The Catechol-O-Methyltransferase Genotype, Frailty and Gait speed: The Cardiovascular Health Study

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Abstract

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: 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). The interaction of *COMT* by frailty and *COMT* by race predicting gait speed were p=0.02 and p=0.01, respectively. Gait speed differences by genotype 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, but statistically significant 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 frail adults should be further examined. This is significant to public health as it could improve quality of life of older adults and decrease adverse health outcomes.

Table of Contents

List of Tables

List of Figures

Preface

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1.0 Introduction

1.1 Aging

The United States has an aging population, with the number of those aged 65 and older in 2018 expected to double by 2060.[1] It is also expected that the number of older adults in America will outnumber children by 2035.[2] With a higher proportion of the population living longer, it will be a challenge to maintain the health and quality of life of this subset of the population. The increase in older adults in our country will create unique health problems, so focusing public health efforts on aging should be a top priority. Older adults face many age-related changes. Some changes are expected while others are unexpected and troubling signs of disease. Focusing on these issues may ease the burden of the aging population and increase the quality of life of older adults.

1.2 Frailty

One prevalent problem in older adults is frailty. Frailty is defined as a state of increased vulnerability. This increase in vulnerability leads to a reduction in the ability to cope with everyday stressors and increases the risk of adverse health outcomes.[3] This increased risk leaves older adults susceptible to disability, hospitalization, falls, and even death.[4] It may also affect

independence due to decreased capacity to complete activities of daily living. Frailty is not inevitable for older adults, as not everyone develops it. Some older adults are referred to as resilient. Resilience is defined as the ability to adapt to acute and ongoing stressors, making it the opposite of frailty.[4] A minor illness may minimally affect a resilient person while devastating a person with frailty. Likewise, frailty is not irreversible. With intervention, frailty may be attenuated. However, without treatment, frailty will worsen over time.[3] Many affected by frailty will have fluctuations. They may have a positive screen followed by a negative screen.

Several methods are used to screen for frailty in older adults. The Fried physical frailty phenotype assesses for the presence of five factors: unintentional weight loss, weakness, exhaustion, slow gait speed, and low physical activity.[5] Another method, the Edmonton Frail Scale[6] includes more categories, such as nutrition, cognition, medication use, and others. The Rockwood model, or the Clinical Frailty Scale, classifies frailty based on cumulative illness and deficits.[7] There is a lack of consensus as to which method is best for screening or research use.

The cause of frailty remains unknown, though some factors are associated with an increased risk of frailty. These risk factors include illness, poor appetite, older age, female sex, poverty, lower education levels, smoking, extremely high or low body mass index (BMI), chronic illness, and chronic pain.[8] Frailty is thought to be linked to various pathologies in body systems, such as inflammation, glucose processing, and cortisol secretion, which lead to damage to skeletal muscle and the immune system overtime, but the exact cause is unknown.[3] The central nervous system (CNS) has also been linked with frailty.

Frailty is a complex condition, likely resulting from an interplay of genetics and environmental factors. A recent genome-wide association study (GWAS) using the Frailty index score found only one genome-wide significant hit and 31 other associations at the suggestive

($p<0.0001$) level.[9] The significant hit was a single nucleotide polymorphism (SNP) related to synaptic transmission in the CNS. This study also assessed pathways that genes were associated, finding multiple significant pathways.[9]

1.3 Central Nervous System and Dopamine

Older adults may experience anatomical changes to their CNS. Overall, brain atrophy may occur in both the white and grey matter of the brain.[10] Brain atrophy and altered volume have been associated with mobility problems.[11] Specifically, the prefrontal cortex (PFC) becomes more susceptible to gray matter atrophy with age.[10] The PFC is located at the front of the frontal lobe and has been implicated in executive functioning, memory, perception, and diverse cognitive processes.[12] Changes occur in the brain's white matter, with both the quantity and quality of the white matter degrading along with altered connections between the two hemispheres of the brain through the corpus callosum.[10,13] White matter hyperintensities (WMH), which can be found on neurological imaging and are associated with cognitive impairment, have also been noted to be related to poor gait and balance performance as well as increased risk of falls.[11]

In addition to anatomical changes, older adults experience biochemical changes in their CNS. Older adults may have decreased levels of acetylcholine, serotonin, and norepinephrine.[10] Arguably, the most important age-related biochemical change in the CNS is decreased dopamine. Dopamine has been highly studied for its involvement in mobility and movement after it was discovered to be related to Parkinson's disease.[14] Dopamine plays an important role in many of the neurocognitive domains.

Dopamine may also play a role in frailty of older adults. Dopamine levels begin to decrease after early adulthood at a rate of up to 10% per decade.[15] Recent studies support the idea of a frailty-related heightened vulnerability to stressors acting on the CNS. For example, recent studies show that individuals with frailty are more vulnerable to amyloid accumulation, with cognitive impairment manifesting even at a lower burden of neuropathology in those considered to be frail.[16] A role for frailty-related vulnerability has also been suggested for Parkinson's disease and depression.[17,18] Frailty can make a person more vulnerable to minor changes in the CNS, thus slight differences in the dopaminergic system could have more detrimental effects than the minor change would have on a non-frail person. This relationship, however, has not been thoroughly studied and has mostly been theoretical.

1.4 Gait Slowing

Mobility changes with age and is, additionally, a component of frailty. Slower gait is a common and especially disabling condition in older age. Slowed gait may result in an increased risk of falls and reduced independence.[19] There may also be an accelerated conversion to dementia and disability resulting from slowed gait and its associated risks.[19] These effects can result in severe declines in quality of life and health. Gait may also be a predictor of psychological status as well, demonstrating that it is interrelated to all parts of health.[13] Gait is also a contributor to frailty, being one of the components of the Fried phenotype.

Gait slowing can result from changes in many body systems, including the musculoskeletal, central nervous, and sensory systems.[13] Tendon stiffness, reduction of skeletal muscle mass, and diminished reflexes all relate to musculoskeletal functioning and may

contribute to gait troubles. Hearing and vision impairments as well as changes in systems that play a role in balance, such as vestibular and proprioceptive, may all contribute to slowing of gait from a sensory standpoint.[13] While age-related changes in peripheral nervous and musculoskeletal systems are well-known contributors of gait slowing,[20] recent evidence suggests an important role for the CNS.[10,11,21,22] It is, therefore, important to examine the CNS as an important risk for gait and mobility problems.

The central nervous system is highly involved in gait through multiple domains. Neurocognitive domains important in gait include attention, planning, visuospatial, and motor processing.[23] Executive functioning also contributes to gait through its support of working memory, attention, multitasking, and awareness.[24] Changes in executive functioning are especially important to gait speed.[13] The coordination of these many neurocognitive domains are critical for the performance of gait and in regulating gait speed. A specific region of the brain, the prefrontal cortex, plays an important role in many of the neurocognitive domains involved in gait. The prefrontal cortex (PFC) processes and integrates information from these domains.[12]

Consistent data suggest that dopaminergic signaling plays an important role in age-related gait slowing in older adults who are free from Parkinson's disease or other clinically overt neurological conditions.[10,25–27]

In younger adults, gait is highly automated involving complex neural processes.[13] The automaticity of gait, however, diminishes in older adults. As a result, older adults rely on additional processes and neural systems and are more dependent on their prefrontal cortex for gait.[10,24] Older adults use additional brain activity in order to complete motor tasks compared to younger adults.[10] This need for additional focus and brain activity can lead older adults to

impaired gait. The PFC is associated with motor behavior, with poor movement being noted as associated with impairments of the PFC.[12,24]

1.5 Catechol-O-Methyltransferase Polymorphism

Consistent data, including from our research team, suggest dopaminergic signaling plays an important role in age-related gait slowing in older adults who are free from Parkinson's disease or other clinically overt neurological conditions.[10,25–27] The Val(158)Met polymorphism of Catechol-o-methyltransferase (*COMT*) regulates tonic release of dopamine in the prefrontal cortex with reciprocal reductions in phasic dopamine (D2 receptors) in subcortical regions and increased D1 transmission cortically.[28] The Met/Met genotype yields the highest dopamine levels, followed by the heterozygous genotype Val/Met, with the lowest levels among Val homozygotes.[28,29] Given the importance of cortical control of gait functions and effect of COMT on tonic dopamine, it would be expected that those with Met/Met genotype would have faster gait speed compared to those with the Val/Val genotype. We,[30–32] and others,[33,34] have examined the association between the *COMT* genotype and gait speed in older adults without Parkinson's disease. Associations between *COMT* polymorphism and gait speed are of variable strength across studies, with some reporting positive associations for the heterozygous genotype, but not for Met/Met. These discrepancies suggest that other factors might affect the relationship between *COMT* genotype and gait speed; specifically, some people may be more vulnerable than others to the effects of *COMT* polymorphism on gait speed.

Race may be another factor modifying the relationship between the effect of *COMT* genotype and gait speed in older persons. For example, the two primary races identified in the

CHS cohort, White and Black, have different allele frequencies for the polymorphism.[35] Those of European descent have a reference allele frequency (Val) of 0.48 while those of African descent have a frequency of 0.69.[36] Race and frailty have previously been found to be associated in the CHS cohort with Blacks having a higher odds of frailty compared to Whites.[37] Due to its relation to both frailty and genotype, race could be a modifier of the relationship between genotype and gait speed. We hypothesize that due to differing allele frequencies and differing rates of frailty between races, there will be differences in gait speed between the two groups.

1.6 Gaps in Knowledge

A major gap in knowledge lies in lack of information about dopamine and the frailty phenotype in older adults without signs of Parkinson's disease. Much of the literature on this relationship is theoretical. A recent research study by Brown et al. has pointed toward slight changes to the CNS being more detrimental to frail older adults when compared with non-frail in regards to depression.[17] This study modeled a relationship between depression and frailty with the theory of frailty putting those at greater risk for negative outcomes. The investigators reported that the depressed frail phenotype was at high risk for mortality later in life and modeled the clinical manifestations that were associated.[17] This study demonstrates a relationship between depression, a problem originating in the CNS, and frailty. This demonstrates that there could be a pathway between dopamine and frailty that has yet to be explored.

There is also a gap in knowledge of how the effects of the *COMT* genotype differs between frail and non-frail individuals. Studies by Metti et al. and Holtzer et al. have assessed the relationship of the *COMT* genotype with gait speed.[30,34] The study by Metti et al. was

longitudinal in nature and found that those with homozygous genotypes, Met/Met and Val/Val, had greater gait slowing over 10 years than heterozygotes.[30] The results from Holtzer et al. are not consistent with this study. Holtzer et al. found that Met/Met had the slowest gait and that the relationship was more pronounced in men.[34] These studies assessed the relationship between *COMT* and gait speed but did not account for the relationship of frailty by stratification of participants by frailty status. This leaves a possible gap in knowledge.

1.7 Public Health Significance

Given the United States' aging population, gait slowing and frailty are major public health issues. Gait disorders have a high prevalence (35%, 95% CI: 28.6-42.1%) in community-dwelling older adults over the age of 65.[38] In the United States, one study found that frailty has an estimated prevalence of 15.3% (95% CI: 14.2-16.4%). The same study found being pre-frail to have a prevalence of 45.5% (95% CI: 44.0-46.9%).[39] Both gait slowing and frailty can limit the independence of older adults and leave them exposed to adverse health outcomes. Limiting the effects of these issues will be critical to preserving the health of our aging population.

2.0 Objectives

We propose that the *COMT* polymorphism, specifically the Val/Val genotype, predisposes to lower cortical dopamine functions, may act as a risk factor with potential detrimental effects on gait speed, and that the presence of frailty would increase vulnerability to such *COMT*-related effects. Our overarching hypothesis is that the association between *COMT* polymorphism and gait speed differs by frailty status, with associations stronger among those with frailty as compared to those without frailty. Given the high prevalence of frailty, and the clinical implications of slow gait, understanding the contributors of gait slowing in this at-risk group of older adults is critical. Additionally, due to its relation to both frailty and genotype, race could be a modifier of the relationship between genotype and gait speed. We hypothesize that due to differing allele frequencies and differing rates of frailty between races, there will be differences in gait speed between the two groups.

3.0 Methods

3.1 Participants and Sampling

The Cardiovascular Health Study (CHS) is a prospective, population-based cohort study that began in 1989 with a goal of identifying risk factors for cardiovascular disease in adults over the age of 65.[40] The CHS cohort includes a mixture of urban and rural populations recruited from four locations in the United States: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania.[40] Eligible subjects over the age of 65 were sampled randomly within age strata from the communities using Medicare eligibility lists.[40] A total of 5,201 participants were enrolled during the initial recruitment phase from 1989-1990, followed by an additional 687 Black participants recruited using identical methods in a later phase in 1992-1993.[41]

Participants were initially eligible to enroll in the CHS if they were sampled using the designated sampling frame or living in the same household as someone who was sampled, were 65 years or older at the time of examination, were non-institutionalized, were expected to remain in the area for the next three years, and were able to give informed consent without a proxy.[40] Otherwise eligible persons who were wheelchair bound at baseline, were receiving hospice treatment, or were receiving radiation or chemotherapy were also excluded.[40] Fifty seven percent of the eligible persons contacted enrolled in the study.[42]

3.2 Data Collection

Baseline characteristics were obtained from phone contact and initial examinations took place during the first clinic visit, conducted between 1989 and 1992.[43] Initial baseline measures conducted during this time included those from a brief physical examination, cognitive function measures, electrocardiograms, respiratory measures, and blood samples.[40] Participants were followed by annual clinic visits and semi-annual phone contacts through the year 1999.[40] For this analysis, all discussed measurements were taken from baseline data.

Since beginning the study, the CHS has expanded its research mission to include the study of genetic factors of cardiovascular disease. DNA was collected from blood samples from most participants and thousands of single nucleotide polymorphisms (SNPs) for candidate gene regions have been genotyped.

3.3 Analytic Sample

Of 5888 total CHS participants, 4043 participants had complete data for the *COMT* gene as well as the walk time measurement. From these we excluded: 291 for having missing data on the frailty measure, as this was a main variable of focus for analysis; 2 participants having Parkinson's disease at the time of assessment, 1 participant due to taking a Parkinson medication; 5 participants due to missing data on taking medications for Parkinson's disease. See Figure 1 for details.

3.4 Measurements

Single nucleotide polymorphisms of the *COMT* Val158Met (rs4680) gene were obtained from previous genome-wide genotyping in the Cardiovascular Health Study. Briefly, blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai among CHS 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 African-American participants, in 2010). All African-American participants were genotyped; European ancestry participants were excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack or lack of available DNA. 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. In CHS, 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. Since Blacks and Whites have different allele frequencies, interactions by race were tested and models were repeated stratified by race.

Participants had been grouped previously as frail, pre-frail, or non-frail based on the Fried physical frailty phenotype.[5] CHS measures used to classify frailty were obtained at study entry and included: dominant hand grip strength (lowest 20% at baseline; below 20 kilograms in our sample), self-reported exhaustion, self-reported unintentional weight loss of 10 pounds or greater in one-year, gait speed (slowest 20% at baseline; under 0.76 m/s), and physical activity (lowest quintile; under 315 kilocalories). Participants with three or more of these characteristics were classified as having frailty, those with one or two were pre-frail and those with none were classified as non-frail.

Gait speed was measured as a 15-foot walk at a usual pace starting from standing still. The time it took to walk 15 feet at usual pace was converted to a speed measurement in meters per second (m/sec). Grip strength was measured three times on dominant and non-dominant hands. The average of the three measures on the dominant hand was used in this analysis. Physical activity was recorded in kcals using the Minnesota Leisure Time Activities and Paffenbarger questionnaires.[44,45] Exhaustion was a self-reported measure. Weight change was also a self-reported measure. Those with a response indicating unintentional weight loss of at least 10 pounds were included as a positive response.

Other variables included in the analysis due to their potential association with gait speed were: age, sex, race, and education level as recorded at the initial visit. Education level was converted from year reached in school to a binary variable for analysis, including a high school diploma, GED, or higher education versus not finishing high school. BMI was calculated based on height and weight measures from initial visits. Ankle-arm index was calculated for each participant using supine blood pressures from the right arm and both ankles. Depression was assessed using the Center for Epidemiologic Studies Depression Scale.[46] Cognitive function was

assessed using the Mini-Mental State Examination.[47] Scores were further categorized into "normal" cognition versus impaired cognition with a cutoff of a score of 27 and above on the 30 point exam being considered normal.[48] Presence of vision problems, diabetes, arthritis, chronic lung disease, cerebrovascular and cardiovascular diseases were self-reported measures with adjudication by clinicians.

3.5 Analyses

Mean and standard deviation or median and inter-quartile range (IQR) were computed for continuous variables, depending on normality of the distribution. Differences in frailty status, gait speed, and population characteristics between *COMT* genotypes were tested using two sample t-tests for normally distributed variables, or Mann-Whitney-U tests for skewed variables. Pearson Chi-square p-values were reported except in cases when expected values were less than 5 in at least one cell; fisher's exact values were reported in these cases (Table 1). Similar analytical approaches were used to compare population characteristics by frailty status (Table 2). Correlations were used to assess each variable's correlation with gait speed for the full cohort and stratified by frailty status; Pearson correlation coefficients and p-values were reported for continuous variables and Spearman coefficients and p-values for categorical variables (Table 3). Multivariable linear regression analyses tested the association of *COMT* genotype (with Met/Met as the reference group) with gait speed. Interaction terms of *COMT* genotype by race and frailty status were included 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 $p<0.05$. Statistics regarding the fit of each model were reported. 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[19] of <0.6m/sec (n=384), 0.6-1.0m/sec (n=2565), and > 1.0 m/sec (n=838).

4.0 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. Blacks were most likely to be Val/Val (47.6%), followed by Val/Met (40.6%), and Met/Met (11.8%). Whites were most likely to be Val/Met (50.3%), followed by Met/Met (25.9%), and Val/Val (23.8%). In the full cohort, compared to Met/Met or Val/Met, those with Val/Val genotype were more likely to have frailty than pre-frail or non-frail (Table1); results were similar when the three-level frailty grouping was used (not shown). In the full cohort, 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 statistically significant at $p<0.05$, 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 (Table 2). 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 (Table 3). 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 (Table 3).

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 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 multivariable linear regression models of *COMT* predicting gait speed stratified by frailty status (Table 4), 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 4). Results were similar after further adjustment for other factors associated with gait speed (not shown).

In models stratified by race (Table 5), 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).

5.0 Discussion

In this study of community-dwelling older adults, we observed a significant association of *COMT* polymorphism, an indicator for dopaminergic signaling,[29] with gait speed among adults with frailty but not for pre- or non-frail. Our results suggest frailty may increase vulnerability to the effects of low dopaminergic signaling on slow gait speed.

Frailty might lower the symptomatic threshold of dopaminergic levels needed to cause slow gait, or it could be a marker of impaired compensatory processes that might otherwise allow for lower dopaminergic signaling to be tolerated. Taken together, our results indicate frailty may be used for risk stratification and to better understand the causes of gait slowing and potentially guide the management of older adults at risk of gait slowing. If our findings of a dopamine-gait speed-frailty link are confirmed, that would suggest that frail adults are most vulnerable to the effects of lower dopaminergic signaling on gait slowing.

Could our results be simply due to extreme gait slowing in frail older adults, that is differences in the distribution of gait speed values across groups? Our sensitivity analyses suggest otherwise. We found the association of *COMT* with gait speed among those with gait speed <0.6m/sec was not significant. Thus, there must be other aspects of the frailty syndrome contributing to such heightened vulnerability to a low dopaminergic *COMT* polymorphism. More studies are needed to clarify the mechanisms underlying the influence of frailty on these

associations. Our data indicate studying the dopaminergic system in subgroups of older adults with frailty could help us understand these complex relationships.

Our results contribute to the emerging conceptualization of gait slowing due to poorer dopaminergic signaling among adults with a specific phenotype, that of frailty. We found that, among frail participants, the association of *COMT* genotype with gait speed remained significant when controlling for other health-related factors and locomotor risk factors, underscoring an important role of dopaminergic signaling on gait speed in older age. The dopaminergic system is critical for motor functioning, as well as attention- and reward processing; [28,17] these domains in turn contribute to the regulation of gait speed. Thus, the relationship between *COMT* polymorphism and gait speed could be a result of altered levels of dopamine affecting motor function, the reward system, and/or attention, all of which are compromised among those with frailty. It is possible that even mild decreases in dopaminergic signaling can affect gait speed and other factors if an individual has frailty through any of these pathways, or perhaps all together. For example, dopamine levels could decrease motivation and/or cognitive resources needed to have an active lifestyle, which can lead to decreased physical activity and in turn compromise physical function. We observed significant differences in physical activity and cognition between *COMT* genotypes, thus lending support to this pathway.

The causes of gait slowing in older age are multifactorial, and a single gene's polymorphism is unlikely to explain the variance of gait speed among adults who also have complex multi-system impairments of varying severity. The literature on the causes of age-related gait slowing has not yet identified a factor or group of factors explaining a substantial portion of the variance of gait speed.[49] Poorer integrity of the CNS, as well as muscle-skeletal, cardiopulmonary and other systems, only partially explain the variance of gait speed decline in

older age, even when considered simultaneously in the same model. Interventions targeting these systems have not yet produced strong impactful improvements in gait speed among older adults. Studying the dopaminergic contribution to slowing gait among frail adults can help better understand its causes and provide novel targets for intervention.

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.[34] 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 likely having a relatively higher prevalence of frailty. Our results of a lack of association for the non-frail group are consistent with a recent longitudinal study.[30] This study did, however, find a significant difference in change in walking speed over 10 years.

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.[50] 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. The negative associations of *COMT* with gait speed in non-frail groups could be partially due to lack of variation in gait speed in these subgroups; standard errors were comparatively narrow in the non-frail cohort. 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 major limitation was the small sample size of our population, especially when separated by frailty status. The analyses may not have been adequately powered.

5.1 Conclusions

This study suggests a relationship between *COMT* polymorphism and gait speed in older adults with frailty. Our findings may have the potential to inform novel studies of the dopaminergic contribution to gait slowing. *COMT* genotyping may help to identify frail older adults who may be candidates for future research using dopaminergic drugs to reduce decline in gait speed. This result is significant to public health as it could improve quality of life of older adults and decrease adverse health outcomes.

Appendix Tables and Figures

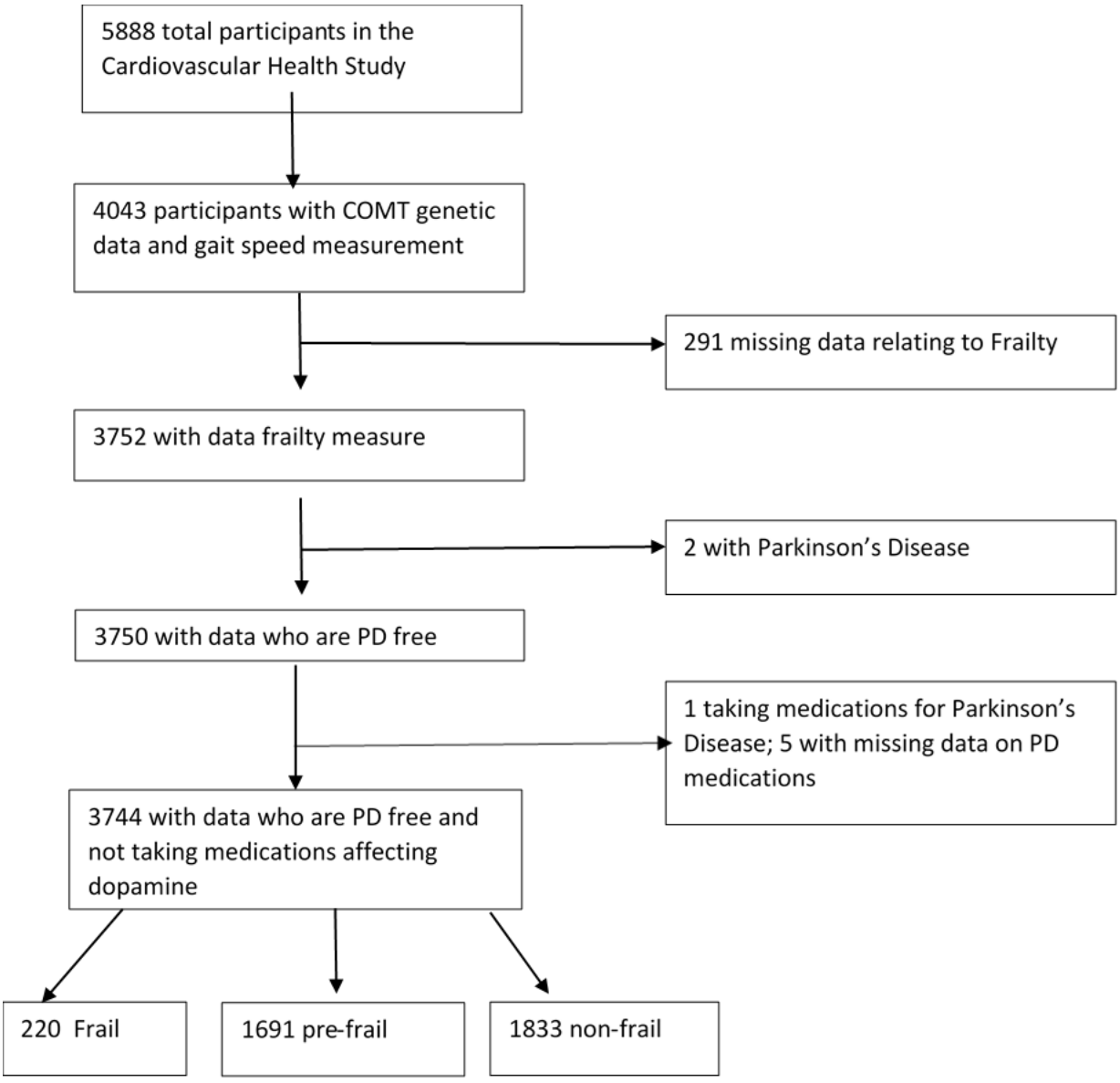

Figure 1. Flowchart illustrating the analytic sample derived from the Cardiovascular Health Study.

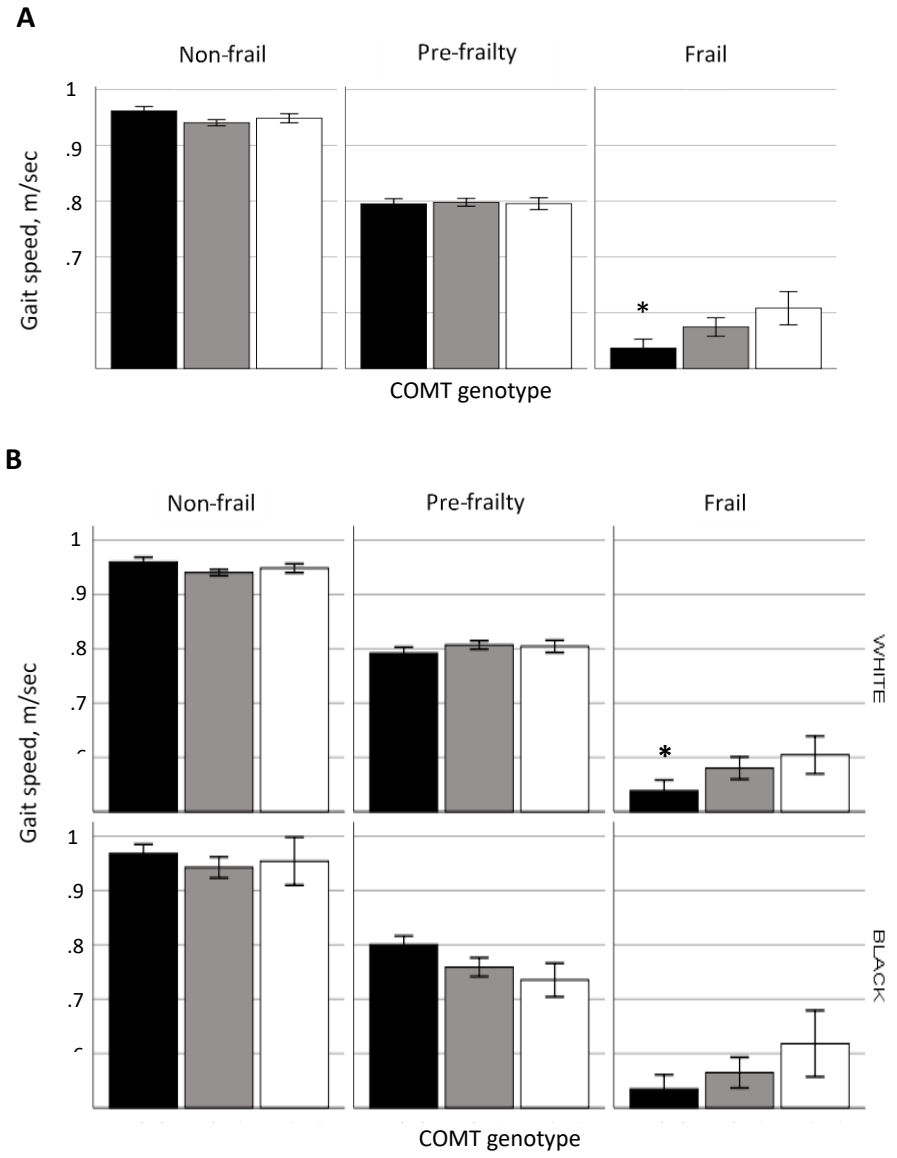

Figure 2. Means and Standard errors of gait speed by *COMT* genotype stratified by frailty (A) and by frailty and race (B).

Legend: Black bars: Val/Val; Gray bars: Val/Met; White bars: Met/Met. Asterisks: significantly different from Met/Met at $p<0.05$

Table 1. Baseline characteristics stratified by *COMT* genotype.

	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						
Frailty (frail vs. pre-frail or non-frail)	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‡‡
Male	423 (40.2)	716 (39.4)	325 (37.2)	0.68	0.28	0.19
Black	326 (31)	278 (15.3)	81 (9.3)	<0.001	<0.001	<0.001
Education ≥HS	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‡‡

Table 1 Continued

Impaired Vision, presence	53 (5)	105 (6)	46 (5)	0.41	0.68	0.75
Arthritis, presence	517 (49)	905 (50)	442 (51)	0.79	0.61	0.49
Diabetes, presence	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

Numbers are *n(%)* unless otherwise specified . P values are from Chi-square test unless otherwise specified; **Two sample t-test; ǂ Kruskal-Wallis test; ǂǂ 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≥ 27

Table 2. Baseline characteristics of participants in full cohort and stratified by frailty status.

	Total Cohort (n= 3744)	Frail (n=220)[a]	Pre-frail (n= 1691)[b]	Non-frail (n= 1833)[c]	P-value [a] vs [b]	P-value [b] vs [c]	P-value [a] vs [c]
(Numbers are *n(%)* unless otherwise specified)							
Demographics							
Age at baseline (median (IQR))	71 (7.75)	76.5 (10)	72 (8)	70 (6)	<0.001 ‡	<0.001 ‡	<0.001 ‡
Male	1464 (39.1)	62 (28.2)	660 (39)	742 (40.5)	0.002	0.38	<0.001
Black	685 (18.3)	87 (39.5)	391 (23.1)	207 (11.3)	<0.001	<0.001	<0.001
Education- high school diploma, GED, or higher	2710 (72.5)	126 (57.3)	1139 (67.4)	1445 (78.8)	0.002	<0.001	<0.001
Frailty measures							
Gait speed (m/sec) (mean(SD))	0.88 (0.21)	0.59 (0.16)	0.82 (0.2)	0.97 (0.17)	<0.001*	<0.001*	<0.001*
Grip strength (kg) (mean (SD))	28.4 (10.3)	19.6 (8.3)	26.5 (9.9)	31.2 (9.9)	<0.001*	<0.001*	<0.001*
Physical activity (total kcals) (median (IQR))	1110 (1967.81)	93.75 (270)	735 (1545)	1635 (2171.6)	<0.001 ‡	<0.001 ‡	<0.001 ‡
Presence of Exhaustion	1158 (30.9)	99 (45)	600 (35.5)	459 (25.0)	0.006	<0.001	<0.001
Unintentional weight loss ≥ 10 lbs	401 (10.7)	69 (31.4)	207 (12.2)	125 (6.8)	<0.001	<0.001	<0.001
Health Related factors							
BMI (kg/m2) (mean (SD))	26.7 (4.7)	27.7 (6.6)	27.1 (5.0)	26.1 (4.1)	0.21*	<0.001*	0.001*
Ankle-arm index (%) (mean (SD))	1.08 (0.16)	1.00 (0.19)	1.07 (0.16)	1.1 (0.14)	<0.001*	<0.001*	<0.001*
Depression score on CES-D Scale (median (IQR))	3 (5)	7 (7)	4 (5)	2 (4)	<0.001 ‡	<0.001 ‡	<0.001 ‡
Presence of Vision problem	204 (5.4)	26 (11.8)	106 (6.5)	72 (4.0)	0.001	0.001	<0.001
Presence of Arthritis	1864 (49.8)	149 (67.7)	916 (54.2)	799 (43.6)	<0.001	<0.001	<0.001
Presence of Diabetes	377 (10.1)	33 (15.0)	211 (12.5)	133 (7.3)	0.29	<0.001	<0.001
Presence of	9 (0.2)	1 (0.5)	7 (0.4)	1 (0.1)	<0.001 †	<0.001 †	<0.001 †

Table 2 Continued

Chronic lung disease							
Presence of Cerebrovascular disease	66 (1.8)	10 (4.5)	39 (2.3)	17 (0.9)	0.048	0.001	<0.001 †
Presence of Cardiovascular disease	419 (11.2)	41 (18.6)	228 (13.5)	150 (8.2)	0.04	<0.001	<0.001
Normal cognitive function	2969 (79.3)	126 (57.3)	1284 (75.9)	1559 (85.1)	<0.001	<0.001	<0.001

Chi-square test unless otherwise specified. **** = Two Sample T- Test***

‡ = Mann-Whitney U test ***† = Fischer's Exact***

Frailty status determined by Fried physical frailty phenotype

Gait speed measured as 15-foot walk at usual pace, later converted to meters/second.

Grip strength measured as an average of three trials on dominant hand.

Physical activity measured in kcals using Minnesota Leisure Time Activities and Paffenbarger Questionnaires

Exhaustion and weight loss were self-reported

Ankle-arm index calculated using supine blood pressures from the right arm and both ankles.

Cognitive function based on assessment with 30-point Mini-Mental State Examination with "normal" cognitive function being a score of 27 or greater.

Table 3. Correlations of population characteristics with gait speed for the full cohort and stratified by frailty status.

	Total Cohort (n=3744)		**Frail (n=220)**		**Intermediate (n=1691)**		**Non-frail (n=1833)**	
	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value
Demographics								
Age	-0.27*	<0.001	-0.30*	<0.001	-0.19	<0.001*	-0.15*	<0.001
Male	0.14	<0.001	0.24	<0.001	0.13	<0.001	0.13	<0.001
Black	-0.12	<0.001	-0.04	0.53	-0.06	0.02	0.01	0.66
Education ≥HS	0.21	<0.001	0.18	0.008	0.17	<0.001	0.16	<0.001
Frailty measures								
Grip strength (kg) (mean (SD))	0.24*	<0.001	0.18*	0.009	0.07	0.004*	0.14*	<0.001
Physical activity (total kcals) (median (IQR))	0.16*	<0.001	0.03*	0.67	-0.04	0.08*	0.08*	0.001
Presence of Exhaustion	-0.07	<0.001	-0.01	0.93	0.01	0.69	-0.02	0.34
Unintentional weight loss ≥ 10 lbs	-0.06	<0.001	-0.02	0.75	0.04	0.08	0.03	0.24
Health-Related factors								
BMI (kg/m2)	-0.15*	<0.001	-0.10*	0.13	-0.12	<0.001*	-0.09*	<0.001
Ankle-arm index (%)	0.14*	<0.001	0.12*	0.09	0.06	0.02*	0.11*	<0.001
Depression score (CES-D) Scale	-0.17*	<0.001	0.22*	0.001	0.007	0.77*	-0.10*	<0.001
Impaired Vision	-0.08	<0.001	-0.15	0.03	-0.07	0.009	-0.02	0.41
Arthritis	-0.13	<0.001	-0.06	0.35	-0.08	0.001	-0.06	0.01
Diabetes	-0.08	<0.001	-0.05	0.44	-0.06	0.02	-0.02	0.30
Chronic lung disease	-0.03	0.08	0.04	0.52	-0.04	0.08	-0.06	0.01
Cerebrovascular disease	-0.05	0.005	-0.01	0.85	-0.03	0.25	-0.02	0.37
Cardiovascular disease	-0.09	<0.001	-0.06	0.38	-0.05	0.03	-0.02	0.42
Normal cognition	-0.18	<0.001	-0.14	0.06	-0.11	<0.001	-0.11	<0.001

Spearman correlation coefficient unless otherwise specified. * = Pearson correlation coefficient.

Cognitive function based on assessment with 30-point Mini-Mental State Examination with "normal" cognitive function being a score of 27 or greater.

Table 4. Multivariable linear regression of *COMT* genotype predicting average gait speed (m/s) for the full cohort and stratified by frailty status.

	All Cohort (n=3744)		**Frail (n=220)**		**Pre-Frail (n=1691)**		**Non-Frail (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.

Table 5. Multivariable linear regression of *COMT* genotype predicting average gait speed (m/s) stratified by race in the full cohort and among frail subgroups.

	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**
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.

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