline variables were: education (converted from year reached in school to high school diploma, GED, or higher education versus not finishing high school); 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] cognitive function (Mini-Mental State Examination[32] , with scores >27 classified as normal.[33] Presence of vision problems, diabetes, arthritis, chronic lung disease, 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 inter-quartile 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's exact values for N>5) as appropriate (Table 1). Similar approaches were used to compare population characteristics by frailty status (Supplemental Table 1). 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 (Supplemental Table 2).

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 $p<0.05$. Additional potential covariates were considered for adjustment if they were significantly associated with gait speed at $p<0.05$. Associations of *COMT* with frailty were also tested in logistic regression models; odds ratios are reported for *COMT* predicting being frail vs. pre-frail, as well as predicting frail vs. non-frail, and pre-frail vs. non-frail. Given the association between frailty and gait speed (slow gait is also one of the Fried criteria to classify frailty), it is possible that 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 cut-offs[1] of <0.6m/sec (n=384), 0.6-1.0m/sec (n=2565), and > 1.0 m/sec (n=838).

Results

Genotype distributions were consistent with Hardy-Weinberg Equilibrium in the full sample (p=0.10) as well as in the Black (p=0.06) and White (p=0.69) participants' races. In the full cohort, 7% of those with Val/Val genotype (indicating lower dopamine) also had frailty (Table1); gait speed differences between Val/Val and Met/Met were marginally significant (Table 1). Compared to Val/Met and Met/Met, Val/Val were more likely to be black, to have lower physical activity, higher BMI, higher proportion having diabetes, cerebrovascular disease, cardiovascular disease, and abnormal cognitive functioning (all p<0.05, Table 1). Difference in age, gender or education were not statistically significant (Table1).

As expected, the frail group had a worse profile on all variables examined, compared to the non-frail or pre-frail group (Supplemental table 1). The unadjusted mean gait speed for the frail group was about 30% slower, compared to those in the pre- or non-frail group. In the total cohort, the factors predicting slower gait were consistent with what we and others have previously shown: older age, female gender, lower education, lower grip strength, and generally worse health (Supplemental Table 2). Results were similar in the frail group, but less strong in the pre-frail or non-frail groups; all variables except weight loss, chronic lung disease, and cerebrovascular disease were significantly correlated with gait speed at p<0.05 and in the expected direction (Supplemental Table 2).

In multivariable logistic regression models predicting frailty, the association between *COMT* and frailty became not significant after adjustment for demographics (p>0.23).

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=0.03) and by race (interaction between *COMT* and race p=0.02). The three-way interaction of *COMT* by frailty and by race was not significant (p>0.1).

In models stratified by frailty status (Table 2), the association of *COMT* with gait speed was significant among those with frailty, but not for pre-frail (p> 0.81) or non-frail (p>0.2). Among frail participants, Met homozygotes walked approximately 13% faster compared to those with Val homozygous status, with a between group difference of about 0.10 m/sec (Table 2). Results were similar after further adjustment for factors associated with gait speed, specifically depression and vision (Supplemental Table 2).

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 betas were between 0.05 and 0.06, corresponding to about 0.01 m/sec 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 betas were between 0.17 to 0.24, corresponding to about 0.07 m/sec 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 cut-offs of gait speed instead of frailty status, the associations of *COMT* with gait speed were not significant for any of the groups (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 pre- or non-frail; and for Whites but not Blacks. Results were robust to adjustment for health-related factors and known locomotor risk factors; sensitivity analysis indicate 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 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 adults[36]; 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 very 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 frails compared to non or intermediate frail, with standard errors comparatively narrow in the non-frail cohort. Indeed, in sensitivity analyses stratified by gait speed cut-offs 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 to 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 non-frail 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 genes polymorphism is unlikely to completely explain the variance of gait speed among adults who also have complex multi-system impairments of varying severity. A simultaneous study of the dopaminergic and multi-system contribution to slowing gait among frail adults can help better understand its causes and help design multi-modal 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 to 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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Figure 1: Flowchart illustrating the participants included in the analysis.

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<0.05

Supplemental Table 1: Baseline characteristics of participants in the full cohort and
stratified by frailty status.

Supplemental Table 2: Correlations of population characteristics with gait speed, for the
full cohort and stratified by frailty status.

Table 1. Baseline characteristics stratified by COMT genotype. Numbers (%) are reported, unless otherwise specified

	Val/Val[a] (n=1053)	Val/Met[b] (n=1818)	Met/Met[c] (n=873)	P-values [a] vs [b]	P-values [b] vs [c]	P-values [a] vs [c]
Frailty measures						
Frail (severe vs. moderate or none), present	77 (7.3)	107 (5.9)	36 (4.1)	0.13	0.056	0.003
Gait speed (m/sec) (mean(SD))	0.87 (0.22)	0.88 (0.21)	0.89 (0.2)	0.55	0.10	0.051**
Grip strength (kg) (mean (SD))	28.8 (10.9)	28.2 (10.2)	28.1 (9.9)	0.21	0.81	0.20**
Physical activity (total kcals) (median (IQR))	893.8 (1702.5)	1215 (1950)	1207 (2155.5)	<0.001	0.38	<0.001‡‡
Exhaustion, present	312 (29.6)	573 (31.5)	273 (31.3)	0.29	0.89	0.44
Unintentional weight loss ≥ 10 lbs, present	111 (10.5)	210 (11.6)	80 (9.2)	0.49	0.09	0.32
Demographics						
Age (median (IQR))	71 (8)	71 (7)	71 (8)	0.36	0.82	0.57‡‡
Gender, Male	423 (40.2)	716 (39.4)	325 (37.2)	0.68	0.28	0.19
Race, Black	326 (31)	278 (15.3)	81 (9.3)	<0.001	<0.001	<0.001
Education ≥high school	740(70.3)	1335 (73.4)	635 (72.7)	0.08	0.74	0.24
Health Related Factors						
BMI (kg/m^2), mean (SD)	27 (4.7)	26.6 (4.7)	26.5 (4.7)	0.02	0.71	0.02**
Ankle-arm index (%), mean (SD)	1.1 (0.2)	1.1 (0.2)	1.1 (0.1)	0.40	0.90	0.53**
Depression score (CES-D) (median (IQR))	3 (5)	3 (5)	3 (5)	0.52	0.87	0.69‡‡
Impaired Vision, present	53 (5)	105 (6)	46 (5)	0.41	0.68	0.75
Arthritis, present	517 (49)	905 (50)	442 (51)	0.79	0.61	0.49
Diabetes, present	124 (12)	181 (10)	72 (8)	0.13	0.16	0.01
Chronic lung disease, present	4 (0)	4 (0)	1 (0)	0.19	0.22	0.09+
Cerebrovascular disease, present	28 (3)	28 (2)	10 (1)	0.04	0.42	0.02
Cardiovascular disease, present	156 (15)	177 (10)	86 (10)	<0.001	0.93	0.001

Normal cognitive function, present	790 (75)	1471(82)	705(81)	<0.001	0.78	0.003

P values are from Chi-square test unless otherwise specified; **Two sample t-test; ‡ Kruskal-Wallis test; ‡‡ Mann-Whitney U Test; +Fischer's exact test. Prevalence: rounded to nearest decimal point.

Normal cognitive function based on assessment with 30-point Mini-Mental State Examination$\geq$ 27

Table 2. Multivariable linear regression of genotype predicting average gait speed (m/s), for the full cohort and stratified by frailty status.

	All Cohort (n=3744)		Frailty (n=220)		Moderate Frailty (n=1691)		No Frailty (n= 1833)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	β (95%CI)* p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value
Val/Val	-.031 (-.03,.006) p=.19	-.030 (-.03,.007) p=.23	**-.201 (-.13, -.01) p=.03**	**-.198 (-.13, -.01) p=.03**	.001 (-.03,.03) p=.99	-.002 (-.03,.03) p=.94	.012 (-.02,.03) p=.71	.013 (-.02,.03) p=.68
Val/Met	-.027 (-.03,.004) p=0.14	-.028 (-.03,.003) p=.23	-.079 (-.09,.03) p=.31	-.068 (-.09,.03) p=.35	.007 (-.21,.03) p=.81	.004 (-.22,.03) p=.88	-.035 (-.31,.006) p=.18	-.037 (-.31,.005) p=.16

* Standardized beta coefficient (95% confidence interval), referent group= Met/Met

Model 1: adjusted for age, gender, education, race

Model 2: further adjusted for variables bivariately associated with COMT genotype: body mass index, diabetes, cerebrovascular diseases, cardiovascular diseases, cognitive status.

Bold text indicates statistically significant results (p<0.05).

Table 3. Multivariable linear regression of genotype predicting average gait speed (m/s), stratified by race for the full cohort and among frail subgroup
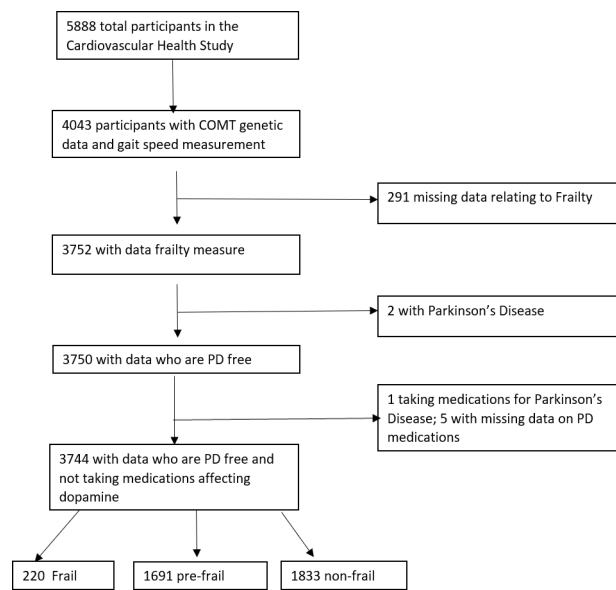
	White, All cohort (n=3059)		Black, All cohort (n=685)		White, Frail (n=177)		Black, Frail (n=87)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	β (95%CI)* p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value	β(95%CI) p-value
Val/Val	**-.06 (-.04, -.003) p=.02**	**-.05 (-.04, -.003) p=.02**	-.06 (-.02, .09) p=.17	-.06 (-.02, .09) p=.17	**-.23 (-.14, -.006) p=.03**	**-.24 (-.14, -.004) p=.04**	-.18 (-.20, .05) p=.23	-.17 (-.20, .06) p=.26
Val/Met	-.03 (-.03, .004) p=0.13	-.03 (-.03,.003) p=.11	-.005 (-.05,.06) p=.91	-.000 (-.05, .05) p=.99	-.04 (-.08, .05) p=0.68	-.03 (-.08,.06) p=.75	-.14 (-.18, .06) p=.32	-.11 (-.17, .07) p=.41

* standardized beta coefficient (95% confidence interval) , referent group= Met/Met
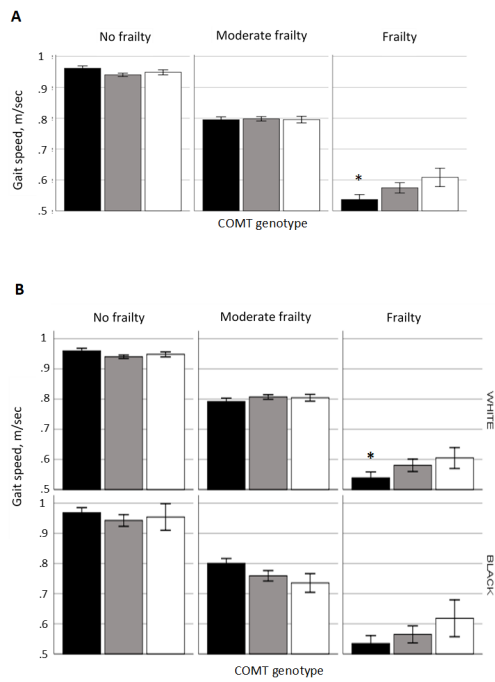
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29

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┌─────────────────────────────┐
│ 5888 total participants in the │
│ Cardiovascular Health Study │
└─────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐
│ 4043 participants with COMT genetic │
│ data and gait speed measurement │
└─────────────────────────────┘
              │
              │────────────────────►┌──────────────────────────────┐
              │                      │ 291 missing data relating to Frailty │
              ▼                      └──────────────────────────────┘
┌─────────────────────────────┐
│ 3752 with data frailty measure │
└─────────────────────────────┘
              │
              │────────────────────►┌──────────────────────────┐
              │                      │ 2 with Parkinson's Disease │
              ▼                      └──────────────────────────┘
┌─────────────────────────────┐
│ 3750 with data who are PD free │
└─────────────────────────────┘
              │
              │────────────────────►┌──────────────────────────────────┐
              │                      │ 1 taking medications for Parkinson's │
              │                      │ Disease; 5 with missing data on PD │
              ▼                      │ medications │
┌─────────────────────────────┐    └──────────────────────────────────┘
│ 3744 with data who are PD free and │
│ not taking medications affecting │
│ dopamine │
└─────────────────────────────┘
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220 Frail   1691 pre-frail   1833 non-frail

JGS_16842_Figure1FINAL.rev.tiff

A

No frailty   Moderate frailty   Frailty

Gait speed, m/sec

COMT genotype

B

No frailty   Moderate frailty   Frailty

Gait speed, m/sec

WHITE

BLACK

COMT genotype

JGS_16842_Figure2FINAL.rev.tiff

Table 1. Baseline characteristics stratified by COMT genotype. Numbers (%) are reported, unless otherwise specified

	Val/Val[a] (n=1053)	Val/Met[b] (n=1818)	Met/Met[c] (n=873)	P-values a vs b	P-values b vs c	P-values a vs c
Frailty measures						
Frail (severe vs. moderate or none), present	77 (7.3)	107 (5.9)	36 (4.1)	0.13	0.056	0.003
Gait speed (m/sec) (mean(SD))	0.87 (0.22)	0.88 (0.21)	0.89 (0.2)	0.55	0.10	0.051**
Grip strength (kg) (mean (SD))	28.8 (10.9)	28.2 (10.2)	28.1 (9.9)	0.21	0.81	0.20**
Physical activity (total kcals) (median (IQR))	893.8 (1702.5)	1215 (1950)	1207 (2155.5)	<0.001	0.38	<0.001‡‡
Exhaustion, present	312 (29.6)	573 (31.5)	273 (31.3)	0.29	0.89	0.44
Unintentional weight loss ≥ 10 lbs, present	111 (10.5)	210 (11.6)	80 (9.2)	0.49	0.09	0.32
Demographics						
Age (median (IQR))	71 (8)	71 (7)	71 (8)	0.36	0.82	0.57‡‡
Gender, Male	423 (40.2)	716 (39.4)	325 (37.2)	0.68	0.28	0.19
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Normal cognitive function based on assessment with 30-point Mini-Mental State Examination≥ 27

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Val/Val	**-.06** **(-.04, -.003)** **p=.02**	**-.05** **(-.04, -.003)** **p=.02**	-.06 (-.02, .09) p=.17	-.06 (-.02, .09) p=.17	**-.23** **(-.14, -.006)** **p=.03**	**-.24** **(-.14, -.004)** **p=.04**	-.18 (-.20, .05) p=.23	-.17 (-.20, .06) p=.26
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