**The Genetic Correlation Between Cardiometabolic Disease and Functional Status in Long-lived Adults**

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BS, University of Pittsburgh, 2018

Submitted to the Graduate Faculty of the

Epidemiology

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2020

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

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**Abstract**

**Background:** Although measures can be taken to prevent or improve the outcomes of cardiometabolic diseases, they continue to be the leading causes of death among individuals aged 65 years or older. Because cardiometabolic disease is often accompanied by other aging comorbidities, like declines in cognitive and physical function, clinical research has begun evaluating the genetic determinants and joint etiologies of these comorbidities. The significance of studying these aging-based diseases enables us to better prepare for and improve the public health of a largely aging population.

**Hypothesis:**We hypothesize that cognitive and physical function measures share a common genetic basis with cardiometabolic disease measures including the common carotid intima-media thickness (IMT), inter-adventitial diameter (IAD), BMI, and systolic (SBP) and diastolic (DBP) blood pressure.

**Methods:**Participants for this study included a subset of families from the Long Life Family Study (n=4,953) who were recruited based on the family’s exceptional longevity (mean age=71.87years, 44% female). The carotid measures, IMT and IAD, were assessed using B-mode ultrasound. A number of physical and cognitive function measures (i.e., gait speed, grip strength, chair stand time, digital symbol substitution test (DSST), overall and working memory, semantic fluency, trail making tests, and fatigability), were also collected the time of cardiometabolic assessment. We used SOLAR to estimate the heritability and the genetic and phenotypic correlation between each pair of cardiometabolic and functional measures and adjusted for age, age2, sex, field centers, height, weight and smoking.

**Results:** All measures were significantly heritable (h2 range 0.133 to 0.621, all p$\leq $0.01).

There were significant genetic correlations (all p<0.05) between cognitive tests and blood pressures (DSST and semantic fluency with both SBP and DBP, overall memory with SBP, and Trail Time with DBP), BMI was genetically correlated with DSST and overall memory, and IMT with working memory. No significant genetic correlations were found between physical function and cardiometabolic disease measures.

**Conclusion:**These results suggest that cardiometabolic disease shares a common genetic basis with cognitive function, which allude to a potential biologic relationship between these aging-related traits. This finding may be particularly important in the clinical care of older adults with multiple chronic diseases.

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# **1.0 Introduction**

Although significant strides have been made in reducing the burden of cardiometabolic disease through treatment and prevention-based strategies, it remains highly prevalent within the United States and is the leading cause of death among men and women who are 65 years or older ([Benjamin et al., 2019](#_ENREF_10); [Flegal, Kruszon-Moran, Carroll, Fryar, & Ogden, 2016](#_ENREF_25); [Fryar CD, 2016](#_ENREF_29); ["Leading Causes of Death," 2017](#_ENREF_46)). Due to a largely aging population the prevalence of dementia, frailty, and cardiometabolic disease will likely continue to increase as time goes on, therefore motivating various scientists to investigate whether a biological link exists between these aging-related diseases. By elucidating the joint etiologies of cardiometabolic disease and the impairments in cognitive or physical function experienced due to aging, we may help prompt development of certain treatments which work to relieve the burden of disease.

## **1.1 Subclinical CVD**

A number of conditions or major cardiac events come to mind when the term *cardiovascular disease* is used in scientific literature—the most common being, myocardial infarction, stroke, hypertension or coronary artery disease. However, this essay will primarily focus on subsets of subclinical CVD, particularly atherosclerosis and elevated blood pressure. Atherosclerosis is defined as the buildup up of hardened fatty deposits termed as plaques within the artery wall, which may result in stenosis of the arteries (["Atherosclerosis,"](#_ENREF_7)). As the plaques continue to accumulate, they may rupture, subsequently causing a blood clot to form, thus impeding blood flow (["Atherosclerosis,"](#_ENREF_7)). The blood clot may then break off and travel to another part of the body, ultimately resulting in an ischemic stroke or heart attack (["Atherosclerosis,"](#_ENREF_7)). The detrimental effects of elevated blood pressure include an increased risk for stroke, myocardial infarction, aneurysms, and heart failure (["HBP and the Cardiovascular System,"](#_ENREF_37)). High blood pressure requires arteries to stretch in order to accompany the increased cardiac output. Excessive stretching can cause microscopic tears within the endothelial lining of the vasculature (["HBP and the Cardiovascular System,"](#_ENREF_37)). Those tears allow monocytes and LDL cholesterol to accumulate beneath the endothelial lining, thus causing plaques to form. In other words, hypertension may prompt the development of atherosclerosis (["A Mechanism by Which Hypertension Accelerates Atherosclerosis," 2018](#_ENREF_48)).

## **1.3 Obesity as a Risk Factor for Atherosclerosis and Cardiovascular Disease**

Obesity is most often numerically defined as having a BMI$\geq 30$ (kg/m2) but is more clearly defined as having excess fat, with excess visceral and abdominal fat being more closely tied to complications such as cardiometabolic disease. But obesity is not only a serious risk factor for cardiovascular and metabolic disease, it itself is a chronic condition that can result in serious debilitation. Prior research illustrates that obesity is a primary risk factor for a variety of clinical and subclinical cardiovascular conditions including dyslipidemia, hypertension, atherosclerosis, coronary artery disease, stroke and myocardial infarction([Akil & Ahmad, 2011](#_ENREF_1)). Multiple studies ([De Michele et al., 2002](#_ENREF_20); [Freedman et al., 2004](#_ENREF_27); [Rashid & Mahmud, 2015](#_ENREF_60)) have illustrated how BMI—a standardized measure of obesity—is positively associated with a particular surrogate measure of atherosclerosis—the intima media thickness (IMT) of the common carotid artery (CCA).

The common carotid artery—of which there is a right and left—extends from the aortic arch or brachiocephalic artery and branches off into smaller internal and external carotid arteries. Plaque can potentially accumulate all throughout the carotid artery including the CCA, the carotid bifurcation and internal carotid artery. Atherosclerotic severity can be assessed by measuring the intima-media thickness (IMT) of any of these regions. However, while fewer plaques tend to develop within the CCA, it is the region commonly used as a surrogate measure of subclinical atherosclerosis because it is easier to visualize using ultrasound compared to other regions such as the carotid bifurcation.

Because the arteries are enveloped in smooth muscle cells and elastic collagen, they can engage in vascular remodeling, in which they can expand or contract in order to maintain a certain level of homeostasis. Previous research ([Bots Michiel, Hofman, & Grobbee Diederick, 1997](#_ENREF_12)) has shown that when the IMT of the CCA measures 1.0 mm or greater, it suggests that there is some atherogenesis and not only vascular remodeling taking place. Therefore IMT can be used as a surrogate measure of atherosclerosis ([Bots Michiel et al., 1997](#_ENREF_12)). The accumulation of plaques beneath the intima layer of the artery can lead to a narrowing of the arterial lumen, and may be associated increased blood pressure or cardiac output, however elevations in blood pressure may occur prior to the onset of atherogenesis ([Bots Michiel et al., 1997](#_ENREF_12); [Kozakova et al., 2015](#_ENREF_43)). In fact, a study conducted by Kozakova et al., (2015) and colleagues identified that among obese patients who are at risk for cardiovascular events such as strokes and myocardial infarction, the common carotid artery may undergo adaptive remodeling. This form of remodeling may prompt IMT to increase in order to preserve circumferential wall stress which may affected by hemodynamic changes such as elevations in blood pressure ([Kozakova et al., 2015](#_ENREF_43)). Yet, the CCA IMT is still utilized as a surrogate measure for atherosclerosis, in which a greater value may be indicative of more severe atherosclerosis. Perhaps the excess fat which characterizes obesity may contribute to atherosclerosis and cardiometabolic disease risk, however the logistics as to how obesity may be related to atherogenesis ought to be more thoroughly investigated.

While some researchers were focused on the association between BMI and IMT, others ([Wildman, Mehta, Thompson, Brockwell, & Sutton-Tyrrell, 2004](#_ENREF_78)) chose to evaluate the relationship between obesity and another common carotid artery measure—the inter-adventitial diameter (IAD). The IAD does not only capture the arterial or lumen diameter, but it can also represent changes in IMT and the adventitial layer. As we age and with increased blood pressures and hemodynamic forces, the external layer of elastic collagen surrounding our blood vessels (which comprise the adventitia), begins to thin and our arteries’ ability to stretch is subsequently limited. This results in an inability of arteries to respond to increased cardiac output, and in turn, leads to increased blood pressure and hypertension risk ([Saba et al., 2016](#_ENREF_61)). Multiple studies have shown that greater carotid IAD is associated with an increased BMI ([Wildman, Mehta, Thompson, Brockwell, & Sutton-Tyrrell, 2004](#_ENREF_28)). This means that the presence of excess fat may speed up the process of vascular aging, thereby increasing the risk of hypertension. Taken together, these results suggest that excess fat stimulates the accumulation of atherosclerotic lesions thus increasing the rigidity of arteries, decreasing their ability to expand in response to hemodynamic forces, and subsequently increasing the risk for hypertension.

## **1.3 Heritability of Cardiometabolic diseases**

In order to elucidate the etiology of cardiometabolic diseases, researchers have been investigating whether there is a genetic cause to these diseases. Prior research has illustrated that obese, atherosclerotic, and hypertensive phenotypes may in fact by heritable. As indicated by prior genome-wide association studies (GWAS) and family-based studies ([Coady et al., 2002](#_ENREF_19); [Fox et al., 2003](#_ENREF_26); [Juo et al., 2004](#_ENREF_39); [Kuipers et al., 2019](#_ENREF_44); [North Kari et al., 2002](#_ENREF_53); [Rampersaud et al., 2008](#_ENREF_59)) BMI, IMT and IAD measurements are significantly influenced by genetics, and there may be certain variants which can be passed on from one generation to the next.

Using data on European and Hispanic populations, researchers Fox et al., (2003) and Juo et al., (2004) estimated the heritability of common carotid artery IMT to range from 0.35 to 0.39. These results indicate that almost 40% of the variation that occurs in IMT may be attributable to genetics. A similar study conducted in Native American populations yielded heritability estimates of 0.44 and 0.21 for the common carotid artery IAD and IMT, respectively ([North Kari et al., 2002](#_ENREF_53)). And, the heritability of the common carotid IMT among asymptomatic, Amish adults was estimated to be 0.29 ([Rampersaud et al., 2008](#_ENREF_59)).

In a study of multigenerational families with exceptional longevity (i.e., families with multiple siblings who were at least 79 years old), Kuipers et al., (2019) examined the heritability of subclinical-CVD measures by using linkage analysis to determine if any chromosomal regions throughout the genome may be linked to a particular phenotype or chronic disease. In these analyses certain regions along chromosomes 3 and 17 were linked to IAD and plaque severity, thus reinforcing the notion that there may be genetic variants associated with vascular aging and atherosclerosis. In addition to the linkage analysis, researchers estimated the heritability of common carotid artery’s IAD (h2r=0.68) and a range of values for the IMT measurements (0.38$\leq $ h2r $\leq $ 0.50). In culmination, these findings highlight that even into late adulthood, a significant component of an individual’s IAD and IMT may be determined by genetics.

Several family studies ([Coady et al., 2002](#_ENREF_19); [Juo et al., 2004](#_ENREF_39)) have also shown that the magnitude of an adult’s BMI may be partially determined by genetics. Coady estimated a heritability value of 0.39 among the families of the Framingham Heart Study and in a systemic review of 27 family studies, Elks estimated a range of heritability values from 0.24 to 0.81 ([Elks et al., 2012](#_ENREF_23)).

## **1.4 Aging and Functional Decline**

 As a whole, aging represents a major risk factor for the development of cardiometabolic, cardiovascular and cerebrovascular diseases. One pertinent complication of aging is the decline in cognitive and physical function. Using data from the Cardiovascular Health Study, Freid et al., defines frailty, a morbid state of declining physical function, as attributing to at least three out of the five phenotypic criteria: low grip strength, reduced gait speed, unintentional weight loss, greater physical fatigability, and a low energy expenditure ([Dolenc & Rotar-Pavlič, 2019](#_ENREF_22); [Fried et al., 2001](#_ENREF_28)). Reduced physical function or frailty among older adults can increase the risk for a variety of adverse health outcomes such as disability, falls, institutionalization and death ([Fried et al., 2001](#_ENREF_28)). Frailty has also been shown to accompany a variety of aging-related diseases, particularly heart failure, cardio and cerebrovascular disease, and chronic renal disease ([Weiss, 2011](#_ENREF_77)). The underpinnings for these associations stem from the fact that frail individuals are increasingly vulnerable to biological stressors, due to the decline in functional reserve among multiple physiological systems ([Bellumkonda, Tyrrell, Hummel, & Goldstein, 2017](#_ENREF_9)).

Cognitive decline, which is often associated with dementia, is characterized as a decrease in semantic fluency and general cognitive abilities, deficits in episodic and overall memory, and reductions in psychomotor speed and visual scanning ability ([Harada, Natelson Love, & Triebel, 2013](#_ENREF_35)). Researchers have partially attributed cognitive decline to grey matter atrophy within the prefrontal cortex and hippocampal regions ([Harada et al., 2013](#_ENREF_35)), which are partially caused by vascular risk factors such as hypertension and hypercholesteremia ([Zonneveld et al., 2015](#_ENREF_81)). Moreover, vascular dementia—a disease characterized by cognitive impairment due to reduced cerebral blood flow—is shown to be a serious complication of strokes which, are major cardiovascular events (["Vascular Dementia,"](#_ENREF_71)). This therefore leads to the question of whether aging-related decline in cognitive and physical function are associated with vascular aging and cardiometabolic disease in older lived adults.

## **1.5 Cardiometabolic Disease and Functional Decline among Older Adults**

Prior research has shown that aging-related functional decline appears to be associated with a number of cardiometabolic diseases, such as atherosclerosis, hypertension and obesity. Various studies have shown that measures of cognitive function—such as working memory, general cognition, and executive function—to be inversely associated with IMT among older lived adults ([Cerhan et al., 1998](#_ENREF_16); [Muller, Grobbee, Aleman, Bots, & van der Schouw, 2007](#_ENREF_49)). Thus, the presence of subclinical atherosclerotic depositions is negatively associated with cognitive function. Several longitudinal studies have also shown that having a larger IMT value during mid-life is associated with a greater incidence of dementia ([Komulainen et al., 2007](#_ENREF_42); [Sander et al., 2010](#_ENREF_63)), thus suggesting that atherosclerosis may be a causal factor in the pathophysiology of cognitive decline.

A study conducted in participants from the Cardiovascular Health Study found that frailty status was positively associated with clinical CVD—particularly congestive heart failure—as well as non-invasive subclinical CVD measures like carotid stenosis ([Newman et al., 2001](#_ENREF_51)). An additional study in 2017 replicated these observations, finding that carotid IMT was positively associated with frailty status ([Chang et al., 2017](#_ENREF_17)).

To our knowledge, no previous studies have tested for an association between IAD and cognitive decline, and there is conflicting evidence regarding an association between blood pressure and dementia. Several cross-sectional studies indicate an inverse association between blood pressure and measures of executive functioning such as psychomotor speed among older-lived adults ([Cacciatore et al., 1997](#_ENREF_15); [Harrington, Saxby, McKeith, Wesnes, & Ford, 2000](#_ENREF_36); [Kuo et al., 2004](#_ENREF_45); [Starr, Whalley, Inch, & Shering, 1993](#_ENREF_65); [Stewart, Richards, Brayute, & Mann, 2001](#_ENREF_67)), whereas others denote a positive association between late-life blood pressure and cognitive function ([Budge, De Jager, Hogervorst, Smith, & Ageing, 2002](#_ENREF_14); [Guo, Viitanen, Fratiglioni, & Winblad, 1996](#_ENREF_33); [Pandav, Dodge, DeKosky, & Ganguli, 2003](#_ENREF_55); [Qiu, Winblad, & Fratiglioni, 2005](#_ENREF_58)). Although hypertension was not used to exclude or categorize participants in any of the studies, the Budget et al., (2002) cohort (in which lower SBP was associated with impaired cognitive function) had a lower proportion of hypertensive patients compared to studies by Kuo et al., (2004) and Stewart et al., (2001) who reported blood pressure was inversely related to cognitive function. Moreover, when examining the difference in demographics across these studies, neither race nor education level appear to be influencing the associations shown.

Unlike cross-sectional studies, longitudinal studies have consistently shown mid-life hypertension to precede the onset of dementia, with measures of higher blood pressure commonly associated with declines in executive function, overall memory and semantic or categorical fluency ([Esme et al., 2017](#_ENREF_24); [Hajjar, Goldstein Felicia, Martin Greg, & Quyyumi Arshed, 2016](#_ENREF_34); [Oveisgharan & Hachinski, 2010](#_ENREF_54); [Qiu et al., 2005](#_ENREF_58); [Waldstein Shari et al., 2008](#_ENREF_75)).

Existing research indicates clinical frailty is positively associated with a few atherosclerotic measures including but not limited coronary artery calcification, IMT, IAD and the degree of carotid stenosis ([Avila-Funes et al., 2014](#_ENREF_8); [Newman et al., 2001](#_ENREF_51); [Veronese et al., 2017](#_ENREF_72)). Avila-Funes et al., specifically observed a positive cross-sectional association between clinical frailty and the atherosclerotic markers IMT and IAD and then hypothesized that frailty may accelerate vascular aging and atherogenesis. In addition to atherosclerosis, a few longitudinal studies have focused on how greater blood pressure at baseline is associated with a greater incidence in dementia ([Aprahamian et al., 2018](#_ENREF_5); [Vetrano et al., 2018](#_ENREF_73)). However, the reason for this association may be partly due to the reduction physiological reserves that frail individuals often experience.

Several studies have also reported a strong association between BMI and cognitive impairment. However, much like with blood pressure, these results appear to be conflicting. One study shows that having an obese BMI (BMI$\geq $30) during mid-life may predispose one to developing dementia in late life ([Anstey, Cherbuin, Budge, & Young, 2011](#_ENREF_4); [Veronese et al., 2017](#_ENREF_72)), while others show that a lower BMI during late-life is related to greater cognitive decline ([Arvanitakis, Capuano, Bennett, & Barnes, 2017](#_ENREF_6); [S. Kim, Kim, & Park, 2016](#_ENREF_40)). However, several studies report that among older adults, obesity may exacerbate aging-related declines in physical function therefore increasing the risk of frailty, reducing quality of life and increasing nursing home admissions ([Blaum, Xue, Michelon, Semba, & Fried, 2005](#_ENREF_11); [Porter Starr, McDonald, Weidner, & Bales, 2016](#_ENREF_57); [Villareal, Banks, Siener, Sinacore, & Klein, 2004](#_ENREF_74)). These results were confirmed by a Medicare beneficiary study which found that obese patients are more likely to suffer impairments in the ability to conduct daily living activities ([Wee et al., 2011](#_ENREF_76)).

## **1.6 Heritability of Cognitive and Physical Function**

Prior research ([Taporoski et al., 2019](#_ENREF_69); [Wilson et al., 2011](#_ENREF_79)) shows some measures of cognitive function, particularly working memory (h2r=0.42) and semantic fluency (h2r=0.21), are significantly heritable. Wilson et al., (2011) found that among a family-based cohort of older individuals, both episodic (h2r=0.47) and working memory (h2r=0.42) function have a significant genetic component, independent of *APOE* genotype, which is a variant that predisposes individuals to Alzheimer’s Disease. Taporoski et al., (2019) utilized a Brazilian family-based study to estimate the genetic influence exerted over semantic fluency. Although the Brazilian study does not place an inherent focus on aging populations, they are one of the few studies to estimate heritability values for a cognitive function measurement. This result is in contrast to measurements of frailty or physical function, in which there are almost no studies evaluating the potential heritability of reduced physical function indicators. However, an existing twin study ([Young, Glaser, Spector, & Steves, 2016](#_ENREF_80)) identified that an individual’s frailty score—as determined by the Rockwood Frailty Index--is significantly attributable to both genetic (h2r=0.45) and environmental (percent explained by covariates=52%) effects, with monozygotic twins experiencing significantly greater similarity in frailty scores compared to dizygotic twins.

## **1.7 Pleiotropy of Functional Decline and Cardiometabolic Disease**

 Pleiotropy is traditionally regarded as a phenomenon in which a single locus affects two or more phenotypic traits ([Stearns, 2010](#_ENREF_66)). Investigating potential pleiotropy between chronic diseases can help us better understand the underlying pathology of a disease and the biological function of affiliated genes. Genetic correlation is a quantitative parameter of genetic similarity between phenotypes or a numerical estimate of pleiotropy ([van Rheenen, Peyrot, Schork, Lee, & Wray, 2019](#_ENREF_70)). Calculating genetic correlation provides insight into the degree of genetic similarity between chronic diseases, thus suggesting that there may common mechanisms in terms of disease causality ([van Rheenen et al., 2019](#_ENREF_70)).

Although the ε4 allele of the *APOE* gene is considered as one of the most common genetic risk factors for Alzheimer’s Disease and many studies have looked at its impact on cognitive decline, this allele has also been extensively researched in regard to its association with lipid metabolism. A recent study found that APOE gene encodes a lipid transport protein utilized in cholesterol metabolism ([Broce et al., 2019](#_ENREF_13)), thus suggesting that this gene may be implicated in the causality of both Alzheimer’s disease and atherosclerosis. Similarly, a meta-analysis found that a certain *FTO* genetic variant associated with high BMI is simultaneously associated with structural brain atrophy within the prefrontal cortex among older-lived adults, thus leading to impairments in semantic fluency and general cognition, as well as an increased risk for Alzheimer’s disease ([Ganeff, Bos, Heemst, & Noordam, 2019](#_ENREF_30)). These results suggest that there is a common genetic determinant between cognitive decline and obesity. Currently limited information is available on the potential pleiotropy underlying frailty or reduced physical function and cardiometabolic disease.

## **1.8 Purpose**

Many existing studies point to a phenotypic association between cardiometabolic disease and cognitive decline and frailty. However, the literature lacks information regarding the potential pleiotropic effects or shared genetic determinants between these conditions. Investigating the degree to which there may be a shared etiology between functional decline and cardiometabolic disease may help to elucidate the pathophysiology of said diseases. Therefore, the purpose of this study was to determine the extent to which measures of cardiometabolic disease and genetically and phenotypically correlated with functional status in long-lived adults from the Long Life Family Study (LLFS).

# **2.0 Methods**

## **2.1 Long Life Family Study (LLFS) Cohort**

 The LLFS cohort is comprised of multigenerational families selected for exceptional longevity. The study recruited participants from three sites across the United States (Pittsburgh, PA; Boston, MA; New York, NY) and Denmark, beginning in 2005. Among those recruited include long-lived siblings (aged 80+ years in the US and 90+ years in Denmark), and additional siblings, and all interested spouses, as well as any interested offspring. Subjects underwent extensive examinations to determine which key phenotypes impact longevity, including chronic diseases, risk factors, cognitive function, and physical function. For the purpose of this analysis, we used data on a subset of 2,050 participants who participate in the second study visit conducted from 2014 to 2017 and who had data on all necessary characteristics described below. Detailed characteristics of the cohort have been described elsewhere ([Newman et al., 2011](#_ENREF_50); [Sebastiani et al., 2009](#_ENREF_64)).

## **2.2 Data Collection**

All cardiometabolic and functional measures were collected during an in-home visit. For this analysis, the cardiometabolic measures we chose to focus on include the IMT and IAD of the common carotid artery, systolic and diastolic blood pressure, and BMI. The carotid measures were obtained via B-mode ultrasound imaging and calculated as a mean of the right and left common carotid arteries. The imaging was conducted by centrally trained and certified research assistants using a GE LOGIQ 3 BT12 Ultrasound System. The IMT and IAD measurements are obtained when 50% of the bulb is visible, as to capture the common carotid artery at its widest point. A certification protocol of at least 10 re-scans was conducted per technician to ensure reproducibility and accuracy. Systolic and diastolic blood pressure (SBP and DBP, respectively) were obtained sitting with an automated blood pressure machine and averaged over three measurements (BP-tru BPM 300, VMS MedTech, Coquitlam, Canada). For BMI, height was measured using a Handi-stat set (Perspective Enterprises, Portage, MI) to the nearest 0.1 cm and weight was determined using an electronic scale (SECA 841, Hanover, MD). The actual BMI measurement was calculated as weight(kg)/height(m2).

Several validated functional tests—both cognitive and physical in nature—were also administered during the in-home visit. The cognitive tests used in this analysis include the digit symbol substitution test (DSST), the number span test, the animal fluency test, logical memory tests, and the trail making tests. The DSST is used to measure a range of general cognitive operations including executive functions such as planning and strategizing, psychomotor speed, attention, and visuoperceptual functions such as manual dexterity ([Jaeger, 2018](#_ENREF_38)). The number span test estimates verbal working memory (i.e., short-term memory) which is often used in everyday tasks such as remembering a telephone number or understanding long sentences (["Digit Span Brain Task: Cambridge Brain Sciences,"](#_ENREF_21)). The animal fluency test provides a measure of semantic fluency, by asking participants to recall all the animals they can within 60 seconds. Two logical memory tests (IA and IIA) were administered to measure overall and episodic memory by asking the participant to immediately recall a story verbatim (immediate recall) and then 20 to 30 minutes (delayed recall) ([Chapman et al., 2016](#_ENREF_18)). The trail making tests (part A and part B) were then used to measure psychomotor speed and visual scanning ability ([Salthouse, 2011](#_ENREF_62)). In part A, participants were asked to draw lines connecting 25 randomly distributed circles on a sheet of paper. The circles were labeled 1-25 and they were instructed to connect the circles in ascending order ([Salthouse, 2011](#_ENREF_62)). In Part B, there are circles labelled numerically (1-13) and others are labeled alphabetically (A-L). Participants were asked to connect the circles in an ascending pattern, but to alternate between numbers and letters ([Salthouse, 2011](#_ENREF_62)).

Several physical function exams were also administered. Among those included in the analysis were grip strength, gait speed, and chair stand time. Grip strength was calculated using an isometric dynamometer (Jamar Hydraulic Hand Dynamometer, Lafayette, IN) over an average of two measurements and was rounded to the nearest 2 kg. Gait speed is reported in m/s and is the time required to walk 15 meters in a straight-line, on a level indoor surface ([Peel, Kuys, & Klein, 2012](#_ENREF_56)). Chair stand time (s) is how long it takes an individual—namely an older adult—to stand up from a straight-back chair without any assistance (i.e., not using their arms). Lastly, the Pittsburgh Fatigability Scale (PFS) was employed to measure the perceived mental and physical fatigability of participants ([Glynn et al., 2015](#_ENREF_32)).

Potential covariates such as smoking status and type two diabetes were also assessed. Smoking status was defined as past, current or never. For analysis, diabetes was defined as use of diabetes medication or a fasting glucose ≥ 126 mg/dL. Diabetes was confirmed by conducting an inventory of all medications—prescription and over-the-counter—taken over the past two weeks ([Newman et al., 2011](#_ENREF_50)). Additionally, date of birth was validated using an official document such as a driver’s license or birth certificate and sex was self-reported.

## **2.3 Statistical Analysis**

 The program SOLAR enables users to account for family structure (i.e., relatedness) while using maximum-likelihood based methods to estimate the residual heritability (h2r) of outcome measures as well as the variance attributable to fixed covariate effects ([Laura Almasy & Blangero, 1998](#_ENREF_2)). SOLAR can also estimate the genetic and phenotypic correlations between pairs of outcomes, such as cardiometabolic traits and functional measures, as done in the current analysis ([Laura Almasy & Blangero, 1998](#_ENREF_2); [L. Almasy, Dyer, & Blangero, 1997](#_ENREF_3)). Phenotypic correlations (ρ) are based on the estimated heritability (h2r), genetic (ρG), and environmental (ρE) correlation between two traits as illustrated in the following equation, which calculates the phenotypic correlation between trait 1 and trait 2: ρ12 = ρG√h21)(√h22) + ρE(1−√h21)(1−√h22). When estimating the residual heritability and correlation values between trait pairs using covariance methods in SOLAR, we additionally adjusted for age, age2, sex, field centers, height, weight, and whether an individual currently smokes. The only difference was when estimating the residual heritability and correlation values for BMI, we additionally adjusted for type two diabetes mellitus and removed height and weight as potential covariates, as they are used to calculate BMI. If any of the outcome variables utilized in this analysis were non-normal as determined by an abnormal residual kurtosis value in SOLAR, a natural log transformation was used to normalize the distribution. All SOLAR-based calculations were conducted on a Mac OSX 10.14.6.

# **3.0 Results**

 The mean age across multiple generations was 71.87 years (SD$\pm 11.46), $and 44% of all participants were female (Table 1). After adjustment, all studied outcome measures were significantly heritable (range: 0.13 for SBP to 0.62 for IAD; all p$\leq $0.01; Table 2). Model covariates including age, sex, field center, smoking, body size (not for BMI), and diabetes (BMI only) explained between 11% (BMI) and 71% (grip strength) of the variance in outcome measures.

Phenotypic correlations between cardiometabolic traits and functional measures are shown in Table 3. BMI had significant phenotypic correlations with all of the functional measures except for overall memory and time required to complete trail A. Both systolic (ρ=0.061) and diastolic (ρ=0.063) blood pressure were significantly (all p$\leq 0.04)$ phenotypically correlated with grip strength. IAD was negatively correlated with DSST score (ρ=-0.052) and gait speed (ρ=-0.048) but positively correlated with chair stand time (ρ=0.051). IMT was not phenotypically correlated with any functional measure.

Genetic correlations between cardiometabolic traits and functional measures are shown in Table 4). There were significant (p≤ 0.04) genetic correlations between DSST and SBP (ρG =-0.374), DBP (ρG=-0.61), and BMI (ρG=-0.21). Overall memory was genetically correlated with SBP (ρG=-0.454) and BMI (ρG=-0.34); whereas, working memory was genetically correlated with IMT (ρG=-0.264). Semantic fluency was genetically correlated with systolic (ρG=-0.396) and diastolic (ρG=-0.445) blood pressures. The time required to complete Trail A was genetically correlated to diastolic (ρG=0.485) but not, systolic blood pressure. The only significant genetic correlation with physical function measures was with BMI and included gait speed (ρG=-0.393) and chair stand time (ρG=0.297).

Environmental correlations, ie. the correlation due to the included covariates, between cardiometabolic traits and functional measures are shown in Appendix B.

# **4.0 Discussion**

The results from this study provide evidence of shared genetic variance between cognitive function and cardiometabolic disease in long-lived families. This study also confirms previous reports of a phenotypic association between decreased physical function and increased cardiometabolic disease. The significant pleiotropic results suggest a shared pathology among aging-related chronic diseases. Specifically, these results indicate that cardiometabolic disease is not only a risk factor for cognitive decline, but is also partially driven by the same genes.

Even though we have identified a significant genetic correlation between the cardiometabolic and cognitive function, there was a lack of significant phenotypic correlation between those measures. A potential reason for this is that the phenotypic correlation is the aggregate of both genetic and environmental correlations; ρP = ρg\*(√h12)\*(√h22) + ρe\*(√1-h12)\*(√1-h22). As in the case of working memory and IMT, the genetic correlation denotes a negative association, but the environmental correlation obtains a positive correlation coefficient (Appendix B). Therefore, the environmental effect may negate the shared genetic effect in the phenotypic manifestation of working memory and IMT.

Another potential reason for this incongruity is the wide age range in LLFS. Due to this being a multigenerational, family-based study, the participants range in age from 42 to 100 years, which may influence the measured phenotypes. BMI is an excellent example of the incongruity seen among different age groups. Among younger adults, an increased BMI is often associated with an increased risk of chronic disease and mortality. However, a lower BMI among older, frail adults is often associated with an increased risk of morbidity and mortality. Therefore, when trying to compare the effects of BMI on some physical function measurements, the phenotypic correlations integrate all of the varied effects a greater BMI represents depending on age. Moreover, recent research has found that obesity can cause similar declines in physical function as frailty. These results indicate that obesity among younger adults can exacerbate the effects of aging ([Strandberg et al., 2013](#_ENREF_68)). Nonetheless, given the family study design, we were able to identify significant pleiotropic effects regardless of the measured chronic disease phenotypes.

When trying to provide a biological explanation for the genetic correlations observed between cardiometabolic disease and cognitive function, the answer may lie in the anatomy. In this analysis, IMT is a surrogate measure for atherosclerosis within the common carotid artery. The common carotid artery branches off into the internal and external carotid arteries and the internal carotid artery is responsible for delivering oxygenated blood to the anterior cerebrum. When plaque accumulates at the bifurcation of the common carotid artery or within the internal or common carotid artery, this may increase stenosis, impeding blood flow to the cerebrum and resulting in neuron dysfunction or death ([Komulainen et al., 2007](#_ENREF_42)). Similarly, mid-life hypertension may increase the risk for late-life cognitive decline by limiting neurovascular blood flow. Therefore, some of the shared pathophysiology between IMT and cognitive function could be mechanisms related to plaque accumulation. Researchers from longitudinal studies have also theorized that limited blood flow as a result of hypertension may increase the reactivity of CO2 thus causing a failure in cerebral autoregulation which increases the risk of microvascular brain damage (Gąsecki, Kwarciany, Nyka, & Narkiewicz, 2013).

Prospective studies primarily report obesity as a risk factor for cognitive decline. They suggest that obesity can impact cognitive function by promoting atrophy of the hippocampal neurons, which are responsible for the consolidating information from our short-term and long-term memory. Based on their study results, Nyugen and colleagues specifically state that a high fat diet, which may cause obesity, is associated with greater apoptosis within the hippocampus and hypothalamus ([Nguyen, Killcross, & Jenkins, 2014](#_ENREF_52)). Obesity has also been documented as a prominent risk factor for atherosclerosis. When atherosclerotic lesions develop in the large cerebral arteries this may impair cerebral blood flow and cause oxidative stress thus triggering apoptosis of the hippocampal neurons ([Nguyen et al., 2014](#_ENREF_52)).

The results of this study suggest that cardiometabolic disease may not only increase the risk for cognitive impairments as prior phenotypic studies have observed, but there may be a common genetic mechanism causing both cardiometabolic disease and cognitive decline. Moreover, due to the cross-sectional nature of this study design, a lack of temporality prevents us from knowing whether cardiometabolic disease occurred prior to the onset of cognitive impairment, or if they occurred contemporarily. Therefore, the results of this study posit cardiometabolic disease as not only a pertinent risk factor for cognitive impairment, but it implies that both subclinical CVD and obesity are system-wide diseases that may theoretically share etiology with aging-related, cognitive dysfunction.

Importantly, because the main objective of the LLFS is to discover factors associated with exceptional longevity, the older-lived subjects may be healthier compared to the general population. Moreover, because this is a family-based study, an inherent genetic similarity may already exist between family members and therefore we may be at risk of overestimating the genetic correlation or heritability of certain traits ([Y. Kim et al., 2015](#_ENREF_41); [Mayhew & Meyre, 2017](#_ENREF_47)). Nonetheless, these novel results add to the existing literature on the phenotypic association between cardiometabolic disease and functional decline, and should motivate researchers to investigate the shared pathophysiology between these aging-related diseases.

## **4.1 Public Health Significance**

 Cardiometabolic disease is the largest cause of mortality among men and women within the United States and the number of older individuals is increasing (["Leading Causes of Death," 2017](#_ENREF_46)), thus, the burden of substantial functional decline and cardiometabolic disease will only continue to rise. A deeper understanding of the etiology of aging-related disorders such as dementia, CVD and frailty, may help to develop revolutionary practices that can ease the burden of such diseases through treatment or prevention strategies. Moreover, simply understanding that diseases such as dementia and CVD may share some of the same molecular underpinnings, can help prepare investigators and clinicians in treating an aging population.

## **4.2 Conclusion**

 The overall findings of this study suggest that cardiometabolic disease and cognitive function share common genetic determinants; and, therefore may have some pathophysiological mechanisms in common. The next step for this line of research will include identifying genes and/or pathways responsible for the pleiotropy in these traits. In addition, it will be important to replicate these findings in other family-based studies that are more reflective of the general adult population.

# **Appendix A Tables**

**Table 1. Characteristics of LLFS Participants**

|  |  |
| --- | --- |
|  | **Mean (SD) or Frequency** |
| Age (years) | 71.87 (11.46) |
| Female (%) | 44% |
| Current Smoking (%) | 4.2% |
| Diabetes (%) | 1.2% |
| Height (cm) | 166.32 (10.04) |
| Weight (kg) | 75.99 (16.56) |
| IMT (mm) | 0.858 (0.16) |
| IAD (mm) | 7.82 (0.89) |
| SBP (mmHg) | 134.23 (18.62) |
| DBP (mmHg) | 73.87 (10.46) |
| BMI (kg/m2) | 27.36 (4.93) |

**Table 2. Residual Genetic Heritability Estimates**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **H2** | **H2 p-value** | **% explained by covariates** |
| **Cardiometabolic Measures** |  |  |  |
| Mean IMT (mm) | 0.478 | 2.83E-17 | 39.9% |
| Mean IAD (mm) | 0.621 | 3.94E-22 | 41% |
| SBP (mmHg) | 0.133 | 0.01 | 11.1% |
| DBP (mmHg**)** | 0.142 | 0.004 | 25.2% |
| BMI (kg/m2) | 0.497 | 1.07E-16 | 5.82% |
| **Cognitive Function** |  |  |  |
| DSST | 0.417 | 5.38E-15 | 49% |
| Overall Memory | 0.285 | 4.63E-08 | 21.3% |
| Working Memory | 0.518 | 2.25E-17 | 28% |
| Semantic Fluency | 0.397 | 4.77E-13 | 25.5% |
| Mental Fatigability | 0.218 | 9.4E-06 | 28% |
| Time to Complete Trail A | 0.220 | 6.8E-06 | 43.7% |
| Time to Complete Trail B | 0.319 | 1.0E-07 | 46.4% |
| **Physical Function** |  |  |  |
| Physical Fatigability | 0.290 | 5.4E-09 | 37.2% |
| Grip Strength (kg) | 0.454 | 5.93E-18 | 71.1% |
| Gait Speed (m/s) | 0.164 | 0.002 | 54.2% |
| Chair Stand Time (s) | 0.264 | 1.1E-05 | 25.5% |

Covariate adjustments for carotid, BP, and functional measures: age, age2, sex, field centers, height, weight, and whether an individual currently smokes;

Covariate Adjustments for BMI: age, age2, sex, field centers, diabetes and whether an individual currently smokes

**Table 3. Adjusted Phenotypic Correlations between Cardiometabolic Disease Measures and Functional Decline Measures**

|  |  |
| --- | --- |
|  | **Phenotypic Correlation (ρP)** |
| **IMT** | **IAD** | **SBP** | **DBP** | **BMI** |
| **DSST** | -0.042 | -0.052 | -0.029 | -0.033 | -0.092 |
| **Overall Memory** | -0.003 | 0.027 | -0.043 | -0.018 | -0.016 |
| **Working Memory** | -0.013 | 0.024 | -0.020 | -0.026 | -0.067 |
| **Semantic Fluency** | -0.003 | -0.003 | -0.023 | -0.017 | -0.065 |
| **Mental Fatigability** | -0.032 | 0.028 | -0.008 | 0.004 | 0.10 |
| **Time to Complete Trail A** | -0.009 | 0.005 | 0.028 | 0.034 | 0.019 |
| **Time to Complete Trail B** | 0.024 | 0.012 | 0.035 | 0.032 | 0.065 |
| **Physical Fatigability** | 0.005 | 0.069 | -0.036 | -0.031 | 0.211 |
| **Grip Strength** | -0.035 | -0.034 | 0.061 | 0.063 | 0.053 |
| **Gait Speed** | -0.026 | -0.048 | 0.009 | -0.006 | -0.207 |
| **Chair Stand Time** | 0.013 | 0.051 | -0.024 | -0.034 | 0.149 |

Values in red indicate a statistically significant correlation estimate (p$\leq $0.04);

Covariate adjustments for carotid and BP measures: age, age2, sex, field centers, height, weight, and whether an individual currently smokes;

Covariate Adjustments for BMI: age, age2, sex, field centers, diabetes and whether an individual currently smokes

**Table 4. Adjusted Genetic Correlations between Cardiometabolic Disease Measures and Functional Decline Measures**

|  |  |
| --- | --- |
|  | **Genetic Correlation****ρG (SE)** |
| **IMT** | **IAD** | **SBP** | **DBP** | **BMI** |
| **DSST** | -0.015 (0.104) | -0.026 (0.098) | -0.374 (0.19) | -0.61 (0.186) | -0.21 (0.105) |
| **Overall Memory** | 0.11 (0.32) | 0.065 (0.092) | -0.454 (0.223) | -0.355 (0.215) | -0.34 (0.134) |
| **Working Memory** | -0.264 (0.102) | 0.064 (0.093) | -0.236 (0.184) | -0.121 (0.172) | -0.175 (0.10) |
| **Semantic Fluency** | 0.054 (0.111) | 0.188 (0.123) | -0.396 (0.202) | -0.445 (0.196) | -0.143 (0.112) |
| **Mental Fatigability** | 0.075 (0.139) | 0.095 (0.13) | 0.231 (0.237) | 0.159 (0.232) | 0.022 (0.147) |
| **Time to Complete Trail A** | -0.071 (0.136) | 0.089 (0.105) | 0.168 (0.238) | 0.485 (0.232) | 0.129 (0.137) |
| **Time to Complete Trail B** | 0.083 (0.125) | -0.071 (0.12) | 0.18 (0.225) | 0.264 (0.209) | 0.208 (0.129) |
| **Physical Fatigability** | 0.101 (0.126) | 0.055 (0.117) | -0.002 (0.219) | -0.101 (0.206) | 0.129 (0.126) |
| **Grip Strength** | -0.089 (0.102) | -0.008 (0.095) | -0.238 (0.206) | -0.277 (0.189) | 0.017 (0.102) |
| **Gait Speed** | 0.01 (0.163) | 0.135 (0.162) | 0.027 (0.305) | -0.217 (0.269) | -0.393 (0.154) |
| **Chair Stand Time** | -0.064 (0.137) | -0.01 (0.13) | 0.257 (0.263) | 0.198 (0.235) | 0.297 (0.13) |

Values in red indicate a statistically significant correlation estimate (p$\leq $0.04);

Covariate adjustments for carotid and BP: age, age2, sex, field centers, height, weight, and whether an individual currently smokes;

Covariate Adjustments for BMI: age, age2, sex, field centers, diabetes and whether an individual currently smokes

# **Appendix B Supplemental Table**

**Table 5. Environmental Correlations between Cardiometabolic Measures and Functional Decline Measures**

|  |  |
| --- | --- |
|  | **Environmental Correlation****ρE (SD)** |
| **IMT** | **IAD** | **SBP** | **DBP** | **BMI** |
| **DSST** | -0.064 (0.076) | -0.081 (0.092) | 0.087 (0.063) | 0.173 (0.062) | 0.0009 (0.08) |
| **Overall Memory** | -0.07 (0.075) | -0.014 (0.081) | 0.066 (0.073) | -0.071 (0.058) | -0.182 (0.076) |
| **Working Memory** | 0.231 (0.089) | -0.03 (0.108) | 0.063 (0.06) | 0.011 (0.07) | 0.044 (0.092) |
| **Semantic Fluency** | -0.048 (0.079) | -0.158 (0.09) | 0.098 (0.064) | 0.125 (0.063) | -0.004 (0.081) |
| **Mental Fatigability** | -0.088 (0.067) | -0.01 (0.081) | -0.06 (0.054) | -0.029 (0.052) | 0.148 (0.067) |
| **Time to Complete Trail A** | 0.022 (0.065) | -0.08 (0.095) | -0.001 (0.053) | -0.064 (0.052) | -0.037 (0.068) |
| **Time to Complete Trail B** | -0.014 (0.077) | 0.085 (0.094) | -0.003 (0.062) | -0.032 (0.06) | -0.03 (0.08) |
| **Physical Fatigability** | -0.053 (0.071) | 0.089 (0.085) | -0.046 (0.056) | -0.013 (0.054) | 0.27 (0.068) |
| **Grip Strength** | -0.011 (0.077) | -0.065 (0.093) | 0.166 (0.062) | 0.189 (0.060) | 0.087 (0.083) |
| **Gait Speed** | -0.044 (0.067) | -0.160 (0.081) | 0.006 (0.054) | 0.034 (0.053) | -0.144 (0.068) |
| **Chair Stand Time** | 0.059 (0.076) | 0.105 (0.091) | -0.091 (0.62) | -0.092 (0.059) | 0.061 (0.08) |

Values in red indicate a statistically significant correlation estimate (p$\leq $0.048)

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