THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2023, Vol. 78, No. 11, 2083–2093
https://doi.org/10.1093/gerona/glad052
Advance Access publication February 9, 2023

OXFORD

Research Article

The Study of Muscle, Mobility and Aging (SOMMA): A Unique Cohort Study About the Cellular Biology of Aging and Age-related Loss of Mobility

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Received: June 13, 2022; Editorial Decision Date: January 27, 2023

Decision Editor: Lewis A. Lipsitz, MD, FGSA

Abstract

Background: The Study of Muscle, Mobility and Aging (SOMMA) aims to understand the biological basis of many facets of human aging, with a focus on mobility decline, by creating a unique platform of data, tissues, and images.

Methods: The multidisciplinary SOMMA team includes 2 clinical centers (University of Pittsburgh and Wake Forest University), a biorepository (Translational Research Institute at Advent Health), and the San Francisco Coordinating Center (California Pacific Medical Center Research Institute). Enrollees were age ≥70 years, able to walk ≥0.6 m/s (4 m); able to complete 400 m walk, free of life-threatening disease, and had no contraindications to magnetic resonance or tissue collection. Participants are followed with 6-month phone contacts and annual in-person exams. At baseline, SOMMA collected biospecimens (muscle and adipose tissue, blood, urine, fecal samples); a variety of questionnaires; physical and cognitive assessments; whole-body imaging (magnetic resonance and computed tomography); accelerometry; and cardiopulmonary exercise testing. Primary outcomes include change in walking speed, change in fitness, and objective mobility disability (able to walk 400 m in 15 minutes and change in 400 m speed). Incident events, including hospitalizations, cancer diagnoses, fractures, and mortality are collected and centrally adjudicated by study physicians.

Results: SOMMA exceeded its goals by enrolling 879 participants, despite being slowed by the COVID-19 pandemic: 59.2% women; mean age 76.3 ± 5.0 years (range 70–94); mean walking speed 1.04 ± 0.20 m/s; 15.8% identify as other than Non-Hispanic White. Over 97% had data for key measurements.

Conclusions: SOMMA will provide the foundation for discoveries in the biology of human aging and mobility.

Keywords: Cohort study design, Epidemiology, Sarcopenia

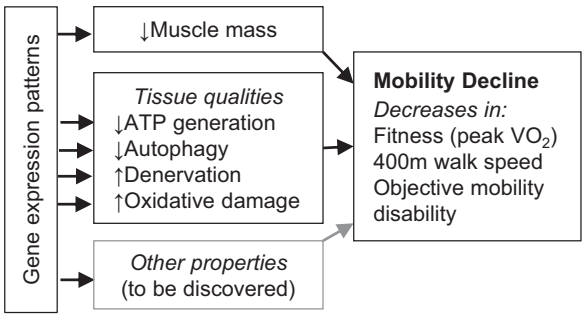

Figure 1. A paradigm for biological causes of mobility decline, slowing of 400 m walk speed, and declines in fitness by VO_2 peak from cardiopulmonary exercise testing. The initial conceptual framework for SOMMA posited that declines in walking speed and fitness and development of mobility disability, result from a combination of the loss of skeletal muscle mass and adverse changes in qualities of muscle tissue. The paradigm recognized that many determinants of loss of fitness and mobility remain to be discovered and specifies that gene expression in muscle will be used to identify some of these pathways.

Numerous large cohort studies have examined facets of aging including declines in muscle function and mobility. They have been limited to collection of data from questionnaires and interviews, physical assessments such as walking speed, imaging, and samples of blood and urine. The Study of Muscle, Mobility and Aging (SOMMA) is unique: in addition to participant-reported data, physical and cognitive assessments, and whole-body imaging, it obtains muscle tissue in all and adipose tissue in many participants to examine the tissue specific, cellular (and molecular) basis of aging and mobility.

The SOMMA Study will provide information necessary to fill important gaps in research. Experiments in rodents have manipulated single properties to the effects on muscle mass or function (1–4). Studies using muscle biopsies in humans have been small, analyzed only cross-sectional associations between one or two properties and physical performance, and did not include older adults at risk of mobility disability (1,5–7). Large human studies have not included biopsies. The primary focus of SOMMA is to investigate the role of muscle biology in the decline of mobility with age. As illustrated in Figure 1, we postulated that primary biological determinants of mobility decline would be aging-related loss of muscle mass and diminished qualities of muscle tissue, including its decreased capacity to generate adenosine triphosphate (ATP) energy, denervation, and increases in molecular damage exacerbated by age-related declines in autophagy to clear damage. In addition to mobility decline, SOMMA aims to understand the biological basis of decreases in cardiorespiratory fitness (measured as peak oxygen uptake [VO_2 peak] by exercise testing). The SOMMA paradigm explicitly acknowledges that there is a limited understanding of the biological pathways that determine how muscle mass and qualities of muscle tissue lead to mobility decline. SOMMA has specified detailed examination of only some of the many biological pathways that may lead to mobility disability; other biological properties remain to be discovered. Thus, the study employs RNA sequencing in muscle tissue as one approach to discovering new biological pathways involved in loss of mobility with aging.

In addition to its focus on muscle and mobility, SOMMA aims to build a unique resource of tissue, blood, images, and data for understanding human aging and its consequences. For example, extra muscle and adipose tissue and an extensive array of blood specimens are archived for a wide variety of potential future assays while the digital repository contains both clinical and laboratory imaging data. Whole-body magnetic resonance (MR) and computed tomography (CT) imaging enables the study of many conditions in addition to impaired mobility, and histological cassettes prepared from muscle and adipose biopsies enable countless future scientific inquiries with staining techniques. Extensive objective measurements of physical and cognitive performance build a platform for research on an unlimited array of aging-related outcomes, such as dementia, fatigue, fractures, and osteoarthritis (OA). SOMMA is already a platform for many funded ancillary studies to address these diverse aging related conditions. Herein, we describe the design of SOMMA.

Method

Study Design

SOMMA was designed to test 3 specific aims. First, to test hypotheses that decreased muscle mass, decreased capacity to generate ATP, denervation of muscle cells, oxidative damage to components of muscle cells, and impaired autophagic flux individually and in combination, predict rapid rates of loss of fitness (by peak VO_2) and slowing of 400 m walking speed over 3 years. Second, SOMMA is designed to test the hypothesis that the same properties of muscle—mass, capacity to generate ATP, denervation, oxidative damage, and autophagy would also increase the risk of mobility disability. Third, we would use RNAseq to profile gene transcription in muscle to test hypotheses that levels of expression of genes that control essential properties of muscle predict major mobility disability, decreased fitness, and slower walking speed. We will use these data to explore and discover new patterns of gene expression that predict major mobility disability, rates of decreases in fitness, walking speed, and muscle mass.

At the time of the writing of this report, the baseline visit was complete (final participant enrolled in December 2021) and the follow-up visits (annual in-person visits for 3 years and interim phone contacts) are ongoing, with follow-up scheduled to conclude in May 2024. The SOMMA plans to extend follow-up after May 2024 when secure additional funding.

SOMMA is a prospective longitudinal cohort study of participants aged 70 years and older funded by grant R01AG059416 (PIs: Cummings, Newman, Kritchevsky, Hepple). After a baseline examination that took place April 2019 to December 2021, participants return every year for 3 years for repeat measurements.

Study Setting

SOMMA represents a multidisciplinary team, notably experts in epidemiology and basic science, built on a foundation of highly experienced staff. It is conducted by clinical sites at University of Pittsburgh and Wake Forest University. Biospecimen storage, chain of custody, and quality control are managed at the Translational Research Institute at Advent Health. The study is managed by the San Francisco Coordinating Center (SFCC) at the California Pacific Medical Center Research Institute. The Executive Committee oversees all scientific decisions in the study and is supported by the larger Steering Committee (see Supplementary Table 2 for a list of SOMMA investigators and key study staff.) An Observation Study Monitoring Board provides external oversight of the study. WIRB-Copernicus Group (WCG) Institutional Review Board (WCGIRB, study number 20180764) approved the study as the single Institutional Review Board (IRB) and all participants provided written informed consent.

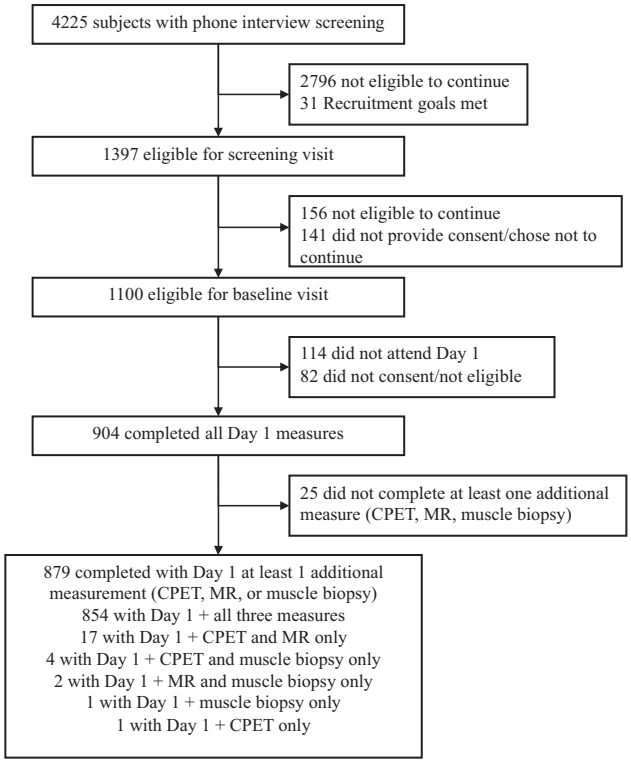

Figure 2. Flow of enrollment in SOMMA.

Recruitment: Inclusion and Exclusion Criteria

Men and women aged 70 years and older were eligible for inclusion in SOMMA. Participants also were required to be eligible for and willing to complete the muscle tissue biopsy and MR scans, which excluded some individuals with implants that had not been determined to be safe for MR. During the initial eligibility telephone screening questionnaire, we also excluded individuals on chronic anticoagulation therapy because of bleeding risk with muscle biopsy. Participants taking aspirin were asked to withhold it for 3 days prior to the biopsy if acceptable to their physician. Anyone who reported an inability to walk ¼ mile or climb a flight of stairs was also excluded, as were individuals with active cancer or with an advanced chronic disease such as heart failure, renal failure on dialysis, Parkinson's disease, or dementia. Those initially eligible attended an informational screening visit that was held in person, by video conference, or telephone. In some cases, medical records were required to determine safety for MR or other conditions by the Study Medical Safety Officers. Final eligibility for enrollment included the demonstration of the ability to walk 400 m at a usual pace at the first day of 3 examination days that comprised the baseline visit. The Baseline Visit generally consisted of 3 days of assessments: Day 1 (the 400 m walk plus most other in-person assessments, 5 hours); Day 2 (cardiopulmonary exercise testing [CPET] and MR, 2–3 hourss); and Day 3 (muscle biopsy, 2 hours); participants also completed a self-administered questionnaire. Occasionally, due to scheduling difficulties, the "Day 2" visit was split into 2 visits on different days; 371 participants had the CPET and MR on different days. For a participant to be considered enrolled, he or she must have had a complete "Day 1 visit," plus at least one of the other major examinations (CPET, MR, or muscle biopsy, Figure 2).

Recruitment Methods

Potential SOMMA participants were reached by mailing a postcard or letters to age-eligible adults using purchased mailing lists, voter registration lists, and university-sponsored research registries, with over sampling of zip codes with greater racial and ethnic diversity. Community outreach events were planned but were not permitted due to COVID-19 pandemic restrictions. If provisionally eligible by telephone screening, potential participants were invited to participate in an information session in person, by video conference, or telephone after providing consent for further screening. Participants who appeared to be unable to complete the 400-m walk were asked to complete the 4-m walk at the screening visit. If participants walked slower than 0.6 m/s on the 4-m walk, they were not eligible as those who walk at this speed would have been very unlikely to be able to complete the 400-m walk. People with a body mass index (BMI) exceeding 40 kg/m^2 were not eligible because of the weight limitations of MR scanners. Once the information session was completed, a full study consent was presented, and if consent was obtained, the first of 3 examination days was scheduled. Initially, during recruitment, we also excluded anyone whose 4-m gait speed was greater than 1.0 m/s to increase the rate of the study outcome of mobility disability by enrolling those at the highest risk. In February 2020, we decided to eliminate this as an exclusion as the range of gait speed to that point in recruitment was very narrow with 219/274 participants (80%) having gait speed of 0.8–1.0 m/s. Participants receive $200 compensation for completing all measures for the baseline visit (ancillary studies involving participant assessments provided additional compensation); $25 for the first and second annual visits, and $75 for the third annual visit. No compensation was provided for 6-month phone contacts.

Recruitment Results

Despite the COVID-19 pandemic, SOMMA exceeded its recruitment goal of 875 participants, with 879 participants age 70 or over (Table 1); 23% of these were over age 80. Consistent with a greater proportion of women in the population of older adults, more women than men were enrolled. The proportion of 13% of Black participants reflects the proportion of older Black residents in the communities around the clinical sites. The distribution of gait speed was nearly normal, with a median of 1.0 m/s. Of those enrolled, the vast majority (n = 854, 97%) completed the Day 1 measures (400 m walk plus in-person assessments) and all 3 other major examination elements (muscle biopsy, CPET, and MR). Seven hundred and ninety-eight (91%) provided at least 100 mg of muscle tissue, sufficient for all the planned assays and archiving of the specimen.

COVID-19: Impact and Mitigation Measures

There were 282 participants recruited before pandemic-related site closures of 4–8 months, resuming with mitigation which extended the recruitment period for an additional year. Mitigation was site-specific and included the use of face masks and/or face shields for staff and participants; priority vaccination of staff; reduced number of staff and participants on site ("social distancing"); and isolation of staff when exposed to infectious cases. CPET exams were completed with staff wearing full personal protective equipment; the spirometry measure was discontinued. SOMMA also added questionnaires about COVID infection and vaccination history to each annual contact.

Primary and Secondary Outcomes

The primary outcomes of SOMMA are a change in walking speed over 400 m, a change in fitness (VO_2 peak) defined by repeating

Table 1. Characteristics of the SOMMA Cohort, Overall and by Sex

Characteristics	All Participants (*N* = 879) (100%)	Men (*N* = 359) (41%)	Women (*N* = 520) (59%)
Site, *N* (%)			
University of Pittsburgh	439 (49.9)	173 (48.2)	266 (51.2)
Wake Forest University	440 (50.1)	186 (51.8)	254 (48.9)
Age groups, years, *N* (%)			
70–74	402 (45.7)	165 (46.0)	237 (45.6)
75–79	273 (31.1)	110 (30.6)	163 (31.4)
80–84	134 (15.2)	54 (15.0)	80 (15.4)
85+	70 (8.0)	30 (8.4)	40 (7.7)
Race, *N* (%)			
American Indian/Alaskan native	2 (0.2)	1 (0.3)	1 (0.2)
Asian	6 (0.7)	4 (1.1)	2 (0.4)
Native Hawaiian or other Pacific Islander	0	0	0
Black	116 (13.2)	33 (9.2)	83 (16.0)
White	745 (84.8)	314 (87.5)	431 (82.9)
More than one race	5 (0.6)	4 (1.1)	1 (0.2)
Unknown or not reported	5 (0.6)	3 (0.8)	2 (0.4)
Hispanic/Latino, *N* (%)	9 (1.0)	5 (1.4)	4 (0.8)
Education, *N* (%)			
High school or less or other	129 (14.8)	44 (12.4)	85 (16.5)
Some college	427 (49.1)	172 (48.3)	255 (49.6)
College graduate	314 (36.1)	140 (39.3)	174 (33.9)
Marital status, *N* (%)			
Married	444 (50.7)	255 (71.4)	189 (36.5)
Widowed	201 (23.0)	44 (12.3)	157 (30.3)
Separated	6 (0.7)	4 (1.1)	2 (0.4)
Divorced	167 (19.1)	39 (10.9)	128 (24.7)
Single, never married	57 (6.5)	15 (4.2)	42 (8.1)
Self-rated health good/very good/excellent, *N* (%)	829 (95.0)	335 (94.1)	494 (95.6)
Body mass index (kg/m^2), mean ± *SD*	27.6 ± 4.6	27.8 ± 4.2	27.4 ± 4.8
4 m Gait speed (m/s), *N* (%)			
0.6–0.79	81 (9.2)	24 (6.7)	57 (11.0)
0.8–0.99	348 (39.6)	129 (35.9)	219 (42.1)
1.0–1.19	268 (30.5)	118 (32.9)	150 (28.9)
≥1.2	182 (20.7)	88 (24.5)	94 (18.1)

CPET at 3 years of follow-up; and 400-m walking speed to quantify mobility disability (8). Table 2 lists the schedule of assessments. Because of the extensive phenotyping of SOMMA participants, this study will serve as a platform for many secondary analyses. These will be governed by a publications review process (described below).

Clinic Visits and Assessments

Table 2, the Schedule of Assessments, lists the array of assessments and specimens that are collected as part of SOMMA at baseline and follow-up visits. At the baseline and third annual visits, participants have a wide array of measures repeated; at the first and second annual visits, a much shorter list of measures are completed. Interim 6-month phone calls assess functional status and other key measures.

400 m walk

At baseline and in-person annual follow-up visits, participants are asked to walk at their usual pace for 400 m. Major mobility disability is defined as the inability to walk 400 m within 15 minutes without assistance (use of cane is allowed) (9).

Cardiopulmonary exercise testing

CPET at baseline and the third annual visit is used to measure VO_2 peak. This is considered to be the gold standard measure for fitness (10). In men and women >70 years old, the mean loss in VO_2 peak over 3 years is 6%–8% (11). Using a modified Balke or manual protocol, we encourage participants to reach a respiratory exchange ratio (RER) ≥1.05 (a measure of exertion) and a self-reported perceived exertional fatigue (RPE) of ≥17 (range of scale 6–20) (12). Technicians performing CPET have Basic Life Support certifications and certifications as American College of Sports Medicine exercise physiologist certifications. The CPET protocol also includes an electrocardiogram (ECG) and measurements of heart rate, blood pressure, and pulse oximetry, both resting and during the treadmill testing. Perceived exertion and energetic costs of walking at both steady state (1.5 MPH) and at the participant's preferred walking speed (derived from the 400-m walk) are collected during the treadmill testing.

Other strength and physical performance tests

We use an expanded version of the *Short Physical Performance Battery* (SPPB) (13), which includes a timed 4 m walk, chair stands, balance

Table 2. Schedule of Assessments for SOMMA

	Interval (month)						
Assessment	0	6	12 First Annual	18	24 Second Annual	30	36* Third Annual‡
400 m walk (usual pace)	●		●		●		●
Expanded Short Physical Performance Battery	●		●		●		●
4 m walk	●		●		●		●
Chair stand	●		●		●		●
Balance test	●		●		●		●
Narrow walk	●						●
Keiser Leg Extensor (power, 1RM)	●		†				●
Four square step test	●						●
Stair climbing test	●		†				●
Grip strength	●		●		●		●
Height and weight; BMI	●		●		●		●
Waist circumference	●						●
Blood pressure	●		●		●		●
Ankle/arm blood pressure	●						●
Processing speed (Digit-symbol coding test)	●		●		●		●
Global cognitive function (MoCA)	●						●
Executive function (Trails B)	●		●		●		●
MAT-sf	●		●		●		●
California Verbal Learning Test (CVLT-sf)	●						●
Smell/olfaction	●						●
Peripheral neuropathy (monofilament testing)	●						●
Vision assessment	●						●
Diet recall	●						●
Accelerometry: ActivPal	●						●
Accelerometry: ActiGraph GT9x	●		●		●		●
Magnetic resonance	●						●
Imaging: total thigh volume, quadriceps muscle volume; abdominal subcutaneous and visceral; liver fat	●						
^{31}P Spectroscopy: ATPmax, PCr/ATP	●						
CT (whole body)*	●						
High resolution peripheral QCT: radius and tibia†			●				
Proximal femur DXA†			●				
D_3Cr muscle mass	●		●		●		●
Cardiopulmonary exercise testing	●						●
Resting ECG, pulse, blood pressure, oximetry	●						●
ECG, blood pressure, pulse, oximetry during the treadmill testing	●						●
Energetic costs of walking (during preferred walking speed and steady-state phases of treadmill testing)	●						●
VO_2 peak	●						●
Perceived exertion	●						●
Spirometry (subset)	●						
Muscle biopsy	●						
Adipose tissue biopsy (subset)	●						
Blood and urine collection	●						●
Stool collection†	●						
Blood collection for bioenergetics profile	●						●
Complete blood count	●						
Hemoglobin A1c	●						
Race and ethnicity	●						
Gender	●						
Marital status	●		●		●		●
Living arrangement/neighborhood	●		●		●		●
Limited activity days	●	●	●	●	●	●	●
Education level	●						
Occupational history	●						
Self-reported health	●	●	●	●	●	●	●
Weight history, intention to lose weight	●						
History of falls	●	●	●	●	●	●	●
Hospitalizations	●	●	●	●	●	●	●

Table 2. Continued

Assessment			Interval (month) 0	6	12 First Annual	18	24 Second Annual	30	36* Third Annual‡
Self-reported memory change	●	●	●		●	●		●	●
Medical conditions	●		●			●			●
Self-reported visual function	●								●
Self-reported hearing	●								●
Urinary symptoms	●		●			●			●
Tobacco and alcohol use	●		●			●			●
Quality of life (EQ-5D)	●	●	●		●	●		●	●
Adverse life events	●								
Moods/Feelings (CESD-10)	●		●			●			●
Meaning and purpose of life	●		●			●			●
Pittsburgh Fatigability Scale	●		●			●			●
Finances and income	●								●
Women: pregnancy history, hormonal use, etc.	●								
Lifespace	●		●			●			●
Activities of daily living (ADL), instrumental ADL (IADL)	●	●	●		●	●		●	●
Physical Activity Questionnaire (CHAMPS)	●								●
Hip and knee pain	●								●
Stiffness	●								●
Prescription medications	●		●			●			●
Peripheral nerve pain	●								●
Daily schedule	●								●
New cancer diagnosis		●	●		●	●		●	●
Incident fractures		●	●		●	●		●	●
New diet or physical activity programs		●	●		●	●		●	●
New use of walking aids		●	●		●	●		●	●
New moderate/intense exercise program		●	●		●	●		●	●

Notes: BMI = body mass index; DXA = dual-energy x-ray absorptiometry.

*Added as part of an ancillary study

†Added as part of an ancillary study at one clinical center only

‡The last visit of this wave of SOMMA (either third annual, 2.5-year visit, or second annual) will have an expanded set of assessments as the baseline exam, except for muscle biopsies and MR (which will only be completed in a small subset.) In this table, that full visit assessment is depicted as the third annual visit, but this will vary based on date of enrollment (ie, this full visit will occur between 2 and 3 years after baseline, and replace the second annual and/or 2.5-year follow-up contact).

test, and short narrow walk. *Leg extension power and strength (one repetition max, 1RM)* are assessed using the Keiser AIR300 or A420 Leg Press system. *Grip strength* (14) is measured with a Jamar hand-held dynamometer. Participants perform the *four-square step test* (15) where participants were asked to step forward, backward, and sideways into different quadrants to test balance, and a *stair climbing task*, where participants were asked to climb up and down 4 stairs 3 times without stopping to measure functional leg power (16).

Whole-body imaging

An approximately 6-minute long MRI scan is taken of the whole body to assess body composition including quadriceps muscle volume, muscle fat infiltration (% fat by proton density fat fraction); total thigh muscle volume, fatty liver, distribution of adipose tissue in intra-abdominal and subcutaneous compartments (AMRA Medical). Whole-body CT was obtained at Wake Forest only.

D3-creatine dilution method

Whole-body D_3Cr muscle mass is measured in participants using a d_3-creatine dilution protocol. Briefly, participants take a tablet with 30 mg of d_3-creatine and provide a fasting, morning urine sample 72–144 hours later (17,18). In urine, D_3-creatinine, unlabeled creatinine, and creatine are measured using high-performance liquid chromatography and tandem mass spectroscopy (MS/MS); these measures are then included in an algorithm to determine total body creatine pool size and thus skeletal muscle mass as previously described. Importantly, because the enrichment of creatinine is measured (ie, the ratio of D_3-creatinine to unlabeled creatinine), this method is not dependent on creatinine clearance or renal function. The method does not require any special dietary control other than the need for a fasting morning spot urine sample.

Physical activity

Two devices are used to assess activity: the thigh-worn *activPal* that records times sitting or lying, standing, and stepping (19,20) and the wrist-worn *ActiGraph GT9x* (21–24), which collects raw accelerometry data along 3 orthogonal axes at 80 hertz (observations per second). These data are used to calculate sleep parameters, including measures of circadian rhythms, and time spent in sedentary, light, moderate-to-vigorous physical activity (21,25,26). Devices are placed on the participants at the baseline Day 1 visit at the time of the 400 m walk, with a data collection period of 7 full days. Both devices are re-worn at various follow-up visits. We use the Community Healthy Activities Model Program for Seniors

(CHAMPS) questionnaire to assess specific types and the context of physical activities at the baseline and annual visits (27,28).

Anthropomorphic measures

Weight is assessed by balance beam or digital scales and *height* by wall-mounted stadiometers; BMI is calculated as weight (kg)/height (m^2). We also measure *waist circumference*.

Blood pressure, heart rate, and ankle-brachial index

We obtained *resting blood pressure* and *heart rate* in a seated position after 5 minutes of rest and repeated prior to the CPET protocol and tissue biopsy. This is performed multiple times according to study protocols for safety checks. We also obtain an *ankle-arm index* (AAI) or ankle/brachial index, which is the ratio of the ankle-to-arm systolic blood pressure. The AAI is a noninvasive measure of atherosclerotic obstruction in the legs and is a general marker of atherosclerotic burden (29,30).

Fatigability

We assess perceived physical and mental fatigability using the *Pittsburgh Fatigability Scale* (31,32) and record perceived exertional fatigue (*Borg scale* (12)) during the 3 phases of CPET testing (preferred walking speed, VO_2 peak, steady state), and at the end of the 400-m walk. We also measure performance fatigability with the *Pittsburgh Performance Fatigability Index* using raw accelerometry data collected during the usual-pace 400-m walk (33).

Medications

Participants bring in all prescription medications they had taken in the 30 days prior to their baseline Day 1 clinic visit. If a participant forgets to bring one or more medications, clinic staff obtain this information over the telephone. The prescription medications are reviewed and updated at the additional baseline visit days where CPET and tissue sampling were done. Each medication is matched to a medication code and generic ingredient name(s) based on RxTerms, a standardized nomenclature for clinical drugs (National Library of Medicine, Bethesda, MD). Using RxMix2, these medication codes were then matched to the WHODrug Anatomical Therapeutic Chemical (ATC) classification system (Uppsala Monitoring Centre [UMC], Uppsala, Sweden) to create indicator variables for specific medications and classes of medications (34,35). Medication use is also collected at each annual in-person follow-up exam.

Dietary intake

Dietary intake was baseline only using the publicly available National Cancer Institute Automated Self-Administered 24-Hour (*AS24*) tool: (https://epi.grants.cancer.gov/asa24/) with staff assistance as needed, for 2 non-consecutive 24-hour periods.

Cognitive performance

Standard measures of cognitive function include processing speed (*Digit-Symbol Coding Test* (36),); global cognition (*the Montreal Cognitive Assessment [MoCA]* (37)), executive function (*Trails B test* (38)), and memory (*California Verbal Learning Test-short form* (39)). These are assessed at baseline and repeated at annual follow-up exams.

Sensory function

We use 4.17 and 5.07 monofilaments to detect *nerve impairment* at the dorsum of the big toe (40,41). We measure *smell* using the 12-item Brief Smell Identification Test (42), which is a rapid and effective 5-minute screening test that has been widely used in studies of olfaction in older adults. Binocular vision assessments include *contrast sensitivity* (43) and *acuity* (44). We also ask participants about impairments in eyesight and hearing.

Spirometry

Lung function was measured in participants whose baseline exam was before March 2020 using the NDD EasyOneTM Spirometer to determine forced vital capacity and forced expiratory volume (45). The exam was not completed in other participants due to inability to provide mitigation in a field setting during the COVID-19 pandemic.

Clinic interview and self-administered questionnaire

Information collected include questions about life space (46,47); functional status; knee, hip, foot/ankle and lower back pain; peripheral nerve pain; joint stiffness; demographics; education; finances and income; occupation; medical history; adverse life events (48), urinary symptoms (*LURN-SI10* (49)); tobacco and alcohol; quality of life (*EQ5D* (50)); and depressive symptoms (51). Functional status was also assessed with the Mobility Assessment Tool-short form (*MAT-sf*), which uses videos that depict a wooden mannequin performing a wide range of physical activities, and the measurement item consists of a question about the participant's self-reported ability to perform the task (52–54).

Magnetic resonance spectroscopy

^{31}P MR spectroscopy includes a measurement of the rate of synthesis of ATP from adenosine diphosphate (ADP) in the quadriceps muscle (55). A phosphorus magnetic resonance coil is secured over the thigh muscle. Data are acquired during rest and during brief exercise (~30 seconds) that depletes phosphocreatine (PCr), thereby elevating ADP. The time constant of the PCr recovery following exercise is used to calculate the maximum ATP production (ATPmax) (56). The exercise involves isometric kicking against Velcro straps positioned tight across the leg and thigh and measurements are collected before, during and after the exercise.

Biospecimens: Muscle Biopsies

At the baseline exam only, percutaneous biopsies of the *vastus lateralis* were obtained between 9 am and 11 am on Day 3 of the baseline visit. Participants were eligible for tissue collection after confirming that they were not currently taking blood thinners, had avoided strenuous physical activity for the prior 48 hours, had systolic blood pressure lower than 180 mm Hg and diastolic blood pressure lower than 110 mm Hg, recorded no use of aspirin or anti-inflammatory medications over the prior 3 days, and confirmation that participant was fasted (at least 8 hours). Biopsy samples were obtained using a Bergström trocar (5 or 6 mm) with suction applied using a 60cc syringe and using a local anesthetic (1 or 2% lidocaine HCL) as previously described (6,57). The goal was to obtain 300 mg of muscle tissue. If the yield was insufficient after the first insertion of the trocar, the trocar could be inserted up to 4 additional times (for a maximum of 5 insertions) contingent on the operators best medical safety judgment and ensuring that the participant was comfortable and provided verbal consent. Following the biopsy procedure, the skin was held closed with sterile adhesive strips, an antibiotic ointment was applied, and the area was covered.

Processing of Muscle Tissue

At the baseline exam, the biopsy specimen was immediately blotted dry of blood and interstitial fluid and dissected free of any connective tissue, subcutaneous tissue, and intermuscular fat (this dissected

tissue was archived if present). The preparation of the biopsy specimen for specific assays are listed in Supplementary Table 1. It was estimated that 140 mg of tissue was sufficient for all planned assays and any remaining tissue would be prepared and stored for future ancillary science.

High-resolution Respirometry

In the baseline muscle tissue specimen, electron transport system function was assayed in permeabilized muscle fibers from freshly collected muscle biopsy specimens in a highly controlled ex vivo experiment, removed from other potentially limiting physiological factors, including supplies of substrates and oxygen. Briefly, ~10 mg of the biopsy specimen was obtained and placed it into a cryovial containing biopsy preservation solution on wet ice. Fiber bundles were prepared by mechanical and chemical permeabilization, and mitochondrial respiration was assayed using the O2k-respirometer (Oroboros Instruments) (58,59). Two respirometry protocols were performed in duplicate for each muscle biopsy specimen. Following completion of the assays, the calibration and assay DatLab files from both clinical sites were uploaded to the SOMMA website. Quality control and review of the data collected at each study site was performed using the DatLab software by experienced staff at the Translational Research Institute at Advent Health.

Histology

A portion of the baseline muscle biopsy was prepared for histological analysis (~30 mg) which includes myosin heavy chain immunostaining to determine fiber type proportion, cross-sectional area, and grouping. Other staining protocols include neural cell adhesion molecule as a marker of denervation, CD31 to identify and measure capillary density, and Oil red O staining to measure neutral triglyceride content in a fiber type specific manner.

Gene Expression: RNA Sequencing

A portion of the baseline muscle biopsy was flash frozen in liquid nitrogen for RNA sequencing (~15 mg). Each muscle piece was homogenized in Trizol using the Bullet Blender at 4°C. At the time of writing of this manuscript, the RNAseq assays and processing were ongoing. Chloroform was used to separate the phases, and RNA precipitated from the aqueous phase using 100% cold isopropanol. Following centrifugation, the pellet was washed and resuspended in Corning Sterile RNAseq water. Samples were DNase treated using the TURBO DNase kit and frozen and stored at −80°C. Purified RNA was checked for integrity using an Agilent Bioanalyzer, and all samples for sequencing with an RNA integrity number > 6.0. Poly-A selected RNAseq libraries were prepared using Illumina mRNA Prep kit (Illumina, San Diego, CA). Libraries were pooled to equal molarity and sequenced on an Illumina NovaSeq, paired-end 100 bp sequencing, with a goal of > 80M reads per sample. Reads were be mapped to a reference genome, GRCh38.p14, and mRNA quantification and normalization will be done using standard analysis pipelines (60).

Additional Biospecimen Collection

At the baseline exam, blood was drawn after an overnight fast of at least 8 hours from an antecubital vein using a blood collection set (BD, 367326). The following blood tubes were filled. (i) Plasma (10 mL ethylenediaminetetraacetic acid [EDTA]), for measurement of a complete blood count and HbA1c in the site's local clinical laboratories; (ii) plasma (10 mL EDTA, single spin); (iii) plasma (10 mL) with double spin to obtain platelet poor plasma; (iv) serum (10 mL); (v) plasma from 2 ACD tubes; (vi) PAXgene RNA (2.5 mL); and (vii) CPT Sodium Heparin (8 mL). The PAXgene and CPT tubes were drawn using a syringe to prevent cross-contamination of blood tube additives. Urine samples were collected after the venipuncture for both the D_3-creatine dilution method and for archiving in the SOMMA biorepository. The first-morning void was not collected. Participants used the Sterile Midstream Urine Collection Systems kit (Covidien 2090SA) for urine collection. Blood and urine specimens were aliquoted and stored at −80°C at the SOMMA biorepository.

"Expanded subsample" for Histology and RNAseq

Originally, SOMMA had intended to use a case-cohort design to study mobility disability, where histology and RNAseq would be completed in a random cohort and all cases of mobility disability. However, given the low event rates and slow recruitment due to the COVID-19 pandemic, the primary study outcome was expanded to include not only mobility disability but also a change in 400 m walk speed and change in VO_2 peak. (The SOMMA is currently working to secure funding to complete all histology and RNAseq assays in all incident cases that occur within 8 years of baseline to allow case-cohort analysis of mobility disability). Histology and RNAseq are only completed in the "expanded subsample" in SOMMA, given the high cost of histology and RNAseq, and the fact that these measures can be completed in archived specimens. The expanded subsample includes a random sample of all SOMMA participants (N = 402), plus additional participants who reported a race or ethnicity other than Non-Hispanic White (N = 42) and/or were aged ≥90 years (N = 6). A total of 450 participants were selected for the expanded subsample. (Selection is depicted in Supplementary Figure 1.)

Data Management and Analysis

The SFCC staff, along with SOMMA Investigators, wrote the study operations manual and are responsible for managing, editing, storing, and analyzing data generated by the clinical sites. Except where external data are generated by a specific instrument, the SFCC produced all data collection instruments to be machine-readable using Teleform software (OpenText, Waterloo, Canada) or to be electronically captured using the Medrio platform (Medrio, Inc., San Francisco, CA). All data forms and questionnaires were pretested to ensure the clarity, efficiency, and reliability of the instruments and to test the distributions of responses. Study data also underwent daily error-checking programs following submission. Select research staff had permission to resolve edits and update data as necessary via the website. These changes to the data were recorded in an audit trail. The study website was password protected and only accessible with a direct link. This website listed forms that were expected to have been submitted, which helped ensure data completeness. Numerous reports were generated monthly to summarize data completeness and timeliness. We ensure the rigor of results by requiring analysis plans to be reviewed and approved by the Publications Committee before analyses begin for manuscripts. Prior to submission for publication, analyses must also be verified by a code review process (61).

Training and Validation

Prior to implementation, all study protocols are reviewed and approved by the Executive Committee. In addition, prior to beginning recruitment, each site sent staff members to a centralized training session. A separate training session was held for muscle tissue biopsies and processing and for ^{31}PMRS acquisition. At training, or shortly thereafter at the clinical center, each staff member was

observed completing the non-invasive, non-imaging clinical exams by at least one other trainer and was certified to complete the measure after completing the protocol without error. Videos of the training sessions at baseline were made and are reviewed by clinic staff intermittently and by all staff hired after baseline.

Follow-up Assessments

Annual follow-up visits include the 400-m walk and other select measures (Table 2). Annual visits were initially planned at 1, 2, and 3 years after baseline to assess mobility and function, with the first and second annual visits including a short list of measures (such as 400-m walk and functional status), and the third annual follow-up visit ("expanded visit") including repeating many assessments collected the baseline exam, except for muscle biopsies and MR (which will only be completed in a small subset). To shorten the recruitment window for follow-up visits from 33 months to 24 months, this "expanded visit" will occur between 2 and 3 years after baseline and will replace the originally planned second annual and/or 2.5-year interim follow-up contact depending on the enrollment date.

Follow-up also includes approximately 6-month interim phone or mail contacts. At each study contact (6-month interim contacts as well as annual visits), participants are asked about health events. A physician adjudicator centrally adjudicates fractures, incident cancer diagnoses, overnight hospitalizations, and deaths. Clinical centers obtain medical records and death certificates to aid in the central adjudication of these events. If we are unable to contact a participant or if the participant becomes incapacitated, we contact the proxy designated by the participant at the baseline visit to inquire about the participant's status and answer the same questions about the functional status that we would have asked the participant to determine mobility disability status prior to death.

Participant Safety

The SOMMA team is dedicated to ensuring participant safety. The study is overseen by an Observational Study Monitoring Board (OSMB). Each clinical center has a Medical Safety Officer, a clinician who reviews eligibility for the biopsy, CPET, and MR. Adverse events (AEs) are tracked and reported to the Executive Committee and OSMB. At baseline, 41 AEs and 2 serious AEs (SAE) were reported. AEs were mostly biopsy related, with pain (N = 20) or vasovagal episodes (N = 4) the most common; no infections were reported. Non-biopsy-related AEs were mostly skin irritation from activity devices or minor falls during examination. Two SEAs were reported: one fall during the 400-m walk requiring overnight hospitalization, and one participant who experienced an atrial fibrillation event during CPET (despite a normal EKG and no known cardiac history) that also required overnight hospitalization. Training sessions provide information on how to safely assess older adults during physical performance tasks and how and when to report AEs and SAEs. SOMMA also carefully considers participant data confidentiality. Identifying information, including names, addresses, and contact information is locally stored at the clinic and not shared with the Coordinating Center. Limited identifiers (date of birth) and all other data are transmitted securely; data use agreements govern sharing of data with both internal and external collaborators.

Ancillary Studies

In line with its goals, SOMMA encourages ancillary studies that address the determinants of mobility disability, the biology of aging, and age-related health outcomes. SOMMA has a formal process for applying to use data, specimens, or images that begins with the completion of a form that details the request along with a description of the proposed study. The proposals are reviewed by the SOMMA Executive Committee. If the new project involves additional participant burden, it is also reviewed by the Observational Study Monitoring Board. If approved, the study must also be reviewed and approved by the single IRB. All data from SOMMA ancillaries are securely sent to the SFCC and incorporated into the overall SOMMA data archives.

Several ancillary studies have been funded to add novel measures to the SOMMA assessments, including adipose tissue collection for the abdominal subcutaneous region (N = 241) and processing (R01AG66474, principal investigators [PIs]: Sparks, Justice, and Kershaw); high resolution peripheral quantitative computed tomography (HR-pQCT, R0AR1076752, PIs: Cauley, Strotmeyer); knee osteoarthritis (R01AG070647, PI: Lane); blood bioenergetics including respirometry on peripheral blood mononuclear cells (R01AG072734, PIs: Molina, Shiva) and mitochondrial DNA heteroplasmy (R01AG075081, PIs: Coen, Delaney, Tranah). An administrative supplement to the parent award was made to support preliminary data collection for brain imaging (lead investigator, Rosano). Institutional and philanthropic funds were used to recruit a younger reference population ("SOMMA Jr") with the same baseline measures as the parent SOMMA study repeated in 80 men and women aged 30–70 to serve as a younger reference cohort. SOMMA has also served as a platform for several funded career development awards to add measures of the built environment/neighborhood (K99AG066846, PI: Duchowny); urinary symptoms (K76AG074903, PI: Bauer), and fecal microbiome (K01AG071855, Pittsburgh participants only, PI: Farsijani). Many more ancillary studies have been proposed and are under review at funding agencies.

Discussion

SOMMA is unique among cohort studies of aging for inclusion of biopsies of muscle and adipose tissue along with archives of blood and a wide array of examinations, including MR and CT imaging, actigraphy, and batteries of physical and cognitive performance tests. The spectrum of examinations has been extended by ancillary studies that, for example, added bone imaging with peripheral quantitative computed tomography (pQCT) and dual-energy x-ray absorptiometry, and knee x-rays for OA.

The study has important limitations. Although the participants are representative of the racial and ethnic composition of the clinical sites (mostly White and some Black participants), the number of participants from some race and ethnic groups is insufficient to determine whether the association of mitochondrial function or other biologic pathways and measurements of mobility varies by race or ethnicity. Plans to expand the representation of the SOMMA are under development, but contingent on additional funding. The requirement for a gait speed of at least 0.6 m/s constrains the inclusion of individuals with mobility limitations. Consequently, SOMMA includes very few individuals over age 90 (n = 17), limiting the near-term ability of SOMMA to study determinants of mobility decline in the oldest old. Further, the MR machines had BMI limits of 40 kg/m^2; we were unable to enroll those with class III obesity limiting our ability to generalize to this population.

SOMMA is particularly well-suited for studies of crosstalk between tissues, including skeletal muscle, subcutaneous abdominal adipose, bone, and joints. The addition of brain imaging and

biomarkers of neurodegeneration and cognitive decline would create unprecedented resources for studies of how aging tissues interact and contribute to detrimental multisystem manifestations such as multimorbidity and frailty or, conversely, as the maintenance of healthy, disease and disability-free aging.

In summary, SOMMA is a new cohort that, as renewals and ancillary studies add new resources and measurements and follow-up continues, will be a growing resource for the study of many facets of the biology of healthy human aging.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

SOMMA is funded by the National Institute on Aging (NIA) grant number R01AG059416. Ancillary studies to SOMMA have been funded by NIA for adipose tissue collection and assessment (R01AG66474, Principal Investigators [PIs]: Sparks, Justice, and Kershaw); knee osteoarthritis (R01AG070647, PI: Lane); blood bioenergetics including respirometry on peripheral blood mononuclear cells (R01AG072734, PIs: Molina, Shiva), single nucleus RNAseq (PI: Xu, funded as a pilot study by the Pepper OAIC Coordinating Center, U24AG059624), and mitochondrial DNA heteroplasmy (R01AG075081, PIs: Coen, Delaney, Tranah0, and by the National Institute for Arthritis and Musculoskeletal disease for high-resolution peripheral quantitative computed tomography for bone structure and strength (R01AR076752, PIs: Cauley, Strotmeyer). Career development awards from NIA support trainees and specific measures including built environment/neighborhood, (K99AG066846, PI: Duchowny); urinary symptoms (K76AG074903, PI: Bauer), and fecal microbiome (K01AG071855, PI: Farsijani). Pre- and post-doctoral trainees using SOMMA data at the University of Pittsburgh are supported by training grant T32AG000181. Study infrastructure support was funded in part by NIA Claude D. Pepper Older American Independence Centers at University of Pittsburgh (P30AG024827) and Wake Forest University (P30AG021332) and the Clinical and Translational Science Institutes, funded by the National Center for Advancing Translational Science, at Wake Forest University (UL1 0TR001420) and University of Pittsburgh (UL1TR001857).

Conflict of Interest

S.R.C. and P.M.C. are consultants to Bioage Labs. All other authors report no conflict of interest.

Acknowledgments

The members of the SOMMA team also acknowledge the important contribution that Kevin Conley made to the study design and implementation for SOMMA before he passed away in 2019.

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