Mechanisms of Ageing and Development

The Aging Imageomics Study Rationale, design and baseline characteristics of the study population

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Corresponding Author:	Josep Puig, MD, PhD SPAIN
First Author:	Josep Puig, MD, PhD
Order of Authors:	Josep Puig, MD, PhD
	Carles Biarnes
	Salvador Pedraza
	Joan C. Vilanova
	Reinald Pamplona
	José Manuel Fernández-Real
	Ramon Brugada
	Rafel Ramos
	Gabriel Coll-de-Tuero
	Laia Calvo-Perxas
	Joaquin Serena
	Lluis Ramió-Torrentà
	Jordi Gich
	Lluis Gallart
	Manel Portero-Otin
	Angel Alberich-Bayarri
	Ana Jimenez-Pastor
	Eduardo Camacho-Ramos
	Victor Pineda
	Raquel Font
	Anna Prats-Puig
	Mariano-Luis Gacto
	Gustavo Deco
	Anira Escrichs
	Bonaventura Clotet
	Roger Paredes
	Eugenia Negredo
	Bruno Triaire
	Manuel Rodríguez

	Rafael Coronado
	Wolter de Graaf
	Anca Mitulescu
	Pepus Daunis-i-Estadella
	Santiago Thió-Henestrosa
	Felip Miralles
	Vicent Ribas-Ripoll
	Manel Puig-Domingo
	Marco Essig
	Chase R. Figley
	Teresa D. Figley
	Benedict Albensi
	Ahmed Ashraf
	Johan HC Reiber
	Giovanni Schifitto
	Md Nasir Uddin
	Carlos Leiva-Salinas
	Max Wintermark
	Joan Vilalta-Franch
	Jordi Barretina
	Josep Garre-Olmo
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Suggested Reviewers:	Henry Völzke voelzke@uni-greifswald.de One of the main investigators of the German National Cohort MRI Study. Huge expertise on this topic.
	Fabian Bamberg fabian.bamberg@med.uni-muenchen.de Good expertise on this topic.
	Katrin Hegenscheid katrin.hegenscheid@uni-greifswald.de
	Xi Zhang yliu@nlpr.ia.ac.cn
	Taeho Jo tjo@iu.edu
Opposed Reviewers:	

Dear Prof. Efstathios Gonos;

Following your recommendation in a previous mail on March 1, 2019 please find enclosed our manuscript entitled *'The Aging Imageomics Study: Rationale, design and baseline characteristics of the study population'* which we would like to be considered for publication in your journal. We think that our manuscript might be of interest to the Mechanisms of Ageing and Development.

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Looking forward to hearing from you and thank you in advance for your kind attention.

Sincerely,

Josep Puig, MD PhD

Biomedical Research Institute (IDIBGI), University Hospital Dr Josep Trueta, Girona, Spain.
Institut de Diagnostic per la Imatge (IDI), Girona, Spain.
University of Manitoba, Health Sciences Center, Winnipeg, Canada
Email: jpuigmd@gmail.com

Highlights

- This population-based study aims to identify biomarkers of aging.
- Structural and functional whole-body MRI was used to evaluate multiple parameters.
- Ultrasonography was used to determine carotid stenosis.
- Data will be analyzed with cross-sectional approach.

Abstract

Biomarkers of aging are urgently needed to identify individuals at high risk of developing age-associated disease or disability. Growing evidence from population-based studies points to whole-body magnetic resonance imaging's (MRI) enormous potential for quantifying subclinical disease burden and for assessing changes that occur with aging in all organ systems. The Aging Imageomics Study aims to identify biomarkers of human aging by analyzing imaging, biopsychosocial, cardiovascular, metabolomic, lipidomic, and microbiomic variables. This study recruited 1030 participants aged ≥ 50 years (mean 67, range 50-96 years) that underwent structural and functional MRI to evaluate the brain, large blood vessels, heart, abdominal organs, fat, spine, musculoskeletal system and ultrasonography to assess carotid intima-media thickness and plaques. Patients were notified of incidental findings detected by a certified radiologist when necessary. Extensive data were also collected on anthropometrics, demographics, health history, neuropsychology, employment, income, family status, exposure to air pollution and cardiovascular status. In addition, several types of samples were gathered to allow for microbiome, metabolomic and lipidomic profiling. Using big data techniques to analyze all the data points from biological phenotyping together with health records and lifestyle measures, we aim to cultivate a deeper understanding about various biological factors (and combinations thereof) that underlie healthy and unhealthy aging.

The Aging Imageomics Study: Rationale, design and baseline characteristics of the study population

Josep Puig[1,2,3,4], Carles Biarnes[1,2], Salvador Pedraza[1,2,3], Joan C. Vilanova[1,23], Reinald Pamplona[5], José Manuel Fernández-Real[2,3,6], Ramon Brugada[2,3,7], Rafel Ramos[2,3,8,9], Gabriel Coll-de-Tuero[10,11,12], Laia Calvo-Perxas[2], Joaquin Serena[2,3,13], Lluis Ramió-Torrentà[2,3,13], Jordi Gich[2,13], Lluis Gallart[14], Manel Portero-Otin[5], Angel Alberich-Bayarri[15], Ana Jimenez-Pastor[15], Eduardo Camacho-Ramos[15], Victor Pineda[1,2], Raquel Font[16], Anna Prats-Puig[16], Mariano-Luis Gacto[16], Gustavo Deco[17,18], Anira Escrichs[17], Bonaventura Clotet[19], Roger Paredes[19], Eugenia Negredo[20], Bruno Triaire[21], Manuel Rodríguez[21], Rafael Coronado[21], Wolter de Graaf[21], Anca Mitulescu[22], Pepus Daunis-i-Estadella[22], Santiago Thió-Henestrosa[22], Felip Miralles[24], Vicent Ribas-Ripoll[24], Manel Puig-Domingo[25], Marco Essig[4], Chase R. Figley[4], Teresa D. Figley[4], Benedict Albensi[26], Ahmed Ashraf[27], Johan HC Reiber[28], Giovanni Schifitto[29], Md Nasir Uddin[29], Carlos Leiva-Salinas[30], Max Wintermark[31], Joan Vilalta-Franch[2,3,32], Jordi Barretina[2], Josep Garre-Olmo[2,3,32]

(1) Department of Radiology (IDI), Hospital Universitari de Girona Dr Josep Trueta. Girona, Spain

(2) Girona Biomedical Research Institute (IDIBGI), Hospital Universitari de Girona Dr Josep Trueta. Girona, Spain

(3) Department of Medical Sciences, School of Medicine, University of Girona. Girona, Spain

(4) Department of Radiology, University of Manitoba. Winnipeg, Canada

(5) Department of Experimental Medicine, Faculty of Medicine, University of Lleida-IRBLleida. Lleida, Spain

(6) Department of Diabetes, Endocrinology and Nutrition, IDIBGI, Hospital Universitari de Girona Dr Josep Trueta, and CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn). Girona, Spain

(7) Cardiovascular Genetics Center, IDIBGI. Girona, Spain

(8) Vascular Health Research Group of Girona (ISV-Girona), Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol). Girona, Spain

(9) Primary Care Services, Catalan Institute of Health (ICS). Girona, Spain

(10) Research Support Unit, University Institute of Research in Primary Care JordiGol (IdIAPGol). Girona, Spain

(11) Research Group on Statistics, Econometrics and Health (GRECS), University of Girona. Girona, Spain

(12) CIBER of Epidemiology and Public Health (CIBERESP). Madrid, Spain

(13) Department of Neurology, Hospital Universitari de Girona Dr Josep Trueta. Girona, Spain

(14) Biobanc, Girona Biomedical Research Institute (IDIBGI). Girona, Spain

(15) Quantitative Imaging Biomarkers in Medicine (QUIBIM). Valencia, Spain.

(16) Department of Physical Therapy, EUSES University School, Salt, Spain.

(17) Center for Brain and Cognition, Universitat Pompeu Fabra. Barcelona, Spain

(18) ICREA Institut Catala de Recerca i Estudis Avançats. Barcelona, Spain

(19) Servei de Malalties Infeccioses; Fundació Irsicaixa; Hospital Universitari Germans Trias i Pujol, Badalona, Spain. Universitat de Vic-Universitat Central de Catalunya (UVIC-UCC), Universitat Autònoma de Barcelona.

(20) Servei de Malalties Infeccioses; Fundacio de la Lluita contra la sida; Hospital Universitari Germans Trias i Pujol, Badalona, Spain. Universitat de Vic-Universitat Central de Catalunya (UVIC-UCC), Universitat Autònoma de Barcelona.

(21) Canon Medical Systems

(22) Olea Medical. La Ciotat, Marseille, France.

(23) Department of Computer Science, Applied Mathematics and Statistics, University of Girona. Girona, Spain

(24) EURECAT, Technological Center of Catalonia, Barcelona, Catalonia, Spain

(25) Department of Endocrinology and Nutrition, Hospital Universitari Germans Trias i Pujol (UAB) Badalona, Barcelona, Spain

(26) Division of Neurodegenerative Disorders, St. Boniface Hospital Albrechtsen Research Centre. Winnipeg, MB, Canada

(27) Manitoba Learning and AI Research (MLAIR), University of Manitoba
(28) Department of Radiology, Division of Image Processing, Leiden University Medical Center, Leiden, The Netherlands
(29) Department of Neurology, University of Rochester, Rochester, NY, USA
(30) Department of Radiology, University of Missouri, Columbia, MO 65212, USA
(31) Department of Radiology, Neuroradiology Section, Stanford University School of Medicine, Stanford, USA
(32) Institut d'Assistència Sanitària. Salt, Spain

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Corresponding authors

Josep Puig MD PhD
Girona Biomedical Research Institute (IDIBGI)
Hospital Universitari de Girona Dr Josep Trueta
Girona, Spain

Rafel Ramos MD PhD
Vascular Health Research Group of Girona (ISV-Girona)
Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol)
Girona, Spain

Highlights:

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- Structural and functional whole-body MRI was used to evaluate multiple parameters.
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Abstract

Biomarkers of aging are urgently needed to identify individuals at high risk of developing age-associated disease or disability. Growing evidence from population-based studies points to whole-body magnetic resonance imaging's (MRI) enormous potential for quantifying subclinical disease burden and for assessing changes that occur with aging in all organ systems. The Aging Imageomics Study aims to identify biomarkers of human aging by analyzing imaging, biopsychosocial, cardiovascular, metabolomic, lipidomic, and microbiomic variables. This study recruited 1030 participants aged ≥ 50 years (mean 67, range 50-96 years) that underwent structural and functional MRI to evaluate the brain, large blood vessels, heart, abdominal organs, fat, spine, musculoskeletal system and ultrasonography to assess carotid intima-media thickness and plaques. Patients were notified of incidental findings detected by a certified radiologist when necessary. Extensive data were also collected on anthropometrics, demographics, health history, neuropsychology, employment, income, family status, exposure to air pollution and cardiovascular status. In addition, several types of samples were gathered to allow for microbiome, metabolomic and lipidomic profiling. Using big data techniques to analyze all the data points from biological phenotyping together with health records and lifestyle measures, we aim to cultivate a deeper understanding about various biological factors (and combinations thereof) that underlie healthy and unhealthy aging.

1. Introduction

Aging is a complex process characterized by a time-dependent decline in functional capacity and stress at different biological levels, associated with increased risk of morbidity and mortality [1]. The rate of aging in humans, varies widely due to genetic heterogeneity and environmental factors. The concept of biological age, unlike chronological age, takes these factors into account [2]. Quantifiable age-related changes in body structure or function that could serve as measures of biological age are termed biomarkers of aging [3]. By definition, these biomarkers predict the trajectory of biological aging, thus the onset of age-related diseases. As age is a major risk factor for many degenerative diseases, these biomarkers could help identify individuals at high risk of developing age-associated diseases or disabilities [3,4]. To date, most biomarkers used are not related to the aging process, so they cannot be considered true biomarkers of biological aging [5].

Radiomics aims at developing imaging biomarkers by extracting information about quantitative features from different medical imaging modalities in population-based studies [6-8]. The choice of imaging modality depends primarily on the research focus, although other aspects such as reproducibility, availability, costs, general legal considerations, or risks are also important. Computed tomography, used to develop the first radiomic biomarkers in oncological studies, is limited by its use of ionizing radiation [7]. Ultrasonography is inexpensive, convenient, and totally noninvasive, but has limited reproducibility. Nevertheless, ultrasonography measurement of carotid artery intima-media thickness is an established imaging biomarker for overall atherosclerotic burden [9]. Magnetic resonance imaging (MRI) is being used increasingly in population-based studies because it provides high tissue contrast without using ionizing radiation [10,11]. MRI has generated substantial scientific knowledge about the human brain in population studies, such as the UK Biobank prospective epidemiological study [12], the Rotterdam Study [13], the Three-City Dijon Study [14] or the 1000BRAINS study [15]. MRI is also a routine clinical standard for examining the spine, cardiac structures and function, large blood vessels, and abdominal organs [16]. Technological advances such as parallel acquisition technologies and continuous table feed have made it possible to examine the entire body in approximately 1 hour. As a result, it is now feasible to incorporate whole-body MRI examinations into the design of population-based studies to acquire multiple datasets that, taken together, provide a holistic view of the human body [16]. These studies can be used to characterize in an integrated manner the morphological and functional alterations of different organ systems, increasing our understanding of diseases in the community and providing knowledge about risk factors and outcomes.

Population-based cohort studies generally monitor participants through follow-up examinations. Two broad approaches are used to explore imaging datasets. Cross-sectional approaches correlate baseline image-based phenotypic features with non-imaging parameters, while longitudinal approaches correlate phenotypic features at different time points with clinical outcomes to determine their prognostic relevance. The inclusion of a large number of participants helps ensure adequate power to identify and verify associations [17,18]. Radiomics can reveal subtle microstructural alterations in tissues by analyzing variables such as volume, intensity, texture, and shape of neighboring voxels [6]. Machine learning can be used to determine which extracted image-based features and combinations of features are associated with different outcomes [7]. Radiomics allows the development of image-based systems for risk stratification that promise to be useful for personalized medicine and prevention [6,8].

The multidisciplinary and multi-institutional Aging Imageomics Study set out to create a large repository of imaging datasets from advanced structural and functional whole-body MRI to enable the analysis of associations between imaging biomarkers and biopsychosocial parameters, cardiovascular indexes, metabolomics, lipidomics, microbiomics, frailty, and other age-related variables. Analyzing what is normal

and abnormal during aging will allow to establish new reference ranges for variables related to aging. The ultimate goal is to combine data from whole-body imaging with data from other fields to develop a panel of biomarkers of biological aging that can identify individuals at high risk of developing age-associated diseases or disabilities. Here we report on the rationale, study design and logistics, technical background, and baseline characteristics of participants in the Aging Imageomics Study.

2. Methods

2.1 Aging Imageomics consortium. A consortium of 14 partners was formed to enable an interdisciplinary approach to establishing biomarkers of biological aging in humans. The different partners have expertise in clinical radiology, epidemiology, primary care, bioengineering, neuroscience, physiology, endocrinology, cardiology, neurology, psychology, physiotherapy, cell biology, and human genetics.

2.2 Study design, population and sample recruitment. The Aging Imageomics Study is an observational study that includes participants from two ongoing cohort studies of individuals residing in the province of Girona (Northeast Catalonia, Spain): the Maturity and Satisfactory Ageing in Girona study (MESGI50 study) [19] and the Improving interMediAte RisK management study (MARK study) [20]. The MESGI50 study is a population-based cohort linked to the Survey of Health, Ageing and Retirement in Europe project (SHARE), which included a representative sample of the population of the province of Girona aged ≥50 years [21]. The MARK study included a random sample of patients aged 35 to 74 with intermediate cardiovascular risk recruited in public primary care centers in the province of Girona [20]. Members of both cohorts were contacted by telephone to be invited to participate in the Aging Imageomics Study. During this standardized telephone call, potential candidates were informed about the study and were encouraged to request more detailed information if they so desired. Subjects that agreed to participate were asked to choose a date and time to complete the enrollment procedures. To be eligible for the study, potential participants had to meet the following criteria: age ≥50 years, dwelling in the community (i.e., not institutionalized), no history of infection during the last 15 days, no contraindications for MRI (electronic cardiac implants, cochlear implants, incompatible prosthetic heart valves, incompatible vascular clips, metallic foreign bodies, or claustrophobia), and consent to be informed of potential incidental findings.

2.3 Study procedures and ethical aspects. The Aging Imageomics Study protocol was approved by the ethics committee of Dr. Josep Trueta University Hospital. Data were collected between 14 November 2017 and 19 June 2019. Candidates were scheduled for two appointments. The first visit consisted of three parts. First, candidates were informed in detail about the study aims and characteristics. Second, candidates who provided informed written consent were assigned a personal identification code and then underwent whole body-MRI and carotid ultrasound studies. Third, participants were scheduled for the next examination (15 days later), and a research assistant provided them with a kit and detailed step-by-step instructions for collecting and transporting morning urine and stool samples to be presented on the day of the following visit. The second visit consisted of three parts. First, morning urine and stool samples were collected from participants, and blood samples were drawn between 8:00 a.m. and 10:00 a.m. After basic processing, specimens were transported to the IDIBGI's Biobank central laboratory by cold chain and were frozen at −80°C for future use. Second, participants underwent an anthropometric examination, a clinical interview, and a cardiovascular examination by a trained nursing team. Third, participants completed standardized tests and questionnaires administered by the nursing team and trained psychology students to measure cognitive-, mood-, and personality-related variables. Participants from the MARK study were also invited to further collaborate by using a device to measure ambient air pollution in the 2 weeks between visits. Table 1 lists the parameters

assessed in each domain and the instruments used to measure them. At the end of the study, participants received a detailed report with the main findings of the MRI, carotid ultrasound, electrocardiogram, and blood test.

2.4 Whole-body MRI acquisition protocol. MRI examinations were performed on a mobile 1.5T scanner (Vantage Elan, Toshiba Medical Systems at the beginning of the study, now from Canon Medical Systems) using a head coil and two body coils to cover the entire body, with a maximum gradient amplitude of 35mT/m-1. Table 2 summarizes the MRI protocol. In brief, the acquisition protocol included (a) coronal T2-weighted short-tau inversion recovery (STIR) sequences from the head to middle third of the thighs; (b) sagittal T2-weighted turbo spin-echo (TSE) of the entire spine; (c) short-axis 3D steady-state free precession (SSFP) sequences of the myocardium; (d) 2D phase-contrast magnetic resonance angiography (MRA) of the aortic arch; (e) time-of-flight MRA of the abdominal aorta; (f) coronal 4p Dixon acquisition from the liver to the symphysis pubis; and (g) diffusion tensor imaging (DTI) using spinecho echo-planar imaging (SE-EPI), resting-state functional MRI (rs-fMRI) using gradient echo EPI, R2* mapping using multiecho gradient echo sequence, high resolution 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) and 2D T2-weighted fluid attenuated inversion recovery (FLAIR) sequences of the brain.The complete whole-body MRI protocol took about 50 minutes. Figure 1 is a graphic representation of each of the acquisitions; Figure 2 shows the imaging variables collected in each body region.

2.5 Quality control of the MRI examinations. The four medical imaging technologists involved in MRI acquisition completed a one-month training program on the imaging platform provided by the vendor and further training. That additional training included theobservation and hands-on whole-body MRI acquisition in different MRI units at several university institutions before starting the project. These technologists checked the quality of the images obtained (up to about 25% of images during the initial pilot phase). A dedicated MRI physicist and a radiologist (13 years' experience) reviewed subsets of the images to ensure acquisition standards were met. The MRI physicist supervised regular MR phantom measurements for quality control.

2.6 Carotid ultrasound study. A radiologist (13 years' experience) performed all carotid ultrasound examinations on a Siemens Acuson S2000 system (Mochida Siemens Medical System; Tokyo, Japan) system with a 7.5 mHz linear array transducer, measuring carotid stenosis percentage on B-mode (common carotid artery and internal carotid artery). After capturing a transverse scan of the most stenotic segment, the original diameter and residual diameter were measured using electronic calipers. The residual diameter was defined as the shortest diameter of the residual lumen at the most stenotic carotid segment. On the other hand, the original diameter was defined as the measured diameter from the outer media to the outer media of the diseased artery on the same plane and at same direction with the residual diameter. This value was calculated using the following equation: Carotid stenosis percentage = (1-[residual diameter/original diameter]) x 100, as previously described [22-24]. The carotid intima-media thickness and plaques will be measured according to the Mannheim Consensus [25].

2.7 Data collection and storage. Two databases were used. The participant's name and study identification code were inputted with individual passwords in an encrypted database. All data from questionnaires and medical devices were entered in another anonymous electronic database using the personal study identification code. A data manager checked the entries for completeness and plausibility and amended incomplete or implausible data when possible. Further data from biological samples and MRI postprocessing were linked through the personal study identification code. Encrypted backups of both databases were periodically stored on two external hard disks kept at different sites.

***2.8 Ongoing data analysis*.** To extract biomarkers of aging and construct a healthy aging model, correlation analyses will be used to identify relationships between different measurements and machine learning methods will be used to estimate biological age from the imaging data and other measurements. Neural networks and decision/regression trees will be applied to find more local relationships within the data. Besides, dimensionality reduction techniques (e.g., principal component analysis) are needed to reduce the number of measurements required and variance in the predictions. Machine learning tools make it possible to combine diverse predictors to generate models with lower variance. Data visualization techniques and interactive methods such as visual clustering models might further help uncover unexpected relationships and reduce variance in the models by improving the characterization of subgroups. One end-product will be the creation of a structural and functional imaging atlas to model the aging of organs.

2.9 Incidental findings. Potentially clinically relevant abnormalities discovered on examinations done for unrelated purposes are referred to as incidental findings. Two certified radiologists with 25 and 13 years' experience reviewed all whole-body MRI and carotid ultrasound images for incidental findings. Following the approach used in the German National Cohort [27], incidental findings were classified as "notification urgently required", "notification required", and "notification not required", based on the likelihood of false-positive findings, clinical consequences of the finding, and potential negative consequences for the participant if unaware of the finding.

2.10 Statistical analysis. For participants' demographic and health characteristics, qualitative variables are expressed as absolute and relative frequencies and quantitative variables as measures of central tendency and dispersion. For bivariate comparisons of these variables between cohorts, chi-square tests, Mann-Whitney U tests, or Kruskall-Wallis tests are used. To assess the effect size for differences between proportions, Cramer's V was applied, the value of which depends on the degrees of freedom (df=1; small [0.10], medium [0.30], large [0.50]; df=2; small [≤0.07], medium [0.21], large [≥0.35]; df3=small [≤0.06], medium [0.17], large [≥0.29]). The effect size for differences between two means was assessed by Cohen's *d* (small=0.2; medium=0.5; large=0.8) [28]. Ninety-five percent confidence intervals (95% CIs) for incidental finding prevalence rates were calculated assuming a Poisson distribution. For all analyses, we used STATA 12 SE (STATA Corp. College Station, TX, USA) and a two-tailed alpha level for statistical significance of 0.05.

3. Results

The Aging Imageomics Study finished the recruitment of participants by June 2019. All participants in the MARK and MESGI studies (n=2181) were considered potential candidates; 1741 met the inclusion criteria. Figure 2 is a flowchart showing the process of inclusion in the study. The final study population consisted of 1030 participants [mean age, 67.1±7.3 years; range, 50-98 years; 54.1% male]; 567 (55.0%) were recruited from the MARK study cohort (57.1% of all candidates in that study) and 463 (45.0%) from the MESGI study cohort (61.8% of all candidates from that study). Education level was classified as low in 57.3%, intermediate in 30.7%, and high in 12.0%; 71.3% were retired, 23.1% employed, and 5.6% unemployed or on sick leave. These variables differed slightly between women and men: educational level was slightly higher in men, and a slightly higher proportion of women were unemployed or sick (Table 3).

Table 4 summarizes participants' anthropometric characteristics, vascular system health status, medical history, basic biochemistry results, and carotid ultrasound examination results, stratified by gender. As expected, anthropometric characteristics (weight, height, waist circumference, heart rate, and blood pressure) differed between women and men. A greater percentage of women had a personal history of depressive episodes (42.3% vs. 18% in men). Differences with moderate effect size were observed in some biochemistry

results (HDL cholesterol, creatinine, sodium, potassium, and serum ferritin). Severe carotid stenosis was more common in men (13.1% vs. 6.3% in women).

Table 5 reports lifestyle indicators (e.g., Mediterranean diet adherence, physical activity pattern), personality traits, affective status, and neuropsychological examination results, stratified by gender. A greater proportion of women had the personality trait "neuroticism" and depressive symptoms. Women outperformed men in memory-related neuropsychological tasks.

Supplemental tables S1 to S3 report the demographic, social, and clinical characteristics of the participants, stratified by the cohort of origin (MARK vs. MESGI). As expected, participants from the two cohorts differed in some clinical and demographic characteristics. Although MARK study participants were recruited from primary care centers on a random basis, only those with intermediate cardiovascular risk were candidates; consequently, characteristics related to cardiovascular health status differed between the two cohorts. Compared to participants recruited from the MESGI cohort, those recruited from the MARK study had higher weight (77.8 kg vs. 73.1 kg), lower HDL cholesterol (49.3 mg/dL vs. 57.6 mg/dL), and higher serum glucose (116.4 mg/dL vs. 104.8 mg/dL) and blood glycated hemoglobin (6.1% vs. 5.7%). Lifestyle and personality characteristics in participants from the two cohorts were similar, but participants coming from the MESGI study outperformed those coming from the MARK study in all the neuropsychological tasks.

The prevalence of incidental findings on whole-body MRI requiring notification was 4.44% (96% CI = 3.28-5.91); the most frequent incidental findings requiring notification were located in the brain (1.35%), followed by the abdomen (1.16%), spine (0.77%), thorax (0.58%), and genitourinary regions (0.58%). A more detailed classification of incidental findings is provided in Table S4.

4. Discussion

The Aging Imageomics Study used multiple imaging modalities to acquire data about the brain, spine, abdomen, heart, musculoskeletal system, and large blood vessels with sufficient statistical power for reliable assessment of associations between imaging phenotype measures and a wide range of parameters related to aging. By analyzing these associations, we aim to develop a panel of combined biomarkers of aging that will be useful for characterizing biological age and identifying individuals at high risk of developing age-associated diseases or disabilities. Participants were drawn from two population-based cohorts, one representative of the general population and another comprising individuals with intermediate cardiovascular risk. Comparing these two cohorts will help in identifying and validating potential biomarkers of aging.

4.1 'Biomarkers of aging' and 'biological age score'. The rate of aging, measured as the decline of functional capacity and stress resistance, differs significantly among individuals, thus giving rise to differences between biological and chronological age in some of them [2]. Classically, the rate of aging of a given population has been quantified by calculating the slope of the mortality curve. However, in this approach, it is only possible to determine individuals' biological age at a given point in their lifetime retrospectively (i.e., after they have died),thus precluding reliable assessment of aging, risk prediction of the onset of morbidity, and residual lifetime for a given living individual. One strategy to overcome this problem is to identify age-related changes in the body (biomarkers of aging) that could serve as surrogate measures of biological age and predict the onset of age-related diseases and/or residual lifetime more accurately than chronological age [3,5].

The American Federation for Aging Research has proposed that biomarkers of aging should fulfill the following criteria [29]: (1) They must predict the rate of aging, signaling an individuals' exact point in their total lifespan better than chronological age; (2) Rather than focusing on the effects of disease, they must focus on basic processes underlying the process of aging; (3) They must be noninvasive (e.g., imaging or blood tests) to allow repeated testing; (4) They must work in laboratory animals as well as in humans so that they can be tested in animals before being validated in humans.

In recent years, various biomarkers of aging have been proposed, but all have shown considerable variability in cross-sectional studies [2-5,29,30]. No single measurement has proven capable of accurately determining biological age. However, the process of aging is complex, involving multiple causes and multiple systems, so a panel of biomarkers reflecting this complexity is likely to measure biological age better than any single marker alone. Thus, the Aging Imageomics Study aims to devise a "biological aging score" by using multivariate analysis and modern Machine Learning techniques to optimize the weighting of predictors from imaging (radiomics) and other tests (other -omics).

4.2 Precision medicine, radiomics, and aging phenotyping. Artificial intelligence techniques are enabling progress toward precision medicine that takes differences among individuals into account to improve the prevention and treatment of disease [31]. Precision medicine depends on the availability of knowledge that allows differentiation among individuals. Determining a given individual's state of health requires combining data about many factors beyond chronological age, such as genetic, microbiomic, clinical, psychosocial, and lifestyle-related characteristics [32]. In aging, precision medicine should aim to classify individuals into subpopulations with different burdens of subclinical disease or susceptibilities to a disease according to observable phenotypes that reflect both genomic variation and accumulated lifestyle and environmental exposures that impact biological function [33]. Genomics has been a useful approach for finding useful biomarkers for precision medicine, but non-genetic factors account for 70% to 90% of the phenotypic variation in chronic and age-related diseases [34]. Thus, effective and efficient approaches incorporating data from noninvasive medical tests are necessary to better define phenotypes of health and aging. National and international efforts such as the Aging Imageomics Study seek to collect a wide array of individual data, including genomic, proteomic, microbiomic, and/or imaging data.

Computer analysis of medical images is a promising source of information for precision medicine initiatives. Medical images contain dense, objective data that can be useful for phenotyping [35]. Radiomics uses high-throughput computational techniques to analyze data from medical images, considering both "traditional" image analysis with human-defined image features and "deep learning", where computer algorithms automatically discover features that are useful for specific purposes through a process of optimization incorporating data from different levels [36]. Deep Learning methods can potentially discover aging biomarkers without any human input, conceivably generating truly unexpected discoveries. Including more variables and more data is likely to better reflect underlying aging process and improve phenotyping [37-39]. Although radiomics-based phenotyping has unmatched potential, its inherent complexity and lack of firmly established standards can lead to methodological variability and consequent risk of irreproducible results. It can be difficult to incorporate multiparametric data. Moreover, the large number of features extracted increases the risk of overfitting the data, so one of the first steps in analyzing radiomics data is to reduce the number of dimensions of the parameters to allow more robust and reliable analyses of a given dataset. One strategy is to select features based on technical qualities such as reproducibility across different settings or readers. Although the research community agrees that radiomics techniques need to be validated to ensure the repeatability, reproducibility, robustness, and accuracy of the biomarkers derived from them as recommended

by the Quantitative Imaging Biomarkers Alliance, there is no consensus about the best approach to data dimensionality reduction [40-42].

***4.3 MRI and radiomics*.** Extracting radiomics features from multimodal MRI sequences promises to advance aging phenotyping. MRI enables examiner-independent visualization of morphologic and functional processes without the need for contrast agents or ionizing radiation, providing simultaneous coverage of major organ systems in a single, whole-body examination requiring less than 1 hour [43,44]. These examinations enable comprehensive quantitative assessment of adipose tissue distribution, brain and heart morphology and function, thoracic and abdominal organs, major blood vessels, and the musculoskeletal system with high sensitivity and specificity [16]. The capability of detecting subclinical disease and normal variants of the different organ systems have enormous potential for phenotyping in population-based studies assessing asymptomatic individuals. Although gadolinium-based contrast agents could provide additional useful information in MRI studies, their use requires the assessment of kidney function and the placement of an intravenous line and also involves a very small risk of allergic reactions [45,46]. For these reasons, we decided not to use them in this population-based study.

4.4 Whole-body in MRI population-based studies. In recent years, several population-based studies have identified novel imaging biomarkers of preclinical disease [47-51]. Examples include computed tomography assessment of coronary calcification [52,53], MRI assessment of left ventricular function/fibrosis or hepatic steatosis [54,55], and ultrasound assessment of carotid intima-media thickness [56]. However, imaging in population-based studies requires a robust and convenient modality that can be applied in many consecutive participants without major deviations, interruptions, or cancellations; it also needs to be extremely safe, because the large sample size means that even very rare adverse events may occur. Moreover, the selected imaging modality should not alter the natural development of disease or potentially increase the risk for study endpoints (e.g., exposure to radiation from computed tomography and development of cancer). Finally, it should cover a large area of the body and provide high spatial resolution to assess subtle pathologic changes indicative of subclinical disease in different organ systems. Whole-body MRI meets these criteria, although contraindications may limit the target population and introduce a selection bias.

In addition to Aging Imageomics Study, various population-based studies are currently using whole-body MRI. In Germany, the German National Cohort aims to recruit 30,000 participants [11], the Study of Health in Pomerania (SHIP) has 3400 participants [56], and the Cooperative Health Research in the Augsburg Region [Kooperative Gesundheitsforschung in der Region Augsburg] (KORA) has 18,000 participants [57]. In the United Kingdom, an extension of the UK Biobank [12,58] study was funded in 2016 to collect imaging data (MRI of the brain, heart and body, low-dose X-ray bone and joint scans, and ultrasound of the carotid arteries) from 100,000 subjects from the existing cohort by 2022. In the Aging Imageomics Study, integrating data from imaging with data from various sources is expected to provide unique insights into the biological mechanisms of aging. For example, structural and functional brain connectivity and cognitive performance may be linked to factors related to the microbiome, heart structure and function, carotid plaques, or body fat. The Aging Imageomics Study's multimodality imaging and multidisciplinary approach might identify intertwining risk factors.

***4.5 Incidental findings*.** Whole-body MRI is bound to detect incidental findings in any large cohort of asymptomatic, supposedly healthy volunteers. The significance of these findings can be difficult to discern and might be considerably different from that of similar abnormalities in symptomatic individuals. How to deal with incidental findings is an ethical and practical quandary, because although these findings may identify

potentially treatable disease, they may also represent false-positive findings or conditions that might never cause problems in the individual's life, in which case any further workup or follow-up would cause unnecessary psychological and/or physical suffering [59,60].

4.6 Usefulness of biomarkers of biological aging. Since the ultimate goal of population-based studies is to learn about the overall health of the population and how to improve it, the data collected in the Aging Imageomics Study will be available to the national and international scientific community. Furthermore, the study has been designed to enable pooling of MRI data with other European and non-European cohorts to make it possible to identify small observable variations between subgroups of participants. Increased life expectancy of human beings worldwide will probably be accompanied by an increase in the prevalence of age-related diseases, thus increasing the need for effective strategies to prevent these conditions and diagnose them early. If biomarkers of aging identified individuals with high risk of developing age-associated disease or disability, detecting a faster-than-normal rate of aging, additional diagnostic and prophylactic measures (e.g., changes in lifestyle) might be indicated and early-stage treatment of age-related disease could be offered when available. Biomarkers would also be useful for assessing the efficacy of interventions to decrease the risk of age-associated disease in the entire population. Therefore, the results of these projects can be useful for public health officials, researchers, healthcare providers, and health-related industry, as well as for the general public. Health managers need solid tools to assess overall community health so they can apply health plans and direct financial resources. Imaging biomarkers based on whole-body MRI and related data can be useful for monitoring the effects of future primary prevention strategies and for stratifying the population for specific health promotion and primary prevention programs.

Conclusions. In summary, the population-based Aging Imageomics Study represents an opportunity to better understand the physiological processes associated with aging in the human body. This data might be useful to quantify biological aging using as biomarkers tissue changes, as measured by MRI and US, and metabolic changes and relating them to clinical outcomes. This project will allow us to determine a range of normal values for each of the many variables derived from the advanced whole-body MRI protocol and to create a structural and functional imaging atlas to model the aging of organs. All this information will be useful in developing advanced imaging biomarkers to identify biopsychosocial risks associated with aging and in generating new hypotheses for further study. Identifying risk factors for health problems through advanced imaging biomarkers based on whole-body MRI could help stratify subjects in the population who could benefit most from primary prevention.

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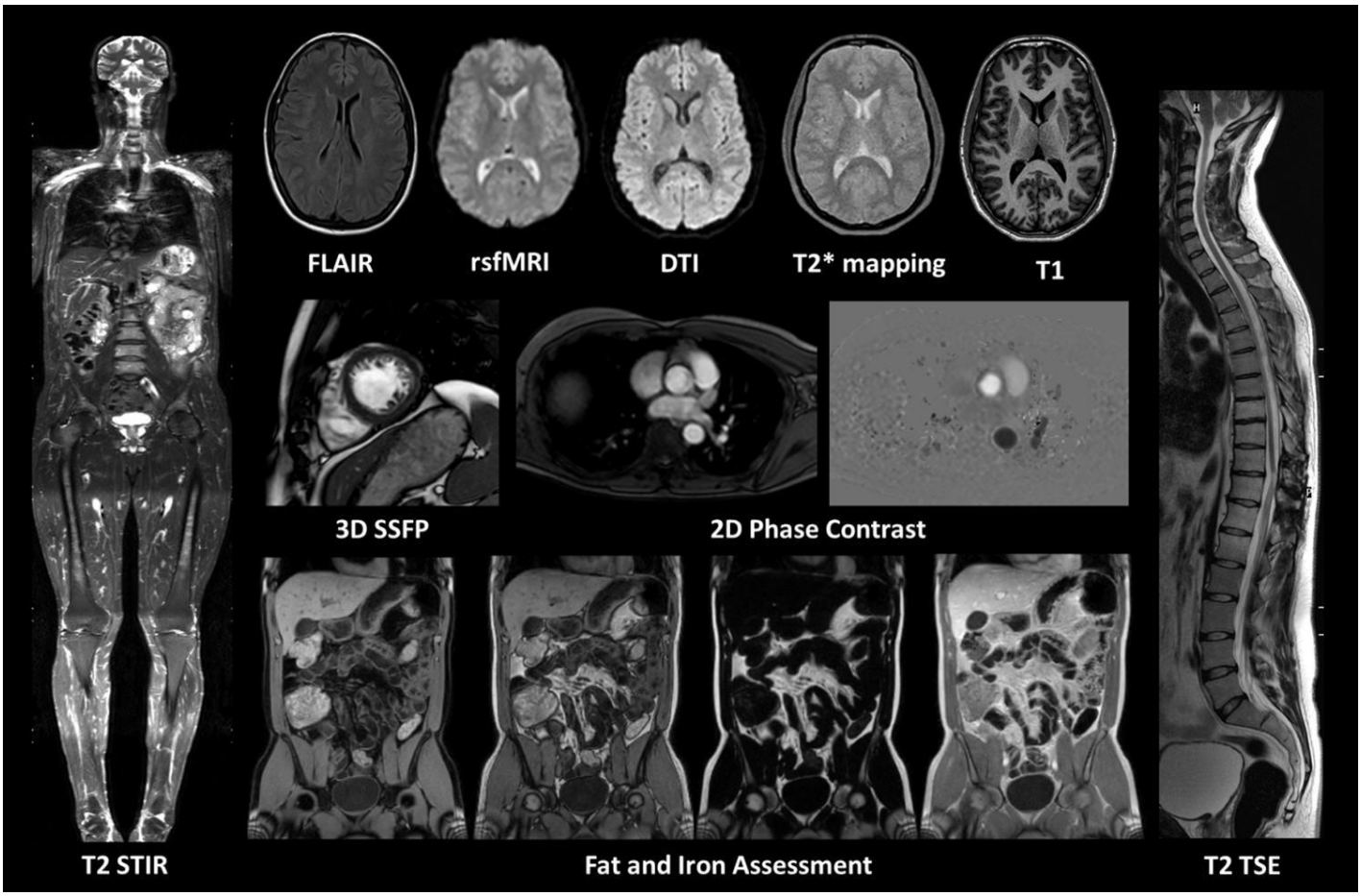

Figure 1. Magnetic resonance imaging acquisition protocol.

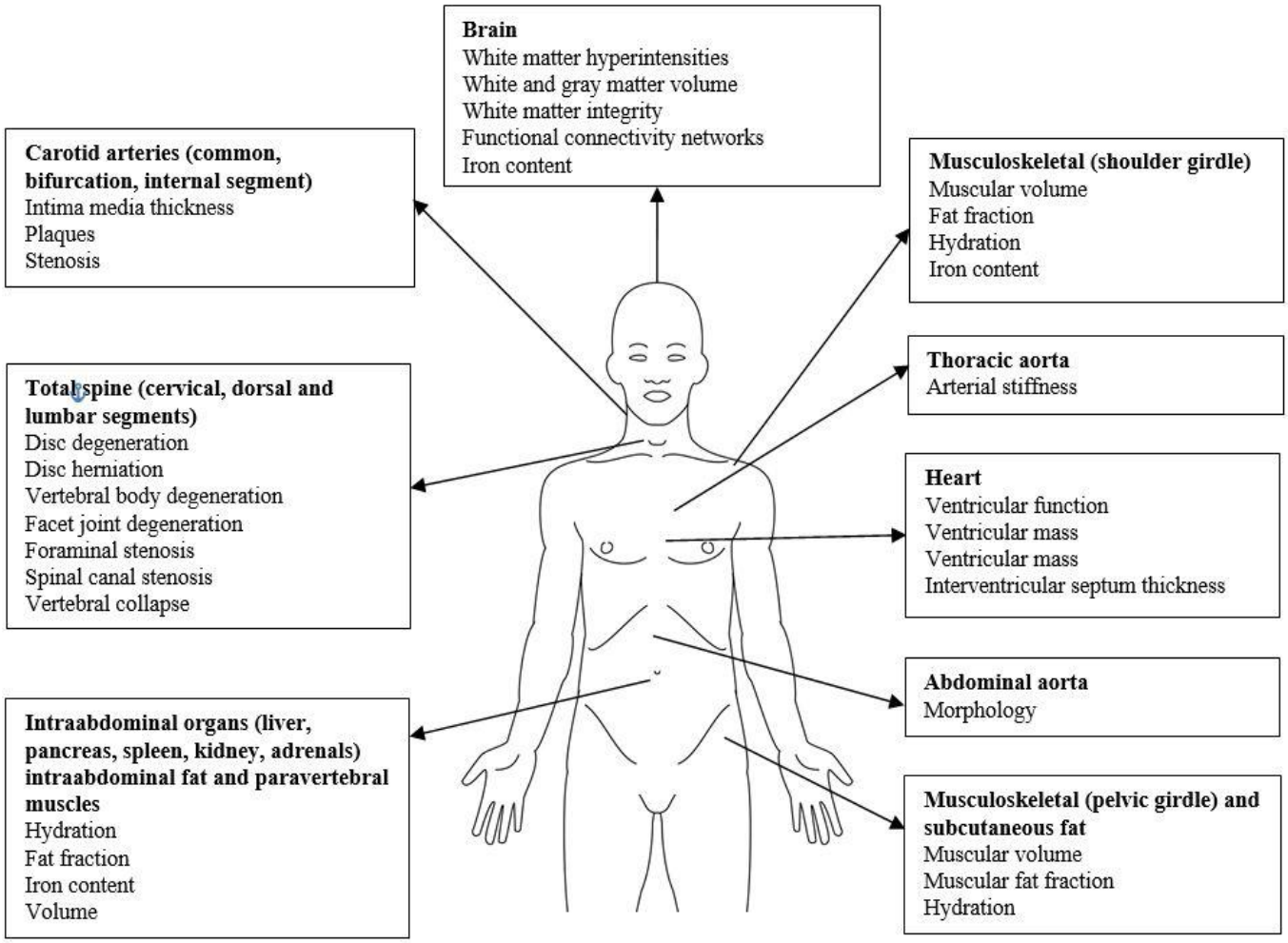

Figure 2. Major phenotypic features analyzed in the Aging Imageomics Study

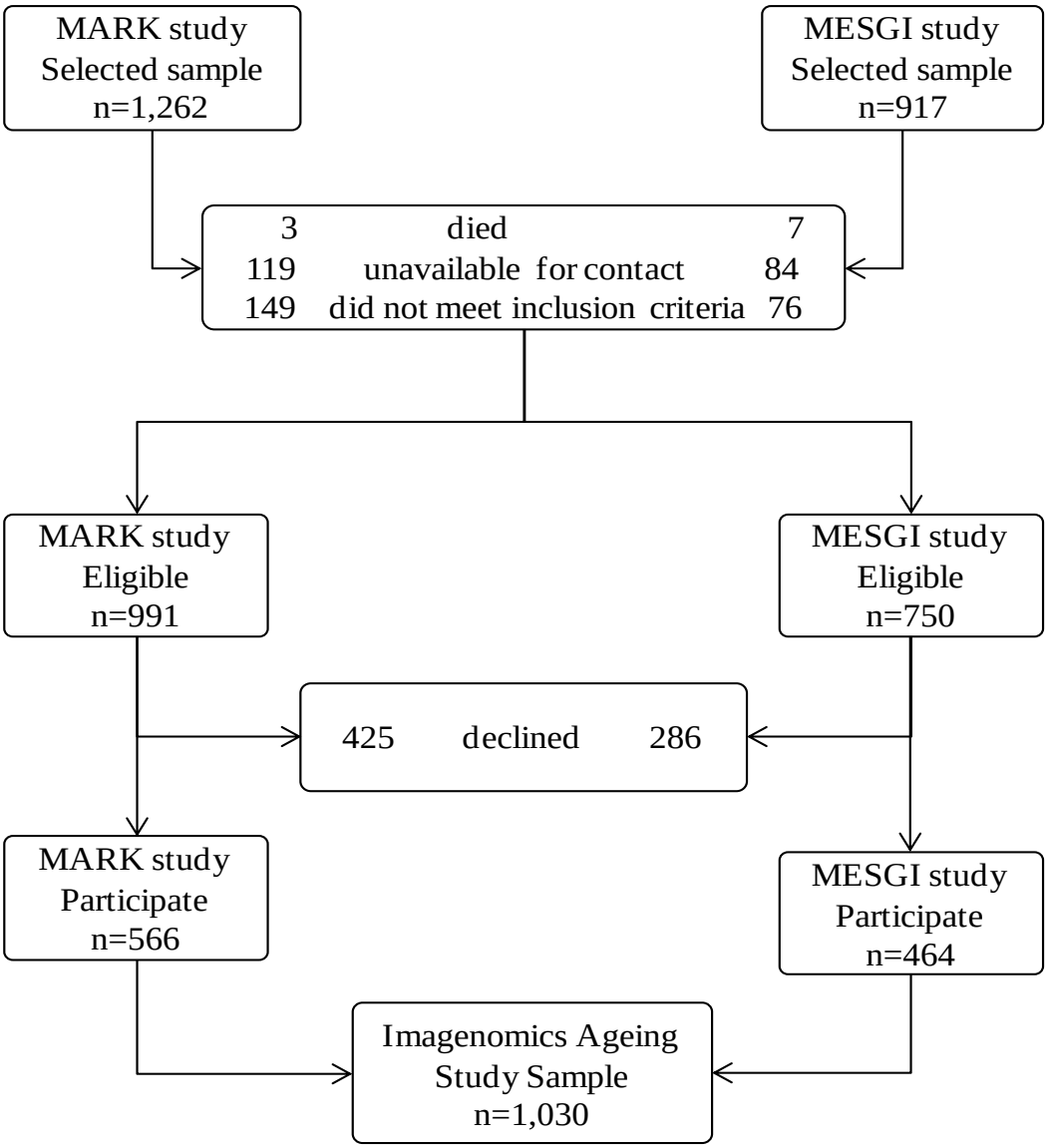

Figure 3. The Aging Imagenoma Study participation flow-chart

Table 1. Domain, parameters and techniques to data gathering

Domain	**Parameter**	**Instrument / technique**
Anthropometry	Body height and weight Waist circumference	Scale and tape measure
Medical history	Self-reported diseases Medication use	Ad hoc questionnaire
Cardiovascular system	Blood pressure Ankle-brachial index Heart rate, PQ, QRS, QT, ST, Q Pulse wave velocity Carotid arteries characteristics Retina vascular characteristics*	 Electrocardiogram Ultrasound Retinography
Cognitive function	Memory Processing speed Automatic response inhibition Attention Working memory Executive control and verbal ability	Memory Binding Test [61,62] Symbol Digit Modality Test [63] Color Word Stroop Test [64] Forward Digit Span Test [65] Backward Digit Span Test [65] Fluency Tasks [66]
Personality	Extraversion Agreeableness Contentiousness Neuroticism Openness	Big Five Inventory-10 [67]
Emotion	Depressive symptoms Maniac symptoms Suicidal ideation	Patient Health Questionnaire-9 [68] Mini International Neuropsychiatric Interview (Hypo)Manic Episode and Suicidality Modules [69]
Lifestyle	Diet Physical activity	PREDIMED Adherence to Mediterranean diet [70] International physical activity questionnaire-SF [71]
Ambient air pollution*		
Basic biochemistry	Serum glucose, blood glycated hemoglobin, serum total, LDL and HDL cholesterol, fasting triglycerides, serum creatinine, sodium, potassium, calcium, phosphate, serum ferritin, serum thyroid stimulating hormone	Blood sample
Metabolomics, lipidomics, transcriptomics, and proteomics	Circulating metabolites, proteins, and mRNA from peripheral blood mononuclear cells	Blood and urine samples
Gut microbiota	Composition and metagenomics	Stool sample

* Only assessed in MARK sample participants

Table 2. Magnetic resonance imaging protocol

Anatomic coverage	**Sequence**	**Imaging parameters* (TR; TE; FA; VS, FOV)**
Whole body**	T2-STIR	3000; 80; 90; 1.5×1.5×5; 250
Brain	2D FLAIR	8000; 120; 90; 0.8×0.8×5; 125
	Resting-state EPI BOLD	3000; 50; 90; 3.5×3.5×4; 125
	Diffusion tensor imaging (SE-EPI)	4500; 75; 90; 2×2×2.5; 125
	R2* (multiecho gradient echo)	1300; 4.6 Δ4.6; 1.5×1.5×5; 125
	3D T1-weighted (MPRAGE)	8.3; 3.8; 8; 1×1×1; 125
Heart	Cine SSFP short axis	4.6; 2.3; 55; 1.5×1.8×8; 80
Thoracic aorta	2D Phase-contrast	7.4; 3; 20; 1.8×1.8×8; 8
Abdominal aorta	Time of flight	24; 2.7; 20;1.2;250
Abdomen	T1-weighted 4D Dixon	10; 1.3 Δ2.3; 1.5×1.5×5; 250
Total spine	T2-weighted 2D fast spin echo	3000; 120; 90; 1×1×4; 60

*TR, Repetition time (ms); TE, echo time (ms); FA, flip angle (degree); VS, voxel size (mm^3); FOV, field of view (mm).
** From the top of the skull to the knees.

Table 3. Demographic and social characteristics

	Female (n=473)	**Male** (n=557)	***p* value (effect size)**
Age, mean (SD)	66.5 (7.7)	67.5 (7.0)	0.035 (<0.1[a])
Age groups			0.152 (0.06[b])
50-64	209 (44.2)	210 (37.7)	
65-74	201 (42.5)	260 (46.7)	
75+	63 (13.3)	87 (15.6)	
Education level completed			<0.001 (0.14[b])
None	24 (5.2)	8 (1.5)	
Primary (ISCED 1)	248 (53.4)	295 (54.5)	
Secondary (ISCED 2)	55 (11.9)	93 (17.2)	
Professional (ISCED 3-4)	87 (18.8)	74 (13.7)	
University (ISCED 5-8)	50 (10.8)	71 (13.1)	
Working status			0.021 (0.08[b])
Retired	314 (67.8)	403 (74.2)	
Employed	114 (24.6)	118 (21.7)	
Other (unemployed/sick)	35 (7.6)	22 (4.1)	

ISCED: International Standard Classification of Education, 1997 levels;
[a] Cohen's *d*; [b] Cramer's V

Table 4. Physical anthropometrics and health characteristics

	Female (n=473)	**Male** (n=557)	***p* value** (effect size)
Weight (kg), mean (SD)	69.5 (14.0)	81.2 (11.8)	<0.001 (0.90[a])
Height (cm), mean (SD)	158 (6,6)	170 (6.8)	<0.001 (1.7[a])
Waist circumference (cm), mean (SD)	95.6 (13.0)	101.8(10.2)	<0.001 (0.51[a])
Number of medications, mean (SD)	2.6 (2.3)	2.2 (1.9)	0,066 (0.18[a])
Heart rate (bpm), mean (SD)	67.2 (11.8)	63.6 (12.7)	<0.001 (0.29[a])
Systolic arterial pressure (mmHg), mean (SD)	138.2 (19.5)	140.4 (19.3)	0.070 (0.11[a])
Diastolic arterial pressure (mmHg), mean (SD)	82.9 (11.1)	84.7 (10.4)	<0.001 (0.16[a])
Ankle-brachial index test, n (%)			
Left, normal 1.0 to 1.4	422 (92.5)	510 (94.8)	0.114 (0.04[b])
Right, normal 1.0 to 1.4	423 (92.8)	504 (94.2)	0.227 (0.06[b])
Personal medical history, n (%)			
Hypertension	193 (41.6)	278 (51.2)	0.002 (0.09[b])
Diabetes mellitus	94 (20.3)	119 (21.9)	0.533 (0.02[b])
Dyslipidemia	127 (27.4)	166 (30.6)	0.265 (0.03[b])
Congestive heart failure	4 (0.9)	10 (1.8)	0.192 (0.04[b])
Atrial fibrillation	9 (2.0)	11 (2.0)	0.934 (<0.01[b])
Chronic kidney disease	20 (4.3)	26 (4.9)	0.682 (0.01[b])
Chronic obstructive pulmonary disease	5 (1.1)	10 (1.9)	0.314 (0.03[b])
Depressive episode	192 (42.3)	94 (18.0)	<0.001 (0.26[b])
HDL cholesterol (mg/dL), mean (SD)	58.2 (16.5)	48.6 (13.2)	<0.001 (0.64[a])
LDL cholesterol (mg/dL), mean (SD)	122.0 (30.5)	115.9 (31.4)	0.003 (0.19[a])
Fasting triglycerides (mg/dL), mean (SD)	118.6 (63.0)	125.1 (81.2)	0.275 (<0.01[a])
Serum glucose (mg/dL), mean (SD)	108.5 (32.1)	113.7 (25.8)	<0.001 (0.17[a])
Fasting plasma insulin, (mg/dL), mean (SD)	9.7 (6.7)	11.2 (8.4)	<0.001 (0.19[a])
Blood glycated hemoglobin (%), mean (SD)	5.9 (0.9)	5.9 (0.8)	0.697 (<0.01[a])
Serum creatinine (mg/dL), mean (SD)	0.73 (0.16)	0.96 (0.20)	<0.001 (1.26[a])
Sodium (mEqu/L), mean (SD)	142.1 (2.1)	141.5 (2.0)	<0.001 (0.29[a])
Potassium (mEqu/L), mean (SD)	4.5 (0.4)	4.7 (0.4)	<0.001 (0.50[a])
Calcium (mg/dL), mean (SD)	9.5 (0.4)	9.4 (0.4)	<0.001 (<0.01[a])
Phosphate (mg/dL), mean (SD)	3.6 (0.4)	3.2 (0.4)	<0.001 (1.0 [a])
Serum ferritin (ng/dL), mean (SD)	102.5 (80.7)	205.1 (171.2)	<0.001 (0.76 [a])
Thyroid stimulating hormone (mUI/L), mean (SD)	3.0 (5.7)	2.4 (2.4)	<0.001 (0.13 [a])
Carotid ultrasound examination, n (%)			<0.001 (0.18 [b])
Normal	204 (45.6)	154 (29.7)	
Non-severe stenosis (<70%)	215 (48.1)	297 (57.2)	
Severe stenosis (≥70%)	28 (6.3)	68 (13.1)	

[a] Cohen's *d*; [b] Cramer's V

Table 5. Lifestyle, personality characteristics, emotional status, and cognitive function

	Female (n=473)	**Male** (n=557)	***p* value** (effect size)
Adherence to Mediterranean diet, n (%)			0.663 (0.02[b])
Low	33 (7.6%)	46 (8.8)	
Moderate	256 (59.0)	314 (60.0)	
High	145 (33.4)	163 (31.2)	
Physical activity, n (%)			<0.001 (0.13[b])
Low (<600 MET-minutes/week)	43 (9.9)	36 (6.9)	
Moderate (600-2,999 MET-minutes/week)	213 (49.0)	200 (38.3)	
High (≥3,000 MET-minutes/week)	179 (41.1)	286 (54.8)	
Personality traits			
Extraversion, mean (SD)	6.8 (1.7)	6.7 (1.8)	0.305 (0.05[a])
Agreeableness, mean (SD)	7.0 (1.6)	6.9 (1.6)	0.476 (0.06[a])
Conscientiousness, mean (SD)	7.6 (1.7)	7.6 (1.8)	0.870 (<0.01[a])
Neuroticism, mean (SD)	5.9 (1.8)	5.4 (1.7)	<0.001 (0.28[a])
Openness, mean (SD)	6.7 (1.8)	6.6 (1.8)	0.661 (0.05[a])
Patient health questionnaire-9, mean (SD)	5.2 (4.6)	3.0 (3.3)	<0.001 (0.54[a])
Cognitive function, mean (SD)			
MBT – total paired recall	21.7 (5.1)	20.4 (5.0)	<0.001 (0.25[a])
MBT – total free recall	12.5 (4.9)	10.7 (4.8)	<0.001 (0.37[a])
MBT – total delayed paired recall	21.2 (5.3)	19.3 (5.2)	<0.001 (0.36[a])
MBT – total delayed free recall	12.4 (5.1)	10.8 (4.8)	<0.001 (0.32[a])
Forward digit span test	7.5 (2.9)	7.9 (2.1)	0.003 (0.15[a])
Backward digit span test	4.1 (1.8)	4.7 (1.9)	0.017 (0.32[a])
Symbol digit modality test	46.7 (19.7)	47.1 (17.2)	0.493 (0.02[a])
Letter fluency task	12.1 (4.8)	12.2 (4.8)	0.984 (<0.01[a])
Category fluency task	16.5 (5.2)	16.7 (5.0)	0.190 (0.03[a])
Stroop test – words	81.7 (19.9)	82.2 (18.6)	0.802 (0.02[a])
Stroop test – colors	58.9 (13.9)	56.2 (14.1)	0.002 (0.19[a])
Stroop test – words/colors	32.6 (11.2)	33.1 (12.3)	0.750 (0.26[a])
Stroop test - interference	-1.4 (9.3)	-.03 (10.6)	0.040 (0.13[a])

[a] Cohen's *d*; [b] Cramer's V

Table S1. Demographic and social characteristics

	MARK study (n=566)	**MESGI study** (n=464)	***p* value** (effect size)
Gender (female), n (%)	226 (39.9)	247 (53.2)	<0.001 (0.13[b])
Age, mean (SD)	67.2 (6.4)	66.7 (8.3)	0.256 (0.06[a])
Age groups			<0.001 (0.13[b])
50-64	209 (36.9)	209 (45.0)	
65-74	286 (50.5)	175 (37.7)	
75+	71 (12.5)	80 (17.2)	
Education level*			<0.001 (0.18[b])
Without studies	22 (4.0)	10 (2.2)	
Primary (ISCED 1)	322 (58.7)	221 (48.5)	
Secondary (ISCED 2)	78 (14.2)	70 (15.4)	
Professional (ISCED 3-4)	89 (16.2)	89 (15.8)	
University (ISCED 5-8)	38 (6.9)	83 (18.2)	
Working status**			0.008 (0.097[b])
Retired	405 (73.6)	312 (68.4)	
Employed	108 (19.6)	124 (27.2)	
Other (unemployed/sick)	37 (6.7)	20 (4.4)	

ISCED: International Standard Classification of Education, 1997 levels
[a] Cohen's d; [b] Cramer's V

Table S2. Physical anthropometrics and health characteristics

	MARK study (n=566)	**MESGI study** (n=464)	***p* value** (effect size)
Weight (kg), mean (SD)	77.8 (13.6)	73.1 (13.7)	<0.001 (0.34[a])
Height (cm), mean (SD)	164 (9.0)	164 (9.1)	0.627 (<0.01[a])
Waist circumference (cm), mean (SD)	100.1 (11.3)	97.6 (12.5)	0.003 (0.20[a])
Number of medications, mean (SD)	2.7 (2.1)	2.1 (2.0)	<0.001 (0.29[a])
Heart rate (bpm), mean (SD)	66.6 (12.0)	63.5 (12.7)	<0.001 (0.25[a])
Systolic arterial pressure (mmHg), mean (SD)	140.8 (18.3)	137.6 (20.6)	0.003 (0.16[a])
Diastolic arterial pressure (mmHg), mean (SD)	84.6 (10.8)	82.9 (10.6)	0.019 (0.15[a])
Ankle-brachial index test, n (%)			
Left, normal 1.0 to 1.4	487 (90.0)	445 (98.2)	<0.001 (0.17[b])
Right, normal 1.0 to 1.4	483 (89.4)	444 (98.4)	<0.001 (0.18[b])
Personal medical history, n (%)			
Hypertension	290 (52.8)	181 (39.5)	<0.001 (0.13[b])
Diabetes mellitus	159 (28.9)	54 (11.9)	<0.001 (0.20[b])
Dyslipidemia	179 (32.5)	114 (24.9)	0.008 (0.08[b])
Congestive heart failure	10 (1.8)	4 (0.9)	0.192 (0.04[b])
Atrial fibrillation	9 (1.7)	11 (2.4)	0.405 (0.02[b])
Chronic kidney disease	31 (5.8)	15 (3.3)	0.068 (0.05[b])
Chronic obstructive pulmonary disease	8 (1.5)	7 (1.5)	0.957 (<0.01[b])
Depressive episode	156 (29.5)	130 (29.0)	0.857 (<0.01[b])
HDL cholesterol (mg/dL), mean (SD)	49.3 (14.1)	57.6 (16.1)	<0.001 (0.54[a])
LDL cholesterol (mg/dL), mean (SD)	119.3 (31.5)	118.0 (30.7)	0.427 (0.04[a])
Fasting triglycerides (mg/dL), mean (SD)	132.1 (72.9)	109.5 (72.1)	<0.001 (0.31[a])
Serum glucose (mg/dL), mean (SD)	116.4 (32.4)	104.8 (22.3)	<0.001 (0.41[a])
Fasting plasma insulin, (mg/dL), mean (SD)	11.6 (7.9)	9.2 (7.2)	<0.001 (0.31[a])
Blood glycated hemoglobin (%), mean (SD)	6.1 (1.0)	5.7 (0.7)	<0.001 (0.46[a])
Serum creatinine (mg/dL), mean (SD)	0.86 (0.21)	0.86 (0.22)	0.259 (<0.01[a])
Sodium (mEqu/L), mean (SD)	141.6 (2.1)	142.0 (1.9)	0.010 (0.19[a])
Potassium (mEqu/L), mean (SD)	4.6 (0.4)	4.6 (0.4)	0.905 (<0.01[a])
Calcium (mg/dL), mean (SD)	9.4 (0.4)	9.6 (0.4)	<0.001 (0.5[a])
Phosphate (mg/dL), mean (SD)	3.4 (0.4)	3.4 (0.4)	0.167 (<0.01[a])
Serum ferritin (ng/dL), mean (SD)	155.9 (142.8)	160.5 (151.0)	0.739 (0.03[a])
Thyroid stimulating hormone (mUI/L), mean (SD)	2.9 (5.8)	2.5 (2.5)	0.128 (0.08[a])
Carotid ultrasound examination, n (%)			<0.001 (0.18[b])
Normal	153 (29.8)	205 (45.4)	
Non-severe stenosis (<70%)	294 (57.2)	218 (48.2)	
Severe stenosis (≥70%)	67 (13.0)	29 (6.4)	

[a] Cohen's *d*; [b] Cramer's V

Table S3. Lifestyle, personality characteristics, emotional status, and cognitive function

	MARK study (n=566)	**MESGI study** (n=464)	***p* value** (effect size)
Mediterranean diet adherence, n (%)			0.054 (0.07[b])
Low	53 (10.1)	26 (6.0)	
Moderate	311 (59.4)	259 (59.8)	
High	160 (30.5)	148 (34.2)	
Physical activity, n (%)			<0.001 (0.14[b])
Low (<600 MET-minutes/week)	33 (6.3)	46 (10.6)	
Moderate (600-2,999 MET-minutes/week)	203 (38.8)	210 (48.4)	
High (≥3,000 MET-minutes/week)	287 (54.9)	178 (41.0)	
Personality traits			
Extraversion, mean (SD)	6.7 (1.7)	6.7 (1.7)	0.813 (<0.01[a])
Agreeableness, mean (SD)	6.9 (1.6)	7.0 (1.6)	0.268 (0.12[a])
Conscientiousness, mean (SD)	7.6 (1.7)	7.6 (1.8)	0.926 (<0.01[a])
Neuroticism, mean (SD)	5.6 (1.8)	5.6 (1.8)	0.770 (0.0[a])
Openness, mean (SD)	6.5 (1.9)	6.8 (1.7)	0.037 (0.16[a])
Patient health questionnaire-9, mean (SD)	4.1 (4.4)	3.8 (3.7)	0.781 (0.07[a])
Cognitive function, mean (SD)			
MBT – total paired recall	20.5 (5.0)	21.5 (5.1)	0.002 (0.19[a])
MBT – total free recall	10.7 (4.4)	12.5 (5.3)	<0.001 (0.37[a])
MBT – total delayed paired recall	19.6 (5.2)	20.9 (5.3)	<0.001 (0.24[a])
MBT – total delayed free recall	10.7 (4.4)	12.5 (5.5)	<0.001 (0.36[a])
Forward digit span test	7.5 (1.9)	8.1 (2.2)	<0.001 (0.29[a])
Backward digit span test	4.3 (1.7)	4.8 (2.0)	<0.001 (0.27[a])
Symbol digit modality test	44.1 (17.4)	50.3 (18.8)	<0.001 (0.34[a])
Letter fluency task	11.5 (4.5)	12.8 (5.1)	<0.001 (0.29[a])
Category fluency task	16.0 (4.7)	17.3 (5.4)	<0.001 (0.26[a])
Stroop test – words	80.2 (18.4)	84.1 (19.8)	<0.001 (0.20[a])
Stroop test – colors	55.6 (12.6)	59.5 (15.4)	<0.001 (0.27[a])
Stroop test – words/colors	32.0 (10.2)	33.8 (13.4)	0.081 (0.15[a])
Stroop test - interference	-0.6 (8.0)	-0.7 (12.0)	0.612 (<0.01[a])

[a] Cohen's *d*; [b] Cramer's V

Table S4. Incidental findings classified as 'notification required'

Region	Finding	n	% (95% CI)
Brain	Non-invasive meningioma	6	0.58 (0.21-1.26)
	Invasive meningioma	2	0.19 (0.02-0.70)
	Low-grade glioma	2	0.19 (0.02-0.70)
	Arachnoid cyst	1	0.09 (<0.01-0.54)
	Cavernoma	1	0.09 (<0.01-0.54)
	Cortical dysplasia	1	0.09 (<0.01-0.54)
	Pituitary macroadenoma	1	0.09 (<0.01-0.54)
	Total brain findings	***14***	***1.35 (0.74-2.27)***
Spine	Syringomyelia	3	0.29 (0.06-0.85)
	Symptomatic disc herniation	2	0.19 (0.02-0.70)
	Schwanoma	1	0.09 (<0.01-0.54)
	Intramedullary cyst	1	0.09 (<0.01-0.54)
	Arachnoid web	1	0.09 (<0.01-0.54)
	Total spine findings	***8***	***0.77 (0.33-1.52)***
Thorax	Lung nodule < 10 mm	4	0.39 (0.10-0.99)
	Lung nodule ≥10 mm	1	0.09 (<0.01-0.54)
	Thymus squamous carcinoma	1	0.09 (<0.01-0.54)
	Total thorax findings	***6***	***0.58 (0.21-1.26)***
Abdomen	Indeterminate liver lesion *	4	0.39 (0.10-0.99)
	Adrenal myelolipoma > 20 mm	1	0.09 (<0.01-0.54)
	Indeterminate adrenal lesion **	1	0.09 (<0.01-0.54)
	Renal oncocytoma	1	0.09 (<0.01-0.54)
	Adrenal pheochromocytoma	1	0.09 (<0.01-0.54)
	Abdominal aortic aneurysm ≤ 5cm	2	0.19 (0.02-0.70)
	Abdominal aortic aneurysm > 5cm	2	0.19 (0.02-0.70)
	Total abdomen findings	***12***	***1.16 (0.60-203)***
Genitourinary	Bladder cancer	3	0.29 (0.06-0.85)
	Paravesical leiomyoma	1	0.09 (<0.01-0.54)
	Ovarian fibroma	1	0.09 (<0.01-0.54)
	Uterine fibroid > 6 cm	1	0.09 (<0.01-0.54)
	Total genitourinary findings	***6***	***0.58 (0.21-1.26)***
Incidental findings		***46***	***4.44 (3.28-5.91)***

* All indeterminate liver lesions were hemangiomas.

** This indeterminate lesion was an adenoma.