

# Nancy Chiles Shaffer

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## **EDUCATION:**

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**University of Maryland, Baltimore (UMB), Department of Epidemiology and Public Health, Division of Gerontology, Baltimore, MD**

PhD in Gerontology, December 2014

Coursework: Theory and Methods of Gerontology, Epidemiology of Aging, Biology of Aging, Psychology of Aging, Issues in Aging Policy, Sociocultural Gerontology

Dissertation Title: Diabetes, Sarcopenia, Peripheral Nerve and Lower Extremity Functions in Older Adults.

*Honors:* Meyerhoff Graduate Fellowship, Epidemiology of Aging T32 Award

**UMB, Department of Epidemiology and Public Health, Baltimore, MD**

MS in Epidemiology, December 2014

Coursework: Principles of Biostatistics, Principles of Epidemiology, Regression Analysis, Health Survey Research Methods, Responsible Conduct in Research, Statistical Methods in Epidemiology, Pharmacoepidemiology, Infectious Disease Epidemiology, Survival Analysis, Observational Studies in Epidemiology, Longitudinal Analysis

**University of Maryland Baltimore County (UMBC), Baltimore, MD**

BS in Biological Science, May 2009

*Honors:* Meyerhoff Scholar, MARC U\*STAR T34 Award

## **PROFESSIONAL RESEARCH EXPERIENCE:**

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2009-Present Graduate Research Assistant

### **Baltimore Hip Studies, UMB**

- Data Management: data filing and organization, data entry, data cleaning using SAS, maintain data codebooks
  - Specialization in AHFS Drug Codes
- Data Analyst: developed and conducted all analyses using SAS for independent research projects: Education and recovery from a hip fracture, Sarcopenia after hip fracture, Sarcopenia and BMD after hip fracture
- Laboratory Assistant: processing blood, processing urine, DNA extraction, maintain Freezerworks database
- Reviewer in Training for several manuscripts in the Journals of Gerontology
- Presented oral presentations at conferences for independent research projects
- Manuscripts in preparation for independent research projects
- Submitted and was scored on NRSA F31 Grant (awaiting funding decision)

- Assisted in preparing presentations on risk factors for hip fracture for community education and outreach

2011- 2012 Research Assistant

**Alliance for Aging Research and UMB**

- Evaluated the validity and reliability of a broad range of physical performance measures in aging population and determined recommendations
- Reviewed methodological issues with clinical trials on physical function and disability and determined recommendations
- Reviewed current issues, documents, and Federal Drug Administration (FDA) regulations and procedures for studies of lower extremity function and disability and developed new methods to ensure optimum research results
- Contributed to discussions and planning sessions on FDA programmatic and policy related issues
- Developed, analyzed, and reviewed operation policies for clinical trials of lower extremity function and disability in older adults.
- Prepared written correspondence regarding clinical trial outcomes and methodology and recommended changes for a Letter of Intent submitted to the FDA

2008 MARC Scholar Summer Research Assistant

**National Institute on Aging (NIA), Laboratory of Epidemiology, Demography, and Biometry, T34 08663**

- Data entry using Microsoft Access
- Developed independent research project on diabetes, nerve function, and physical function in older adults.
- Developed and conducted analysis using SAS for research project
- Publication: **Chiles, N., Phillips, C., Volpato, S., Bandinelli, S., Ferrucci, L., Guralnik, J., Patel, KV.** Diabetes, Peripheral Neuropathy, and Lower Extremity Function. Journal of Diabetes and its Complications, October 2013

Summer 2007 MARC Scholar Research Assistant

**UMB, Department of Epidemiology and Public Health, Division of Gerontology, T34 08663**

- Developed independent research project on education and its role in recovery from a Hip Fracture
- Developed and conducted analysis using SAS
- Manuscript in preparation

2006- 2007 Meyerhoff Scholarship Research Assistant

**UMBC, Biological Sciences Department**

- Conducted research on Bovine Melanopsin and Stomatopod Opsin

using several techniques

- PCR; DNA ligation; Cell transformation; DNA sequencing

Summer 2006 Meyerhoff Scholarship Summer Research Assistant

**NIA**

- Researcher for the HANDLS epidemiology Study
  - Enrolled and consented participants
  - Administered questionnaires to participants in person and via phone
  - Data collection of objective measures of neighborhood characteristics for 12 Baltimore city neighborhoods
  - Communicated directly with participants, community members and leaders, researchers, and NIA investigators and staff.

2005-2006 Meyerhoff Scholarship Research Experience

**UMBC, Department of Sociology and Anthropology**

- Researcher with the HANDLS epidemiology Study
  - Data collection of objective measures of neighborhood, grocery store, and market characteristics for 12 Baltimore city neighborhoods
  - Youngest research team leader for the study
  - Managed and trained junior researchers, and developed and evaluated current study practices, operations, and organization structure to determine best practices and improve effectiveness and efficiency of data collection
  - Participated in and presented at study meetings to discuss best practices and current problems or concerns
  - Reviewed legal legislative laws and polices outlining available assistance and programs for participants
  - Conducted independent study assessing the health and quality of care received by study participants and assessed their utilization of assistance programs

#### **MANUSCRIPT PUBLICATIONS:**

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1. **Chiles, N.**, Phillips, C., Volpato, S., Bandinelli, S., Ferrucci, L., Guralnik, J., Patel, KV. Diabetes, Peripheral Neuropathy, and Lower Extremity Function. Accepted, Journal of Diabetes and its Complications, October 2013 (E-published ahead of print).
2. Orwig D., **Chiles N.**, Jones M., Hochberg, M. Osteoporosis in Men: Update 2011. Rheum Dis Clin North Am 2011 37 (3): 401-14.

## **MANUSCRIPTS IN PREPARATION:**

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1. **Chiles, N.,** Alley, D., Hawkes, W., Orwig, D. Sarcopenia and Functional Recovery after a Hip Fracture.
2. **Chiles Shaffer, N.,** Orwig, D., Magaziner, J. Changes in Body Composition and Function after Hip Fracture: Interventions and their Timing to Address Deficits and Desired Outcomes.
3. **Chiles, N.,** Gruber-Baldini, A., Orwig, D., Magaziner, J. Education and Its Role in Recovery from a Hip Fracture.
4. **Chiles, N.,** Huang, Y., Guralnik, J., Strotmeyer, E., Ryan, A., Orwig, D. Prevalence of Sarcopenia by Diabetes Status in Older Adults.
5. **Chiles, N.,** Huang, Y., Guralnik, J., Strotmeyer, E., Ryan, A., Orwig, D. The Effect of Peripheral Nerve Function on Sarcopenia by Diabetes Status among Older Adults.
6. **Chiles, N.,** Huang, Y., Guralnik, J., Strotmeyer, E., Ryan, A., Orwig, D. The Effects of Sarcopenia and Peripheral Nerve Function on Lower Extremity Function by Diabetes Status among Older Adults.

## **PUBLISHED ABSTRACTS AND PRESENTATIONS:**

---

1. **Chiles, N.,** Alley, D., Hawkes, W., Orwig, D. Sarcopenia and Functional Recovery after a Hip Fracture. *Gerontologist* 2011 51: 230.
2. **Chiles, N.,** Gruber-Baldini, A., Orwig, D., Magaziner, J. Education and Its Role in Recovery from a Hip Fracture. *Gerontologist* 2010 50: 502. \*Also presented at Research on Aging Showcase, Johns Hopkins University; Graduate Research Conference, University of Maryland Baltimore.
3. **Chiles, N.,** Guralnik, J., Phillips, C., Patel, K. Diabetes, Peripheral Neuropathy, and Lower-Extremity Function. *Gerontologist* 2010 50: 335. \*Also presented at Annual Biomedical Research Conference for Minority Students; NIA STAR Poster Day, National Institute on Aging; NIA Intramural Summer Internship Program Poster Day.

## **PRESENTATIONS:**

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1. **Chiles Shaffer, N.,** Huang, Y., Strotmeyer, E.S., Guralnik, J., Harris, T.B., Newman, A.B., Ryan, A.S., Orwig, D. Diabetes, Sarcopenia, Peripheral Nerve and Lower Extremity Function among Older Adults. “Baltimore Longitudinal Study on Aging Longitudinal Studies Section Lecture”, National Institute on Aging, Summer 2014.
2. **Chiles Shaffer, N.,** Huang, Y., Strotmeyer, ES., Guralnik, J., Harris, TB., Newman,

AB., Ryan, AS., Orwig, D. Sarcopenia Prevalence by Diabetes in Older Adults in the Health ABC Study. Johns Hopkins Research on Aging Showcase

3. **Chiles, N.**, Gruber-Baldini, A., Orwig, D., Magaziner, J. Education and Its Role in Recovery from a Hip Fracture. Poster presentation URCAD, UMBC, Baltimore, MD, Spring 2008
4. **Chiles, N.**, Blasic, J., Porter, M., Robinson, P. The Role of Bovine Melanopsin and Stomatopod Opsin. Poster presentation at “A Look Ahead”, UMBC, Baltimore, MD, Fall 2007 \*Also presented at “NIDDK Step Up” Research Conference, National Institutes of Health; URCAD at University of Maryland Baltimore County.

#### **MAJOR INVITED SPEECHES:**

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1. **Chiles Shaffer, N.**, Huang, Y., Strotmeyer, E.S., Guralnik, J., Harris, T.B., Newman, A.B., Ryan, A.S., Orwig, D. Diabetes, Sarcopenia, Peripheral Nerve and Lower Extremity Function among Older Adults. “GGEAR Research Seminar Series”, University of Maryland Baltimore, Spring 2014.
2. **Chiles, N.**, Gruber-Baldini, A., Orwig, D., Magaziner, J. Education and Its Role in Recovery from a Hip Fracture. “Baltimore Hip Study Seminar Series”, University of Maryland Baltimore, Spring 2011.

#### **COMPLETED GRANT SUPPORT:**

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2010-2013	Epidemiology of Aging Predoctoral Research Fellow, University of Maryland School of Medicine, Department of Epidemiology, Baltimore, MD, T32 AG000262, P.I. Dr. Jay Magaziner
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2007-2009	MARC U*STAR Training Grant, University of Maryland Baltimore County, T34 08663, P.I. Dr. Lasse Lindahl
2005-2007	Meyerhoff Scholarship, University of Maryland Baltimore County, Private Funding

#### **PROFESSIONAL SOCIETY MEMBERSHIPS:**

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- Gerontological Society of America
- National Society of Collegiate Scholars
- Sigma Phi Omega – Delta Lambda Chapter

#### **HONORS AND AWARDS:**

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2013	Recipient of the Renee Royak-Schaler Memorial Endowment Award from the UMB Department of Epidemiology and Public Health for Excellence in Health Disparities Research
2012	1 <sup>st</sup> Place, Session Award, UMB Graduate Research Conference
2012	1 <sup>st</sup> Place, Research in Aging Award, UMB Graduate Research Conference
2011	3 <sup>rd</sup> Place, Predoctoral Poster Award, Johns Hopkins Research on Aging Showcase
2010-Present	Epidemiology of Aging Predoctoral Research Fellow, University of Maryland School of Medicine, Department of Epidemiology, Baltimore, MD T32 AG000262, PI Dr. Jay Magaziner
2009-2010	Meyerhoff Graduate Fellow, Doctoral Program in Gerontology, University of Maryland School of Medicine, Department of Epidemiology, Baltimore, MD, PI Dr. Mark Summers
2007-2009	MARC U*STAR Trainee, UMBC, Department of Biological Sciences, Baltimore, MD T34 08663, PI Dr. Lasse Lindahl
2005-2007	Meyerhoff Scholarship, UMBC, Department of Biological Sciences, Baltimore, MD

#### **PROFESSIONAL SERVICE:**

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2014	Peer reviewer, Clinical Interventions in Aging
2013-Present	President, Meyerhoff Fellowship Student Board
2013	Panelist, University of Maryland Baltimore and Baltimore County Aging Forum, “Applying for Funding”
2013	Department Representative for GPILS Awards Committee

2010-2012	Student Member of Department of Gerontology Steering Committee
2010-2011	Coordinator, Epidemiology of Aging Trainee Meetings, University of Maryland School of Medicine, Department of Epidemiology, Baltimore, MD
2009-2010	Department of Gerontology Student Representative for Graduate Student Association
2009-Present	Member, Minority Task Force, Gerontological Society of America (GSA)
2009-Present	Member, Emerging Scholar and Professional Organization, GSA

**LOCAL AND NATIONAL SERVICE:**

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2013	Appointed Member, Regional Advisors Task Force, Eastern Region of Delta Sigma Theta Sorority, Incorporated
2013	Co-Chair, Scholarship Committee, Baltimore Metropolitan Alumnae Chapter of Delta Sigma Theta Sorority, Incorporated
2013	Guest Panelist for Cristo Rey Jesuit High School, “Living the Dream – African Americans in Science”
2012-Present	Advisor for Collegiate Chapter of Delta Sigma Theta Sorority, Incorporated at the UMBC
2012-Present	Member, Meyerhoff Alumnae Board Mentoring Committee
2012	Guest Panelist for Delta Sigma Theta Scholarship Award Ceremony, How to be Successful in College and Beyond
2011-Present	Cohort Representative, Meyerhoff Alumnae Board, UMBC
2011-Present	Interviewer for Meyerhoff Scholarship Program, UMBC
2011	Guest Panelist for MBRS-Rise Program, Morgan State University
2008-Present	Member, Delta Sigma Theta Sorority, Incorporated

## **Abstract**

Title of Dissertation: Diabetes, Sarcopenia, Peripheral Nerve & Lower Extremity Function in Older Adults.

Nancy S. Chiles Shaffer, Doctor of Philosophy, 2014

Dissertation Directed by: Denise Orwig, Assistant Professor, Department of Epidemiology and Public Health, Division of Gerontology

Diabetes is associated with lower extremity dysfunction. Sarcopenia, a geriatric syndrome that indicates loss of muscle mass and strength, is also associated with lower extremity dysfunction. Sarcopenia may be more prevalent among diabetic older adults. Peripheral nerve dysfunction (PND) has been suggested as a mechanistic cause of sarcopenia. This relationship between PND and sarcopenia has not been examined longitudinally in any cohort. Additionally, research has not examined the association between diabetes, sarcopenia, and lower extremity function (LEF) longitudinally. The specific aims of this study were to: 1) Examine the prevalence of sarcopenia among a US population of diabetic and non-diabetic older adults, and effect modification of sex and race, using multivariable logistic regression; 2) Examine the relationship between PND and sarcopenia among diabetic and non-diabetic older adults over time and determine if race and sex modify the relationship using generalized estimating equations; 3) Identify the relationship of PND and sarcopenia on LEF among diabetic compared to non-diabetic older adults, and examine if race or sex modify the relationship, using generalized linear models. A secondary analysis of the Health, Aging, and Body Composition (Health ABC) study (1997-2008) was conducted on 2388 (1884 non diabetics and 504 diabetics) community-dwelling black (932) and white (1456) individuals aged 70 years and older,

over study years 1-11. Diabetes was determined from blood glucose, use of antidiabetic medications, and/or self-report of a previous diagnosis. Sarcopenia classification was based on DXA-measured appendicular lean mass normalized for height, and grip strength. LEF was measured by gait speed. Sarcopenia prevalence was lower for diabetics than non-diabetics older adults. Adjusting for covariates, neither diabetes nor PND were associated with increased prevalence of sarcopenia. Sarcopenia prevalence was significantly associated with a slower gait speed over time. Sex and race did not modify any of the relationships. Our findings indicate that diabetes is not predictive of sarcopenia prevalence over time; however sarcopenia is predictive of slower gait speed. Further refinement of the definition of sarcopenia may be necessary to account for muscle quality, specifically fat infiltration, which may exist among diabetic older adults.

Diabetes, Sarcopenia, Peripheral Nerve & Lower Extremity Function in Older Adults

by

Nancy S. Chiles Shaffer

Dissertation submitted to the Faculty of the Graduate School of the  
University of Maryland, Baltimore in partial fulfillment  
of the requirements for the degree of  
Doctor of Philosophy  
2014

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2014

## **Dedication**

I would first like to dedicate my dissertation to God. “I can do all things through Christ who strengthens me” (Philippians 4:13). I would also like to dedicate my dissertation to my family. My grandfather “Pop” inspired my interest in gerontology. He personifies that remaining physically, mentally, and spiritually healthy in older age can be the strongest preventative measure against mortality. My daddy inspired me to always do my best at whatever I do; never cut corners or seek the easy way out. His life had a lasting impact on my life as a gerontologist. My brother “Billy” has taught me to always remain dedicated to what you love; despite difficulties, it will always be worth it. My mom accomplished so many feats during her career that I am always in awe of her success. Through watching her I have learned that the sky is the limit and I must always continue climbing the ladder. Finally, I thank my wife Demetrius. I have never had a stressful day and not come home to her love and support. She has always been as committed to my studies as I have, and has provided additional confidence at times when I needed it most. The support and influence of my family has propelled me through my studies and the dissertation process. They have all earned honorary doctoral degrees and to them I will forever be grateful.

## **Acknowledgements**

I would like to thank my dissertation committee for all their help, guidance, mentoring, and collaboration on this project. I would like to thank Dr. Denise Orwig for mentoring me throughout my tenure in the Gerontology Doctoral program and for serving as my committee chair. I whole-heartedly appreciate all of the time she has dedicated to helping me produce the best product possible and preparing me to take the next steps towards becoming an independent researcher.

I appreciate my frequent meetings with Dr. Yi Huang to review my statistical analyses. I have left this experience much more confident in my analytic abilities thanks to her help. Dr. Jack Guralnik helped solidify my interest in gerontological research, and my experience interning with him in 2008 laid the groundwork for this project. I appreciate all of his edits, suggestions, and mentoring over the years. I am very thankful to Dr. Alice Ryan who has helped extensively with this project since its inception. I appreciate all of her advice and contributions to the research question and methods, as well as my dissertation. Finally, I would like to thank Dr. Elsa Strotmeyer for her assistance. I was thrilled to meet her at a GSA conference and was very excited when she offered to serve on my committee. I am very thankful for all of her reviews, edits, and contributions. Together, all of my committee members pushed me to be greater and I cannot thank them enough.

I would also like to acknowledge my Gerontology and Epidemiology peers, including Jennifer Lloyd Wolter, Sarah Dutcher, and my “TINCK” cohort Tara McMullen, Iona Johnson, Colleen Bennett, and Kathy Humber. I would also like to

acknowledge all of the Meyerhoff Graduate Fellows and Epidemiology of Aging Trainees who have served as supporters and friends.

Finally I would like to thank the Gerontology Department faculty and staff, as well as the faculty and staff of the Meyerhoff Graduate Fellowship Program, Epidemiology Training Grant, Meyerhoff Undergraduate Scholarship, and MARC U\*STAR. You all have helped shape me over the years, solidified my skillset, and assured that I was able to complete this goal.

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## **Chapter 1 – Introduction**

### **Overview**

Diabetic and non-diabetic adults are at risk of poor lower extremity function, with diabetic older adults at higher risk than non-diabetic older adults. This study aimed to establish if peripheral nerve dysfunction (PND) and sarcopenia explain the relationship between diabetes and lower extremity function over time, as well as the potential effect modification of race and sex on this relationship. All study aims accounted for weight, physical activity, diabetes duration and control, and additional comorbidities, and utilized data from the Health, Aging, and Body Composition study (Health ABC). Understanding this relationship, and understanding if the relationship differs by race and sex, may facilitate the development of improved interventions to enhance lower extremity function in older adults with and without diabetes.

### **Background**

Diabetes is a common condition among older adults, with over 26% of the 65 and older population having the disease<sup>1</sup>. Diabetes is associated with lower extremity dysfunction, as diabetic older adults are 2-3 times more likely to be unable to complete activities of daily living (ADLs) and walk a quarter of a mile<sup>1-3</sup> compared to non-diabetic older adults. Sarcopenia, a geriatric syndrome that indicates the loss of muscle mass and muscle strength, is also associated with lower extremity dysfunction<sup>4,5</sup>. Evidence suggests that sarcopenia may be more prevalent among diabetic older adults<sup>4,6,7</sup>.

While there is recent literature from the Korean Sarcopenia Obesity Study (KSOS) reporting the prevalence of sarcopenia in diabetic older adults as 15.7%, this

research only examined muscle mass and not strength in its measurement of sarcopenia. Additionally, the study population was comprised of Korean older adults and thus was not generalizable to the United States<sup>8</sup>. This present study will use a more comprehensive measure of sarcopenia put forth by the European Working Group on Sarcopenia in Older People (EWGSOP), which defines sarcopenia by low muscle mass and low muscle strength<sup>9</sup>. Also, the Health ABC population consists entirely of older U.S. adults, and allows for exploration of the effect of race because of the large proportion of blacks in the study population.

Prior research has not examined the impact of race or sex on the prevalence of sarcopenia among diabetic and non-diabetic older adults. While blacks 65 years of age and older have a higher prevalence of diabetes than whites 65 years of age and older (31.5% vs. 19.0%)<sup>10</sup>, blacks also have a higher average muscle mass, and thus, may have a lower prevalence of sarcopenia<sup>1,11,12</sup>. While males aged 65 and older have a higher prevalence of diabetes than females 65 and older, (23.5% for males vs. 18.2% for females)<sup>10</sup>, males also have a higher average muscle mass, and may have a lower prevalence of sarcopenia<sup>13,14</sup>. This proposed study examined the prevalence of sarcopenia among both diabetic and non-diabetic older adults in a diverse population of black and white older adults.

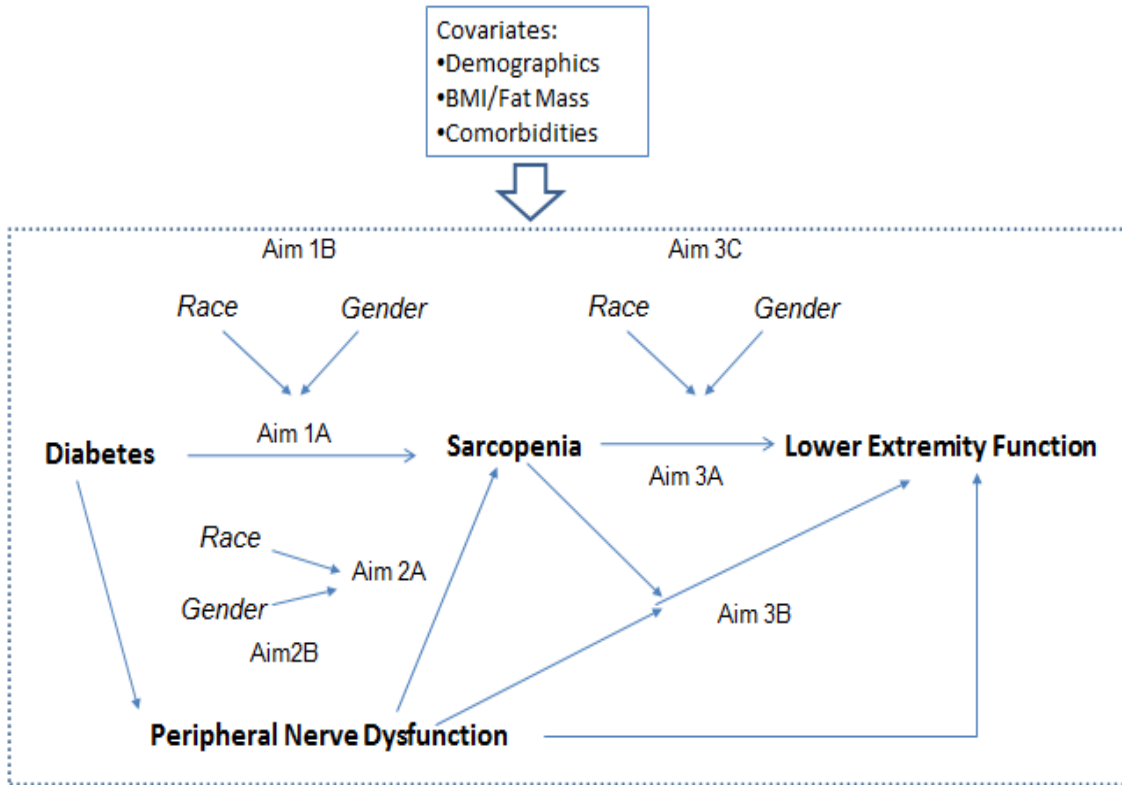
PND has been suggested as a mechanistic cause of sarcopenia, as PND may lead to denervation and atrophy of muscle fibers<sup>15,16</sup>. While this relationship between PND and sarcopenia has been assessed biologically, it has not been examined longitudinally in any cohort; therefore, it is unknown whether or not muscle atrophy resulting from PND is

substantial enough to result in sarcopenia. This proposed study assessed the prevalence of sarcopenia by PND status over a 6-year period.

While studies have shown that diabetes is associated with lower extremity function, research has not examined the association between diabetes, sarcopenia, and lower extremity function longitudinally<sup>15,17-22</sup>. Cross-sectional research has indicated that PND mediates the relationship between diabetes and lower extremity function<sup>15,20,22,23</sup>; however studies have not demonstrated whether PND in addition to sarcopenia results in differences in lower extremity function by diabetes status<sup>15,23</sup>. Examining race and sex as possible effect modifiers of this relationship also has not been analyzed longitudinally. This is particularly important to assess as the prevalence of sarcopenia and PND as well as lower extremity dysfunction may differ by race and sex. This proposed study aimed to examine the relationship between diabetes, sarcopenia, PND, and lower extremity function in light of race and sex differences utilizing longitudinal data from the Health, Aging, and Body Composition Study (Health ABC) years 1 to 11.

Below is a conceptual model depicting the aims of the study (Figure 1).

**Figure 1: Conceptual Model**



## **Specific Aims and Hypotheses**

**Aim 1:** Examine the prevalence of sarcopenia among diabetic and non-diabetic older adults and examine if race or sex modify the relationship.

**Aim 1A:** Determine the prevalence of sarcopenia at year 4 among diabetic and non-diabetic older adults, where diabetes status was determined at year 4.

**H1A.1** Diabetic older adults will have a higher prevalence of sarcopenia at year 4 than non-diabetic older adults.

**Aim 1B:** Investigate if race and sex modify the relationship between diabetes status and sarcopenia at year 4.

**H1B.1** Race will modify the relationship between diabetes status and sarcopenia such that black diabetic older adults will have a lower prevalence of sarcopenia at year 4 than white diabetic older adults.

**H1B.2** Sex will modify the relationship between diabetes status and sarcopenia such that older diabetic women will have a higher prevalence of sarcopenia at year 4 than older diabetic men.

**Aim 2:** Examine the relationship between PND and sarcopenia among diabetic and non-diabetic older adults and determine if race and sex modify the relationship.

**Aim 2A:** Determine the prevalence of sarcopenia at years 6, 8, and/or 10 among participants with PND at year 4.

**H2A.1:** Participants with PND will have a higher prevalence of sarcopenia over time than participants without PND.

**Aim 2B:** Investigate if race and sex modify the relationship between PND at year 4 and sarcopenia at years 6, 8, and/or 10.

**H2B.1** Race will modify the relationship between PND and sarcopenia such that black older adults with PND at year 4 will have a lower prevalence of sarcopenia at years 6, 8, and/or 10 than white older adults with PND at year 4.

**H2B.2** Sex will impact the relationship between PND and sarcopenia such that older women with PND at year 4 will have a higher prevalence of sarcopenia at years 6, 8, and/or 10 than older men with PND at year 4.

**Aim 3:** Identify the relationship of PND and sarcopenia on lower extremity function among diabetic compared to non-diabetic older adults, and examine if race or sex modify the relationship.

**Aim 3A:** Demonstrate that sarcopenia at years 6, 8, and/or 10 is associated with gait speed at years 8, 10, and/or 11 among diabetic and non-diabetic older adults.

**H3A.1:** Diabetic and non-diabetic older adults with sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than diabetic and non-diabetic older adults without sarcopenia at years 6, 8, and/or 10.

**Aim 3B:** Demonstrate that PND at year 4, in addition to sarcopenia at years 6, 8, and/or 10 is associated with gait speed at years 8, 10, and/or 11 among diabetic older adults.

**H3B.1:** Diabetic older adults with PND at year 4 and sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than diabetic older adults with sarcopenia at years 6, 8, and/or 10 without PND at year 4.

**Aim 3C:** Determine whether the relationship between sarcopenia at years 6, 8 and/or 10 and gait speed at years 8, 10, and/or 11 among diabetic and non-diabetic older adults is modified by race and sex.

**H3C.1** Race will modify the relationship between sarcopenia and gait speed among diabetic and non-diabetic older adults, such that black older adults with sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than white older adults with sarcopenia at years 6, 8, and/or 10.

**H3C.2** Sex will impact the relationship between sarcopenia and gait speed among diabetic and non-diabetic older adults, such that older women with sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than older men with sarcopenia at years 6, 8, and/or 10.

## **Contribution of Research**

This proposed study is the first to examine the impact of PND and sarcopenia on lower extremity function of diabetic and non-diabetic older adults over time in a study sample representative of the U.S. population. While previous research had examined associations between these components, none existed examining the impact of the interplay of all of these components together, nor examining the effect of race and sex on the relationships. Understanding whether or not diabetes and sarcopenia, as well as PND and sarcopenia, are associated longitudinally could lay the groundwork for additional research to learn how to prevent sarcopenia among those with diabetes and/or PND.

Understanding how PND and sarcopenia impact the relationship between diabetes and lower extremity function may lead to better understanding of strength and physical function interventions needed for diabetic older adults, as well as better intervention development, specifically focused on muscle mass and strength. Diabetic older adults with PND and sarcopenia may require different functional interventions to prevent decreases in lower extremity function compared to diabetic older adults with PND and no sarcopenia.

This current study also assessed the effect of race and sex on these relationships, thus providing better identification of the populations most at risk for sarcopenia and lower extremity dysfunction. While blacks and males have a greater prevalence of diabetes than whites and females respectively<sup>1,10-14</sup>, they may be at lower risk of lower extremity dysfunction resulting from sarcopenia, thus whites and females may require different functional interventions to improve lower extremity function<sup>1,10,11,13,14,24</sup>.

Many studies of sarcopenia solely assess muscle strength and not muscle mass. The field of sarcopenia research has lacked a standard definition and measurement criteria for sarcopenia, thus resulting in multiple and inconsistent methods employed by researchers<sup>9,14,25-27</sup>. The analysis of mass alone has been associated with neither clinical nor functional outcomes consistently. The definition and measurement criteria put forth by the EWGSOP were developed by a consensus from multiple organizations representative of the field, and the use of this comprehensive definition of sarcopenia will allow for more accurate prevalence ratios, as well as greater clinical relevance of findings<sup>9</sup>.

### **Organization of Dissertation**

Chapter 1 of my dissertation provides an overview and background of the research topic and justification for this study, a conceptual model depicting the research aims of the study and the potential impact of confounders and effect modifiers, lists the specific aims and hypotheses, and discusses the potential contribution of the results of this study to the research field. Chapter 2 provides a literature review detailing the concepts and components that comprise the aims of the study, and how these components are related. Chapter 3 provides the methods of the study, including an overview of the dataset, the measures used, a power analysis, and analysis plans for each aim of the study. Chapter 4 features the study results. Chapter 5 consists of a discussion of the study results and conclusions.

## **Chapter 2: Background and Significance**

### **I. Diabetes**

#### **Etiology**

Diabetes is a common condition among older adults. The Centers for Disease Control and Prevention (CDC) reported a 23.1% prevalence rate of diabetes, diagnosed and undiagnosed, amongst adults 60 years of age and older in the United States<sup>3</sup>. Type 2 diabetes is the most prevalent type of diabetes in the United States, especially among the elderly population, accounting for 90-95% of all diabetes cases<sup>2</sup>. Type 2 diabetes is defined as diabetes resulting from insulin resistance or relative insulin deficiency, as compared to Type 1 diabetes where an autoimmune destruction results in no insulin production<sup>1</sup>. Type 2 diabetes is associated with older age, as well as abdominal obesity and physical inactivity<sup>1,13</sup>. This study focusses on Type 2 diabetes, which will hereafter be referred to as diabetes. Diabetes is a risk factor for morbidity, including decreased physical function leading to disability, as well as mortality<sup>1,13</sup>.

#### **Epidemiology among Older Adults**

##### **Prevalence**

The prevalence of diabetes was estimated as 10.9 million among US adults aged 65 and older in 2010<sup>1,10</sup>. The CDC reported the percentage of adults 65-74, and 75 and older with diabetes in the United States in 2010 as 20.7% and 20.1% respectively<sup>13</sup>. The overall prevalence of diabetes among older adults is expected to increase to 26.7 million by 2050<sup>10</sup>.

## Race and Sex

Blacks have a prevalence of diabetes that is twice that of whites<sup>28</sup>. The highest incidence of diabetes occurs among blacks 65-75 years old<sup>28</sup>. Adjusting for age, black women are the most likely demographic to be diagnosed with diabetes<sup>28</sup>. Similar statistics were reported by the CDC in 2010 stating that among US older adults age 65-74 years of age, 19.1% of whites had diagnosed diabetes compared to 32.4% of blacks. For the 75 years of age and older US population, 19.0% of whites had diagnosed diabetes compared to 30.5% of blacks<sup>13</sup>.

The following are comparisons of sex statistics from the CDC report<sup>13</sup>. Older men 65-74 years of age had a higher percentage of diagnosed diabetic older adults (23.2%) than older women (18.6%). Similarly in the 75 and older population, men had a higher percentage of diagnosed diabetic older adults (23.8%) than women (17.7%). Within sex, race also affected the percentage of diagnosed diabetes. For men age 65-74, white males had a lower percentage of diagnosed diabetes (21.6%) than black males (34.1%). Similarly for men aged 75 and older, white males had a lower percentage of diagnosed diabetes (22.8%) than black males (33.8%). The increased percentage of diagnosed diabetes for blacks existed among women as well, in both the 65-74 year old population (16.9% vs. 31.1%) and the 75 and older population (16.3% vs. 28.9%). While the CDC data indicate that black men, not black women as reported by the Office of Minority Health (OMH)<sup>28</sup>, are the demographic with the greatest percentage of diagnosed diabetes, both reports indicate a greater prevalence of diagnosed diabetes among black older adults compared to white older adults<sup>13,28</sup>.

## Risk factors

Several biological processes may lead to an increased risk of diabetes for older adults. One such process is a change in body composition that occurs with older age. With increasing age, fat distribution throughout the body changes, resulting in an increase in visceral fat and a decrease in subcutaneous fat <sup>29,30</sup>. Increased visceral fat is associated with increased risk of diabetes <sup>29</sup>.

Another biological process that places older adults at increased risk of diabetes is changes in carbohydrate metabolism. The increase in adiposity and decrease in lean body mass that occur with older age increases glucose intolerance <sup>29</sup>. Glucose intolerance is also increased from the increase in visceral fat discussed earlier. Glucose intolerance increases the risk for diabetes <sup>29</sup>.

Increases in inflammatory response in old age are another biological link to the development of diabetes. C-reactive protein (CRP) is an inflammatory marker that non-specifically increases during times of infection, disease, and cellular damage, and it has been associated with multiple comorbidities, including diabetes <sup>31-33</sup>. Inflammation is associated with metabolic syndrome which is also associated with an increased risk for diabetes <sup>18</sup>.

In addition to the age-related biological processes that increase an older adults risk for diabetes, external factors can also increase their risk for diabetes. The prevalence of diabetes in adults has doubled in the last 15 years<sup>34</sup>. External factors have contributed to the increase in the prevalence of diabetes in recent cohorts of older adults, including an unhealthy diets, low physical activity, and obesity<sup>35,36</sup>.

Diet is a major external factor that influences age-related biological processes involved in the development of diabetes. A poor diet, such as one that is high in saturated fat, low in complex carbohydrates, and high in sodium, can influence each of the biological processes of diabetes development. A diet high in saturated fat increases the visceral fat in the body<sup>29</sup>. A diet low in complex carbohydrates increases the risk for glucose intolerance, which in turn increases one's risk of diabetes<sup>29</sup>. A diet high in sodium places one at increased risk of hypertension. Hypertension has been associated with insulin resistance, which is one of the biological processes involved in diabetes development<sup>30</sup>. Hypertension has been found to result in a 2 times higher odds of developing diabetes<sup>37</sup>. These three aspects of a poor diet are not independent of each other and can be exhibited together by an individual, placing the individual at increased risk of diabetes above the biological age-associated risk.

An older adult that does not actively engage in physical activity is also at increased risk of diabetes. Low physical activity is a cause of glucose intolerance<sup>29</sup>. Conversely, physical activity is capable of increasing insulin sensitivity, regardless of body weight or body composition<sup>29</sup>. This means that even if an older adult is incapable of engaging in physical activity at a level that would cause weight loss or an increase in lean muscle mass, physical activity can still lower the risk of diabetes. In the Nurses' Health Study, a prospective cohort study of female registered nurses aged 40 to 65 at baseline, those who engaged in walking were 26% less likely to develop diabetes than sedentary women over an 8 year follow up period<sup>38,39</sup>.

Obesity is a growing problem in the United States for all age groups, including older adults<sup>40</sup>. Obesity, primarily in the central locations of the body, can exacerbate the

consequences of the body composition changes that occur with aging by contributing additional visceral fat to the body<sup>40,41</sup>. The high level of visceral fat in a central location can greatly increase an older adult's risk of glucose intolerance<sup>29,41</sup>. Obesity has been reported to account for up to 60-90% of the risk variance for diabetes<sup>38,42,43</sup>.

Poor diet, low physical activity, and obesity are all correlated with each other and have been increasing in prevalence for older adults in recent years<sup>35,36</sup>. This increase in prevalence is expected to continue through the upcoming decades and may continue to result in a cohort effect, whereby future older adult cohorts may have an increased prevalence of diabetes due to their increased exposure to obesity, low physical activity, and poor diet<sup>35,36</sup>.

### Associated Complications

Many older diabetic adults have additional comorbidities, including heart disease, stroke, vision problems, kidney disease, nervous system disorders, arthritis, dental disorders, and cardiorespiratory disease<sup>10,44</sup>. Diabetes is highly associated with coronary vascular disease (CVD). CVD is the greatest cause of morbidity and mortality for diabetic adults<sup>44</sup>. Adults with diabetes have a 2-4 times higher death rate for heart disease and 2-4 times higher risk for stroke than adults without diabetes<sup>1</sup>.

Diabetes is the leading cause of incident blindness among adults 20-74<sup>1</sup>. Viljoen et al. state that the two primary risk factors for developing diabetic retinopathy are poor glycemic control and high blood pressure<sup>44</sup>. Vision impairment places older diabetic adults at increased risk of depression and may “amplify frailty”<sup>44</sup>. Among diabetics 40

and older, almost 30% had diabetic retinopathy during 2005 through 2008, with 4.4% having advanced diabetic retinopathy, which may result in severe vision loss <sup>1</sup>.

The prevalence of diabetic nephropathy among diabetic patients is 20-40% <sup>44</sup>. In 2008, diabetes was found to account for 44% of all incident cases of kidney failure, making it the leading cause of kidney failure <sup>1</sup>. Diabetic nephropathy places patients at increased risk of cardiovascular disease outcomes, including myocardial infarction (MI) and stroke, thus exacerbating the risks associated with diabetes alone <sup>44</sup>.

Diabetes can also result in damage to the nervous system. Mild to severe nervous system damage, including loss of sensation and or pain in the hands or feet, carpal tunnel syndrome, difficulty digesting food, and erectile dysfunction, exists for 60% to 70% of persons with diabetes <sup>1</sup>. The major contributors to these neuropathies are prolonged hyperglycemia and diabetes duration <sup>44</sup>.

### **Health Care Burden**

Diabetes is associated with high economic costs. The economic cost of diabetes in the US in 2007 was estimated at \$174 billion <sup>10,45</sup>. Costs of care for diabetic older adults accounted for \$64.8 billion of all US health care expenditures <sup>10</sup>. Average medical costs per case for diabetic adults 65 years of age and older were \$9,713, the highest among all adult comorbidity age groups <sup>45</sup>. The primary contributor to the economic cost of diabetes is associated CVD complications <sup>44</sup>.

### **Impact on Lower Extremity Function**

Studies have shown that diabetes is associated with decreased physical function <sup>22,46-48</sup>. Bruce et al. reported that several studies have shown diabetes to be associated

with physical disability<sup>46</sup>. The factors found to result in disability among diabetic older adults included age, sex, obesity, insulin treatment, peripheral neuropathy, coronary heart disease, stroke, peripheral artery disease, vision loss, depression, and arthritis<sup>17,22,46-50</sup>.

Gregg et al. analyzed lower extremity disease among adults age 40 and older in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2000 and found that diabetic adults had over a 1.5 higher prevalence (30.2%) of lower extremity disease than non-diabetic adults (17.6%)<sup>17</sup>. Volpato et al. found that diabetic women in the Women's Health and Aging Study (WHAS) had a 38% greater decline in the Short Physical Performance Battery (SPPB) components, thereby a greater decline in lower extremity function, than non-diabetic subjects<sup>47,51</sup>. They also reported that women with diabetes had a 1.8 relative risk for incident mobility and 1.6 relative risk for incident ADL disability<sup>22</sup>.

## **II. Peripheral Nerve Function**

### **Etiology**

PND can result from genetics, metabolic stress, vascular stress, oxidative stress, chronic disease, environmental toxins, alcoholism, nutritional deficiencies, or side effects of certain medications<sup>52,53</sup>. Diabetes is the chronic disease that most commonly causes PND. While PND is primarily believed to manifest from prolonged hyperglycemia (diabetes), it has also been shown to manifest in persons with abnormal glucose tolerance (pre-diabetes). Head et al. details the pathophysiology of diabetic nerve dysfunction, including increased oxidative stress resulting in increased advanced glycosylated end products (AGEs), an increase in sorbitol accumulation resulting in both a decrease in

(Na<sup>+</sup>/K<sup>+</sup>)-ATPase activity and a decrease in free carnitine and myo-inositol content, and a decrease in nitric oxide as well as homocysteinemia resulting in impaired endothelial function.<sup>52</sup>

Hyperglycemia, resulting from diabetes, causes glucose molecules to combine with proteins, resulting in glycosylated proteins. Glycosylated proteins are at risk of becoming damaged by free radicals and then bonding with fats, resulting in production of AGEs. AGEs are damaging because they easily bond to cells, including smooth muscle cells, and can result in chronic inflammation<sup>52</sup>. Inflammatory markers are associated with diabetes and have been implicated in the development of peripheral neuropathy<sup>53</sup>.

In the absence of insulin, excess glucose is able to passively diffuse into some cell types, nerve cells included. Upon entering the cell, the aldose reductase enzyme converts the glucose into sorbitol or another polyol. These polyols are not able to passively diffuse out of the cells, resulting in concentration within cells, such as neurons. This polyol concentration yields an osmotic gradient, resulting in an influx of excess sodium and water. In addition to the osmotic gradient effect, sorbitol may also be converted to fructose. High fructose levels can result in increased AGE precursors, which are also a source of oxidative stress<sup>52</sup>. Oxidative stress is associated with development of diabetic neuropathy<sup>53</sup>.

The accumulation of sorbitol and fructose in nerve cells also results in a decrease in (Na<sup>+</sup>/K<sup>+</sup>)-ATPase activity, resulting in a decrease in the contraction potential of associated cells, including smooth muscle cells<sup>52</sup>. Polyol accumulation also results in a

decrease in free carnitine and myo-inositol content, leading to a potential decrease in signal reception and secondary messaging between skeletal muscle cells <sup>52</sup>.

Hyperglycemia also can result in reduced nerve blood flow, mediated by nitric oxide metabolism. Nitric oxide stimulation integrally controls (Na<sup>+</sup>/K<sup>+</sup>)-ATPase activity, resulting in the widening of blood vessels and increased blood flow. When exposed to an excess of superoxide radicals, as can result from hyperglycemia, stimulation of nitric oxide on (Na<sup>+</sup>/K<sup>+</sup>)-ATPase is reduced, thereby reducing blood flow <sup>52</sup>. Diabetes can also cause impaired blood flow through blood vessel thickening and occlusion, also potentially resulting in diabetic neuropathy<sup>53</sup>.

### **Epidemiology among Older Adults**

#### Prevalence among diabetic older adults

The prevalence of PND is approximately 20-50% among older adults with diabetes <sup>2,52</sup>. With the projected increase in the prevalence of diabetes, peripheral neuropathy may affect up to 236 million people worldwide by the year 2030 <sup>54</sup>. The prevalence of PND increases with age <sup>55</sup>.

In the Italian Longitudinal Study on Aging (ILSA), age and sex-specific prevalence and incidence rates of neuropathy were reported. While the overall study prevalence rate of neuropathy was 7% per 1,000 person-years, it was more than 22% per 1,000 person years for the diabetic participants. Among both sexes, the prevalence rate of neuropathy increased with increasing age. While in the 65-69 age group males had a higher prevalence than females, females had the highest prevalence in all other age groups (70-74, 75-79, 80-84). The incidence rate was higher among females than males

in the 65-69 and 80-84 age groups. Among the total sample, the incidence rate was 32.2 per 1,000 person-years among diabetic participants compared to 5.8 per 1,000 person-years among non-diabetic participants.

The prevalence of peripheral neuropathy was also reported from NHANES comparing diabetic and non-diabetic participants age 40 and older<sup>17</sup>. The overall study prevalence of peripheral neuropathy was 14.8% and increased with age. 75% of the population with peripheral neuropathy were asymptomatic, however the percentage of diabetic participants with asymptomatic neuropathy was lower (62%). 28.5% of the population with diabetes had peripheral neuropathy vs. 13.3% of the non-diabetic population.

### Risk factors

Increased age is a risk factor for PND, as age is strongly associated with decrements in large-fiber peripheral nerve function<sup>55</sup>. In WHAS, researchers determined that age was strongly associated with decrements in peripheral nerve function, as the oldest old (those 85 years of age and older) of disabled participants had the greatest prevalence of PND<sup>55</sup>. Similar results of higher prevalence with age were found in the ILSA and NHANES<sup>17,56</sup>. Height is another historical variable that has been found to be associated with slower nerve conduction velocity and decreased vibration sensitivity<sup>57,58</sup>.

Among diabetics, prolonged hyperglycemia and diabetes duration are major risk factors for PND<sup>44,57</sup>. In a study assessing risk factors of peripheral neuropathy among diabetic adults, 1 unit increase in glycohemoglobin was associated with a 15% increase in risk of peripheral neuropathy<sup>57</sup>. The study as hypothesized that the association between

diabetes duration and risk of peripheral neuropathy may be confounded by age. Poor glycemic control is also a risk factor for peripheral neuropathy<sup>59</sup>, and it can result in lower capillary blood flow.

Exposure to several toxins has been found to result in increased risk of peripheral neuropathy<sup>60</sup>. Certain poisons and heavy metals, toxins in cigarettes, as well as medications and treatments (chemotherapy<sup>61</sup>) can lead to vitamin deficiencies and associated nerve detriments<sup>60</sup>. Poor diet, smoking, and excess alcohol can also result in vitamin deficiencies<sup>60</sup>.

Cardiovascular-associated conditions and risk factors are also risk factors for peripheral neuropathy, including hypertension, elevated triglycerides, and high BMI<sup>54,57,59,62</sup>. Occupational hazards, microvascular diseases (retinopathy, nephropathy)<sup>62</sup>, as well as autoimmune diseases (such as rheumatoid arthritis, lupus<sup>63</sup>, sarcoidosis, AIDS, and Guillain-Barre syndrome), other disease (kidney disease, liver disease, hypothyroidism, and amyloidosis), and infections (Lyme disease, shingles, hepatitis C<sup>64</sup>, and HIV) are also associated with an increased risk of PND<sup>60</sup>.

### Race and Sex

Blacks have been found to have a higher age-adjusted prevalence of PND than whites (21.9% vs 14.4%)<sup>17</sup>. In the Health ABC study, Strotmeyer et al. reported that blacks had both a greater percentage unable to detect sensory measures of nerve function (10-g monofilament), and a lower average threshold vibration; however

Gregg et al. reported from NHANES a higher prevalence of PND among men (18.2%) than women (12.6%)<sup>17</sup>. Similarly, Strotmeyer et al. reported from Health ABC that men performed poorer on all sensory and motor nerve function measures than women, however not all of the sex differences held after adjustment<sup>65</sup>. Within sex, race also affected prevalence of peripheral neuropathy, as black women had a significantly higher percentage of peripheral neuropathy (21.2%) than white women (11.2%).

### Associated complications

PND is associated with muscle weakness that can alter a person's gait; this can result in hammertoes and the midfoot collapsing<sup>66</sup>. Additionally, loss of balance and coordination can occur, which can increase an older adult's risk of falls<sup>66-68</sup>.

The loss of sensation in the feet resulting from PND increases the risk of foot ulcers, also known as diabetic foot<sup>19,57,66,69,70</sup>. Foot ulcers that go untreated can become severely infected, often resulting in the need for amputation. More than half of all lower-limb amputations in the United States occur among persons with diabetes<sup>66</sup>. It is estimated that half of these are attributable to peripheral neuropathy<sup>66</sup>. Both the muscle weakness and loss of sensation impact lower extremity function, and place older adults with PND at increased risk of disability.

### Impact on Lower Extremity Function

Peripheral nerve function has been associated with lower extremity function in many studies<sup>15,20,21,55,71,72</sup>. Investigators using the WHAS dataset found a group of findings related to PND and lower extremity function<sup>20</sup>. PND was associated with a trend

of increasing impairment for all balance tests, chair stands, and the walking speed assessment. Severity of PND was also indicative of poorer physical function, as 56% of participants with severe PND could not complete the balance test compared to 23% of participants with moderate PND who were unable to complete the balance test. Similarly with the chair stand test, 30.6 % of participants with severe PND could not complete the test compared to 8.8% of participants with moderate PND. Usual walking speed for the mild (0.57 m/s), moderate (0.58), and severe (0.51 m/s) PND groups were all slower than the normal peripheral nerve function group (0.65 m/s). However, the functional impairments resulting from PND did not explain all of the association between PND and functional limitations, indicating that PND may either have independent effects on functional limitations or influence them through other pathways <sup>20</sup>.

Similar findings were seen in the Health ABC and the Invecchiare in Chianti (InCHIANTI) studies. In Health ABC, diabetes was associated with poorer chair stand performance, a shorter standing balance time, slower usual walking speed, slower narrow walking speed, and lower performance battery score <sup>15</sup>. Poor peripheral nerve function was found to account for a portion of these functional limitations <sup>15</sup>. In InCHIANTI, older adults with diabetes had significantly decreased physical performance compared to older non-diabetic adults (1.0 lower SPPB score ( $p < 0.01$ ))<sup>23</sup>. Previous studies have shown that declines of this magnitude are associated with a 2-fold increased risk of death in older adults <sup>73</sup>. The effect of diabetes on SPPB was reduced by 8.1% when adjusting for nerve conduction velocity <sup>23</sup>. The association between diabetes and lower extremity function was concluded to be partially attenuated by peripheral nerve function.

## **Impact of Peripheral Neuropathy on muscle mass and strength**

Motor nerve axons and skeletal muscle fibers communicate at the neuromuscular junction (NMJ) <sup>74</sup>. The NMJ is made up of four different cell types: motor neurons, Schwann cells, muscle fibers, and kranocytes <sup>74</sup>. Its function is to transmit signals from the axon of motor neurons to skeletal muscle fibers. It is essential that these signal transmissions occur “quickly and reliably, to ensure precise control of skeletal muscle contraction and therefore voluntary movement” <sup>74</sup>. The structure of the NMJ aids in the reliability of transmission, in that its architecture includes active zones and junction folds that “promote high levels of transmitter release, large and reliable postsynaptic responses to transmitter binding and rapid termination of signaling events” <sup>74</sup>.

Changes occur to the NMJ with age, as in an older adult the NMJ is “in a state of low nutrients, low metabolism, accumulated inflammation, oxidative stress, and reduced axonal transport” <sup>75</sup>. This environment can result in a decrease in the number of motor neurons<sup>76</sup>, changes in size of motor units, innervation, and a loss of muscle fibers <sup>75</sup>, all of which can result in decreased control of muscular contractions and weakness. Peripheral neuropathy can exacerbate this as it can result in impaired Schwann cells, which can result in demyelination thus decreasing the speed at which signals are transmitted along the associated fiber <sup>5</sup>. Beyond the decreases in number and diameter of motor axons that can occur with age<sup>76</sup>, peripheral neuropathy can also result in damaged axons, which would result in loss of signal transmission to associated muscle fibers <sup>5</sup>. All of these changes can result in losses in muscle mass, muscle strength, muscle power, and muscle quality <sup>5</sup>. Lexell et al. determined that the decrease in size and number of fast-twitch muscle fibers attribute to decrease in muscle mass in older adults<sup>77</sup>.

### **III. Sarcopenia**

#### **Etiology**

Sarcopenia, classically, is the age-associated related loss of muscle mass. Muscle mass and muscle strength are correlated components of muscle which play an important role in physical function<sup>78</sup>. With age there is a decrease in both muscle mass and muscle strength<sup>77</sup>. Muscle mass and muscle strength are related<sup>78</sup>; this relationship can be seen in part by analyzing muscle fibers. Human skeletal muscle is comprised of type I and type II muscle fibers. Type I fibers are also known as slow twitch fibers and type II are known as fast twitch fibers. Type I fibers have “greater mitochondrial density, capillary density, and myoglobin content”<sup>79</sup>. These fibers are the source of endurance, and are the driving force of low-intensity exercise. Conversely, type II fibers have “a lower oxidative capacity, greater glycolytic potential and a faster twitch response than ... type I fibers”<sup>79</sup>. High-intensity exercise involves type I as well as type II fibers. Muscle mass is proportional to the total number of muscle fibers as well as the area of the fibers<sup>79,80</sup>.

The age-associated loss of muscle mass occurs from loss of both type I fibers and type II fibers, with the latter experiencing accelerated loss<sup>5,81</sup>. In order to adapt to the loss of type I fibers, and to decrease the burden placed upon surviving slow motor units, the body converts denervated type II muscle fibers into type I fibers<sup>5</sup>. Compounding the loss of type II muscle fibers is the decrease in the power-generating capacity of the remaining type II muscle fibers, resulting in a great decrease in the power-generating capacity<sup>5</sup>. The loss of type II muscle fibers results in a decrease in muscle mass, as type II muscle fibers have a greater mass than type I fibers<sup>5</sup>. Therefore, the age-associated

loss of muscle mass indicates a loss in type II muscle fibers as well as a loss in power-generating capacity, which results in a loss in muscle strength.

## **Definitions and Measures**

### Definitions

With no universal definition of sarcopenia, studying its consequences is difficult. Some of the difficulty in agreeing upon a definition stems from whether aspects of muscle strength should be encompassed in a sarcopenia definition. Some definitions of sarcopenia solely state it is the age-related loss of muscle mass<sup>82</sup>, while others experts contend sarcopenia encompasses muscle function, particularly strength<sup>27,83-85</sup>.

Consensus amongst sarcopenia investigators is that an aspect of muscle mass should be used to measure sarcopenia, as sarcopenia is by all definitions the loss of muscle mass. However, no consensus exists with regard to inclusion of muscle strength in a definition of sarcopenia, as there are arguments for and against its inclusion. One argument for the inclusion of muscle strength in a sarcopenia definition is that while the amount of muscle mass is correlated to muscle strength, it may be possible that muscle strength is more of a predictor of physical function and physical disability than muscle mass<sup>14,27</sup>. Strength, and not mass, is a functional measure of muscle, and measurement of function is important for determining disability risk. If this is true, it would be important to include aspects of muscle function in a definition of sarcopenia.

Conversely, arguments are made against the inclusion of muscle strength in a sarcopenia definition. Some studies have found that muscle mass accounts for variation in muscle strength, indicating that even if muscle strength is a stronger predictor of

physical function, it is still reflective of actual muscle mass<sup>25</sup>. Thus, it would not be necessary to include muscle strength in the definition of sarcopenia since measuring muscle mass alone would reflect the relevant components of muscle strength. In addition, research has shown that less than 5% of variance in change in muscle strength was attributed to sarcopenia, indicating that change in muscle strength is not reflective of sarcopenia and thus should not be included in its definition<sup>25</sup>.

The definition of sarcopenia, specifically whether to include muscle strength, has recently been debated by the International Working Group on Sarcopenia task force (IWGS). This task force decided upon sarcopenia being defined as “the age associated loss of skeletal muscle mass and function”<sup>86</sup>. Given this definition, measures of muscle function should be included when assessing a participant for sarcopenia. The commonly used measure of sarcopenia, defined by Baumgartner et al. considers only relative lean muscle mass in defining one as being sarcopenic<sup>82</sup>. Based on the findings of the task force, another measure that incorporates muscle strength should be used.

### Measures

As stated earlier, the historically used measure to define sarcopenia is the measure defined by Baumgartner et al. This measure, analogous to the body mass index, is an index of skeletal muscle mass relative to height. The values of this index are then compared to the values for the population aged 50, the young-normal. Sarcopenia is defined by this measure as having a relative skeletal mass less than two standard deviations from young-normal mean<sup>82</sup>. Muscle mass is most commonly determined via dual energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis, as these

are the lowest in cost<sup>87</sup>. The gold standards are magnetic resonance imaging (MRI), computerized tomography (CT), and creatinine excretion<sup>87</sup>, yet they are not used as much due to cost.

Muscle strength is quantified using grip strength or knee extension strength<sup>14,88-90</sup>. While cutpoints were recently established for grip strength<sup>91</sup>, those scoring in the lowest quartile or quintile are frequently considered to have low muscle strength. While grip strength is correlated with mortality, knee extension strength has a greater correlation with lower extremity function<sup>92</sup>. Many of the studies that assess sarcopenia separately assess grip strength or knee extension strength; however, these measures are not used in conjunction with relative skeletal muscle mass to define sarcopenia. In order to appropriately measure sarcopenia as it is defined by the IWGS task force, it is necessary to assess muscle mass and muscle strength together.

Recently, the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project combined nine cohort studies to establish evidence-based cutpoints to identify participants with sarcopenia for clinical trials<sup>91</sup>. While the evidence-based approach by which these cutpoints were established is an improvement over previous work, they are very conservative as they are meant to identify those most at risk of mobility impairment. The Health ABC study population is healthier than many older adult cohort study populations; therefore the FNIH cutpoints are too stringent for this study.

For this study, sarcopenia is measured based on an amended definition from the European Working Group on Sarcopenia in Older People (EWGSOP). This amended definition defines sarcopenia as those that have both low appendicular lean muscle mass

and low handgrip strength<sup>9</sup>. The definition has been amended for these analyses to exclude low gait speed, as gait speed is the outcome of interest in Aim 3.

## **Epidemiology among Older Adults**

### **Prevalence**

Due to the varying definitions of sarcopenia, prevalence rates for this geriatric syndrome vary. Using the Baumgartner et al. operational definition of sarcopenia, and using DXA measurement of lean mass<sup>82</sup>, the prevalence of sarcopenia for adults age 60-69 was 8.8% for women and 13.5% for men. The prevalence increased for adults age 80 and over to 16% for women and 29% for men. Morley et al. reported a range in the prevalence of sarcopenia for adults age 60-70 of 5-13%, and 11-50% for adults age 80 and over<sup>4,9</sup>.

### **Risk factors**

After age 50, declines in muscle mass and muscle strength occur annually. Muscle mass declines at an annual rate of 1-2%<sup>93</sup>. Strength declines at a rate of 1.5% per year from age 50-60, after which the rate of decline accelerates to approximately 3% for adults 60 years of age and older<sup>93</sup>. Declines in muscle mass differ for men and women, as men experience gradual declines in muscle mass while women after menopause experience a steeper decrease in muscle mass<sup>93</sup>.

Several diseases also place older adults at increased risk of sarcopenia. Kidney disease in men and osteoporosis in men and women have been found to be associated with development of sarcopenia<sup>94</sup>. Kidney disease is associated with a decrease in testosterone, and kidney disease and osteoporosis are associated with decreased vitamin

D, both of which are associated with decreases in muscle. Cognitive impairment has also been found to be a risk factor for sarcopenia<sup>95</sup>.

Low BMI, low physical activity, low physical function, and ADL limitations have all been cited as risk factors for sarcopenia in several studies<sup>94-97</sup>. As well, behavioral characteristics such as smoking and excessive drinking, and socioeconomic factors (income, malnutrition), are associated with an increased risk of sarcopenia<sup>94-96</sup>.

### **Impact on Lower Extremity Function**

Studies have reported sarcopenia as being negatively associated with lower extremity function and osteoporosis<sup>12,98,99</sup>. Sarcopenia has been associated with decreased physical function as well as physical disability<sup>82</sup>. Similarly, muscle strength has also been associated<sup>90,100,101</sup> with and predictive<sup>102</sup> of functional decline, as well as mortality. Recent studies hypothesized that muscle strength could be mediating the relationship between muscle mass and physical function due to the high correlation between muscle mass and muscle strength<sup>25,27,101</sup>.

Cross-sectional studies have shown a relationship between sarcopenia and physical disability and lower extremity function. Baumgartner et al. found that sarcopenic older adults had a 4 times higher likelihood of having physical disability<sup>82,103</sup>. Likewise, older adults with severe sarcopenia in the NHANES study had a 2-3 times higher likelihood of functional impairment and physical disability<sup>103,104</sup>. Specifically, Janssen et al. found in NHANES II that severe sarcopenia resulted in a 2-fold likelihood of functional impairment and disability in men, and a 3-fold likelihood in women<sup>104</sup>.

Similar findings were also confirmed in longitudinal studies. In Health ABC, mid-thigh muscle size was a predictor of loss of physical function over a follow-up period of 2 to 3 years<sup>89,101,103</sup>. Visser et al. concluded that the association of muscle mass to function resulted from muscle strength<sup>80</sup>. Also in the Cardiovascular Health Study, those with severe sarcopenia, defined by cutpoints of relative muscle mass<sup>99,105</sup>, had 79% greater likelihood of having physical disability at baseline. Moreover, those with severe sarcopenia had a 27% higher risk of developing physical disability over 8 years in the same cohort<sup>99,103</sup>.

### **Impact of Diabetes on muscle mass and strength**

Diabetes leads to accelerated loss of muscle function<sup>4</sup>. Diabetes results in a decrease in insulin growth factor IGF-1, leading to a decrease in protein synthesis and increase protein catabolism, all of which results in lower muscle mass<sup>4</sup>. Diabetes is also associated with insulin resistance, which leads to a decrease activity of protein kinase systems, which are important for maintaining and developing muscle mass<sup>4</sup>. Diabetes also may result in decreased testosterone, which has been associated with loss of muscle mass, strength, and function<sup>93</sup>. Diabetic older adults have been shown to have lower muscle quality<sup>7</sup> and excessive loss of appendicular lean mass<sup>6</sup> compared to non-diabetic older adults.

Several complications from diabetes discussed in Chapter 2 can also impact muscle mass and strength, including vision impairment, kidney disease, nervous system disorders, and arthritis. Vision impairment has been hypothesized to increase frailty<sup>44</sup>. Nephropathy has been found to be a risk factor for sarcopenia<sup>95</sup>. Loss of sensation and or pain in the hands or feet, can result in decrease physical activity, thereby resulted in

decreases in muscle mass and strength<sup>1</sup>. Similarly, arthritis can also result in decreases in physical activity<sup>48</sup>.

#### **IV. Summary**

While studies have shown the physiological association between diabetes and muscle mass, they have not quantified the prevalence of sarcopenia among diabetic older adults, nor examined this association using the newer definitions of sarcopenia including muscle strength and muscle mass. Also, while PND has been shown to moderate the relationship between diabetes and lower extremity function, and PND is physiologically associated with decreased muscle mass and strength, the association between sarcopenia and PND and its potential impact on lower extremity function is unknown.

Understanding how sarcopenia and PND impact lower extremity function, and how these complications may be impacted by race and sex, is critical to the development of interventions to improve the lower extremity function of older adults with and without diabetes.

## Chapter 3 – Methods

### Overview of Methods

This analysis aimed to establish the relationship between diabetes, PND, sarcopenia, and lower extremity function over time, while accounting for important confounding variables such as weight, physical activity, and comorbidities. Cross-sectional and longitudinal analyses were utilized in three aims to examine the relationship between these components.

### Overview of Dataset

#### Health Aging and Body Composition Study

This study utilized data from the Health ABC, a prospective cohort study investigating changes in body composition as a common pathway by which multiple diseases contribute to disability<sup>15,71</sup>. Participants were enrolled and measured at baseline in 1997 and 1998, and re-assessed every year with interviews and measurements. The study is currently in its 17<sup>th</sup> year, allowing for longitudinal examination of many study variables. All participants were physically well-functioning older adults aged 70 to 79 when enrolled. Of the 3,075 total participants, 48.4% were male and 41.6% black<sup>71</sup>.

Participants were recruited via large mass mailing to a random sample of white, Medicare beneficiaries and all age-eligible black community residents in and surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee<sup>71</sup>. All participants were screened to determine their eligibility via a phone interview. Participants needed to report no difficulty walking one-quarter of a mile (400 m), no difficulty walking up 10 steps, no use of walking equipment such as a cane or walker, and no difficulty performing

ADLs<sup>71,106</sup>. Additionally, all eligible participants were required to have had no active cancer treatments in the prior 3 years, and they were required to report no intention of moving outside of the eligibility area in the next 3 years<sup>106</sup>.

All Health ABC participants enrolled gave informed consent before study measures were collected. After the screening interview, eligible participants completed the baseline home interview during which they provided information on their health status; physical function; physical activity and exercise; work, volunteer and caregiving activities; appetite and eating behavior; weight history; smoking and alcohol usage; sleep habits; joint and bone pain or disease; female health history; cardiovascular, pulmonary, cancer, gastrointestinal, urinary, oral, visual, and hearing health history; health care usage; social and psychological well-being; and socioeconomic factors. Following the home survey, participants were scheduled for clinic visits where height and weight were measured as well as blood pressure, blood tests, strength and performance measures, DXA scanning, oral glucose tolerance, ECG, and medication inventory.

### **Analytic Sample**

The Health ABC study population consists of well-functioning individuals 70 years of age and older which provides an appropriate sample to examine change in lower extremity function over time. Overall, the Health ABC study population is 51.6% female and 41.6% black, therefore, this dataset allows for the examination of race and sex as potential effect modifiers. The analytic sample was restricted to participants with complete data to assess diabetes status at year 4, as well as complete peripheral nerve function at year 4, body composition at years 4, 6, 8, and/or 10, gait speed at years 8, 10, and/or 11, and covariate data at baseline for the covariates listed in table 1.

## Measures

Table 1 lists the dependent and independent variables, effect modifiers, and confounders that were analyzed for each aim of the study.

### Measurement of Diabetes

Diabetes status (bivariate) was determined at baseline by blood glucose levels, use of antidiabetic medications, or self-reported diagnosis at baseline. For determination by blood glucose levels, participants were defined with diabetes if they had a fasting blood glucose level  $\geq 126$  mg/dl, consistent with current American Diabetes Association's (ADA) guidelines<sup>107</sup>.

Additionally, categorical diabetes variable was created to account for control. Control was defined by Hemoglobin A1c (HbA1c) levels based off of ADA recommendations<sup>107</sup>. Diabetic participants with a HbA1c less than 7% were defined as having controlled diabetes, while diabetic participants with a HbA1c greater than 7% were defined as having poorly-controlled diabetes.

### Measurement of Sarcopenia

Sarcopenia was defined as a binary measure based on having low muscle mass, measured from whole body dual-energy X-ray absorptiometry (DXA), *and* low muscle strength, measured from isometric handgrip strength. Low muscle mass via DXA was defined as less than  $7.23 \text{ kg/m}^2$  for men and  $5.67 \text{ kg/m}^2$  for women<sup>24</sup>. Low muscle strength via measured grip strength was defined as less than 30 kg for men and less than 20 kg for women<sup>92</sup>. Whole body DXA and grip strength measurements were used from year 4 for aim 1, and from years 6, 8, and 10 for aims 2 and 3.

For each aim, using an amended European Working Group on Sarcopenia in Older People (EWGSOP) definition, participants were classified as sarcopenic (bivariate) for that time point if they had both low muscle mass and low muscle strength<sup>9</sup>. Participants were defined as not sarcopenic at each time point if they have low muscle mass and normal muscle strength, normal muscle strength and low muscle mass, or normal muscle mass and normal muscle strength.

#### Measurement of Peripheral Nerve Dysfunction

PND (bivariate) was defined as having 2 or more of the following during the year 4 measurement: inability to detect vibration, inability to detect either a 4.17 or 5.07 monofilament, nerve conduction velocity less than 40 m/s, and/or motor nerve conduction amplitude less than 1 mV.

#### Measurement of Lower Extremity Function

Lower extremity function (continuous) was defined using gait speed (m/s). Gait speed is an objective measure of lower extremity function and was used as the outcome measure in Aim 3 to assess lower extremity function. Gait speed was calculated by dividing the length of a walking course (4m at year 8; 3, 4, or 6m at years 10 and 11) by the total time necessary for a participant to complete the distance of the walking course at their usual pace. This measurement was used from years 8, 10, and 11 for aim 3.

#### Confounders

Confounding may occur if variables are associated with both the independent and dependent variable. Several variables could confound the association between the

independent variables diabetes (Aim 1), PND (Aims 2 and 3), and sarcopenia (Aim 3), and the respective dependent variables of the three research aims: sarcopenia (Aims 1 and 2), and lower extremity function (Aim 3). These include demographics and comorbidities, all listed in Table 1.

Age is associated with diabetes status, as older adults are at greater risk of diabetes than younger adults<sup>3,10,13</sup>. Age is also associated with sarcopenia, as older adults are at greater risk of loss of muscle mass and strength, leading to sarcopenia<sup>9,103,106</sup>. Additionally, older adults are at greater risk of decreases in nerve function and lower extremity function<sup>20,55,73,108-110</sup>. Behavioral demographic factors such as smoking status and alcohol intake frequency may affect the relationship between diabetes, peripheral nerve function, sarcopenia, and lower extremity function. Smoking status is associated with increased risk of diabetes, peripheral neuropathy, and a sedentary lifestyle<sup>38,111-113</sup>. Alcohol intake frequency is also associated with increased risk of diabetes, peripheral neuropathy, and a sedentary lifestyle<sup>38,114,115</sup>. Socioeconomic factors like family income, highest level of education attained, and marital status may impact the relationship between diabetes and sarcopenia.

Diabetes duration and control (maintaining a low hemoglobin A1c and low blood glucose) are associated with having complications from diabetes<sup>3,10</sup>. Longer duration and poorer control of diabetes can place one at greater risk of sarcopenia, as they both may lead to a stronger decrease in protein kinase systems, which aid in maintaining and developing muscle mass<sup>84</sup>. Longer diabetes duration and poorer diabetes control can place one at greater risk of PND, as prolonged glucose intolerance is the primary risk

factor for PND<sup>2</sup>. Longer diabetes duration and poorer control are also associated with greater decreases in lower extremity function<sup>17,48</sup>.

BMI is associated with diabetes, and diabetic older adults have a higher BMI than non-diabetic older adults<sup>3,13</sup>. BMI is also associated with sarcopenia, as obese older adults may be at increased risk of sarcopenia<sup>9,79,84</sup>. While obese older adults may experience an increase in fat mass, and therefore maintain overall mass, this increase in fat mass results in decreases in lean mass. Decreases in lean mass in conjunction with increases in fat mass are characteristic of sarcopenic obesity<sup>9</sup>. BMI also increases the risk for the development of PND<sup>2</sup>. Additionally, BMI results in increased risk of lower extremity dysfunction<sup>116</sup>.

Self-reported physical function, measured by reported difficulty with functional activities such as walking, and climbing, is associated with diabetes and lower extremity function, in that diabetic older adults have lower self-reported physical function than non-diabetic older adults<sup>117</sup>. Additionally, self-reported physical function has been found to be predictive of objectively measured lower extremity function<sup>118</sup>.

Medication usage, particularly bone medications and diabetes medications, may also help explain the association between diabetes and sarcopenia. Depression is associated with lower adherence to lifestyle changes for diabetes, poorer diabetes control, and is also associated with a sedentary lifestyle and poorer physical function<sup>119-121</sup>. Comorbidities may differently affect muscle loss and strength in diabetes, thus arthritis, cardiovascular disease, hypertension, osteoporosis, and osteoarthritis will also be controlled for<sup>94-96</sup>.

**Table 1: Variables for Analysis**

	Type	Aims		
		1	2	3
<b>Dependent Variables</b>				
Sarcopenia (year 4)	Binary (1=Sarcopenic)	X		
DXA total lean mass (kg/m)				
Isometric handgrip strength (kg)				
Sarcopenia (years 6, 8, and/or 10)	Binary (1=Sarcopenic)		X	
DXA total lean mass (kg/m)				
Isometric handgrip strength (kg)				
Lower Extremity Function (years 8, 10, and/or 11)				
Gait Speed (m/s)	Continuous			X
<b>Independent Variables</b>				
Diabetes status (year 4)	Binary (1=Diabetic)	X		
Categorical Diabetes Status (year 4) (Defined by HbA1c $\geq$ 7% for diabetic older adults)	Categorical (0=No diabetes, 1=Controlled diabetes, 2=Poorly-controlled diabetes)	X		
PND (year 4)	Binary (1=PND)		X	
Sarcopenia (years 6, 8, and/or 10)	Binary (1=Sarcopenic)			X
DXA total lean mass (kg/m)				
Isometric handgrip strength (kg)				
Sarcopenia (years 6, 8, and/or 10) <i>and</i> PND (year 4)	Binary (1=Sarcopenic and PND)			X
<b>Effect Modifiers</b>				
Sex	Binary (1=Female)	X	X	X
Race (White, Black)	Binary (1=White)	X	X	X
<b>Confounders (Baseline)</b>				
Age	Continuous ( $\geq$ 70)	X	X	X
Centered Age	Centered around the mean (73.48)	X	X	X
Sex	Binary (1=Female)	X	X	X

**Table 1 Continued**

Race (White, Black)	Binary (1=White)	X	X	X
BMI	Continuous	X		
Categorical Diabetes Status	Categorical (0=No diabetes, 1=Controlled diabetes, 2=Poorly-controlled diabetes)		X	X
Diabetes ≥ 5 years	Binary (1= Diabetes Duration ≥ 5 years)	X	X	X
Family income	Categorical			
	(1= <10K, 2= ≥ 10K to 25K, 3= >25K to 50K, 4= >50K)			
		X	X	X
Highest level of education attained	Categorical			
	(1=Less than HS, 2=HS Grad, 3=Postsecondary)	X	X	X
Self-reported physical activity	Continuous (Kcal/kg/week)	X	X	X
Current Smoker	Binary (1=Yes)	X	X	X
Drinking Frequency	Categorical			
	(1=No consumption in past year, 2=Less than once per week, 3= More than once per week)	X	X	X
Cardiovascular disease	Binary (1=CVD)	X	X	X
Depressive Symptoms (CES-D)	Binary (1=Depression)	X	X	X
Arthritis	Binary (1=Arthritis)	X	X	X
Hypertension	Binary (1=Hypertension)	X	X	X
Osteoporosis	Binary (1=Osteoporosis)	X	X	X
Symptomatic Osteoarthritis				
Hand	Binary (1=Osteoarthritis)	X	X	X
Hip	Binary (1=Osteoarthritis)	X	X	X
Knee	Binary (1=Osteoarthritis)	X	X	X
Other	Binary (1=Osteoarthritis)	X	X	X
Use of medications				
Bone medications	Binary (1=Yes)	X	X	X
Diabetes medications	Binary (1=Yes)	X	X	X

## **Analytic Methods**

### **Specific Aim 1**

**Aim 1**: Examine the prevalence of sarcopenia among diabetic and non-diabetic older adults and examine if race or sex modify the relationship.

**Aim 1A**: Determine the prevalence of sarcopenia at year 4 among diabetic and non-diabetic older adults, where diabetes status was determined at year 4.

**H1A.1** Diabetic older adults will have a higher prevalence of sarcopenia at year 4 than non-diabetic older adults.

**Aim 1B**: Investigate if race and sex modify the relationship between diabetes status and sarcopenia at year 4.

**H1B.1** Race will modify the relationship between diabetes status and sarcopenia such that black diabetic older adults will have a lower prevalence of sarcopenia at year 4 than white diabetic adults.

**H1B.2** Sex will modify the relationship between diabetes status and sarcopenia such that older diabetic women will have a higher prevalence of sarcopenia at year 4 than older diabetic men.

## **Rationale**

Recent literature reports that 15.7% of diabetic older adults have sarcopenia<sup>8</sup>. However, this estimate is based on a simplistic measure of muscle mass that does not incorporate strength in its measurement of sarcopenia. Sarcopenia measurements that do not include strength are lacking because strength has been found to be more predictive of functional outcomes than mass alone<sup>9</sup>. This is critical among older adults but can be potentially important among diabetic older adults because recent research has found functional muscular components (including strength and quality) to account for 25% of the association between diabetes and functional outcomes<sup>122</sup>. Prior estimates on the prevalence of sarcopenia among diabetics were based on a non-US sample which may have limited applicability to US older adults<sup>8</sup>.

It was therefore the aim of the current study to use a more comprehensive measure of sarcopenia put forth by the European Working Group on Sarcopenia in Older People (EWGSOP), which defines sarcopenia by low muscle mass *and* low muscle strength<sup>9</sup>. This is still important to understand in relation to diabetic older adults because of the physiological associations between diabetes, muscle mass, and muscle strength.

## **Analytic Sample**

For Aim 1, participants must have had a diabetes status at year 4 as well as DXA and handgrip measurements at year 4. The sample must also not have missing data on the covariates of interest listed in table 1.

### **Independent and Dependent Variable**

Aim 1 assessed the prevalence of sarcopenia among diabetic and non-diabetic participants at year 4. The independent variable was diabetes status, while sarcopenia was the dependent variable measured at year 4.

### **Sex and Race Differences**

To determine if prevalence of sarcopenia among diabetic participants differed by race and sex, interaction terms were assessed. Previous research that examined the prevalence of sarcopenia by diabetes status had not examined race and sex effects. Black older adults have a higher prevalence of diabetes<sup>10</sup> and higher muscle mass<sup>1,11,12</sup> than white older adults; therefore they may have a lower prevalence of sarcopenia. Older adults males have a higher prevalence of diabetes than older adult females<sup>10</sup>; however older adult males also have a higher average muscle mass<sup>13,14</sup>. It is unknown whether older adult males would have a higher or lower prevalence of sarcopenia.

### **Analytic Strategy**

The multivariable analysis for Aim 1 examined the relationship between diabetes status and sarcopenia. Multivariable logistic regression was used to determine prevalence (odds ratios) of sarcopenia (year 4) by diabetes status. The first model examined sarcopenia by diabetes status. The second model added age, race, sex, and control variables listed in table 1. Backward selection was used to determine which covariates should remain in the model. Some covariates remained in the model regardless of significance due to biological plausibility. The third model examined an interaction term for diabetes and race to determine if race impacts the relationship between diabetes and sarcopenia. Similarly, the fourth model examined an interaction term for diabetes and sex

to determine if sex impacted the relationship between diabetes and sarcopenia. Stratified analyses were to be conducted if either of the interaction terms in the latter two models were significant.

### **Models for Aim 1:**

Model 1:  $\text{Logit}[\text{Sarcopenia}_{\text{yr4}}] = \beta_0 + (\beta_1 * \text{Controlled Diabetes}) + \beta_2 * \text{Poorly-Controlled Diabetes}$

Model 2:  $\text{Logit}[\text{Sarcopenia}_{\text{yr4}}] = \beta_0 + (\beta_1 * \text{Controlled Diabetes}) + \beta_2 * \text{Poorly-Controlled Diabetes}) + (\beta_3 * \text{Race}) + (\beta_4 * \text{Sex}) + (\beta_5 * \text{Covariates}) \dots (\beta_n * \text{Covariates})$

Model 3:  $\text{Logit}[\text{Sarcopenia}_{\text{yr4}}] = \beta_0 + (\beta_1 * \text{Controlled Diabetes}) + \beta_2 * \text{Poorly-Controlled Diabetes}) + (\beta_3 * \text{Race}) + (\beta_4 * \text{Controlled Diabetes} * \text{Race}) + (\beta_5 * \text{Covariates}) \dots (\beta_n * \text{Covariates})$

Model 4:  $\text{Logit}[\text{Sarcopenia}_{\text{yr4}}] = \beta_0 + (\beta_1 * \text{Controlled Diabetes}) + \beta_2 * \text{Poorly-Controlled Diabetes}) + (\beta_3 * \text{Race}) + (\beta_4 * \text{Poorly-Controlled} * \text{Race}) + (\beta_5 * \text{Covariates}) \dots (\beta_n * \text{Covariates})$

Model 5:  $\text{Logit}[\text{Sarcopenia}_{\text{yr4}}] = \beta_0 + (\beta_1 * \text{Controlled Diabetes}) + \beta_2 * \text{Poorly-Controlled Diabetes}) + (\beta_3 * \text{Sex}) + (\beta_4 * \text{Controlled Diabetes} * \text{Sex}) + (\beta_5 * \text{Covariates}) \dots (\beta_n * \text{Covariates})$

Model 6:  $\text{Logit}[\text{Sarcopenia}_{\text{yr4}}] = \beta_0 + (\beta_1 * \text{Controlled Diabetes}) + \beta_2 * \text{Poorly-Controlled Diabetes}) + (\beta_3 * \text{Sex}) + (\beta_4 * \text{Poorly-Controlled Diabetes} * \text{Sex}) + (\beta_5 * \text{Covariates}) \dots (\beta_n * \text{Covariates})$

### **Power Calculation**

Power calculations for these analyses were done based on Aim 1A (Table 2). Parameters for the power calculations were derived from Health ABC and previous

analyses from KSOS of the prevalence of sarcopenia among diabetic (16%) and non-diabetic (7%) older adults, as this is the only known study with quantified prevalence data for sarcopenia among diabetic older adults<sup>8</sup>. Preliminary data from Health ABC provided an estimated cohort of 489 diabetic older adults and 1763 non-diabetic older adults. All power calculations utilized an alpha level of 0.05.

**Table 2: Power Calculations Aim 1A**

**Prevalence of Sarcopenia between Diabetic and non-Diabetic Older Adults**

<b>% Sarcopenia among diabetic older adults (P1)</b>	<b>%Sarcopenia among non-diabetic older adults (P2)</b>	<b>Detectable Difference (P1-P2)</b>	<b>Diabetic older adults sample size</b>	<b>Non-diabetic older adults sample size</b>	<b>Power</b>
16	7	0.090	489	1763	>.999
12	7	0.050	489	1763	0.923
16	11	0.050	489	1763	0.887

Based on the comparison of two proportions using these estimates, power calculations indicated that this sample size was sufficient to detect 9% higher sarcopenia prevalence among diabetic versus non-diabetic older adults (Table 2). Additionally, if the prevalence of sarcopenia among diabetic older adults was lower than previously estimated yet the prevalence among non-diabetic older adults was the same as previous estimates, a 5% higher prevalence rate of sarcopenia between diabetic and non-diabetic older adults could still be detected. Similarly, if the previous prevalence estimates of

sarcopenia among diabetic older adults were correct, and yet the prevalence of sarcopenia among non-diabetic older adults was higher, this sample size would still be sufficient enough to detect a 5% higher rate of prevalence of sarcopenia among diabetic versus non-diabetic older adults.

## **Specific Aim 2**

**Aim 2:** Examine the relationship between PND and sarcopenia among diabetic and non-diabetic older adults and determine if race and sex modify the relationship.

**Aim 2A:** Determine the prevalence of sarcopenia at years 6, 8, and/or 10 among participants with PND at year 4.

**H2A.1:** Participants with PND will have a higher prevalence of sarcopenia over time than participants without PND.

**Aim 2B:** Investigate if race and sex modify the relationship between PND at year 4 and sarcopenia at years 6, 8, and/or 10.

**H2B.1** Race will modify the relationship between PND and sarcopenia such that black older adults with PND at year 4 will have a lower prevalence of sarcopenia at years 6, 8, and/or 10 than white older adults with PND at year 4.

**H2B.2** Sex will impact the relationship between PND and sarcopenia such that older women with PND at year 4 will have a higher prevalence of sarcopenia at years 6, 8, and/or 10 than older men with PND at year 4.

## **Rationale**

PND has been suggested as a mechanistic cause of sarcopenia, as PND may lead to denervation and atrophy of muscle fibers<sup>16,71</sup>. While this relationship between PND and sarcopenia had been assessed biologically, it had not been examined longitudinally in any cohort; therefore, it was unknown whether or not muscle atrophy resulting from PND was substantial enough to result in sarcopenia. This proposed study would determine the association between PND and sarcopenia over a 6-year period. Understanding the impact of PND on sarcopenia could be important for intervention development as it can lead to better targeting of older adults most at risk for the development of sarcopenia. Additionally, understanding the potential effects of race and sex can improve upon targeting for interventions.

## **Analytic Sample**

Aim 2 included those with a known PND status at year 4, and DXA and handgrip measurements at years 6, 8, and/or 10. In addition, participants must have had non-missing covariate data.

## **Independent and Dependent Variable**

Aim 2 assessed the prevalence of sarcopenia by PND status. PND was the independent variable. The dependent variable was sarcopenia status and was determined by low muscle mass measured from DXA and low handgrip strength at years 6, 8, and/or 10.

## **Sex and Race Differences**

Interactions terms were examined to determine if race or sex affected the relationship between PND and sarcopenia. This was particularly important to assess as the prevalence of PND differs by race and sex and the prevalence of sarcopenia may differ as well.

## **Analytic Strategy**

The multivariable analysis for Aim 2 examined the relationship between PND and sarcopenia prevalence. Generalized estimating equations (GEE) were used to predict sarcopenia prevalence over time (years 4-10) by PND status. The first model predicted sarcopenia status by PND status. The second model added age, race, sex, and additional control variables listed in table 1. Backward selection was used to determine which covariates should remain in the model. Some covariates remained in the model regardless of significance due to biological plausibility. The third model examined an interaction term for sarcopenia and race to determine if race impacted the relationship between PND and sarcopenia. Similarly, the fourth model examined an interaction term for sarcopenia and sex to determine if sex impacted the relationship between PND and sarcopenia. Stratified analyses were to be conducted if either of the interaction terms in the latter two models was significant.

Each of the models was fit as a marginal model and a random effect model with a random intercept. The marginal models provide the population average. The random intercept models allow for individual variation. Given the heterogeneity of older adults, we believed that both model types should be fit and compared for goodness of fit.

## **Models for Aim 2:**

Model 1:  $\text{Logit}[\text{Sarcopenia}] = \beta_0 + (\beta_1 * \text{PND}) + (\beta_2 * \text{Time}) + (\beta_3 * \text{PND} * \text{Time})$

Model 2:  $\text{Logit}[\text{Sarcopenia}] = \beta_0 + (\beta_1 * \text{PND}) + (\beta_2 * \text{Time}) + (\beta_3 * \text{PND} * \text{Time}) + (\beta_4 * \text{Age}) + (\beta_5 * \text{Race}) + (\beta_6 * \text{Sex}) + (\beta_7 * \text{Covariates}) + \dots (\beta_n * \text{Covariates})$

Model 3:  $\text{Logit}[\text{Sarcopenia}] = \beta_0 + (\beta_1 * \text{PND}) + (\beta_2 * \text{Time}) + (\beta_3 * \text{PND} * \text{Time}) + (\beta_4 * \text{Race}) + (\beta_5 * \text{PND} * \text{Race}) + (\beta_6 * \text{Covariates}) + \dots (\beta_n * \text{Covariates})$

Model 4:  $\text{Logit}[\text{Sarcopenia}] = \beta_0 + (\beta_1 * \text{PND}) + (\beta_2 * \text{Time}) + (\beta_3 * \text{PND} * \text{Time}) + (\beta_4 * \text{Sex}) + (\beta_5 * \text{PND} * \text{Sex}) + (\beta_6 * \text{Covariates}) + \dots (\beta_n * \text{Covariates})$

Model 5:  $\text{Logit}[\text{Sarcopenia}] = \beta_0 + (\beta_1 * \text{PND}) + (\beta_2 * \text{Time}) + (\beta_3 * \text{PND} * \text{Time}) + (\beta_4 * \text{Sex}) + (\beta_5 * \text{PND} * \text{Diabetes Duration} \geq 5 \text{ Years}) + (\beta_6 * \text{Covariates}) + \dots (\beta_n * \text{Covariates})$

Model 6:  $\text{Logit}[\text{Sarcopenia}] = \beta_0 + (\beta_1 * \text{PND}) + (\beta_2 * \text{Time}) + (\beta_3 * \text{PND} * \text{Time}) + (\beta_4 * \text{Sex}) + (\beta_5 * \text{PND} * \text{Controlled Diabetes}) + (\beta_6 * \text{Covariates}) + \dots (\beta_n * \text{Covariates})$

Model 7:  $\text{Logit}[\text{Sarcopenia}] = \beta_0 + (\beta_1 * \text{PND}) + (\beta_2 * \text{Time}) + (\beta_3 * \text{PND} * \text{Time}) + (\beta_4 * \text{Sex}) + (\beta_5 * \text{PND} * \text{Poorly-Controlled Diabetes}) + (\beta_6 * \text{Covariates}) + \dots (\beta_n * \text{Covariates})$

## **Power Calculation**

Power calculations were not done for aim 2 because it was not possible to properly estimate the prevalence of sarcopenia among older adults with PND, given that this prevalence has not previously been studied.

### **Specific Aim 3**

**Aim 3:** Identify the relationship of PND and sarcopenia on lower extremity function among diabetic compared to non-diabetic older adults, and examine if race or sex modify the relationship.

**Aim 3A:** Demonstrate that sarcopenia at years 6, 8, and/or 10 is associated with gait speed at years 8, 10, and/or 11 among diabetic and non-diabetic older adults.

**H3A.1:** Diabetic and non-diabetic older adults with sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than diabetic and non-diabetic older adults without sarcopenia at years 6, 8, and/or 10.

**Aim 3B:** Demonstrate that PND at year 4, in addition to sarcopenia at years 6, 8, and/or 10 is associated with gait speed at years 8, 10, and/or 11 among diabetic older adults.

**H3B.1:** Diabetic older adults with PND at year 4 and sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than diabetic older adults with sarcopenia at years 6, 8, and/or 10 without PND at year 4.

**Aim 3C:** Determine whether the relationship between sarcopenia at years 6, 8 and/or 10 and gait speed at years 8, 10, and/or 11 among diabetic and non-diabetic older adults is modified by race and sex.

**H3C.1** Race will modify the relationship between sarcopenia and gait speed among diabetic and non-diabetic older adults, such that black older adults with sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than white older adults with sarcopenia at years 6, 8, and/or 10.

**H3C.2** Sex will impact the relationship between sarcopenia and gait speed among diabetic and non-diabetic older adults, such that older women with sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than older men with sarcopenia at years 6, 8, and/or 10.

### **Rationale**

While studies have shown that diabetes is associated with lower extremity function, research has not examined the association between diabetes, sarcopenia, and lower extremity function longitudinally<sup>2,15,17-22</sup>. Cross-sectional research has indicated that PND mediates the relationship between diabetes and lower extremity function<sup>20,22,23</sup>; However studies have not demonstrated whether PND in addition to sarcopenia results in differences in lower extremity function by diabetes status<sup>15,23,71</sup>. Additionally, while studies have shown lower prevalence of sarcopenia among blacks and men, no studies

have shown how race and sex impact the relationship between sarcopenia and lower extremity function with the EWGSOP sarcopenia definition.

### **Analytic Sample**

For Aim 3, participants must have had a diabetes status at baseline and DXA and handgrip measurements, both at years 6, 8, and/or 10. In addition, participants must also have had non-missing peripheral nerve function measures at year 4, had at least one complete performance measure inclusive of gait speed at years 8, 10, and/or 11, and non-missing covariate measures.

### **Independent and Dependent Variable**

Aim 3 examined the longitudinal association between sarcopenia and lower extremity function between diabetic and non-diabetic adults. Sarcopenia was the independent variable for aims 3A and 3C. Sarcopenia in conjunction with PND was the independent variable for aim 3B. Gait speed was the dependent variable.

### **Sex and Race Differences**

Interactions terms were examined to determine if race or sex affected the relationship between sarcopenia and lower extremity function. This was particularly important to assess as the prevalence of sarcopenia as well as gait speed may differ by race and sex.

### **Analytic Strategy**

The multivariable analysis for Aim 3 examined the relationship between sarcopenia and gait speed among diabetic and non-diabetic older adults. Generalized

linear models were used to predict gait speed over time (years 1-11) by sarcopenia status. The first model predicted gait speed by sarcopenia status. The second model added age, race, sex, and additional control variables listed in table 1. Backward selection was used to determine which covariates should remain in the model. Some covariates remained in the model regardless of significance due to biological plausibility.

The third model predicted gait speed by sarcopenia and PND status unadjusted. The fourth model added age, race, sex, and the same additional control variables as in model 2. The fifth model examined an interaction term for sarcopenia and race to determine if race impacted the relationship between sarcopenia and gait speed. Similarly, the sixth model examined an interaction term for sarcopenia and sex to determine if sex impacted the relationship between sarcopenia and gait speed. Stratified analyses were to be conducted if either of the interaction terms in the latter two models is significant.

Each of the models was fit as a marginal model and a random effect model with a random intercept. The marginal models provide the population average. The random intercept models allow for individual variation. Given the heterogeneity of older adults, we believed that both model types should be fit and compared for goodness of fit.

### **Models for Aim 3:**

Model 1: [Gait speed] =  $\beta_0 + (\beta_1 * \text{Sarcopenia Status}) + (\beta_2 * \text{Time Year 10}) + (\beta_3 * \text{Time Year 11}) + \varepsilon$

Model 2: [Gait speed] =  $\beta_0 + (\beta_1 * \text{Sarcopenia Status}) + (\beta_2 * \text{Time Year 10}) + (\beta_3 * \text{Time Year 11}) + (\beta_4 * \text{Age}) + (\beta_5 * \text{Race}) + (\beta_6 * \text{Sex}) + (\beta_7 * \text{Covariates}) + \dots (\beta_n * \text{Covariates}) + \varepsilon$

Model 3: [Gait speed] =  $\beta_0 + (\beta_1 * \text{Sarcopenia Status}) + (\beta_2 * \text{Time Year 10}) + (\beta_3 * \text{Time Year 11}) + (\beta_4 * \text{Sarcopenia and Peripheral Neuropathy}) + (\beta_5 * \text{Age}) + (\beta_6 * \text{Race}) + (\beta_7 * \text{Sex}) + (\beta_8 * \text{Covariates}) + \dots (\beta_n * \text{Covariates}) + \varepsilon$

Model 4: [Gait speed] =  $\beta_0 + (\beta_1 * \text{Sarcopenia Status}) + (\beta_2 * \text{Time Year 10}) + (\beta_3 * \text{Time Year 11}) + (\beta_4 * \text{Sarcopenia} * \text{Race}) + (\beta_5 * \text{Age}) + (\beta_6 * \text{Race}) + (\beta_7 * \text{Sex}) + (\beta_8 * \text{Covariates}) + \dots (\beta_n * \text{Covariates}) + \varepsilon$

Model 5: [Gait speed] =  $\beta_0 + (\beta_1 * \text{Sarcopenia Status}) + (\beta_2 * \text{Time Year 10}) + (\beta_3 * \text{Time Year 11}) + (\beta_4 * \text{Sarcopenia} * \text{Sex}) + (\beta_5 * \text{Age}) + (\beta_6 * \text{Race}) + (\beta_7 * \text{Sex}) + (\beta_8 * \text{Covariates}) + \dots (\beta_n * \text{Covariates}) + \varepsilon$

### **Power Calculation**

Power calculations for these analyses were done based on aims 3A (Table 3). Using data from previous analyses of sarcopenia in Health ABC and the EWGSOP definition of sarcopenia<sup>9,24</sup>, a cohort of 1200 non-sarcopenic older adults was estimated and used to calculate the necessary sample size of sarcopenic older adults to achieve a power of 0.80 (Table 3). Mean gait speed differences and standard deviations were estimated from a previous study of clinically meaningful differences in gait speed<sup>123</sup>. All

power calculations utilized an alpha level of 0.05. With projected estimates of sarcopenia<sup>8</sup> there is sufficient sample size to detect a meaningful difference in gait speed ranging from 0.05, indicating a small meaningful difference, to 0.10, indicating a significant meaningful difference<sup>124</sup>.

**Table 3: Power Calculations Aim 3A**

**Comparing gait speed between sarcopenic and non-sarcopenic older adults**

<b>Mean Gait Speed Difference</b>	<b>Standard Deviation</b>	<b>Sarcopenic older adults sample size</b>	<b>Non-sarcopenic older adults sample size</b>	<b>Power</b>
0.05	0.1	180	1200	>0.999
0.05	0.2	180	1200	>0.878
0.10	0.1	180	1200	>0.999
0.10	0.2	180	1200	>0.999

## Chapter 4 – Results

### Aim 1

#### Specific Aims

**Aim 1**: Examine the prevalence of sarcopenia among diabetic and non-diabetic older adults and examine if race or sex modify the relationship.

**Aim 1A**: Determine the prevalence of sarcopenia at year 4 among diabetic and non-diabetic older adults, where diabetes status was determined at year 4.

**H1A.1** Diabetic older adults will have a higher prevalence of sarcopenia at year 4 than non-diabetic older adults.

**Aim 1B**: Investigate if race and sex modify the relationship between diabetes status and sarcopenia at year 4.

**H1B.1** Race will modify the relationship between diabetes status and sarcopenia such that black diabetic older adults will have a lower prevalence of sarcopenia at year 4 than white diabetic older adults.

**H1B.2** Sex will modify the relationship between diabetes status and sarcopenia such that older diabetic women will have a higher prevalence of sarcopenia at year 4 than older diabetic men.

## **Results**

Table 4 shows the bivariate relationships between baseline study demographics, covariates, and binary diabetes status. Four year sarcopenia prevalence was higher among those without diabetes (6%) than those with diabetes (3.4%). While the mean age was similar between the diabetic and non-diabetic groups, diabetic adults were more likely to be male and black. Diabetic older adults had a significantly higher prevalence of PND, BMI, CVD, hypertension and depressive symptoms. A significantly greater percentage of diabetic participants had a family income less than \$25,000 and less than high school education. Diabetic older adults had a significantly lower self-reported physical activity (total kcal/wk), report of  $\geq 1$  drink per week, and use of osteoporosis medications.

Table 5 shows the main bivariate relationships between study demographics, covariates, and distinguishing those with controlled diabetes and those with poorly-controlled diabetes. Sarcopenia prevalence was highest among those without diabetes and lowest among those with poorly-controlled diabetes. PND was highest among those with controlled diabetes and lowest among those without diabetes. Percentage of male participants was highest in both diabetes groups. Black participants were more likely to be in the poorly-controlled diabetes group. Age was not different across the diabetes groups. Those with poorly-controlled diabetes had the highest BMI while non-diabetics had the lowest. Among those with diabetes, percentage of participants with a diabetes duration greater than 5 years and usage of diabetes medications were higher among the poorly controlled diabetes group than the controlled diabetes group.

The poorly controlled diabetes group had the highest percentage of participants with a family income less than \$25,000 and education less than high school. Percentage of participants who drank more than once a week, and self-reported physical activity was lowest in the poorly-controlled diabetes group, although the difference in physical activity only borders on significance. There was no difference in prevalence of current smokers. CVD prevalence, hypertension, and depressive symptoms were highest among the poorly controlled diabetes group. Prevalence of arthritis, osteoporosis, and osteoarthritis did not differ statistically across the diabetes groups.

The bivariate relationships between study demographics, covariates, and sarcopenia status are displayed in Table 6. Diabetes prevalence was highest among those without sarcopenia at four years. Participants with sarcopenia at 4 years had a higher mean age and higher percentage of female and white participants (although the sex difference was not statistically significant). Those with sarcopenia at 4 years also had a significantly lower BMI, more depressive symptoms, and lower self-reported physical activity. Sarcopenic adults were more likely to be current smokers, have less than a high school education, and family income less than \$25,000 (although family income was not significant). For the comorbidities, only osteoporosis was higher among those with sarcopenia.

**Table 4: Baseline Demographics by Diabetes Status at Year 4**

	No Diabetes	Diabetes	p-value
Mean (SD)	n=1884	n=504	
Sarcopenia at Year 4(%)	6.02	3.4	0.03
Low Muscle Mass (%)	31.2	19	<0.01
Low Muscle Strength (%)	13.4	13.4	0.99
PND (%)	13.67	24.16	<0.01
Sex (%)			<0.01
Male	43.79	52.38	
Race (%)			<0.01
Black	35.35	52.78	
Age	73.48 (2.83)	73.39 (2.77)	0.56
BMI (%)			<0.01
Normal (BMI <25)	35.03	17.46	
Overweight (25> BMI >30)	43.31	41.27	
Obese (BMI ≥ 30)	21.66	41.27	
Diabetes more than 5 years (%)	N/A	58.13	
Family income less than 25K (%)	48.81	57.11	<0.01
Less than HS (%)	21.4	30.88	<0.01
Self-reported total kcal/ <u>wk</u>	88.5 (70.73)	80.93 (71.48)	0.03
Current Smoker (%)	8.45	7.16	0.3
Drinking Frequency more than 1/ <u>wk</u> (%)	31.86	20.83	<0.01
Cardiovascular disease definite (%)	19.86	28.8	<0.01
Depressive Symptoms (CES-D)	4.23 (4.01)	4.81 (4.15)	<0.01
Arthritis (%)	56.74	54.17	0.5
Hypertension (%)	38.98	57.8	<0.01
Osteoporosis (%)	8.98	7.34	0.44
Symptomatic Osteoarthritis (%)			
Hip	1.83	2.21	0.1
Hand	5.82	3.01	0.03
Knee	5.76	5.82	0.95
Other	13.35	10.84	0.24
Use of medications (%)			
Bone medications	4.74	2.19	0.01
Diabetes medications	N/A	51.69	

**Table 5: Baseline Demographics by Diabetes Categories at Year 4**

	No Diabetes	Controlled Diabetes	Poorly Controlled Diabetes	P-value
<b>Mean (SD)</b>	n=1884	n=270	n=66	
Sarcopenia Year 4 (%)	6.02	3.80	2.92	<0.01
Low Muscle Mass	31.20	22.60	13.60	<0.01
Low Muscle Strength	13.40	14.60	11.70	0.64
PND (%)	13.67	26.11	21.05	<0.01
Sex (%)				<0.01
Male	43.79	54.60	55.70	
Race (%)				<0.01
Black	35.35	42.96	63.07	
Age	73.48 (0.06)	73.57 (0.17)	73.05 (0.21)	0.12
BMI (%)				<0.01
Overweight (25> BMI >30)	43.31	38.52	47.73	
Obese (BMI ≥ 30)	21.66	41.48	38.07	
Diabetes Duration ≥ 5 years (%)	N/A	49.63	70.45	<0.01
Family Income ≤ 25K (%)	48.81	50.61	62.43	<0.01
Less than HS Education (%)	21.40	26.39	37.50	<0.01
Self-reported physical activity	88.50 (1.63)	85.36 (4.31)	75.65 (5.34)	0.06
Current Smoker (%)	8.45	6.69	7.95	0.3
Drinking > 1/wk (%)	31.86	24.08	16.48	<0.01
Cardiovascular disease (%)	19.86	26.42	30.64	<0.01
Depressive Symptoms (CES-D)	4.23 (0.09)	4.83 (0.25)	4.95 (0.31)	0.01
Arthritis (%)	56.74	58.15	46.02	0.07
Hypertension (%)	38.98	55.22	58.62	<0.01
Osteoporosis (%)	8.98	8.52	5.68	0.63
Symptomatic Osteoarthritis (%)				
Hip	1.83	2.99	1.73	0.29
Hand	5.82	3.73	2.31	0.07
Knee	5.76	9.33	2.31	0.1
Other	13.35	13.43	6.94	0.12
Use of medications (%)				
Bone medications	4.74	2.97	1.14	0.04
Diabetes medications	N/A	39.03	69.89	<0.01

**Table 6: Baseline Demographics by Sarcopenia Status at Year 4**

	No Sarcopenia	Sarcopenia	P-value
<b>Mean (SD)</b>	n=1971	n=114	
Diabetes (%)			0.03
Diabetes	21.61	13.16	
PND (%)	15.69	14.12	0.7
Sex (%)			0.1
Male	47.44	39.47	
Race (%)			<0.01
Black	38.10	14.91	
Age	73.38 (2.82)	74.32 (2.80)	<0.01
BMI (%)	27.63	23.91	<0.01
Overweight (25 > BMI > 30)	44.78	30.15	
Obese (BMI ≥ 30)	25.96	5.15	
Diabetes Duration ≥ 5 years (%)	12.33	7.02	0.09
Family income ≤ 25K (%)	49.38	40.78	0.06
Less than HS (%)	23.11	12.28	<0.01
Self-reported total kcal/wk	88.85 (71.21)	63.61 (47.99)	<0.01
Current Smoker (%)	7.22	14.04	0.03
Drinking Frequency > 1/wk (%)	29.69	37.16	0.19
Cardiovascular disease (%)	20.81	29.82	0.06
Depressive Symptoms (CES-D)	4.28 (3.99)	4.69 (4.49)	0.04
Arthritis (%)	55.81	60.53	0.58
Hypertension (%)	42.79	41.23	0.44
Osteoporosis (%)	8.38	16.67	<0.01
Symptomatic Osteoarthritis (%)			
Hip	1.90	2.65	0.13
Hand	5.20	9.73	0.11
Knee	6.02	6.19	0.85
Other	12.4	18.58	0.11
Use of medications (%)			
Bone medications	4.32	7.02	0.18
Diabetes medications	10.82	7.89	0.32

Table 7 shows results from the logistic models predicting prevalence of sarcopenia at year 4 comparing the controlled and poorly-controlled diabetic groups to the reference group no-diabetes. After backward selection, cardiovascular disease, drinking frequency, family income, education, arthritis, hypertension, and hip and hand osteoarthritis were removed from the final model due to p-values greater than 0.15. Odds of sarcopenia at year 4 for the controlled diabetic and poorly-controlled diabetic participants were lower than that of the non-diabetic participants (p-value 0.04). After adjusting for covariates, the association between diabetes status and sarcopenia prevalence no longer remained.

Effect modification was assessed for race and sex. White participants had a higher odds of sarcopenia in models 3 and 4 compared to black participant. Neither the interaction between race and controlled-diabetes, nor race and poorly-controlled diabetes were significant. Therefore, there is no differential effect of race on diabetes' association with sarcopenia. Female participants did not have a higher odds of sarcopenia in models 5 and 4 compared to male participants. The results of the effect modification analyses also indicated no differential effect of sex on the relationship between diabetes and sarcopenia prevalence.

As a result of these findings conflicting with our hypotheses, several confirmatory analyses were conducted. Exploratory plots were assessed to view normality, skew, residuals, and slopes. If variables were not normally distributed, Box-Cox transformations were performed to result in normality. Contingency tables were created to check for colinearity between variables. Additionally, confirmatory logistic regressions were fit to look for systematic differences between the diabetic and non-diabetic

populations. Finally saturated models were fit, including transformed, centered, and interaction variables, and stepwise backwards selection was manually performed to determine the appropriate final model. The likelihood ratio test was used to make sure that the full model did not fit statistically significantly better than the final reduced model. These analyses provide us with confidence that the findings we are reporting are accurate.

**Table 7: Logistic Models Predicting Sarcopenia Prevalence**

	OR	Confidence Interval	P-value	-2 log (likelihood)	AIC
Model 1: $\beta_0 + \beta_1 \text{DCAT1} + \beta_2 \text{DCAT2}$				1029.25	1035.25
DCAT1	0.50	(0.26, 0.97)	0.04		
DCAT2	0.42	(0.18, 0.97)	0.04		
Model 2: $\beta_0 + \beta_1 \text{DCAT1} + \beta_2 \text{DCAT2} + \beta_3 \dots \dots \dots \text{B17 Covariates}^*$				601.36	637.36
DCAT1	0.90	(0.31, 2.61)	0.85		
DCAT2	1.53	(0.36, 6.44)	0.56		
Model 3: $\beta_0 + \beta_1 \text{DCAT1} + \beta_2 \text{DCAT2} + \beta_3 \text{DCAT1} * \text{White} + \beta_4 \dots \dots \dots \text{B18 Covariates}^*$				599.55	637.55
DCAT1	2.75	(0.49, 15.46)	0.25		
DCAT2	1.65	(0.40, 6.85)	0.49		
White	4.10	(1.93, 8.72)	<0.01		
DCAT1 * White	0.23	(0.03, 1.76)	0.16		
Model 4: $\beta_0 + \beta_1 \text{DCAT1} + \beta_2 \text{DCAT2} + \beta_3 \text{DCAT2} * \text{White} + \beta_4 \dots \dots \dots \text{B18 Covariates}^*$				598.97	636.97
DCAT1	1.00	(0.96, 1.04)	0.92		
DCAT2	1.01	(0.94, 1.08)	0.86		
White	1.04	(1.01, 1.07)	<0.01		
DCAT2 * White	1.03	(0.94, 1.12)	0.53		
Model 5: $\beta_0 + \beta_1 \text{DCAT1} + \beta_2 \text{DCAT2} + \beta_3 \text{DCAT1} * \text{Female} + \beta_4 \dots \dots \dots \text{B18 Covariates}^*$				598.84	636.84
DCAT1	1.72	(0.51, 5.79)	0.38		
DCAT2	1.62	(0.39, 6.82)	0.51		
Female	1.56	(0.92, 2.65)	0.10		
DCAT1 * Female	0.18	(0.18, 1.87)	0.15		
Model 6: $\beta_0 + \beta_1 \text{DCAT1} + \beta_2 \text{DCAT2} + \beta_3 \text{DCAT2} * \text{Female} + \beta_4 \dots \dots \dots \text{B18 Covariates}^*$				601.36	639.36
DCAT1	0.90	(0.31, 2.61)	0.85		
DCAT2	1.56	(0.29, 8.32)	0.60		
Female	1.45	(0.86, 2.45)	0.16		
DCAT2 * Female	0.96	(0.10, 8.81)	0.97		

\*Covariates included: diabetes duration >5 years, centered age, BMI, race, sex, smoking status, education, self-reported physical activity, CES-D, osteoporosis, osteoarthritis (knee and other), use of osteoporosis medication, use of antidiabetic medication

## **Aim 2**

### **Specific Aims**

**Aim 2:** Examine the relationship between PND and sarcopenia among diabetic and non-diabetic older adults and determine if race and sex modify the relationship.

**Aim 2A:** Determine the prevalence of sarcopenia at years 6, 8, and/or 10 among participants with PND at year 4.

**H2A.1:** Participants with PND will have a higher prevalence of sarcopenia over time than participants without PND.

**Aim 2B:** Investigate if race and sex modify the relationship between PND at year 4 and sarcopenia at years 6, 8, and/or 10.

**H2B.1** Race will modify the relationship between PND and sarcopenia such that black older adults with PND at year 4 will have a lower prevalence of sarcopenia at years 6, 8, and/or 10 than white older adults with PND at year 4.

**H2B.2** Sex will impact the relationship between PND and sarcopenia such that older women with PND at year 4 will have a higher prevalence of sarcopenia at years 6, 8, and/or 10 than older men with PND at year 4.

## **Results**

Table 8 shows the bivariate relationship between PND, covariates, and PND status. The PND group had a higher percentage of male participants and was older than those without PND. Race did not differ by PND status. Those with PND were more likely to have a family income less than \$25,000 and less than a high school education. While the PND group had significantly higher mean BMI of 26.44 vs 27.14 for the non PND group, there was no statistical difference in categorical BMI. Cardiovascular disease, mean depressive symptoms, self-reported physical activity, and current smoking as well as drinking frequency did not differ by PND group.

The PND group had a higher percentage of controlled diabetes and poorly-controlled diabetes participants. Additionally, the PND group had a significantly higher percentage of diabetic older adults with duration of disease more than 5 years compared to the no PND group. Arthritis prevalence did not differ by PND group, nor did hypertension, and osteoporosis. Of the osteoarthritis joint categories, only the knee statistically differed between the two groups, with those without PND having a higher prevalence. Bone medication use did not differ by PND groups, but diabetes medications were more prevalent among participants with PND than those without PND.

Marginal model results for the main analyses are displayed in Table 9. After backward selection, cardiovascular disease, drinking frequency, family income, education, arthritis, hypertension, and hip and hand osteoarthritis were removed from the final model due to p-values greater than 0.15. PND was not associated with increased odds of sarcopenia over time in the unadjusted model, and an interaction term for PND and time was not statistically significant, indicating that association between PND and sarcopenia does not change over time. These findings remained stable with the addition of covariates in Model 2. Interaction terms for PND and race, and PND and sex, PND and diabetes duration, PND and controlled diabetes, and PND and poorly-controlled diabetes were not statistically significant.

Random effect model results for the main analyses are displayed in Table 10. After backward selection, cardiovascular disease, drinking frequency, family income, education, arthritis, hypertension, and hip and hand osteoarthritis were removed from the final model due to p-values greater than 0.15. Results were similar to those from the marginal models. PND was not associated with increased odds of sarcopenia over time in the unadjusted model, and the interaction term for PND and time indicated that the association between PND and sarcopenia is unchanging with time. These findings also remained unchanged with the addition of covariates in Model 2. Interaction terms for PND and race, and PND and sex, PND and diabetes duration, PND and controlled diabetes, and PND and poorly-controlled diabetes were again not statistically significant.

To determine if the random effect models were statistically more appropriate for the data, a test of homogeneity was performed. The test of homogeneity compared the variance of the model with and without the random intercept to determine if the model

without the random intercept fit the data as well as the model with the random intercept.

The small p-value resulting from this test (p-value  $<0.01$ ) indicates that the random intercept model fit the data better than the marginal model.

<b>Table 8: Baseline Demographics by PND Status</b>	<b>No PND</b>	<b>PND</b>	<b>p-value</b>
Mean (SD)	n=1116	n=191	
Diabetes (%)			<0.01
No Diabetes	82.94	71.05	
Controlled Diabetes	9.96	18.42	
Poorly-Controlled Diabetes	7.09	10.53	
Diabetes $\geq$ 5 years (%)	9.05	16.23	<0.01
Sex (%)			<0.01
Male	39.70	67.54	
Female	60.30	32.46	
Race (%)			0.12
Black	35.57	29.84	
White	64.43	70.16	
Age	73.23 (2.83)	73.79 (2.72)	0.01
BMI (%)			0.16
Normal (BMI <25)	31.90	38.74	
Overweight (25 $\leq$ BMI >30)	45.79	42.41	
Obese (BMI $\geq$ 30)	22.31	18.85	
Family income $\leq$ 25K (%)	46.67	46.75	0.05
Less than HS (%)	20.00	24.08	<0.01
Self-reported physical activity (kcal/wk)	89.44 (66.93)	80.33 (69.59)	0.08
Current Smoker (%)	7.00	6.81	0.2
Drinking Frequency > 1/wk (%)	30.12	28.94	0.44
Cardiovascular disease definite (%)	18.69	22.04	0.49
Depressive Symptoms (CES-D)	4.18 (3.92)	4.39 (4.07)	0.48
Arthritis (%)	54.66	59.16	0.51
Hypertension (%)	40.18	41.88	0.84
Osteoporosis (%)	9.32	8.38	0.33
Symptomatic Osteoarthritis (%)			
Hip	2.54	2.65	0.99
Hand	5.35	4.23	0.82
Knee	5.44	4.23	0.02
Other	13.34	14.29	0.44
Use of medications (%)			
Bone medications	5.38	2.63	0.11
Diabetes medications	7.62	16.32	<0.01

**Table 9: Marginal Models**

	OR	SE	Confidence Interval	P-value	QIC
Model 1: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time}$					3898.02
PND	0.77	0.24	(0.41, 1.43)	0.41	
Time	1.13	0.01	(1.11, 1.16)	<0.01	
PND*Time	1.02	0.04	(0.95, 1.11)	0.48	
Model 2: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \dots \dots \dots \beta_{15} \dots \dots \dots \beta_{15} \text{ Covariates}^*$					3330.10
PND	0.81	0.26	(0.44, 1.51)	0.51	
Time	1.15	0.02	(1.12, 1.18)	<0.01	
PND*Time	1.02	0.04	(0.94, 1.10)	0.65	
Model 3: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{White} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					3334.40
PND	1.04	0.40	(0.49, 2.19)	0.92	
Time	1.15	0.02	(1.12, 1.18)	<0.01	
PND*Time	1.02	0.04	(0.94, 1.10)	0.64	
White	2.17	0.44	(1.47, 3.22)	<0.01	
PND*White	0.73	0.33	(0.31, 1.76)	0.49	
Model 4: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{Female} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					3334.22
PND	0.96	0.35	(0.47, 1.95)	0.90	
Time	1.15	0.02	(1.12, 1.18)	<0.01	
PND*Time	1.02	0.04	(0.94, 1.10)	0.64	
Female	1.30	0.23	(0.92, 1.85)	0.14	
PND*Female	0.63	0.30	(0.25, 1.61)	0.33	
Model 5: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{Diab5yrs} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					3334.23
PND	0.81	0.27	(0.42, 1.56)	0.53	
Time	1.15	0.02	(1.11, 1.18)	<0.01	
PND*Time	1.02	0.04	(0.94, 1.10)	0.64	
Diab5yrs	0.78	0.36	(0.32, 1.91)	0.59	
PND*Diab5yrs	0.98	0.67	(0.26, 3.74)	0.98	
Model 6: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{DCAT1} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					3334.55
PND	0.80	0.27	(0.42, 1.54)	0.50	
Time	1.15	0.02	(1.11, 1.18)	<0.01	
PND*Time	1.02	0.04	(0.94, 1.10)	0.65	
DCAT1	0.70	0.28	(0.32, 1.54)	0.38	
PND*DCAT1	1.18	0.79	(0.32, 4.39)	0.80	
Model 7: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{DCAT2} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					3332.55
PND	0.78	0.24	(0.42, 1.44)	0.43	
Time	1.15	0.02	(1.11, 1.18)	<0.01	
PND*Time	1.02	0.04	(0.94, 1.10)	0.63	
DCAT2	0.96	0.40	(0.43, 2.18)	0.93	
PND*DCAT2	1.72	1.45	(0.33, 8.96)	0.52	

\*Controlling for: centered age, sex, race, BMI, diabetes duration  $\geq 5$  years, education, self-reported physical activity, CES-D, and use of osteoporosis medications.

**Table 10: Random Effect Models**

	OR	SE	Confidence Interval	P-value	-2 log (likelihood)	AIC
Model 1: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time}$					2655.16	2665.16
PND	0.68	0.71	(0.17, 2.74)	0.59		
Time	1.36	0.03	(1.29, 1.44)	<0.01		
PND*Time	1.06	0.07	(0.91, 1.22)	0.46		
Model 2: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \dots \dots \dots \beta_{15} \text{ Covariates}^*$					2571.53	2603.53
PND	0.53	0.63	(0.15, 1.81)	0.31		
Time	1.33	0.03	(1.26, 1.40)	<0.01		
PND*Time	1.05	0.07	(0.92, 1.21)	0.44		
Model 3: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{White} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					2571.38	2605.38
PND	1.10	0.94	(0.17, 6.93)	0.92		
Time	1.33	0.03	(1.26, 1.40)	<0.01		
PND*Time	1.04	0.07	(0.91, 1.19)	0.52		
White	2.42	0.44	(1.03, 5.68)	0.04		
PND*White	0.45	0.97	(0.07, 2.98)	0.41		
Model 4: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{Female} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					2571.31	2605.31
PND	0.58	0.69	(0.15, 2.26)	0.43		
Time	1.33	0.03	(1.26, 1.40)	<0.01		
PND*Time	1.05	0.07	(0.92, 1.20)	0.47		
Female	1.09	0.37	(0.53, 2.24)	0.82		
PND*Female	0.75	0.96	(0.12, 4.88)	0.76		
Model 5: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{Diab5yrs} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					2571.41	2605.41
PND	0.57	0.64	(0.16, 2.01)	0.38		
Time	1.33	0.03	(1.26, 1.40)	<0.01		
PND*Time	1.05	0.07	(0.92, 1.21)	0.44		
Diab5yrs	0.84	0.95	(0.13, 5.40)	0.86		
PND*Diab5yrs	0.42	1.51	(0.02, 8.03)	0.56		
Model 6: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{DCAT1} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					2571.54	2605.54
PND	0.53	0.64	(0.15, 1.89)	0.33		
Time	1.33	0.03	(1.26, 1.40)	<0.01		
PND*Time	0.20	0.07	(0.92, 1.21)	0.44		
DCAT1	0.72	0.77	(0.16, 3.27)	0.67		
PND*DCAT1	0.81	1.36	(0.06, 11.60)	0.88		
Model 7: $\beta_0 + \beta_1 \text{PND} + \beta_2 \text{Time} + \beta_3 \text{PND} * \text{Time} + \beta_4 \text{PND} * \text{DCAT2} + \beta_5 \dots \dots \dots \beta_{16} \text{ Covariates}^*$					2571.59	2605.59
PND	0.54	0.64	(0.15, 1.87)	0.33		
Time	1.33	0.03	(1.26, 1.40)	<0.01		
PND*Time	1.05	0.07	(0.92, 1.20)	0.46		
DCAT2	1.16	1.00	(0.16, 8.19)	0.89		
PND*DCAT2	0.70	1.84	(0.02, 25.55)	0.85		

\*Controlling for: centered age, sex, race, BMI, diabetes duration  $\geq 5$  years, education, self-reported physical activity, CES-D, and use of osteoporosis medications.

### **Aim 3**

#### **Specific Aims**

**Aim 3**: Identify the relationship of PND and sarcopenia on lower extremity function among diabetic compared to non-diabetic older adults, and examine if race or sex modify the relationship.

**Aim 3A**: Demonstrate that sarcopenia at years 6, 8, and/or 10 is associated with gait speed at years 8, 10, and/or 11 among diabetic and non-diabetic older adults.

**H3A.1**: Diabetic and non-diabetic older adults with sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than diabetic and non-diabetic older adults without sarcopenia at years 6, 8, and/or 10.

**Aim 3B**: Demonstrate that PND at year 4, in addition to sarcopenia at years 6, 8, and/or 10 is associated with gait speed at years 8, 10, and/or 11 among diabetic older adults.

**H3B.1**: Diabetic older adults with PND at year 4 and sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than diabetic older adults with sarcopenia at years 6, 8, and/or 10 without PND at year 4.

**Aim 3C:** Determine whether the relationship between sarcopenia at years 6, 8 and/or 10 and gait speed at years 8, 10, and/or 11 among diabetic and non-diabetic older adults is modified by race and sex.

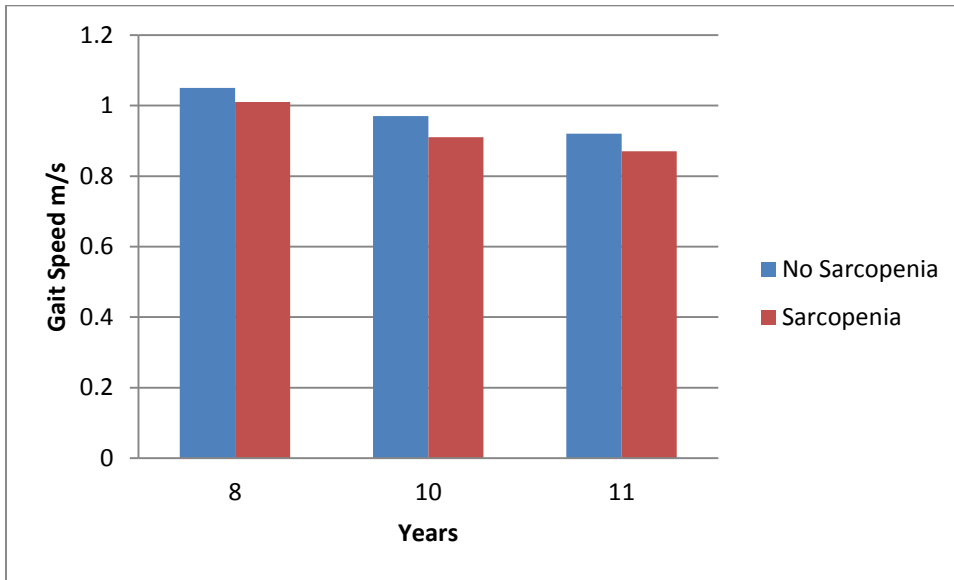
**H3C.1** Race will modify the relationship between sarcopenia and gait speed among diabetic and non-diabetic older adults, such that black older adults with sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than white older adults with sarcopenia at years 6, 8, and/or 10.

**H3C.2** Sex will impact the relationship between sarcopenia and gait speed among diabetic and non-diabetic older adults, such that older women with sarcopenia at years 6, 8, and/or 10 will have slower gait speed over time than older men with sarcopenia at years 6, 8, and/or 10.

## **Results**

The study population's mean gait speed was 1.04 m/s at year 8, and decreased over time to 0.95 m/s at year 10, and 0.89 m/s at year 11. At each time point, gait speed was significantly lower for participants with sarcopenia (Figure 2).

**Figure 2: Mean Gait Speed over time by Sarcopenia Status**



Marginal model results for the main analyses are displayed in Table 11. Following backwards selection, cardiovascular disease, current smoking status, drinking frequency, arthritis, hypertension, osteoporosis, osteoarthritis, use of osteoporosis medications, and use of antidiabetic medications were removed from the model due to their p-values exceeding 0.15. Sarcopenia was associated with a 0.07 unit decrease in gait speed (Model 1) ( $p < 0.01$ ). Time at year 10 was associated with a 0.05 m/s lower gait speed compared to year 8, and a 0.11 m/s gait speed at year 11 compared to year 8. These associations of sarcopenia and time to slower gait speed remained even with the addition of covariates to Model 2 (Sarcopenia  $b = -0.12$ ,  $p < 0.01$ ). In assessing the effect of having sarcopenia and PND, the results indicate that having both is not associated with additional decreases in gait speed (Model 4:  $p = 0.21$ ). Interaction terms for sarcopenia and race (Model 4:  $p = 0.61$ ), and sarcopenia and sex (Model 5:  $p = 0.30$ ) were also not statistically significant.

Random effect model results for the main analyses are displayed in Table 12. The results of the backward selection, and the associations, were the same as for the marginal models. Sarcopenia was again associated with decreased gait speed in the unadjusted model (Model 1) (Sarcopenia  $b = -0.05$ ,  $p < 0.01$ ), and time was also associated with a slower gait speed at years 10 and 11 compared to year 8 ( $p < 0.01$ ). These findings also remained unchanged with the addition of covariates in Model 2 (Sarcopenia  $b = -0.08$ ,  $p < 0.01$ ). Interaction terms for sarcopenia and PND (Model 3:  $p = 0.38$ ), PND and race (Model 4:  $p = 0.61$ ), and PND and sex (Model 5:  $p = 0.79$ ) were not statistically significant as in the marginal models.

The marginal model and random effect models can be compared using the likelihood ratio test, which assesses the difference in the  $-2 \log$  likelihood of each model with a  $\chi^2$  distribution. The difference in  $-2 \log$  likelihood from the full models without interaction terms (model 2), is 370.8. Following a  $\chi^2$  distribution, with 1 degree of freedom, the difference between the models is highly significant ( $\text{Prob} > \chi^2 = 0.00$ ). Therefore, the estimates from the random intercept models should be considered over and above those from the marginal models.

**Table 11: Marginal Models**

	<b>b</b>	<b>SE</b>	<b>P-value</b>	<b>-2 Res log(likelihood)</b>	<b>AIC</b>
Model 1: $\beta_0 + \beta_1 \text{SARC} + \beta_2 \text{Time10} + \beta_3 \text{Time11}$				1404.90	1406.90
<u>Sarc</u>	-0.07	0.02	<0.01		
Time10	-0.05	0.01	<0.01		
Time11	-0.11	0.01	<0.01		
Model 2: $\beta_0 + \beta_1 \text{Sarc} + \beta_2 \text{Time10} + \beta_3 \text{Time11} + \beta_4 \dots + \beta_{16} \text{Covariates}^*$				639.20	641.2
<u>Sarc</u>	-0.12	0.02	<0.01		
Time10	-0.07	0.01	<0.01		
Time11	-0.12	0.01	<0.01		
Model 3: $\beta_0 + \beta_1 \text{Sarc} + \beta_2 \text{Time10} + \beta_3 \text{Time11} + \beta_4 \text{Sarc} * \text{PND} + \beta_5 \dots$ B17 Covariates*				639.20	641.2
<u>Sarc</u>	-0.11	0.02	<0.01		
Time10	-0.07	0.01	<0.01		
Time11	-0.12	0.01	<0.01		
PND	-0.03	0.02	0.17		
<u>Sarc</u> *PND	-0.11	0.08	0.21		
Model 4: $\beta_0 + \beta_1 \text{Sarc} + \beta_2 \text{Time10} + \beta_3 \text{Time11} + \beta_4 \text{Sarc} * \text{White} + \beta_5 \dots$ B17 Covariates*				643.3	645.3
<u>Sarc</u>	-0.15	0.05	<0.01		
Time10	-0.07	0.01	<0.01		
Time11	-0.12	0.01	<0.01		
White	0.07	0.01	<0.01		
<u>Sarc</u> *White	0.03	0.06	0.61		
Model 5: $\beta_0 + \beta_1 \text{Sarc} + \beta_2 \text{Time10} + \beta_3 \text{Time11} + \beta_4 \text{Sarc} * \text{Female} + \beta_5 \dots$ B17 Covariates*				641.8	643.8
<u>Sarc</u>	-0.15	0.04	<0.01		
Time10	-0.07	0.01	<0.01		
Time11	-0.12	0.01	<0.01		
Female	-0.06	0.01	<0.01		
<u>Sarc</u> *Female	0.05	0.05	0.30		

\*Controlling for: Controlled diabetes, poorly controlled diabetes, PND, centered age, sex, race, BMI, diabetes duration  $\geq 5$  years, family income, education, self-reported physical activity, and CES-D.

**Table 12: Random Effect Models**

	<b>b</b>	<b>SE</b>	<b>P-value</b>	<b>-2 Res log(likelihood)</b>	<b>AIC</b>
Model 1: $\beta_0 + \beta_1 \text{Sarc} + \beta_2 \text{Time}_{10} + \beta_3 \text{Time}_{11}$				8.60	12.60
<u>Sarc</u>	-0.05	0.02	<0.01		
Time <sub>10</sub>	-0.07	0.01	<0.01		
Time <sub>11</sub>	-0.14	0.07	<0.01		
Model 2: $\beta_0 + \beta_1 \text{Sarc} + \beta_2 \text{Time}_{10} + \beta_3 \text{Time}_{11} + \beta_4 \dots \dots \dots \beta_{16} \text{Covariates}^*$				-268.40	-264.40
<u>Sarc</u>	-0.08	0.02	<0.01		
Time <sub>10</sub>	-0.07	0.01	<0.01		
Time <sub>11</sub>	-0.14	0.01	<0.01		
Model 3: $\beta_0 + \beta_1 \text{Sarc} + \beta_2 \text{Time}_{10} + \beta_3 \text{Time}_{11} + \beta_4 \text{Sarc} * \text{PND} + \beta_5 \dots \dots \dots \beta_{17} \text{Covariates}^*$				-266.00	-262.00
<u>Sarc</u>	-0.07	0.02	<0.01		
Time <sub>10</sub>	-0.07	0.01	<0.01		
Time <sub>11</sub>	-0.14	0.01	<0.01		
PND	-0.04	0.02	0.05		
<u>Sarc</u> *PND	-0.07	0.08	0.38		
Model 4: $\beta_0 + \beta_1 \text{Sarc} + \beta_2 \text{Time}_{10} + \beta_3 \text{Time}_{11} + \beta_4 \text{Sarc} * \text{White} + \beta_5 \dots \dots \dots \beta_{17} \text{Covariates}^*$				-264.20	-260.20
<u>Sarc</u>	-0.10	0.04	0.02		
Time <sub>10</sub>	-0.07	0.01	<0.01		
Time <sub>11</sub>	-0.14	0.01	<0.01		
White	0.06	0.01	<0.01		
<u>Sarc</u> *White	0.02	0.05	0.61		
Model 5: $\beta_0 + \beta_1 \text{Sarc} + \beta_2 \text{Time}_{10} + \beta_3 \text{Time}_{11} + \beta_4 \text{Sarc} * \text{Female} + \beta_5 \dots \dots \dots \beta_{17} \text{Covariates}^*$				-263.50	-259.50
<u>Sarc</u>	-0.08	0.03	0.01		
Time <sub>10</sub>	-0.07	0.01	<0.01		
Time <sub>11</sub>	-0.14	0.01	<0.01		
Female	-0.06	0.01	<0.01		
<u>Sarc</u> *Female	0.01	0.04	0.79		

\*Controlling for: Controlled diabetes, poorly controlled diabetes, PND, centered age, sex, race, BMI, diabetes duration  $\geq 5$  years, family income, education, self-reported physical activity, and CES-D.

## Chapter 5 – Discussion

### Summary

This study found no association between diabetes status and sarcopenia prevalence when adjusting for covariates, including age, sex, race, BMI, and comorbidities. Similarly, there was no association between PND and sarcopenia over time. While sarcopenia prevalence was predictive of slower gait speed over time, having PND in addition to sarcopenia did not result in further decreases in gait speed. Neither race nor sex modified the effects of the relative independent variables on the outcomes of the three aims.

### Prevalence of Sarcopenia by Diabetes Status

This study found an inverse association between diabetes status and sarcopenia prevalence, however there was no significant association after adjusting for covariates. There are several reasons why diabetes may not result in increased odds of sarcopenia. Older adults with diabetes have a higher body mass than those without diabetes<sup>3,7,13</sup>. A higher BMI may result in a lower prevalence of sarcopenia, since having a higher BMI is associated with having a higher fat free mass<sup>125</sup>. This higher amount of fat free mass may mean a more substantial amount of mass needs to be lost in order for a diabetic adult to be defined as sarcopenic as currently classified. Koster et al. assessed fat mass and changes in lean mass and strength over time and reported that greater fat, while associated with higher lean leg mass at baseline, was associated with greater losses of lean leg mass over time<sup>126</sup>. While these findings would seem to indicate a greater risk of sarcopenia for obese older adults, the study also found that fat mass was associated with higher knee muscle strength<sup>126</sup>; maintaining more strength would prevent sarcopenia as

defined in this study. It is important to note, however, that the Koster study analyzed knee muscle strength while this current study analyzed grip strength. In this current study, similar results were found with grip strength, as it was higher for the diabetic participants who had a higher BMI than the non-diabetic participants. Conversely, another study assessing the association between the history of obesity and hand grip strength, reported that obesity was associated with lower grip strength<sup>127</sup>. The inconsistencies between the findings of these studies highlight the need for further research to elucidate the relationship between obesity, muscle mass, and measures of strength.

This current study found no significant difference in low muscle mass or low muscle strength by diabetes status after controlling for covariates. A previous study assessing the influence of diabetes on physical functional measures among women from the Study of Osteoporotic Fractures (SOF) similarly found no association between diabetes status and grip strength<sup>128</sup>. Consistent with the findings reported from SOF<sup>128</sup>, Park et al. in Health ABC found that grip strength and knee extension strength were not significantly lower comparing diabetic women to non-diabetic women<sup>7</sup>. Both strength measures, however, were significantly lower in diabetic men compared to non-diabetic men<sup>7</sup>. The presence of a significant difference in baseline strength measures by diabetes status in Park et al. and no difference in this current study may indicate that the weakest participants were not retained throughout later follow-up time points in the study. Park et al. later conducted a longitudinal analysis comparing multiple measures of muscle mass by diabetes status, including undiagnosed diabetes from baseline to year 6<sup>6</sup>. Participants with diagnosed and undiagnosed diabetes had a steeper decline in lower appendicular lean mass than those without diabetes<sup>6</sup>. Additionally, older women with diabetes had a

significantly greater decline in thigh muscle cross-sectional area than older women without diabetes<sup>6</sup>. These findings could indicate that it may be more informative to assess muscle mass continuously, versus defining sarcopenia by cutpoints as in this current study, when assessing diabetes' impact on muscle mass.

In addition to the body mass and strength characteristics of diabetic older adults, the Aim 1.A hypothesis that sarcopenia prevalence would be greater among diabetic participants compared to non-diabetic participants may not have been supported because the mechanism by which diabetes can cause sarcopenia is still not clear. It is unknown how long it would take for diabetes to result in muscle atrophy. While the majority of this study's diabetic participants have had the disease for at least 5 years, the disease may require more time to result in decreases in muscle necessary to result in sarcopenia. Additionally, the changes that are needed to impact muscle may occur in the end stages of the disease. Conversely, it is possible that diabetes does not affect muscle to the threshold that would result in sarcopenia as currently defined. The findings from the SOF studied previously mentioned similarly found no association between diabetes status and grip strength over a 4.9 year period<sup>128</sup>.

In Aim 1, non-diabetic older adults had a higher prevalence of sarcopenia than diabetic older adults (6.0 vs. 3.4 respectively). The prevalence of sarcopenia among the diabetic participants was approximately 5 times less than reported by KSOS<sup>8</sup>. Sarcopenia was defined in KSOS solely by low muscle mass, which may explain the difference in prevalence of sarcopenia between the two studies. The difference in prevalence may also be due to the selection of Health ABC participants, as these older adults were required to be physically well-functioning at the time of study entry. Also, the Health ABC cohort is

older than the KSOS cohort, with a mean age of 73 compared to 59. This difference in age may reflect a survival bias, as those who develop diabetes in older age may differ in health and comorbidities than younger diabetic adults. The potential for survival bias when studying older diabetic adults can be seen by comparing demographics from three studies aimed at lowering HbA1c levels for diabetic older adults: 1) a study of US older military veterans, with a mean participant age of 60 and a mean diabetes duration of 11.5 years<sup>129</sup>, 2) the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study conducted at 77 clinical centers in the US and Canada, with a mean participant age of 62 and mean diabetes duration of 10 years<sup>130</sup>, and 3) the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial conducted at 215 centers in 20 countries across Asia, Australasia, Europe, and North America with a mean participant age of 66 and mean duration of diabetes of 8 years<sup>131</sup>. Comparing the mean ages and years of diabetes duration across these three studies, there is an inverse relationship between age and duration of diabetes; specifically the youngest cohort (the veteran's study) had the longest duration of disease and the oldest cohort (ADVANCE) had the shortest duration of disease<sup>129-131</sup>. There was also an inverse relationship between mean age of cohort and mean HbA1c levels, as the youngest cohort had the highest mean baseline HbA1c levels (9.4%) and the oldest cohort had the lowest mean baseline HbA1c levels (7.2%)<sup>129-131</sup>. These comparisons demonstrate potential survival bias, as those who obtain diabetes in older age have had the disease for a shorter duration and maintain better control of the disease. Better control of the disease could result in lower disability limitations. Older adults with diabetes but without disability limitations, as in Health ABC at enrollment, would be healthier and possibly stronger

than older adults with diabetes and disability limitations, and older adults without diabetes but with disability limitations.

Kim et al. reported in their discussion that differences in lean muscle mass reported from a previous analysis by Park et al. of Health ABC data may differ from KSOS results due to “ethnic differences in characteristics of type 2 diabetes”<sup>7,8</sup>. One of these differences may be the prevalence of obesity among older adults with diabetes. The mean BMI for men with diabetes was 24.8 among the KSOS study population, corresponding to being borderline overweight, compared to 28.4 among the Health ABC study population which corresponds to overweight. Similarly among the women with diabetes, the average KSOS female was overweight with a BMI of 25, compared to the average Health ABC female who was obese with a BMI of 30.4. The higher prevalence of overweight and obese participants in Health ABC could explain the lower prevalence of sarcopenia in this population.

In addition to the main findings from Aim 1, there were several significant associations with diabetes control, specifically race, obesity, markers of socioeconomic status (family income and education), and depression. Blacks were more likely to have poorly-controlled diabetes than whites, which is consistent with findings from a meta-analysis conducted among US adults<sup>132</sup>. Similarly, participants with less than a high school education, and family income less than \$25,000 were also more likely to have poorly-controlled diabetes, consistent with previous findings<sup>133</sup>. Race may confound the association between diabetes control and socioeconomic status. These findings could indicate that clinicians might need to more actively encourage lifestyle interventions and monitor medication adherence of black patients to improve their diabetes control. Weight

was also highest among the poorly-controlled diabetes group. This association may result in a paradoxical effect where poorer diabetes control results in greater obesity, which is associated with less sarcopenia. Weight could serve as a proxy for lifestyle intervention adherence, as those with a healthy diet who engage in physical activity should be less likely to be overweight or obese. A study assessing the impact of self-efficacy on medication adherence, diabetes control, diet, and exercise among low-income black participants found that lower self-efficacy was associated with poorer diabetes management and self-care behaviors (diet and exercise)<sup>134</sup>. This corresponds in this study with the assessment of self-reported physical activity, which bordered on significance, with those without diabetes having the highest self-reported physical activity and those with poorly-controlled diabetes having the lowest. Educational interventions aimed at improving confidence in management of health and diabetes, thereby increasing self-efficacy, may decrease the racial and social economic disparities that currently exist in diabetes control.

### **Peripheral Nerve Dysfunction and Sarcopenia**

Results from Aim 2 indicate that PND is also not predictive of sarcopenia over time. It is unclear if the amount of damage to neuromuscular function from PND is substantial enough to manifest as sarcopenia. Additionally, PND may influence lower extremity muscle strength more than grip strength as assessed in this study. PND has been shown to be associated with lower quadricep strength as well as lower ankle strength cross-sectionally<sup>71</sup> and longitudinally<sup>135,136</sup> in the Health ABC study. In the InCHIANTI study, compound muscle action potential (CMAP) was significantly associated with calf muscle density<sup>16</sup>, a measure of lipid content in the calf muscle, also

an indicator of sarcopenia<sup>137</sup>. This association between CMAP and calf muscle density indicated a reduction in the number of motor axons resulting from PND<sup>16</sup>. The assessment of grip strength in this current study, and not lower extremity strength, may explain the lack of association between PND and sarcopenia prevalence. Duration of PND was also not assessed in this study; therefore, we cannot assess the relative contributions of disease progression, or time since diagnosis on changes in muscle mass and strength.

From the results in Table 5, the percentage of poorly-controlled diabetic participants with PND was lower than that of the controlled diabetic participants. This may be a result of retention bias, as poorly-controlled diabetic older adults with PND may be sicker, and thus less likely to be retained in the study over time. The study therefore may be retaining only the healthiest of the poorly-controlled diabetic participants.

The overall prevalence of PND in this study population was 15%, which is similar to that reported from NHANES among adults 40 years of age and older<sup>17</sup>. The similar prevalence of PND observed in this study compared to a study with a younger mean age may provide further evidence of the health status of the participants analyzed in this study. The 29% prevalence of PND among diabetic participants in this study was also consistent with the prevalence range among diabetic older adults of 20-50% previously reported<sup>2,52</sup>. The male participants had a higher prevalence of PND than the females, which is consistent with other findings from Health ABC<sup>15,71</sup> and NHANES<sup>48</sup> but inconsistent with the ILSA<sup>56</sup>. Black participants in Health ABC have previously been found to have a lower average vibration threshold and a higher percentage of individuals

unable to detect a 10g monofilament; however when assessing across all nerve components in this study, there was a lower percentage of black participants with PND compared to without PND<sup>15,71</sup>.

Previous studies have indicated that PND can result in both decreased muscle mass and strength due to its potential to damage muscle axons<sup>5</sup> as well as lower muscle mass due to decreases in the size and number of fast-twitch muscle fibers<sup>77</sup>. It is possible that no association between PND and sarcopenia prevalence was observed in this study due to the better functional status of the Health ABC participants at enrollment. Older adults with PND who at baseline experienced no difficulty walking a quarter of a mile and no ADL limitations may not be representative of the population of older adults with PND most at risk for sarcopenia. Similar analyses should be done in a less physically healthy cohort in order to determine if PND is associated with sarcopenia prevalence in a more generalizable older adult population.

### **Sarcopenia and Lower Extremity Dysfunction**

The results from Aim 3 confirm the negative association between sarcopenia and physical function previously reported<sup>12,99</sup>. Perera et al. categorized a change in gait speed of 0.05 m/s to be indicative of a small meaningful change and a change in gait speed of 0.10 m/s to be indicative of a substantial change<sup>123</sup>. The population average (marginal model) difference between gait speed among those with sarcopenia vs. without sarcopenia (-0.07 m/s) can be categorized as a small meaningful change in the unadjusted model. The effect of time at year 8 vs. 10 (-0.05 m/s) was also consistent with a small meaningful change, while year 8 vs. 11(-0.11 m/s) was consistent with a substantial

change, indicating further decreases in gait speed over time. The meaningful difference in gait speed between sarcopenic and non-sarcopenic participants remained after adjusting for covariates. While the difference between gait speed for sarcopenic vs. non-sarcopenic participants was less when observing individual level relationships (random-effect models), a small meaningful difference still existed in the unadjusted and adjusted models.

### **Sarcopenia, Peripheral Nerve Dysfunction, and Lower Extremity Dysfunction**

The results from this study indicate that having PND in addition to sarcopenia does not result in any greater decreases in gait speed than having sarcopenia alone. While these results could suggest that PND is not as detrimental to lower extremity function as sarcopenia, this may be a function of the outcome solely being gait speed and no other measures of lower extremity function. Gait speed may not be the best outcome for assessment of the impact of PND on lower extremity function; PND may result in further decreases in other measures of lower extremity function, such as balance and chair stands, as has been shown in previous research<sup>15,16,20,23</sup> and may play an important role in falls<sup>67,138-141</sup>.

### **Effect Modification**

Race and sex did not modify the relationships from any of the three aims of this study. We were unable to do a power calculation prior to analyzing the data due to an inability to estimate the prevalence of sarcopenia by diabetes status and race or sex. Due to the low prevalence of sarcopenia, analyzing effect modification resulted in low power to assess the multiplicative interaction between each aim's dependent variable and race or

sex. The existence of an association between race and sarcopenia prevalence in Aims 1 and 2, race and gait speed as well as sex and gait speed in Aim 3 may indicate that in a larger study sample race could modify the relationship between both diabetes status and sarcopenia and PND and sarcopenia, and both race and sex could modify the relationship between sarcopenia and gait speed.

### **Sarcopenia Definition**

This study uses one definition and one set of cutpoints, however, there are several other definitions in the literature. It is possible that the definition used is not the most appropriate for the study population or disease of interest. In particular, the current definition and measures used for this study do not take muscle quality into account, nor do any of the most commonly used definitions. Diabetic older adults have been shown to have greater fat infiltration in muscle<sup>142</sup>, which could decrease the quality of the muscle even if the overall quantity of mass is maintained. Therefore, while two individuals could have the same amount of mass, one individual could have greater muscle fat infiltration, resulting in poorer muscle quality. Muscle quality estimates the amount of muscle strength relative to muscle mass. Previous studies have shown older adults with the highest amount of fat mass have the lowest muscle quality<sup>126</sup>. Muscle quality has been found to be a better indicator of muscle impairment among obese older adults<sup>89,126</sup>; therefore, a definition incorporating muscle quality may better predict older adults most at risk of functional decline by way of muscle impairment.

While there are limitations to the definition used, the data imply that the definition used is more appropriate than the full EWGSOP definition that includes gait speed or the

newer FNIH definition<sup>9,91</sup>. Both of these definitions are more specific, resulting in very low prevalence estimates of sarcopenia in this healthier cohort (0.52% with full EWGSOP and 1.7% with the FNIH definition). It may be more meaningful to develop a definition of sarcopenia based on low muscle quality by assessing the ratio of muscle strength per unit of muscle mass<sup>7,24,143</sup>. This measure would still use a measure of strength (grip or knee extension) as well as DXA measured lean mass used currently, and would not require additional assessments, such as CT scans; however this ratio could be more predictive of muscle impairment and mobility disability than assessing muscle strength and muscle mass independently. Park et al. used a similar assessment of muscle quality in Health ABC and found that this evaluation of muscle provided a better indicator of muscle function than solely assessing muscle mass and muscle strength independently<sup>7</sup>.

### **Limitations**

This study is innovative in that it assesses the interplay between different diabetes complications as well as uses a definition of sarcopenia that utilizes two measures of muscle: muscle mass and muscle strength. However, the assessment of muscle mass and muscle strength resulted in reduced sample sizes for analyses. Assessing a composite score of PND instead of assessing the individual tests independently also presents a limitation, as the individual tests may be associated with different aspects of muscle and function<sup>15,71,144</sup>. Assessing all of the tests together resulted in the inability to examine individual effects of sensory and motor nerve function.

While the Health ABC study has a large sample size with many measures and covariates, the cohort was designed to study healthy aging. All of the participants

enrolled in the study were physically well-functioning in their 70s. Older adults most at risk of sarcopenia and lower extremity dysfunction may not have been enrolled in the study due to physical function limitations. While Health ABC oversampled black participants in order to assess race interactions, the physical function enrollment criteria may have resulted in a smaller percentage of black participants being eligible for enrollment compared to white participants, as black older adults have been shown to have higher mobility disability than white older adults<sup>145-148</sup>.

This study assessed whether sarcopenia in combination with PND explains differences in gait speed between diabetic versus non-diabetic older adults. However, it is possible that older adults without diabetes may have impaired fasting glucose (IFG), differentiating them from the older adults with normal glucose levels. Despite the exclusion of the assessment of IFG, the lack of association between diabetes, as well as diabetes control, and sarcopenia indicates that assessing IFG would not change the results.

### **Strengths**

A strength of this proposed study is that previous research has not examined the impact of PND and sarcopenia on gait speed of diabetic and non-diabetic older adults over time. While previous research has examined associations between these components, none exists examining the impact of the interplay of all of these components together, or examining the effect of race and sex on this relationship.

The Health ABC dataset is comprised of a diverse population of older US adults, and allows for the assessment of race and sex. The data include a large number of important covariates and clinical measures, and multiple follow up visits allows for

longitudinal analyses over several years. Diabetes control was assessed, and both sensory and motor PND measures were analyzed, some of which are used as standard clinical measures.

Moreover, an important innovative strength is the use of a more comprehensive and specific measure of sarcopenia, assessing muscle mass and muscle strength, whereas previous studies solely assessed muscle mass to define sarcopenia. The field of sarcopenia research has lacked a standard definition and measurement criteria for sarcopenia, thus resulting in multiple and inconsistent methods employed by researchers<sup>9,14,25-27</sup>. The definition and measurement criteria put forth by the EWGSOP were developed by a consensus from multiple organizations representative of the field, and the use of a modified version of this comprehensive definition of sarcopenia allows for more accurate prevalence ratios, as well as greater clinical relevance of findings<sup>9</sup>

### **Conclusions and Future Considerations**

Previous research has examined the associations between diabetes, sarcopenia, PND, and gait speed; however, none have examined the impact of the interplay of all of these components together, nor the effect of race and sex. While diabetes was not predictive of sarcopenia, diabetes was associated with lower gait speed over time. Therefore, sarcopenia as defined in this study may not be an appropriate screening measure for identifying diabetic older adults at greatest risk of lower extremity dysfunction. Additionally, seeing no effect modification by race or sex means that there is no differential effect on the relationship by these groups, and they therefore may not require different screening measures.

While PND was not predictive of sarcopenia, PND was also associated with lower gait speed over time. Therefore, sarcopenia as defined in this study may not be an appropriate screening measure for which older adults with PND are at greatest risk of developing lower extremity dysfunction over time. Since there was no significant association between PND and diabetes, diabetic older adults with PND may not require different screening for sarcopenia, or functional interventions to prevent decreases in gait speed compared to non-diabetic older adults with PND.

As discussed previously, many studies of sarcopenia solely assess muscle mass alone and not muscle strength, and mass alone has not been associated with either clinical or functional outcomes consistently. However, this study's results indicate that assessing mass and strength may not be the best way to define sarcopenia for diabetic older adults; an assessment of muscle quality may better classify sarcopenic individuals, particularly among those with a higher BMI. In a previous analysis in Health ABC, Park et al. determined that obesity plays an important role in the association between diabetes and muscle quality due to the finding that older adults with diabetes had lower muscle quality attenuated by BMI<sup>7</sup>. Villareal et al. reported that obese older adults had lower muscle quality than both non-obese non-frail and non-obese frail older adults<sup>149</sup>. Similarly, Vilaça et al. also reported that obese older women in Brazil had poorer force per unit mass, indicating poorer muscle quality<sup>150</sup>. Since the present study found sarcopenia was associated with slower gait speed, and diabetes was associated with slower gait speed, it is possible that a better classification of sarcopenic diabetic older adults may be necessary and should be further explored.

Given the results and conclusions, there are several future directions for this research that would move this area of study forward. Exploring muscle decline over the life-course may indicate that there are several trajectories of decline and different within subject changes. In particular, there may be different trajectories for different BMI categories and races. Additionally, the trajectory of acute loss post trauma, such as a hip fracture, or in the end stages of certain diseases (including diabetes) may differ from gradual decline over time. It is important to understand the role of sarcopenia in predicting recovery of functionality post trauma.

Additionally, further refinement of the definition of sarcopenia may be necessary to account for muscle quality and fat infiltration. Assessment of muscle quality, as opposed to muscle mass, may be a better indicator of who is most at risk of lower extremity dysfunction. Cutpoints for low muscle quality should be determined to best predict mobility disability. Future studies should also assess the relationship between sarcopenia and muscle quality with individual peripheral nerve tests instead of a composite peripheral nerve function score.

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