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Study Protocol of the 10-Year Longitudinal Amersfoort Cohort Study on Functional Decline, Healthy Aging, and Frailty (AMCOHF) in a Community-Dwelling Older Population

Dax Houtkamp[a, b] Sabrina Chettouf[a] Bart C. Bongers[a, c, d] Albert Van de Wiel[a, e] Peter Van Roy[a, f] Patrick Schrama[a] David Beckwée[a, g] Willy H.A.M. Smeets[a] Ivan Bautmans[a, h, i, j] Annelies L. Pool-Goudzwaard[a, b]

[a]SOMT University of Physiotherapy, Amersfoort, The Netherlands; [b]Faculty of Behavioural and Movement Sciences, Amsterdam Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [c]Department of Nutrition and Movement Sciences, Institute of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, The Netherlands; [d]Department of Surgery, Institute of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, The Netherlands; [e]Faculty of Applied Sciences, Radiation Science and Technology, Clinical Medicine and Isotopes for Health, Delft University of Technology, Delft, The Netherlands; [f]Experimental Anatomy Department, Vrije Universiteit Brussel (VUB), Brussels, Belgium; [g]Rehabilitation Research Department, Vrije Universiteit Brussel (VUB), Brussels, Belgium; [h]Gerontology Department, Vrije Universiteit Brussel (VUB), Brussels, Belgium; [i]Frailty and Resilience in Ageing (FRIA) Research Unit, Vitality Research Group, Vrije Universiteit Brussel (VUB), Brussels, Belgium; [j]Geriatrics Department, Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

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Keywords
Frailty · Functional decline · Longitudinal studies · Intrinsic capacity · Older adults

Abstract

Introduction: Frailty, characterized by a reduction in intrinsic capacity across multiple physiological systems, is a key concern in healthy aging. Insight in the trajectory of an individual's functional ability and intrinsic reserve capacity in a relatively younger population of older adults is lacking. This study aims to investigate the early stages of frailty by tracking trajectories of physical indicators of intrinsic capacity before frailty becomes clinically evident. ***Methods:*** The AMersfoort COhort study on functional decline, Healthy aging and Frailty (AMCOHF) is a unique 10-year prospective cohort study evaluating the predictive value of longitudinal trajectories of physical parameters for frailty onset or robustness maintenance. An a-select community-dwelling robust population of Amersfoort (55–75 years) in the Netherlands will undergo baseline assessments for inclusion criteria and will be followed longitudinally every 2.5 years. Frailty status is assessed using the Fried phenotype, Rockwood frailty index, and Groningen frailty indicator. Testing procedures and questionnaire completion include physical performance tests in the domains: (1) musculoskeletal system, (2) articular system, (3) cardiorespiratory system, (4) sensory system, (5) immune

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Correspondence to:
Annelies L. Pool-Goudzwaard, a.pool@somt.nl

system, and 6) uro-gynecological system. Study outcomes focus on intrinsic capacity, functional ability, explanatory data, and frailty. Statistical analyses evaluating the predictive capacity include logistic regression, confirmatory factor or latent class analysis, and structural equation modeling. Nonprobability convenience sampling recruits 2,078 robust participants, estimating a 1-year frailty incidence of 1.5%–6.0%. Ethical approval was obtained, and the trial is prospectively registered on Open Science Framework (DOI: 10.17605/OSF.IO/RMBQV). ***Conclusion:*** The AMCOHF study will contribute to knowledge about markers to predict an accelerated decline in intrinsic capacity in an early stage. This knowledge is important to deploy prevention strategies at an earlier stage in life then those currently undertaken, ultimately reducing healthcare costs and contributing to a healthy aging population.

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Introduction

To date, the World Health Organization considers healthy aging from the perspective of an adult's life course and longitudinal trajectory of functioning [1]. By monitoring intrinsic capacity (i.e., the composite of all the physical and mental capacities that an individual can draw on), a participant's potential for future disease may be recognized at an early stage. The development of preventive interventions, specifically tailored to those individuals who are at risk of developing adverse health outcomes may promote healthy aging. This may subsequently reduce the strain on healthcare systems and improve overall quality of care [2]. Healthy aging is defined as "the process of developing and maintaining the functional ability that enables well-being in older age (e.g., abilities to move around or to meet their own basic needs)" and functional ability encompasses the individual's intrinsic capacity, relevant environmental characteristics, and the interactions between the individual and these characteristics [3]. The dynamic interaction between an individual and the environment results in trajectories of both intrinsic capacity and functional ability [4].

As people age, they experience a gradual accumulation of molecular and cellular damage that results in a general decline in physiological reserves [5]. In addition, dysfunctions in three or more physiological systems (e.g., a pro-inflammatory state, hormonal dysregulation, sarcopenia) are strongly associated with the prevalence of frailty, which is considered one of the most prominent barriers to healthy aging [6]. Conceptually, frailty can be defined as "a condition or syndrome that results from a multisystem reduction in reserve capacity to the extent that a number of physiological systems are close to, or pass, the threshold of symptomatic clinical failure" [7]. Consequently, frail individuals face increased risk of developing negative health outcomes such as premature mortality, hospitalization, and the development of disabilities in basic activities of daily living [8].

Even though several physical factors such as muscle strength, gait speed, and cardiorespiratory fitness decline with increasing age, the natural course of the decline in physical intrinsic capacity (i.e., the physiological and physical reserves on which one can rely) has not yet been considered as a determinant of frailty. To recognize an individual's accelerated decline in intrinsic capacity, a better understanding of the pathways governing the natural progression of physical determinants of functional capacity and frailty is needed. This is of particular significance because the capacity to reverse frailty decreases with age and the effectiveness of preventive interventions in pre-frail older adults may be of greater benefit than in frail older adults [6, 9]. A recent Delphi study has reached consensus about recognizing pre-frailty as a key step in promoting healthy aging [10].

The primary aim of this study was to investigate whether time-related trajectories of intrinsic capacity across six physiological systems (i.e., cardiovascular and respiratory, articular, uro-gynecological, musculoskeletal, immune, and sensory system) can predict maintenance of robustness (healthy aging) or the onset of frailty. The secondary aim was to investigate cross-sectional associations between biomarkers of intrinsic capacity or functional ability and (pre-) frailty (Fig. 1). The innovative aspect of the current study is that, unlike previous studies, it focuses on trajectories of intrinsic capacity and the relationship with the very early stages of (pre-)frailty, when deficits are not yet clinically obvious. When markers for accelerated declining intrinsic capacity can be evaluated at an early stage in life, development of prevention interventions specifically targeting one's individual intrinsic capacity may prevent or delay the onset of (pre-)frailty.

Methods

Design

The AMersfoort COhort study on functional decline, Healthy aging, and Frailty (AMCOHF) is a prospective cohort study in which participants will be followed for

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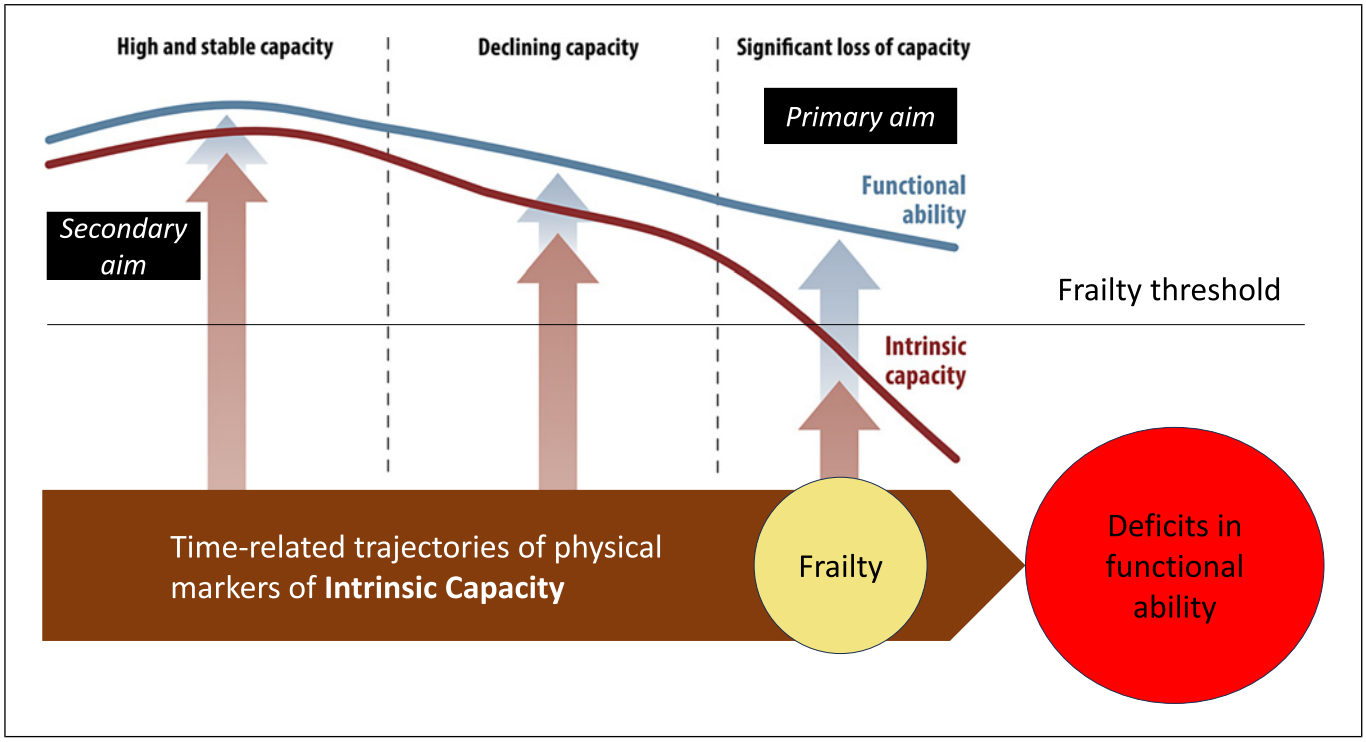


Fig. 1. Schematic representation of how the study complies with the WHO concepts of Healthy Aging (adapted with permission from Beard and colleagues [1]). The primary aim of this study was to find whether time-related trajectories of intrinsic capacity can predict maintenance of robustness (i.e., healthy aging) or the onset of frailty. In the initial stage of the study, cross-sectional associations will be explored between biomarkers of intrinsic capacity or functional ability and (pre-)frailty status.

10 years. Patient inclusion and data collection started in June 2022 and ethical approval was granted by the Medical Ethical Committee Zuyderland (Heerlen, The Netherlands) under reference number NL 70141.096.19 (19 September 2019). The trial has been registered on Open Science Framework (DOI: 10.17605/OSF.IO/RMBQV).

Recruitment

This study applies nonprobability convenience sampling. Different recruitment strategies will be used to ensure a representative study sample: participants will be recruited in collaboration with the city of Amersfoort, by sending monthly open invites to households with inhabitants >55 years old. Additionally, invites can be aimed at demographically underrepresented groups through advertisements in local media, general practices, hospitals, and community centers. Those interested to participate will be informed by information on the website (www.amersfoortstudie.nl). When a participant is interested, six questions will be asked to evaluate initial eligibility to participate, concerning age, walking limits (strength and endurance), comorbidities, weight loss, and self-perceived fatigue. To mitigate the risk of selection bias (e.g., a high response of relatively fit and literate older adults), demographic data will be evaluated continuously throughout the inclusion period, allowing for the recruitment of underrepresented subgroups through specifically targeted advertisements.

Participants

Participants aged between 55 and 75 years will be invited to participate in this cohort study. Those who meet the initial eligibility criteria will be asked to provide written informed consent, after which each participant will be invited for further medical screening by a physician to exclude contraindications and to assess final inclusion for participation in the assessments. This medical evaluation will include anamnesis of medical history and medication use, auscultation of the lungs and heart, baseline evaluation of resting blood pressure and resting electrocardiogram. Furthermore, comorbidities

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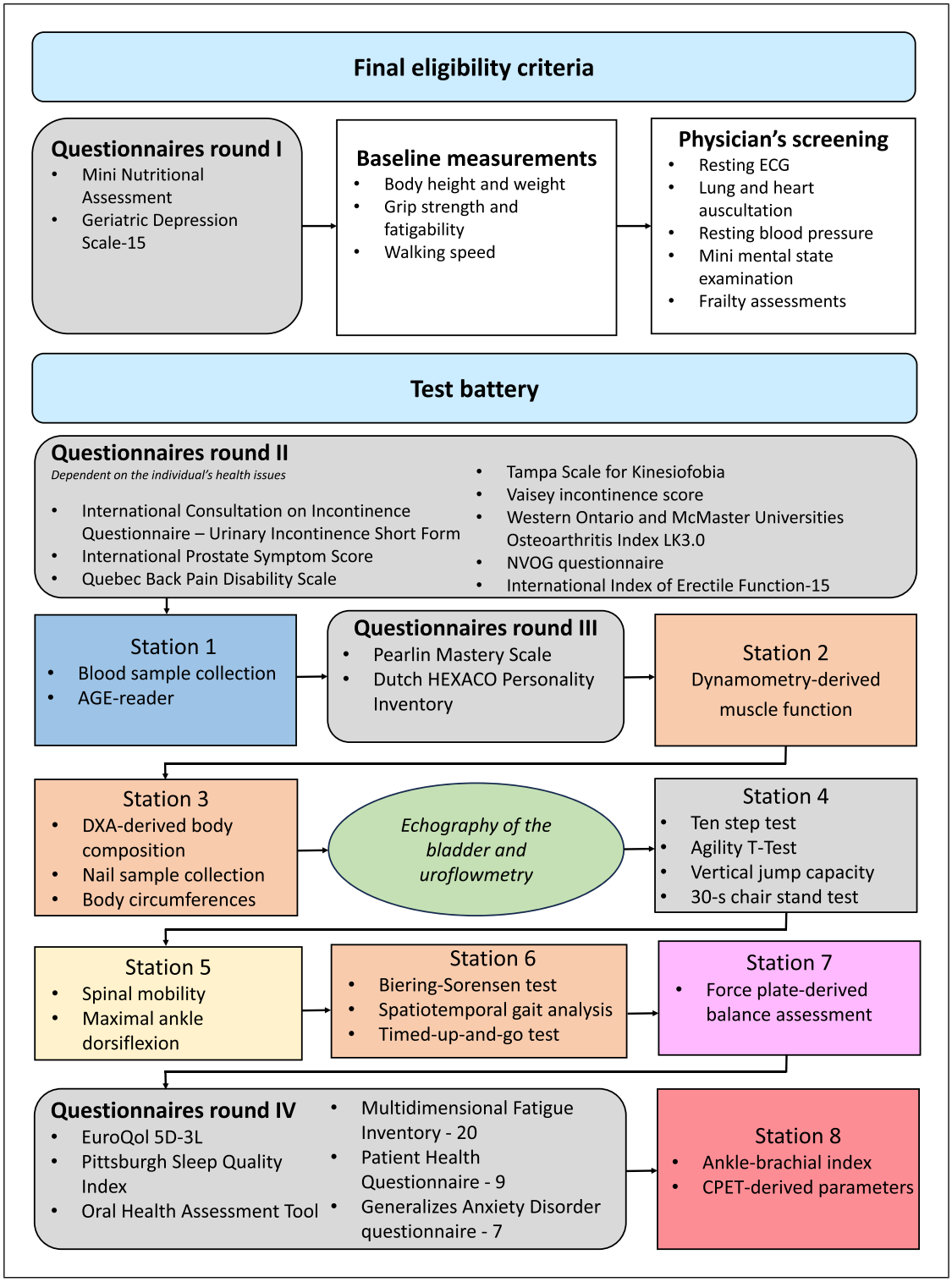


Fig. 2. Overview of the participant journey. Each participant will perform the assessments every 2.5 years. The echography is time-dependent on the participants urge to urinate. Different colors correspond to the different physical domains. Station 4 consists of integrative tests that evaluate a combination of different domains and is therefore colored white.

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will be documented using a self-administered comorbidity questionnaire [11] and frailty status will be assessed. Final exclusion criteria are (1) physical impairment (e.g., unable to stand up or walk), (2) cognitive impairment, defined as a mini mental state examination score <23/30 [12], (3) surgery, cancer, chemotherapy, and/or radiotherapy in the last 6 months, or active cancer and/or severe cardiopulmonary diseases.

After final inclusion by the physician, participants will be eligible to complete the full testing procedure. Study outcomes will be assessed by the research staff of SOMT University of Physiotherapy. The duration of the entire evaluation is maximally 3 hours, including resting moments allowing the participants to recover from the physical tests. The participant journey for the testing procedure is shown in Figure 2.

Those who are non-frail at baseline will be included in the longitudinal study and invited to be reassessed for potential early markers of frailty every 2.5 years for 10 years. The testing procedure will be similar every 2.5 years. When participants become frail after inclusion at baseline, they maintain amenable for participation. Non-frail has been defined in this study as being robust or pre-frail based on all of the three frailty scales: the Fried phenotype [13] as operationalized by the AMCOHF research group, Rockwood frailty index as operationalized by Collerton and colleagues [14], and the Groningen frailty indicator [15]. Frail participants at baseline who do not show any contraindication and are able to perform the tests will still be evaluated at baseline (for cross-sectional analysis), but they will be excluded for the longitudinal follow-up.

Study Parameters

The study parameters can be divided into three main parts: (1) primary endpoints related to frailty status, (2) trajectories of physical intrinsic capacity, and (3) explanatory outcomes, including trajectories of functional ability and nonphysical (i.e., emotional and cognitive) aspects of aging. Furthermore, the following demographic and lifestyle factors will be recorded: sex, age, race, education, marital status, (previous) occupation, ethnicity, body height, body mass, smoking (never, previous, current), and major life events (e.g., having children, major illness or injury, family traumas).

Primary Endpoints: Frailty

The primary endpoint will be either maintenance of robust status or occurrence of (pre-)frailty within 10-year follow-up to at least one out of three complementary frailty reference tools:

- Physical frailty will be evaluated using a modified version of the original Fried phenotype [13]. Frailty will be evaluated using four of the original five criteria in accordance to previous research [16–19]: (un)intentional weight loss, exhaustion, low gait speed, and low handgrip strength. Using four criteria, robustness is defined as having zero components, pre-frailty as having one or two components, and frailty as having three or four components, which is in accordance with the scoring system described elsewhere [20]. Exact operationalization of the four criteria in the AMCOHF study can be found in online supplementary File 1 (for all online suppl. material, see https://doi.org/10.1159/000546943).
- The Rockwood frailty index as operationalized by Collerton and colleagues [14] involves a 40-item deficit accumulation index that evaluates medical, cognitive, and functional aspects of frailty. Each deficit is given a score depending on its presence (0 = absent) and severity (when present either 0.25, 0.50, 0.75, or 1.00), and all deficit scores are summed to a total score which is then divided by 40 expressed as a frailty index score. Frailty is defined as a frailty index score ≥0.25. This index is operationalized through self-reported questions, medical records, and noninvasive clinical tests (e.g., resting electrocardiogram).
- The Groningen frailty indicator is a 15-item self-reported questionnaire covering physical, cognitive, social, and psychological domains of frailty. A score of ≥4 indicates frailty [15].

Trajectories of Intrinsic Capacity

Markers for trajectories of intrinsic capacity (see Fig. 1, red line) will be based on the potential capacity to predict the occurrence of frailty or maintenance of robustness (i.e., healthy aging). Predictors were selected based on several criteria, including (1) tests that measure the construct corresponding to intrinsic capacity, (2) tests that are responsive to change and potentially modifiable via physical interventions, and (3) tests having a high potential to predict the occurrence of frailty or maintenance of robustness. Finally, to make sure that intrinsic capacity (i.e., the physiological and physical reserves on which one can rely) could be captured, a stress test (i.e., a test that aims to challenge the maximal physiological and/or physical capacity) was chosen for each intrinsic capacity component.

Evaluated physical parameters for intrinsic capacity were divided in six body domains: (1) musculoskeletal system, (2) articular system, (3) cardiorespiratory system, (4) sensory system, (5) immune system, and (6)

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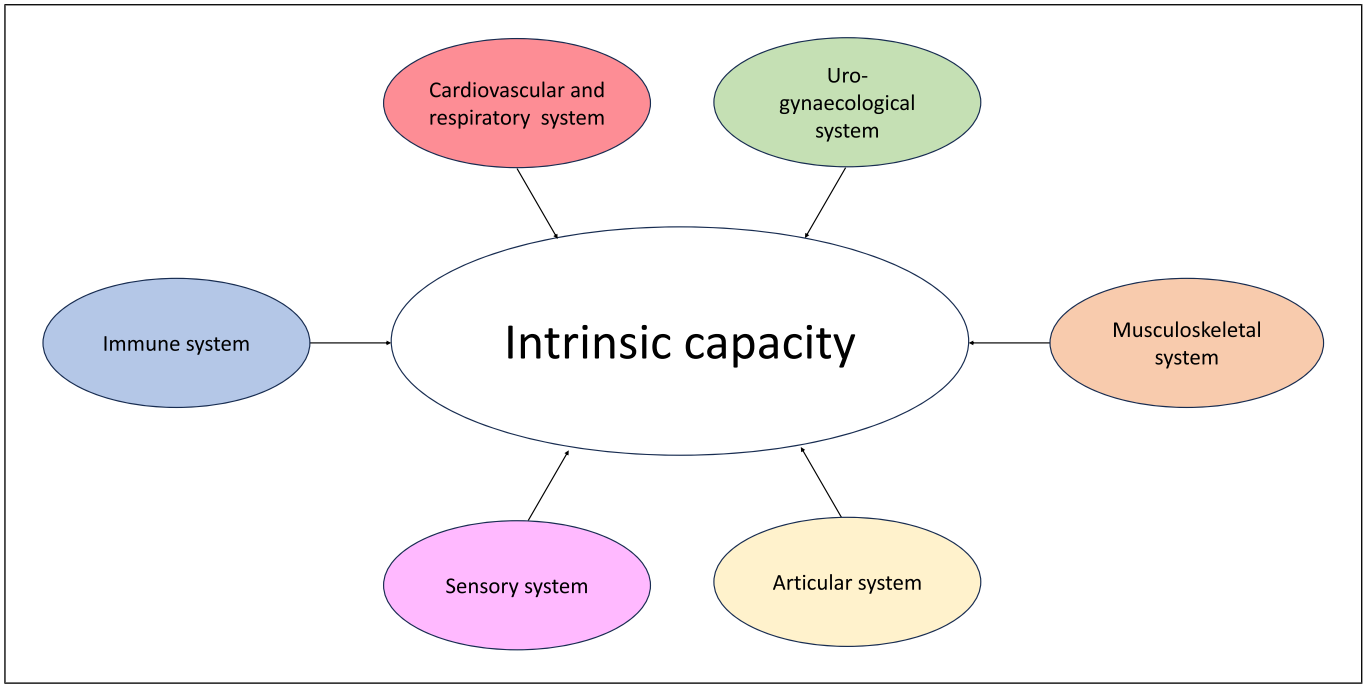


Fig. 3. Physical parameters for intrinsic capacity divided into 6 body domains.

uro-gynecological system. Some tests evaluate a combination of multiple body domains (Fig. 3). Exact operationalization, clinimetric or psychometric quality of all the instruments, tests and questionnaires, and detailed description of instruments can be found in online supplementary Files 1 and 2.

Musculoskeletal System

Handgrip Strength and Fatigue Resistance

Handgrip strength and fatigue resistance will be assessed using the Martin Vigorimeter (KLS Martin Group, Tuttlingen, Germany) or Eforto® system (Uni-Web BV, Meise, Belgium). Handgrip fatigability is a very promising outcome to help elucidating the pathways leading to frailty [17, 19, 21]. It has been shown that muscle fatigue occurs before the onset of muscle weakness in a mouse model of premature aging [22]. This supports the hypothesis that muscle fatigue might be a good early marker for frailty. For handgrip strength, the participant is asked to squeeze the large bulb of the Martin Vigorimeter or Eforto® as hard as possible with the dominant hand for 5 seconds. The highest of three attempts is noted as the maximal handgrip strength in kPa. Fatigue resistance will be measured as the time in seconds during which handgrip strength drops to 50% of its maximal value during sustained maximal contraction [23, 24]. Fatigue resistance allows the calculation of grip work (i.e., the work delivered by the handgrip muscles during the test) [23]. Grip work is calculated as fatigue resistance multiplied by 75% of maximal handgrip strength, corresponding to the area under the curve [23, 25].

Dynamometry

Maximal isometric strength, isokinetic and isotonic dynamometry, and muscle fatigability of the knee extensors and knee flexors of the dominant side will be assessed using a Biodex system 4 dynamometer (Biodex Medical Systems, Inc., Shirley, NY, United States). It has been shown that maximal strength is an important variable to be tested for monitoring loss of muscle strength in the older adults [26]. Main outcome variables include peak torque and rate of torque development and will be evaluated using maximal isometric knee extension. Furthermore, outcome variables for isokinetic dynamometry include peak torque, peak power, and the angle at which peak power will be reached, which will be evaluated at, respectively, 60 and 180° per second for both knee extension and knee flexion. Peak isotonic (quasi) unloaded tests are shown to be a key component in the onset of functional difficulties in older women [27]. In addition, peak torque and peak velocity as well as

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the time it takes to reach these points will be evaluated in isotonic mode at, respectively, 20% of the previously determined maximal isometric peak torque. Main outcome variables include time in seconds to 50% strength decay and the area under the strength-time curve [28].

Trunk Extensor Muscle Endurance

Isometric endurance of trunk extensor muscles will be evaluated using the Biering-Sorensen test as operationalized by Latimer and colleagues [29]. Back extensor muscle strength has been proposed as an alternative frailty marker for grip strength and previous literature has demonstrated its association with frailty [30]. Trunk muscle fatigability is measured as the time in seconds that the participant is able to correctly maintain this position.

Body Composition

Body composition will be measured using a fan beam whole body dual X-ray absorptiometry (DXA) device (GE Medical Systems Lunar, Madison, WI, USA). The DXA machine can distinguish body composition variables such as fat mass, bone mineral content, and lean mass [31, 32], which, in contrast with BMI, have shown to be associated with frailty [33]. Additionally, body circumferences of the waist, hip, calf, and upper arm will be measured (cm).

Internal Trace Elements

An analysis of internal trace elements will be performed using toenail clipping. Internal elements play an essential role in functioning of the human body, for example, in the production of proteins and in enzymatic processes relevant for muscle and nerve function and bone strength [34]. Some internal trace elements are toxic and can have deleterious effects promoting frailty, especially in higher concentrations. An analysis of internal trace elements may therefore contribute significantly to identify determinants that may reflect or predict a decline in muscle and nerve function and bone strength. Elements that will be studied include calcium, potassium, magnesium, zinc (all of which are known to be positively associated with bone and muscle strength), arsenic, cobalt, chromium, iron, manganese, vanadium, mercury, cadmium, and aluminum. Additionally, elements that may be both positively and negatively associated with muscle and nerve function as well as bone strength will be studied for presence (%) and volume, such as arsenic, cobalt, chromium, iron, manganese, and vanadium, as well as elements known to be toxic, such as mercury, cadmium, and aluminum.

Articular System

Spinal Posture and Mobility

Spinal posture and mobility will be assessed using a SpinalMouse (Idiag, Fehraltorf, Switzerland). Poor spinal posture and hypomobility are well-known age-related changes that are related to loss in physical independency in older persons [35]. The SpinalMouse comprises an electronic, hand-held inclinometer connected wirelessly to a computer with inclination angles at each vertebral segment allowing for calculation of posture and flexion-extension mobility of the thoracic spine, lumbar spine, and hip joint (sacral inclination) in degrees [36].

Mobility of the Ankle

Mobility of the ankle will be assessed using a hand-held inclinometer. Since maximal ankle dorsiflexion declines with age and has been associated with fall risk [37], it may serve as a marker for frailty. It will be measured 3 times, and the average ankle dorsiflexion (in degrees) will be used for data analysis.

Mobility of the Mastricatory System

Mobility of the masticatory system will be assessed using a plastic ruler. Poor oral health has been associated to increased loss of muscle performance and health in older adults [38]. To gain further insight in the mobility of the masticatory system, maximum mouth opening and lateral deviation range of motion will be measured (in degrees) and used for data analysis.

Cardiovascular and Respiratory System

Cardiorespiratory fitness will be assessed by an incremental cardiopulmonary exercise test up to maximal exertion in upright position on an electronically braked cycle ergometer (Lode Corival Rehab, Lode BV, Groningen, the Netherlands). Measuring maximal oxygen uptake using respiratory gas analysis during an incremental cardiopulmonary exercise test up to maximal exertion is considered the gold standard for assessing cardiorespiratory fitness by the WHO [39] and others [40]. It has been proposed as an indicator to operationalize the vitality domain of intrinsic capacity [41] and can distinguish frail from non-frail elderly [42]. Before commencing the maximal cardiopulmonary exercise test, forced vital capacity and forced expiratory volume in one s will be obtained from maximal flow-volume curves according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) standards [43]. During the cardiopulmonary exercise test, participants breath through a facemask

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(Hans Rudolph, Kansas City, MO, USA) connected to an ergospirometry system (Metalyzer 3B, Cortex, Leipzig, Germany). Heart rate will be measured by continuous twelve-lead electrocardiography. The maximal cardiopulmonary exercise test allows to generate the following cardiorespiratory outcomes measures at peak exercise: oxygen uptake (L/min or mL/kg/min), work rate (W), respiratory exchange ratio, heart rate (beats/min), oxygen pulse (mL/beat), minute ventilation (L), breathing reserve (%), tidal volume (L), breathing frequency (breaths/min), and peripherally measured oxygen saturation (%). Furthermore, the ventilatory anaerobic threshold (first ventilatory threshold), the respiratory compensation point (second ventilatory threshold), the relationship between the minute ventilation and oxygen uptake up to the ventilatory anaerobic threshold (VE/VO_2-slope), the relationship between the minute ventilation and carbon dioxide production up to the respiratory compensation point (VE/VCO_2-slope), oxygen uptake efficiency slope (OUES), oxygen uptake efficiency plateau (OUEP), and efficiency of work ($\Delta VO_{2peak}/WR_{peak}$) will be determined. Blood pressure response and heart rate recovery will also be assessed.

Sensory System

Center of pressure, postural control, and static balance will be assessed using an AccuGait-Optimized (ACG-O) force platform (502 × 502 × 45 millimeter, Advanced Mechanical Technology Inc., Watertown, MA, USA). Balance performance has been utilized to evaluate the locomotion domain of intrinsic capacity [44] and is associated with all-cause mortality [45]. Outcome measures are anterior-posterior and medial-lateral displacement (cm) and mean velocity (cm/s) of the center of pressure, as well as a 95% predicted ellipse area (cm^2).

Immune System

Biomarkers reflecting low-grade inflammation and immunosenescence will be measured from blood samples obtained by a qualified study nurse via peripheral venipuncture. Aging of the immune system is characterized by elevated circulating inflammatory mediators which indicate a chronic low-grade inflammatory profile [46]. Due to immunosenescence, older persons show reduced immunization following vaccination, are more susceptible for infections, and show an impaired recovery following infection which is probably related to a deregulated inflammatory response [47, 48]. The exact panel of biomarkers reflecting low-grade inflammation and immunosenescence is described in online supplementary File 3. Analyses will be performed by the Frailty and Resilience in Ageing research group, Vrije Universiteit Brussel (Brussel, Belgium), or at the myolab laboratory at the Vrije Universiteit Amsterdam (Amsterdam, the Netherlands).

Uro-Gynecological System

Transperineal ultrasound free flowmetry will be evaluated using the Minze NV Hospiflow uroflowmeter (Minze Health, Antwerpen, Belgium). Changes in uroflowmetry are hypothesized to be a marker of declining strength of the levator ani, a skeletal muscle that helps establish and maintain pelvic support. This manifests as a reduced flowrate and a more hesitative fluctuating flow pattern. Uroflowmetry provides insight into (obstruction of) flow, detrusor overactivity, and the possibility to open the urethra by pelvic floor muscle relaxation. It allows to quantify the peak flow (mL), maximal and average flowrate (mL/s) and voided volume (mL) in both men and women. Additionally, transabdominal ultrasound will be used to measure residual voided volume in the bladder after micturition [49], possible lift of the bladder with pelvic floor muscle contraction [50], and the enlargement of the prostate in men [51, 52].

Integrative Tests (Combining Aspects of Different Domains of Intrinsic Capacity in One Test)

Agility and Reaction Time

Agility and reaction time will be assessed by modified agility *T*-Test using a Microgate Witty SEM system (Witty SEM, Microgate, Bolzano, Italy). Intraindividual variability may represent a sensitive marker for both normal cognitive aging and early cognitive impairment. These neurocognitive parameters are sensitive to late life changes in neurological integrity and may constitute early behavioral markers for preclinical neural changes associated with cognitive decline. Additionally, agility will also be evaluated using the Ten Step test [53]. Time (s) to perform these tests will be used for data analysis.

Vertical Jump Capacity

Vertical jump capacity will be evaluated using a photoelectric cell system (OptoGait, Microgate, Bolzano, Italy). Both jump height and jump power have shown to be reduced in community-dwelling older adults with sarcopenia [54], and may therefore serve as a marker for reduced intrinsic capacity. Participants will perform three maximal attempts and the average height (cm) and peak power (W) will be recorded.

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Functional Lower Extremity Strength

Functional lower extremity strength will be assessed with the 30-s chair-stand test. Besides lower extremity strength, this test also challenges the participant's equilibrium and capacity to transfer body mass. The number of full stands within 30 seconds will be used for data analysis.

Explanatory Outcomes

Explanatory outcomes include markers that relate to functional ability and/or (neuro) physiology (see Fig. 1, blue line) that may explain the pathway through which change trajectories in intrinsic capacity can lead to frailty. Functional ability tests are assumed not to be primarily aimed at evaluating the maximal reserve capacity but rather at assessing the usual level of functioning of an individual during daily activities. Thus, the body systems assessed through intrinsic capacity measurements may differ from those represented in the explanatory outcomes.

Musculoskeletal System

Spatiotemporal Gait Characteristics

Spatiotemporal gait characteristics will be measured with the OptoGait photoelectric cell system (OptoGait, Microgate, Bolzano, Italy). Spatiotemporal gait parameters are known to deteriorate with aging and changes in some spatiotemporal gait parameters might occur before preferred walking speed drops to a critical level. Therefore, they are assumed to be a good candidate as explanatory outcome for this project. Outcome measures include several spatiotemporal step and stride characteristics such as gait speed and stride length.

Functional Mobility

Balance, sit-to-stand, and walking abilities are evaluated using the timed-up-and-go test [55]. It is highly suitable for clinical fall-risk estimation, and it can distinguish between frail and robust older adults. The time necessary to stand up from a seated position and, subsequently, walk 3 meters, turn around, walk back, and sit down again is recorded (seconds).

Articular System

Participants that indicate to suffer from knee or hip pain will be asked to rate their pain on the Western Ontario and McMaster Universities Osteoarthritis Index LK3.0 [56]. Participants that indicate to suffer from low back pain will be asked to rate the level of disability on the Quebec Back Pain Disability Scale [57, 58].

Psycho-Cognitive System

Participants that indicate to suffer from general pain will be asked to fill in the Tampa Scale for Kinesiophobia, a 17-item self-reported questionnaire on kinesiophobia [59]. Anxiety symptoms will be assessed using the Generalized Anxiety Disorder questionnaire, a 7-item self-reported questionnaire [60]. Depressive symptoms will be assessed using the Patient Health Questionnaire, a 9-item self-reported questionnaire [61]. Personality will be appraised by the Dutch HEXACO Personality Inventory [62], a questionnaire allowing to quantify 6 personality traits: integrity, emotionality, extraversion, forbearance, conscientiousness, and openness to experiences. Lastly, locus of control will be assessed using the seven-item Dutch version of the Pearlin Mastery Scale [63]. Subgroups based on the outcome of the questionnaires may be determined using existing cutoff values as described in the literature. A total sum score of each questionnaire will be utilized for statistical analysis.

Uro-Gynecological System

Urinary incontinence in men will be documented using the International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form. The severity of lower urinary tract symptoms (men) will be measured using the International Prostate Symptom Score, a 6-point scale covering voiding symptoms (e.g., hesitancy, weak stream, post-micturition dribble) and storage symptoms (e.g., urgency, frequency or nocturia) [64]. Additional questions on nocturnal enuresis will be added to the questionnaire. Erectile dysfunction complaints (men) will be measured using the International Index of Erectile Function, a questionnaire consisting of 15 questions scored on a six-point scale [65]. The NVOG questionnaire (women) will be used to obtain a standardized assessment of obstetric and gynecological history, as well as complaints related to the pregnancy and birth such as prolapse, urinary incontinence, sexual dysfunction, fear and stress, fecal incontinence, and constipation. The Vaizey incontinence score consists of 7 questions that evaluate frequency and type of stool loss, pad use, and alteration in lifestyle related to obstipation or incontinence of stool [66].

Blood Biomarkers Reflecting General Functioning of Physiological Systems

Biomarkers reflecting different physiological systems can be used to appraise the degree of homeostatic dysregulation, which is a good candidate to explain some pathways leading to frailty [67] or maintenance of robustness [68]. Relevant physiological systems and their

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biomarkers are described in online supplementary File 3. Analysis will be performed by the Frailty and Resilience in Ageing research group at the Vrije Universiteit Brussel (Brussel, Belgium) or the myolab laboratory of the Vrije Universiteit Amsterdam (Amsterdam, the Netherlands).

Other Factors Reflecting Functional Ability

Quality of life will be scored using the EuroQol 5D-3L, which is a 14-item questionnaire covering five health dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression [69]. Risk for malnutrition will be appraised using the Mini-Nutritional Assessment. Oral health will be assessed using the Oral Health Assessment Tool [70], which is a simplified version of the Brief Oral Health Examination [71], and the 14-item Oral Health Impact Profile [72]. The presence of bruxism will be assessed using the BruxScreen questionnaire [73]. Sleep quality will be appraised using the Pittsburgh Sleep Quality Index [74]. Self-perceived fatigue will be assessed by the Multidimensional Fatigue Inventory, which consists of 20 questions and allows the differentiation between five domains: mental fatigue, reduced motivation, reduced activity, physical fatigue, and total fatigue [75]. Physical activity will be quantified using the International Physical Activity Questionnaire which allows for the estimation of the subject's energy expenditure during activities of daily life (e.g., housekeeping, care-giving, gardening, leisure time) and sports over the last week [76]. Sports activities will be further detailed using the Dutch version of the Sports Activity Rating Scale [77]. To rate a participant's activity level, two additional questions will be added from the Physical Activity Assessment Tool [78].

Sample Size Calculation

Frailty incidence rates were based on the earlier reported 7.2% for the Fried phenotype over 4 years in a group of adults aged 65 years or older [13] and an overall 1-year incidence of 13% (95% confidence interval 12.2–13.9%) for the Rockwood frailty index in a group of adults aged 55 years or older, ranging from 6.2% in those aged 55–64 years to 32.2% in those aged 85+ years [79]. Since this study aims to include non-frail individuals for the longitudinal part, as determined by three distinct frailty scales, stratified over a wide age-range, a very conservative 1-year incidence of 1.5%, 3.0%, and 6.0% is estimated for respectively the age cohorts 55–59, 60–69, and 70–75 years. Taking into account a maximum of seven factors that will be entered in the logistic regression model (i.e., one summary score for each system of intrinsic capacity including the combination), 105 frailty participants will be needed after 10 years (i.e., 15 events per factor) [80]. In addition, increasing the number of participants that will develop frailty by 404, a maximum of 15 covariates can be added in the model (i.e., an additional 25% of events per covariate). Thus, after 10 years, 509 frail adults need to be identified. Considering a 1-year incidence of 1.5%, 3.0%, and 6.0% in the age cohorts 55–59, 60–69, and 70–75, respectively [13, 79], 1,600 robust participants need to be recruited. Considering a potential 15%, 20%, 25%, and 30% drop-out in the age cohorts 55–59, 60–64, 65–69, and 70–75 years, respectively, an estimated total of 2,075 non-frail adults need to be included at baseline to ensure sufficient statistical power. Based on these estimations, 2,078 non-frail participants will be recruited, stratified as follows: $n = 472$ for the age cohort 55–59 years (236 males; 236 females), $n = 500$ for the age cohort 60–64 years (250 males; 250 females), $n = 534$ for the age cohort 65–69 years (267 males; 267 females) and $n = 572$ for the age cohort 70–75 years (286 males; 286 females).

Statistical Considerations

The primary study aim will be examined using a logistic regression analysis that relates the change of various intrinsic capacity scores at 2.5-year intervals to the probability on developing frailty by the end of the study. These scores are summary scores that are obtained from sets of factors for each system of intrinsic capacity related to a predefined body system of which there are maximally 7. A confirmatory factor analysis will validate our choice of items or may result in the elimination of some. The resulting model will include all summary scores of intrinsic capacity that provide sufficient unique information on the probability of frailty, as well as those predictors that were retained as significant following a likelihood ratio test. The result will be an evaluation of how important each summary score for intrinsic capacity is for the development of frailty, conditional on other relevant information. Additional statistical analyses (e.g., latent class analysis) may potentially be explored in the future based on renewed statistical recommendations.

Complementary to the main analysis, predictive models will be used to evaluate the importance of each of the individual factors of intrinsic capacity in predicting frailty, irrespective of the body system they relate to. As such, the focus will shift from quantifying the strength of the relation between the intrinsic characteristics and the probability on frailty toward obtaining a maximum

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predictive accuracy for new data and offering an understanding on which items are most relevant for it. Item specific information on the predictive strength can be used to eliminate items too, but here based on frailty. If specific intrinsic characteristics are shown to be important, partial least squares regression analysis should show the relation between those clusters of items and the frailty score. Additionally, the data offer various opportunities to explore the mechanisms underlying the development of frailty in more detail. Even in the early and intermediate stages of the study lacking enough frail participants, the data may offer interesting insights into the structure of intrinsic capacity scores. The actual evolution of each of the factors of intrinsic capacity can, for example, be further modeled using a generalized linear mixed model, which accommodates the repeated measurement structure, so that the full conditional average evolution between the frail and the non-frail participants can be compared. A visualization of the predicted trajectories in combination with the actual observations should give a much better understanding of this evolution. Structural equation modeling will not only consider the relation between items and latent intrinsic capacity variables but will also consider the relation between these latent intrinsic capacity variables, possibly conditional on other relevant information such as participant's sex or age. The result could be the development of validated scales for intrinsic capacity. Regarding the secondary study aim, we will assess the cross-sectional associations between (pre-)frailty status and physical performance outcomes using logistic regression analysis, considering potential confounders such as sex or age. Additionally, odds ratio's and, accordingly to the distribution of the data, Pearson's r or Spearman's rho correlation will be used.

Discussion

The primary aim of the AMCOHF study was to investigate whether time-related trajectories of intrinsic capacity across six physiological systems can predict maintenance of robustness (i.e., healthy aging) or the onset of frailty. The secondary aim was to investigate cross-sectional associations between biomarkers of intrinsic capacity or functional ability (Fig. 1). By doing so, (pre-)frailty can be recognized at an early stage and personalized interventions can be developed aimed at individuals at risk of developing frailty. By preventing frailty, the individual's quality of life can be maintained, and societal health costs may be reduced. As such, this study addresses the increasing challenges associated with the aging global population.

In contrast with previous cohort studies, this study focusses on the investigation of early markers of a declining intrinsic capacity or the determinants of (very) early stages of (pre-)frailty in a younger aging population (55 years and older). The focus of this study will therefore be on the physical aspects of intrinsic capacity and frailty, rather than the influence of environmental factors. Upon inclusion, participants will be non-frail according to three distinct frailty scales (i.e., Fried phenotype, Rockwood frailty index, and Groningen frailty Indicator). This is in contrast to other cohort studies, that either included participants at an higher age [81–83], did not evaluate a robust, community-dwelling population [84], or solely explored the relationship between frailty and specific domains such as mental frailty [85] or nutritional status [86] rather than a comprehensive objective physical evaluation. The latter is of importance because it has been described that early stages of frailty may manifest as early as at middle age [87], as well as the fact that age is recognized as one of the determinants influencing an individual's likelihood of returning to a state of robustness when exposed to a lifestyle intervention [88]. Accordingly, identification of (pre-)frailty at an early stage, before clinically evident deficits emerge, may enable tailored interventions for individuals in the more robust or pre-frail part on the continuum to potentially mitigate the exacerbation of intrinsic capacity. Furthermore, the exploration of markers that can identify vulnerability at an earlier stage may help reveal the exact mechanisms responsible for development of (pre-)frailty, which currently remain to be fully understood [89].

The strengths of this project encompass a thorough assessment of both the presence of (pre-)frailty (utilizing three distinct, well described frailty models), the intrinsic capacity, and functional ability of different physical domains (i.e., musculoskeletal, articular, cardiorespiratory, sensory, immune, and uro-gynecological system) using probability sampling ensuring a study sample that accurately reflects of Amersfoort, which is considered to be a very representative city in the Netherlands. Longitudinal analysis will allow development of prospective prediction models for changes of intrinsic capacity over time and its association with (pre-)frailty. Subsequently, potentially preventive interventions improving intrinsic capacity or frailty status can be developed. Moreover, employing convenience sampling in what is considered a very representative sample area in The Netherlands, together with a substantial sample size

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(>2,000 participants) will generate a representative sample of a community-dwelling population for The Netherlands. Cross-sectional analysis may be prone to confounding effects of for example sex, age, and several demographic and socioeconomic factors. Although regression analysis as included in the study protocol may adjust for well-established confounding effects, the cross-sectional analyses must be interpreted cautiously.

In conclusion, the AMCOHF study is a prospective cohort study with a 10-year follow-up which will generate an extensive, longitudinal dataset consisting of time-related trajectories of biomarkers for intrinsic capacity across six physiological domains. Based on this dataset, maintenance of robustness (i.e., healthy ageing) or the onset of frailty can be predicted in older adults. By doing so, the outcomes of this study contribute to developing targeted preventive interventions to promote healthy aging, thereby enhancing quality of life for individuals at risk of developing adverse health outcomes and decrease the burden on healthcare systems.

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Statement of Ethics

This study was reviewed and approved by the Ethics Committee of Zuyderland Medical Centre Heerlen (NL 70141.096.19, v1.0 on 19 September 2019). Written informed consent was provided by participants prior to enrolment in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.P., A.W., B.B., D.B., I.B., P.R., and W.S. contributed to the design of the study protocol; A.P. acted as principal investigator; A.P., A.W., B.B., I.B., and P.R. collaborated in the election of tools and ethical issues; I.B. wrote the statistical approach of the protocol. D.H. and S.C. are responsible for data acquisition; P.S. is responsible for data management. D.H. formatted the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to information that could compromise the privacy of research participants. Upon reasonable request, data sharing will be considered by Prof. Dr. Annelies Pool-Goudzwaard (a.pool@somt.nl).

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