Universitat de Girona

THREEFOLD ANALYSIS OF THE INDIVIDUAL EFFECTS OF PHYSICAL ACTIVITY, PROCESSING SPEED, AND AGING ON STRUCTURAL AND FUNCTIONAL CARDIAC VARIABLES

From The Aging Imageomics Study

FINAL DEGREE PROJECT

Author: **Aina Foguet Noguer**

Tutor: **Dr. Víctor Pineda Sanchez**

Department of Radiology
Dr. Josep Trueta University Hospital

University of Girona, Faculty of Medicine
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1. ABSTRACT

Background: Aging constitutes a significant risk factor for cardiovascular diseases, which stand as the leading cause of mortality in Spain. Prior studies have underscored the positive impact of physical activity on lifespan extension and the mitigation of cardiovascular risk factors. However, limited research has explored its influence on cardiac structural and functional alterations. Additionally, while dementia has been associated with cardiac changes, the relationship between processing speed and cardiac parameters within a healthy population remains relatively unexplored. Aging is a complex process, and in itself, it has been associated with various structural and functional cardiac changes, some of which ultimately contribute to an increased cardiovascular risk.

Objectives: to analyze the individual effects of physical activity, processing speed, and aging on structural and functional cardiac variables.

Methods: Cardiac structure and function parameters were assessed using cardiovascular magnetic resonance (CMR). The study included a sample of 746 participants of both sexes, with an average age of 66.85 years. Physical activity levels were quantified using the International Physical Activity Questionaire (IPAQ), processing speed was evaluated with the Symbol Digit Test, and aging was recorded in years. Statistical analyses included t-tests, Welch test, and linear regression models for the entire sample, sex-stratified, and adjusted for age, sex and cardiovascular risk factors.

Results: All cardiac variables were found to be significantly higher in males compared to females, except for the EndoGLS and GRS. In the analysis of physical activity, no statistically significant differences were observed in the left ventricle between 'high' and 'moderate-low' levels. The only exceptions were an increase of the LV EndoGCS in females (2.64%), and an increase of the LVCO in males (0.14 l/(min*m^2)). When considering the right ventricle, the overall sample showed a significant increase in the RVEDV (p-value 0.001) and RVESV (p-value <0.001).

Processing speed levels were not found to have any significant associations with cardiac structural and functional variables.

When analyzing the impact of increasing age on cardiac structural and functional variables, several associations were found. Both sexes showed an increased LV M/V ratio (p-value <0.001), and a decrease in the RVEDV and RVSV. Moreover, males exhibited a significant reduction of the LVEDV (-0,27 ml/m^2 each year of age) as well as a significant decrease of the LVSV, LVCO and RVESV.

Conclusions: In a non-athletic community-based population, results suggested a general lack of association between physical activity levels and both structural and functional cardiac variables. Notably, the right ventricle volumes increased with higher activity levels. In contrast, processing speed had no impact on cardiac variables. Increasing age was associated with a decrease in several cardiac parameters. Both males and females had significant changes in LV M/V ratio, RVEDV, and RVSV. However, other variables differed between the sexes.

KEYWORDS: *physical activity, processing speed, aging, cardiac structure, cardiac function, CMR.*

2. ABBREVIATIONS

CMR	Cardiac Magnetic Resonance
CV	Cardiovascular
CVD	Cardiovascular Disease
CVRF	Cardiovascular Risk Factors
EndoGCS	Endocardial Global Circumferential Strain
EndoGLS	Endocardial Global Longitudinal Strain
GRS	Global Radial Strain
HfpEF	Heart Failure with preserved Ejection Fraction
IV	Interventricular
LV	Left Ventricle
LVCO	Left Ventricle Cardiac Output
LVEDV	Left Ventricle End-Diastolic Volume
LVEF	Left Ventricle Ejection Fraction
LVESV	Left Ventricle End-Systolic Volume
LVM	Left Ventricle Mass
LV M/V	Left Ventricle Mass-to-Volume ratio
LVSV	Left Ventricle Stroke Volume
MESA	Multi-Ethnic Study of Atherosclerosis
MESGI50	Maturity and Satisfactory Ageing in Girona study
MARK	Improving interMediAte RisK management study
PA	Physical Activity
RV	Right Ventricle
RVEDV	Right Ventricle End-Diastolic Volume
RVEF	Right Ventricle Ejection Fraction
RVESV	Right Ventricle End-Systolic Volume
RVSV	Right Ventricle Stroke Volume

3. INTRODUCTION

3.1. AGING

Aging is the natural evolution of life. It is a complex, time-dependent process leading to body structure and function decline and thus, being an inescapable comorbidity. It increases the risk for many diseases such as cardiovascular (CV), pulmonary, and oncological and so its morbidity, hospitalizations, and death (1).

In the last century, Spain has experienced a major demographic transformation. While in 1900 life expectancy at birth was 34 years (2), nowadays it is more than 80 years and continues to increase (3). This rise in longevity has resulted in the emergence of a large population of elderly individuals, including many with age-associated diseases and functional limitations.

Age represents the largest risk factor for cardiovascular diseases (CVD) leading to a dramatic increase in its prevalence and morbimortality (4). In 2019, the prevalence of CVD[1] in Spain affected 9.8% of the population, 52.6% women and 47.4% men, with an annual incidence of 1 case per 100 people. The highest rates were reached over 75 years (3). In the same year, CVD ranked as the first cause of hospital admissions and deaths, constituting 27.9% of the total deaths (about 200.000 deaths) (5). Approximately half of them were due to ischemic heart disease and cerebrovascular disease (3). It is also important to emphasize that CVDs stand as the 3rd cause of disease burden, accounting for 12.5% of the total disability-adjusted life years. On a European scale, heart diseases were responsible for 37.4% of all deaths, affecting more than 2 million people (5).

Cardiovascular risk factors (CVRF) also increase with age. They can be classified into behavioral factors, non-modifiable biological factors, and biological factors with metabolic origin (5). See in *Figure 1.*

[1] CVD includes ischemic heart disease, heart failure, atrial fibrillation, sudden death and aortic valve disease, and the incidence of acute cardiovascular events, such as acute myocardial infarction or stroke.

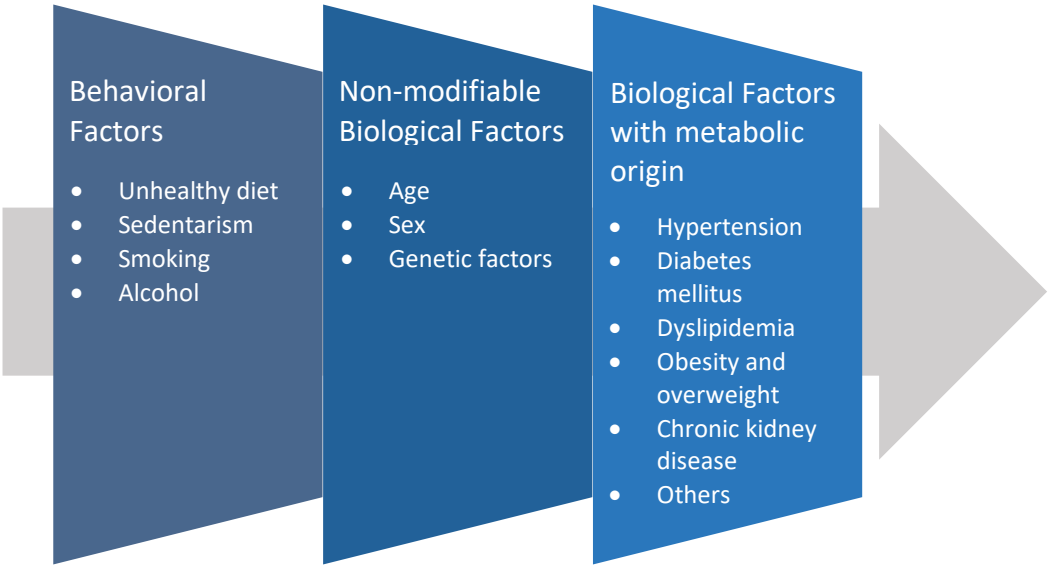

Figure 1. Classification of the risk factors. Extracted from: (5).

The American Heart Association (AHA) has identified 7 risk factors (Life's Simple 7) that maintained at stable and controlled values contribute to achieve optimal CV health. Metrics and desired values are: no smoking, body mass index in the normal range, adequate physical activity, balanced diet, total cholesterol <200 mg/dL, blood pressure <120/80 mm Hg, and fasting blood glucose <100 mg/dL. In order to achieve those, healthy lifestyles are needed. Modifying CVRFs can prevent three out of four CVDs and prevent the appearance of new episodes after suffering an acute CV event (5).

The four clinical presentations that cause the greatest impact on society due to their high incidence, prevalence, morbidity, mortality, and cost generated are ischemic heart disease (prevalence of 2.4%), heart failure (prevalence of 1.1), arrhythmias (most common is atrial fibrillation, present in 1-2% of the population) and valvular heart disease (prevalence greater than 12% in >75 years) (5).

3.1.1. Physical Activity

Physical activity (PA) is defined as 'any situation employing the skeletal muscles, whatever the aim, accompanied by an increase in energy expenditure compared with

the resting state'. It encompasses activities of daily living, leisure, and sport, the latter being defined as a subset of PA characterized by established rules and structured gameplay. On the other hand, the term 'exercise' is more specifically used to describe planned, structured, and repetitive PA to maintain or improve health and fitness (6,7). Both moderate and vigorous-intensity PA improve health (6).

Among the behavioral and lifestyle factors, PA is the most important determinant of the aging process. Its significance extends to various dimensions, encompassing clinical, functional, psychological, and social aspects. It enhances the quality of life and diminishes disability and morbidity in later years (8). Regular exercise is associated with a 30% reduction in the risk of overall mortality. This positive dose-response relationship between PA and longevity indicates that a larger training volume leads to greater mortality benefits. In contrast, low activity and sedentary behavior are associated with a 63% greater risk of developing CVD (7,9).

PA also has beneficial effects on the heart by reducing the risk of CVD and lowering CV mortality rates (7,9,10). Moreover, it leads to improvements in CVRFs by favorably affecting plasma lipoprotein profiles (increasing HDL and reducing LDL) and decreasing body fat and weight (7,10,11). PA also contributes to reduce blood pressure and insulin resistance with an enhanced glucose metabolism (7,8,10,11). Furthermore, there is an improved endothelial function (7,11).

During exercise, the heart is subjected to intermittent hemodynamic stresses including pressure overload, volume overload, or both. In order to normalize such stress and to meet the systemic demand for an increased blood supply, it undergoes morphological adaptation by increasing the thickness of the ventricular chamber wall, and so its mass. This increase is attributed to the growth of already differentiated cardiac muscle cells. The heart's adaptation to exercise is often accompanied by the preservation or enhancement of contractile function, in contrast to pathological remodeling that can proceed to a loss of contractility and heart failure. It can also increase cardiac output and reduce the risk of arrhythmia (11). Exercise has been related to a reduction in LV myocardial stiffness and a lower incidence of heart failure with preserved ejection fraction (HfpEF) compared with those individuals with a sedentary lifestyle (10). In a

community-based population free of clinically apparent CVD, higher PA levels were associated with proportionally greater left ventricular mass (LVM) and end-diastolic volume (LVEDV). The magnitude of this relation was stronger in males (12). These long-term positive effects of exercise on CV health are associated with a more favorable inflammatory marker profile and, in turn, they lower their risk of heart failure (11).

Other beneficial effects of PA are enhanced maximal oxygen uptake (7,10), decreased susceptibility to stroke, reduced risk of colon and breast cancer, as well as reduced risk of falls partly due to a better profile of osteoporosis (7,8).

In relation to the functional status, evidence suggests that PA can improve cognition in people without dementia, reduce the incidence of dementia, and improve health among people with existing dementia (7,8). Both aerobic and resistance training have shown positive effects on executive function, attention, and processing speed with neuroimaging evidence of larger hippocampal volumes and better cerebrovascular flow. Moreover, low muscle mass and muscle strength have been linked to cognitive impairment and brain atrophy (8).

Regarding psychological well-being, PA has been attributed a better mental health with reduced symptoms of depression and possibly reduced anxiety (7,8).

On a cellular level, research indicates that PA helps preserve telomere length, which is a biomarker of aging and so associated with life expectancy. With age, the activity of the telomerase enzyme decreases and telomers shorten. Thus, their length is considered to be a biological indicator of youth (7). Participants who were less physically active had shorter telomeres lengths and more fragmentation, compared with those performing regular exercise (7,8). The average difference in length between exercisers and non-exercisers was 200 nucleotides, which corresponded approximately to ten years (7). This suggests that physically active adults may experience lower levels of oxidative stress or positive epigenetic modifications induced by PA (8).

A summary of the range of health benefits for older adults is shown in *Figure 2.*

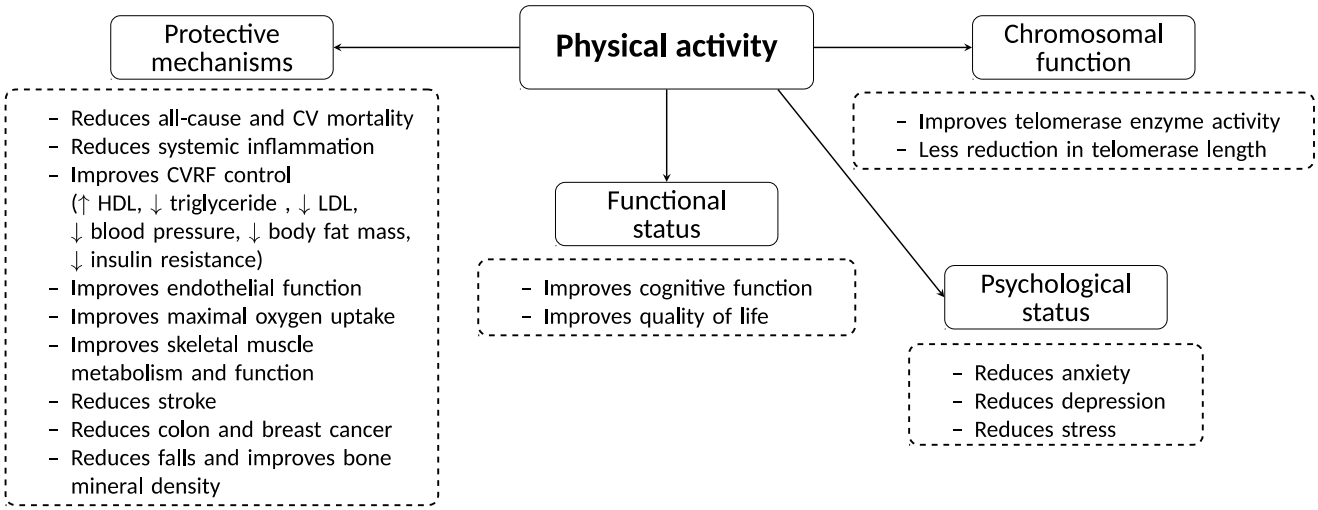

Figure 2. Benefits of physical activity in older adults.

3.1.2. Cognitive Aging

The aging process is associated with declines in specific cognitive abilities, including processing speed, memory, language, visuospatial, and executive functions. Notably, processing speed tends to peak in the third decade of life and then gradually decline at an estimated rate of -0.02 standard deviations per year. Other cognitive functions such as vocabulary, are resilient to brain aging and may even improve with age (13).

In the realm of cognitive aging, two complementary theories have emerged. First, 'The Processing Speed Theory' says that age-related cognitive decline results from a generalized slowing of cognitive processing. This deceleration is believed to stem from a broad deterioration of white matter integrity throughout the brain. According to this theory, cognitive performance suffers because fundamental cognitive operations occur at a reduced pace. Thus, it reduces the amount of simultaneously available information needed for higher level processing. On the other hand, 'The Prefrontal Executive Theory' states that local structural and functional changes in frontal cortex areas lead to specific declines in executive functions, which in turn lead to more general cognitive deficits. Both neuropsychological and neuroimaging studies have shown that executive processes heavily rely on the frontal lobes, making them particularly susceptible to age-

related changes. Therefore, chronological age negatively impacts cognitive measures related to processing speed and executive functions (14).

Cognitive decline and dementia in the elderly population have been associated with CVRF. Better CV health, indicated by high Life's Simple 7 scores, showed a positive relation with a superior global cognitive performance regarding learning, memory, verbal fluency, executive functioning, and processing speed (15,16).

On a functional cardiac level, changes in the left ventricle ejection fraction (LVEF) due to severe cardiomyopathies and heart failure have been related to abnormal brain aging. This includes cognitive impairment, structural neuroanatomic abnormalities, and an increased risk of Alzheimer's disease (17). In fact, after heart transplantation there is a substantial increase in cerebral blood flow (over 50%), resulting in a reduction of cognitive impairment, presumably because of the improved cardiac function. Consequently, it is believed that reduced LVEF influences cerebral perfusion homeostasis contributing to clinical brain injury. The Framingham Heart Study indicated that lower LVEF (including values from 55% to 62%) was associated with decreased cognitive performance in memory and visuoperceptual abilities, in the absence of CVD. Surprisingly, values exceeding 73.2% were also linked to poor cognitive performance, encompassing memory, executive function, and visuoperceptual abilities. It suggested a nonlinear association between systolic function and accelerated cognitive decline (18).

Similar investigations, including the Multi-Ethnic Study of Atherosclerosis (MESA), have also explored subclinical cardiac changes in relation to cognitive aging. It identified associations such as an increased left ventricular mass (LVM) and mass-to-volume ratio (LV M/V). However, none of the left ventricle (LV) diastolic or systolic function parameters, including the LVEF, demonstrated such relationship (19).

Thus, while some evidence suggests a potential link between cardiac morphological and functional changes and accelerated cognitive aging, current research remains limited.

3.2. CARDIAC AGING

Cardiovascular aging is a complex process of adaptive structural and functional changes over time. The arterial tree thickens and decreases in compliance, resulting in increased pulse wave velocity, systolic blood pressure, and left ventricular afterload. Myocardium remodels in order to maintain systolic function and diastolic filling. These adaptive mechanisms are not pathologic but increase the susceptibility to myocardial ischemia, heart failure, and atrial fibrillation if there are common age-associated comorbidities (9,10).

On a structural level, the number of myocytes decreases, possibly driven by an underlying chronic inflammatory state. As a result of a compensatory response, the myocyte size increases, leading to LV hypertrophy. It is characteristically concentric and affects the LV in an asymmetrical way, mostly affecting the IV (interventricular) septum (4,20). Concentric hypertrophy is considered to be a hallmark of HfpEF (4).

The impact of age on cardiac mass remains a topic of debate in the literature. Some studies suggest that the overall cardiac mass remains stable due to the redistribution of cardiac muscle (4,21,22). Others affirm that it is preserved in females, but decreases in males (10), and others explain an age-related reduction (20).

Either the left ventricular end-diastolic volume (LVEDV) or the left ventricular end-systolic volume (LVESV) decreases with age (4,20–23). These changes reflect adverse myocardial remodeling (21) and are hallmarks of HfpEF (4). Other changes described are preserved short axis length and decreased LV long axis length, changing the LV geometry from a conical to a more spherical shape (10).

Older age is associated with a higher mass-volume ratio (4,20,23) reflective of a hypertrophic process occurring in the setting of progressively reduced LV volumes. Increased LV mass-to-volume ratio has been associated with coronary heart disease and stroke (24). There are also lower stroke volumes (SV) (20,23).

Regarding functional changes, the hallmark of cardiac aging is a decrease in LV diastolic function. There are two phases during diastolic filling, which are the passive filling early

during diastole and the active filling late during diastole by atrial contraction. There is a decrease in the early diastolic filling so the latter assumes more portion of the total end diastolic volume. As a consequence, there is an enlargement of the atrium and increased contraction in order to maintain the filling of the ventricle manifested as the fourth heart sound (4,9,10). Actually, LV's early diastolic filling rate progressively slows at the age of 20 years, so that by 80 years the rate is reduced, on average, up to 50% (9,25). Diastolic dysfunction is related to heart failure and it is also a major problem for patients with atrial fibrillation (4). Resume in *Figure 3.*

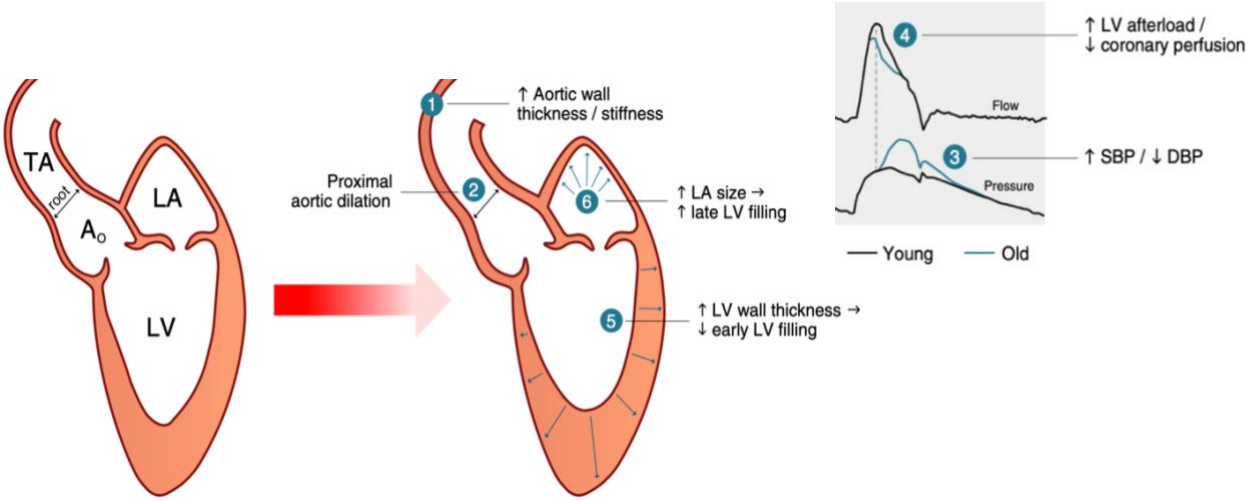

Figure 3. Conceptual framework of age-related changes in CV structure and function. *Abbreviations*: DBP, diastolic blood pressure; EDV, end-diastolic volume; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; PP, pulse pressure; SBP, systolic blood pressure. Extracted from (10).

Aging does not affect the left ventricle ejection fraction (LVEF), which is the most commonly used measure of systolic function (4,10,21,22). However, strain parameters are considered to be more sensitive than the LVEF (10,26) and enable the detection of subclinical LV dysfunction before a reduction in LVEF occurs. Studies have shown a decline in transmural global longitudinal strain (GLS) (10,27). There are discrepancies regarding the global circumferential strain (GCS), some investigations reported its decrease (20,23,27) while others mention an increase as a compensatory mechanism to maintain global LVEF (10).

Right ventricular (RV) volumes have been shown to decrease with age (27).

3.2.1. Cardiovascular Magnetic Resonance

Cardiovascular Magnetic Resonance (CMR) is a non-invasive medical imaging technique that uses powerful magnetic fields and radiofrequency waves in order to produce highly detailed images. Within the realm of CV assessment, CMR has become the contemporary gold standard when evaluating both the cardiac anatomy and function of the heart and great vessels (28).

It is independent of geometrical assumptions with an excellent definition of endocardial and epicardial borders (29). Thus, the distinction lies in its greater spatial resolution, accuracy, and reproducibility which has increased its use in population-based studies (30). Furthermore, it has superior diagnostic and prognostic power than other techniques without ionizing radiation, enhancing its safety profile (28).

3.3. THE AGING IMAGEOMICS STUDY

'The Aging Imageomics Study' is an observational multidisciplinary and multi-institutional study that aims to identify biomarkers of human aging. It wants to cultivate a deeper understanding of different biological factors that underlie healthy and unhealthy aging in order to identify individuals at high risk of developing age-associated diseases.

In the study, participants underwent a whole-body MRI that took about 50 minutes, creating a large repository of advanced structural and functional datasets. Depending on the anatomic coverage, the imaging acquisition protocol encompassed different sequences, collected in *Annex 1*.

The major phenotypic features analyzed were: brain, total spine, abdomen, heart, musculoskeletal system, and large blood vessels such as the aorta and carotid arteries. Carotid intima-media thickness and plaques were also assessed by ultrasonography. Furthermore, the project collected other parameters related to age such as demographic and social characteristics, lifestyle factors, physical anthropometrics, emotional status, cognitive functions, and various additional metrics. Several types of samples were also gathered to allow for microbiome, metabolomic, and lipidomic profiling.

A total of 1030 participants aged ≥50 years followed the inclusion criteria and enrolled in 'The Aging Imageomics Study'.

4. JUSTIFICATION

Over the past century, life expectancy in Spain has increased by more than 50 years, resulting in a substantial elderly population, many of whom are affected by age-related diseases. Since age represents the largest risk factor for cardiovascular diseases, there has been a substantial rise in their prevalence and the corresponding morbidity and mortality. The process of aging has been related to alterations in the cardiac structure and function which predispose to greater cardiovascular risk.

Among various behavioral and lifestyle factors, physical activity (PA) stands out as the most important determinant of successful aging encompassing clinical, functional, psychological, and social aspects. A positive dose-response relationship has been demonstrated in terms of longevity. Exercise reduces cardiovascular risk factors and cardiovascular diseases as well as diminishes age-related cardiac changes. These heart adaptations to PA have mainly been studied in high-performance athletes and usually with echocardiography. However, there is limited knowledge regarding the relationship between PA and the impact on morphological and functional cardiac changes in a non-athletic population over 50 years. To date, only a single study within 'The Multi-Ethnic Study of Atherosclerosis (MESA)' in the United States has examined this association using cardiac magnetic resonance (CMR) (12).

The process of aging is accompanied by a reduction in cognitive abilities such as processing speed, memory, language, visuospatial, and executive function. This decline is partly attributed to 'The Processing Speed Theory', which posits that a generalized slowing of cognitive processing limits the amount of information needed for higher level cognitive tasks. Despite numerous studies have investigated the relationship between cardiac changes and dementia, only two studies the 'Framingham Heart Study' (18) and the 'MESA' (19) have examined the association with processing speed.

The current study, a component of 'The Aging Imageomics Study', aims to examine the relationship between different PA levels and cardiac structural and functional changes. Additionally, it will investigate the association with processing speed. Given that our study's population comprises individuals aged 50 years and older, this research will also

investigate whether the aging process is associated with cardiac changes. CMR will be used, as it offers immense potential for quantifying subclinical disease burden and age-related changes in the heart. Notably, this study is locally focused, with participants residing in the province of Girona.

Thus, through this study our goals are threefold. Firstly, we aim to generate valuable data and evidence that not only reinforces the significance and benefits of PA but also elevates its status within the realm of primary prevention. Secondly, if there is a relationship between cognitive aging and cardiac parameters, it could potentially serve as part of a screening tool for cardiovascular disease in the future. Lastly, we aspire to contribute to the heart aging literature with a dataset specific to the population of Girona.

5. HYPOTHESIS

Main hypothesis

- A higher level of physical activity is associated with increased left ventricle cardiac **morphological** changes, based on the **mass**, **volumes** and **mass-to-volume ratio**, in individuals aged ≥50 years.
- A higher level of processing speed is associated with increased left ventricle cardiac **morphological** changes, based on the **mass**, **volumes** and **mass-to-volume ratio**, in individuals aged ≥50 years.
- Increasing age is associated with left ventricle cardiac **morphological** changes, based on the **mass**, **volumes** and **mass-to-volume ratio**, in individuals aged ≥50 years from Girona region.

Secondary hypothesis

- A higher level of physical activity is associated with increased left ventricle cardiac **functional** changes, based on the **ejection fraction**, **stroke volume**, **cardiac output** and **strains**, in individuals aged ≥50 years.
- A higher level of physical activity is associated with increased right ventricle cardiac **morphological** changes based on the **volumes**, and **functional** changes based on the **ejection fraction** and **stroke volume**, in individuals aged ≥50 years.
- A higher level of processing speed is associated with increased left ventricle cardiac **functional** changes, based on the **ejection fraction**, **stroke volume**, **cardiac output** and **strains**, in individuals aged ≥50 years.
- A higher level of processing speed is associated with increased right ventricle cardiac **morphological** changes based on the **volumes**, and **functional** changes based on the **ejection fraction** and **stroke volume**, in individuals aged ≥50 years.
- Increasing age is associated with left ventricle cardiac **functional** changes, based on the **ejection fraction**, **stroke volume**, **cardiac output** and **strains**, in individuals aged ≥50 years from Girona region.
- Increasing age is associated with right ventricle cardiac **morphological** changes based on the **volumes**, and **functional** changes based on the **ejection fraction** and **stroke volume**, in individuals aged ≥50 years from Girona region.

6. OBJECTIVES

Main objective

- To investigate the association between the level of physical activity and left ventricle cardiac **morphological** changes, focusing on the **mass**, **volumes** and **mass-to-volume ratio**, in individuals aged ≥50 years.
- To examine the association between the level of processing speed and left ventricle cardiac **morphological** changes, focusing on the **mass**, **volumes** and **mass-to-volume ratio**, in individuals aged ≥50 years.
- To investigate the association between increasing age and the extent of left ventricle cardiac **morphological** changes, focusing on the **mass**, **volumes** and **mass-to-volume ratio**, in individuals aged ≥50 years

Secondary objective

- To assess the relationship between the level of physical activity and left ventricle cardiac **functional** changes, based on the **ejection fraction**, **stroke volume**, **cardiac output** and **strains**, in individuals aged ≥50 years.
- To analyze the association between the level of physical activity and right ventricle cardiac **morphological** changes based on the **volumes,** and **functional** changes concerning the **ejection fraction** and **stroke volume**, in individuals aged ≥50 years.
- To evaluate the relationship between the level of processing speed and left ventricle cardiac **functional** changes, based on the **ejection fraction**, **stroke volume**, **cardiac output** and **strains**, in individuals aged ≥50 years.
- To assess the relationship between the level of processing speed and right ventricle cardiac **morphological** changes based on the **volumes,** and **functional** changes concerning the **ejection fraction** and **stroke volume**, in individuals aged ≥50 years.
- To investigate the association between increasing age and the extent of left ventricle cardiac **functional** changes, concerning the **ejection fraction**, **stroke volume**, **cardiac output** and **strains**, in individuals aged ≥50 years.
- To investigate the association between increasing age and the right ventricle cardiac **morphological** changes based on the **volumes,** and **functional** changes concerning the **ejection fraction** and **stroke volume**, in individuals aged ≥50 years.

7. METHODOLOGY

7.1. STUDY DESIGN

Observational, analytical, prospective, cross-sectional research that used data from 'The Aging Imageomics Study', conducted in the province of Girona between 2018 and 2019. It involved the evaluation of participants aged 50 and above using a multimodal magnetic resonance imaging approach.

7.2. PARTICIPANTS

Participants were selected from two separate ongoing cohort studies: the Improving interMediAte RisK management study (MARK) (31) and the Maturity and Satisfactory Ageing in Girona study (MESGI50) (32). Each cohort had independent eligibility criteria, but all members were residing in the province of Girona.

'MESGI50' was a population-based cohort, linked to the Survey of Health, Ageing and Retirement in Europe project (SHARE). It was designed to characterize the aging process according to the demographic characteristics of the municipalities in the province of Girona. The reference population was people aged 50 and over that corresponded to the municipal register data according to the Institut d'Estadística de Catalunya for the year 2012. A two-stage stratified cluster probabilistic sampling method was used based on the population size and the degree of aging in the municipalities of the province of Girona. Stratification was carried out proportionally based on the weight of the reference population in each stratum. In the first stage, sampling units were municipalities, while in the second stage, they were the residents registered in the census. Their selection was done randomly. Inclusion criteria for 'MESGI50' were having been born in 1962 or earlier, as well as being registered and habitually reside in a municipality in the province of Girona. Being in prison or hospitalized during the fieldwork period of the study, living in a geriatric center, the presence of language barriers or a change of address with an unknown address were exclusion criteria. According to the SHARE study criteria, partners of all participants who resided in the

same home were included in the study. The sampling process guaranteed the total representativeness of the sample on the population under study.

In the 'MARK' study, the population's age ranged from 35-74 years (both included) and had low to moderate CV risk. Participants had a coronary risk between 5%-15% at 10 years according to the Framingham adapted risk equation and a vascular mortality risk between 3-5% at 10 years according to the SCORE equation. Exclusion criteria were: terminal illness or institutionalization at the appointment time or a personal history of atherosclerotic disease. The 'MARK' study included a random sample of patients recruited in public primary care centers in the province of Girona. Candidates were cited by telephone at their health center and they were welcomed to participate.

Participants of both cohorts were invited to take part in 'The Aging Imageomics Study' by telephone, and if they accepted, a meeting was organized in order to finish the registration.

7.3. SUBJECTS SELECTION

Inclusion and exclusion criteria agreed by 'The Aging Imageomics Study' are set out below.

Inclusion criteria

- Age ≥50 years
- Dwelling in the community (not institutionalized)
- Signed informed consent, which included a second part where participants had the option to decline being informed about the results of the magnetic resonance explorations performed in the study.

Exclusion criteria

- History of infection the last 15 days.
- Contraindications for MRI: electronic cardiac implants (pacemakers and defibrillators), cochlear implants, incompatible prosthetic heart valves or vascular

clips, metallic foreign bodies in eyes or places with vital risk (intracranial, spinal canal, large vessels or liver).

- Any circumstance that may make it impossible to perform an MRI scan (e.g. claustrophobia).

7.4. STUDY PROCEDURES

Participants were contacted for two visits. During the first visit appointment, they were informed about the goals and procedures of the study they were enrolling in. Once they had understood and accepted it, they had to sign informed consent and personal identification codes were assigned. Moreover, participants underwent a whole body-MRI and carotid ultrasound studies. After this first day, participants were listed for the next evaluation 15 days later. They were provided a kit and detailed instructions for collecting and transporting morning urine and stool samples for the following visit. During the second visit, participants samples were collected and blood samples were taken between 8:00 and 10:00 in the morning. Furthermore, an anthropometric and cardiovascular examination as well as a clinical interview were done by a nursing team. Participants also filled out various standardized tests and questionnaires to measure cognitive function, personality, physical activity, among others. Participants from the 'MARK' study were also invited to measure ambient air pollution in the 15 days between visits with a specific device.

Data were collected between 14th November 2017 and 19th June 2019.

7.4.1. Image Acquisition

All MRI examinations were carried out using a mobile 1.5T scanner (Vantage Elan, Toshiba Medical System at the beginning, but then from Canon Medical Systems). The maximum gradient amplitude was 35mT/m-1 and the imaging setup involved a head coil and two body coils to cover the body. The whole-body MRI procedure took approximately 50 minutes.

In the context of CMR, the acquisition of the study needs to be synchronized with an ECG of the patient. The tracing needs to have tall and peaked R waves to be recognized by the MRI. Prominent T waves should be avoided since might lead to confusion with the R waves. In order to obtain a good ECG, it is necessary to remove hair, dry the skin, and avoid the breast and sternum areas. The examination is performed in a supine position with the arms extended alongside the body.

To locate the heart, *single-shot* sequences were used to obtain quick images despite sacrificing spatial and temporal resolution. Location planes were obtained with a multiplanar multislice protocol (one image per R-R interval) in the strict orthogonal planes (axial, coronal, and sagittal). They were acquired during expiration since the position of the heart is more reproducible.

The cine steady-state free precision (cine SSFP) sequence allowed to have specific cardiac planes based on the multiplanar locators.

- 2 chamber cine SSFP: the locator is placed parallel to the IV septum.
- Short axis cine SSFP: sequences are perpendicular to the IV septum and paralel to the valvular plane.

7.4.2. Post-processing – Fieldwork

The post-processing and segmentation of cardiac images were performed with a specialized platform known as Medis Medical Imaging[2], which uses deep learning methods. The segmentation process involved 4 parts:

1. **Short axis**: the platformed contoured the endocardium and epicardium of the left ventricle (LV) and the endocardium of the right ventricle (RV) in a semi-automated manner. Initially, the platform identified the maximum systole and maximum diastole phases of both LV and RV, and then the software

[2] To read more about Medis Medical Imaging (33): https://medisimaging.com/software-solutions/medis-suite-mr/

automatically segmented these phases throughout all cardiac slices. It required to be reviewed and manually corrected if necessary.

See *Figure 4* and *Figure 5* for an explanation of the procedure through a screenshot of the platform.

The purpose of this whole procedure was to obtain data for the end-diastolic (ED) volume and end-systolic (ES) volumes of both ventricles, as well as the left ventricle mass. Values were computed using the summation of areas on each slice multiplied by the sum of slice thickness and image gap (Simpson's rule).

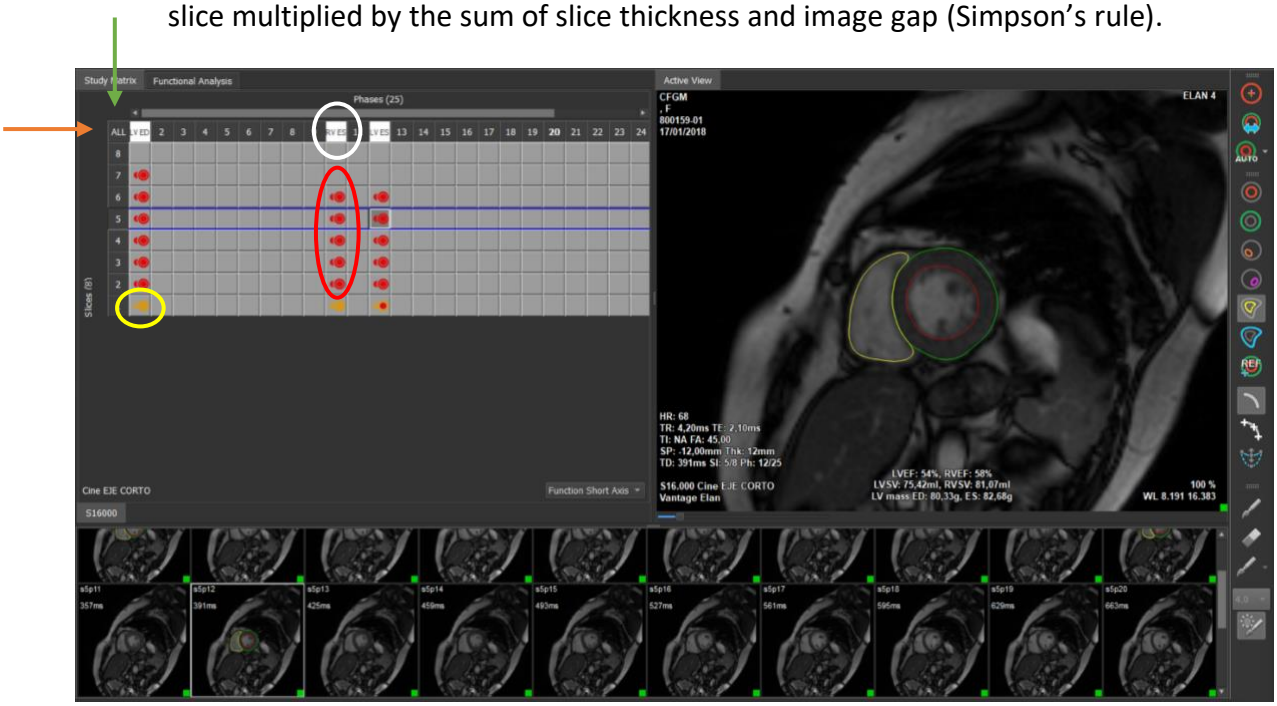

Figure 4. First part of post-processing on the Medis Medical Imaging software.

On the left side of the image, there are horizontal numbers representing different levels of contraction *(orange arrow),* and vertical numbers representing different cardiac slices from more basal to apical *(green arrow).* White boxes *(white circle)* correspond to the maximum systole and maximum diastole of each ventricle (LVED, LVES, RVED, RVES). This selection is provided by the program, and all slices of these phases are automatically segmented. Red marks *(red circle)* correspond to this automatic segmentation, while yellow marks *(yellow circle)* indicate manual changes made for correction or addition.

On the right side of the image, there is the CMR image. This is where the interpretation of the automated segmentation took place, and corrections were made as needed. Contours of the left ventricle endocardium (red) and epicardium (green), as well as the contour of the right ventricle (yellow) were the ones reviewed.

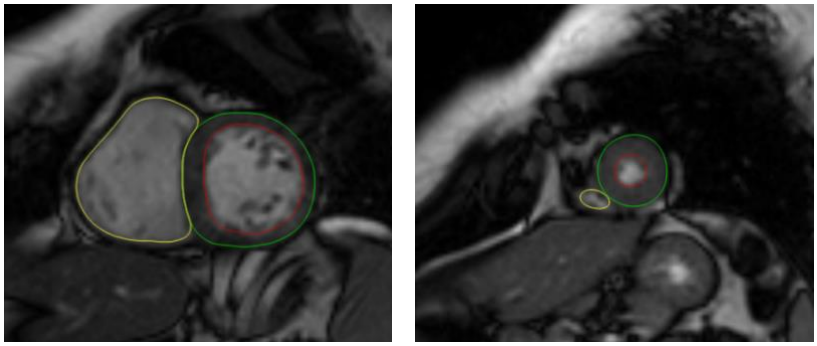

Figure 5. Segmentation of two different slices of the same phase.

2. **Short axis**: three short-axis cuts were selected at basal, middle, and apical levels. This selection enabled to obtain the radial strain.

   See *Figure 6*.

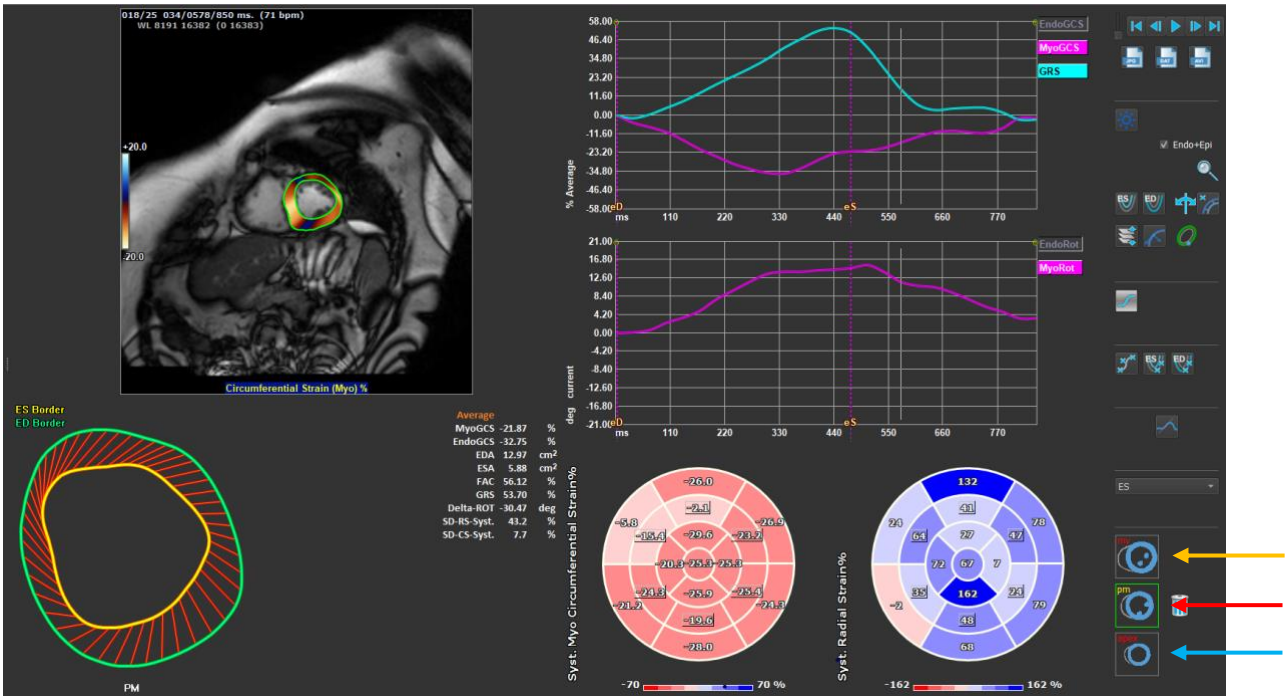

Figure 6. Second part of post-processing on the Medis Medical Imaging software.

In this screenshot, we appreciate the final part of this section, where the different selected cuts were available for analysis. On the right side of the image, the *yellow arrow* corresponds to the basal cut, the *red arrow* to the middle cut, and the *blue arrow* to the apical cut. On the left side, there is the CMR, which in this case was a middle cut.

In this final part of the analysis, this CMR image had movement, allowing us to verify if we had chosen a cut with good contractility or if it was better to opt for another.

3. **Long axis**: manual delineation of the LV was performed.

   This procedure enabled to obtain the longitudinal and circumferential strain.

   See *Figure 7* and *Figure 8.*

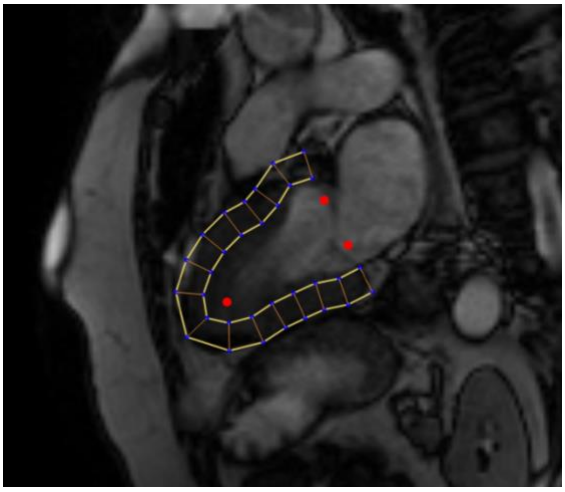

Figure 7. Third part of post-processing on the Medis Medical Imaging software. Manual delineation of the LV in the long axis. The three red points enabled the adjustment of the double yellow line, ensuring it matched the myocardium.

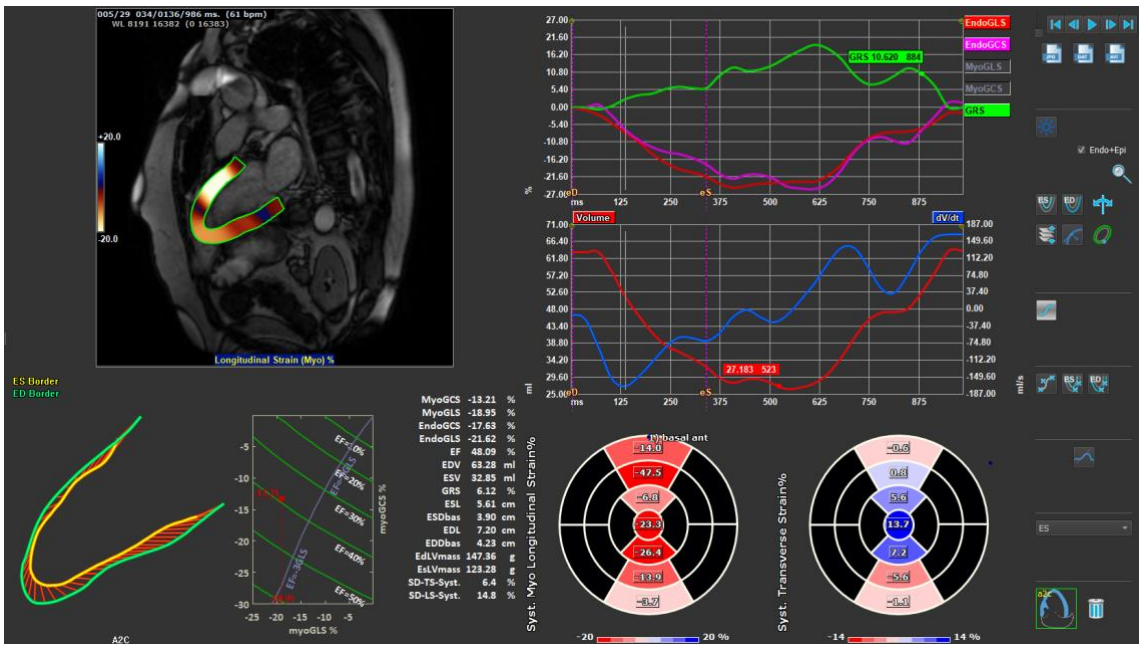

Figure 8. In the final part of this section, we verified myocardial delineation and contractility by observing CMR movement (upper left part of the image).

4. **Long axis**: manual delineation of the left atrium (LA) was performed.

   Variables obtained during this procedure were not ultimately used in this study.

   See *Figure 9* and *Figure 10.*

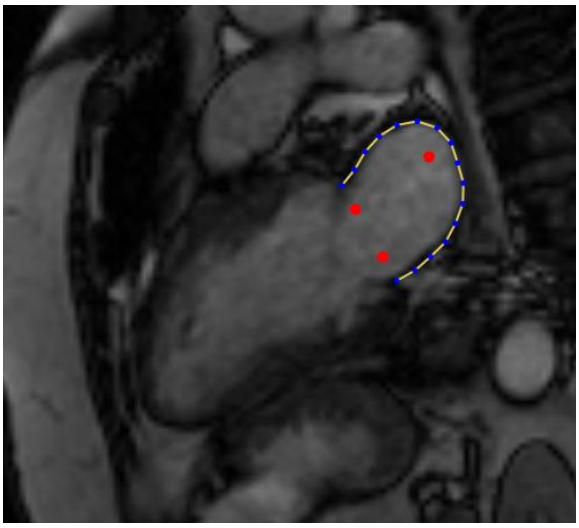

Figure 9. Fourth part of post-processing on the Medis Medical Imaging software.

The three red points enabled the adjustment of the yellow-blue line, ensuring it matched the LA.

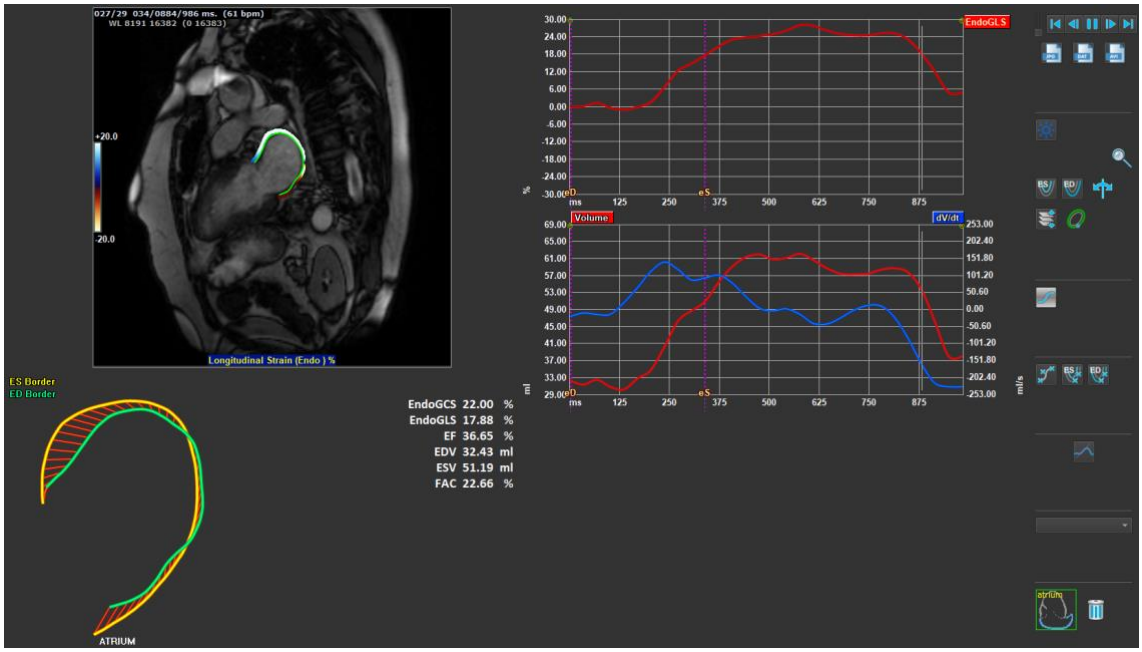

Figure 10. In the final part of this section, we verified atrium delineation and contractility by observing CMR movement (upper left part of the image).

7.5. VARIABLES

7.5.1. Independent Variables

- **Physical Activity (PA)**: assessed using the International Physical Activity Questionnaire (IPAQ), detailed in *Annex 2*. Results were initially obtained as a continuous variable, measured in Metabolic Equivalent of Task (MET) minutes per week. A MET is a multiple of the estimated resting energy expenditure, so to calculate the total METs, walking was considered to be 3.3 METS, moderate PA to be 4 METS and vigorous PA to be 8 METS.

  According to the IPAQ, continuous variables were later categorized into ordinal qualitative levels: low, moderate, and high.

  In this study, due to the limited number of participants in the lowest group, the 'low' and 'moderate' categories were merged into a single 'moderate-low' level, with a separate 'high' level.

  Categories

  - **HIGH level**: PA levels equate to approximately ≥ 1h/day of activity of at least a moderate intensity activity level.

    Those who score **HIGH** on the IPAQ engaged in:

    - ≥3 days of vigorous intensity activity achieving at least 1500 MET minutes a week OR
    - ≥7 days of any combination of walking, moderate intensity or vigorous intensity activities achieving a minimum total PA of at least 3000 MET minutes a week.

  - **MODERATE-LOW level:**

    - **MODERATE**: PA of at least moderate intensity equivalent to 30' on most days.

      Those who score **MODERATE** on the IPAQ engaged in:

      - ≥3 days of vigorous intensity activity and/or walking of at least 30'/day OR
      - ≥5 days of moderate intensity activity and/or walking of at least 30'/day OR

- ≥5 days of any combination of walking, moderate intensity or vigorous intensity activities achieving a minimum total PA of at least 600 MET minutes a week

▪ **LOW:** participants not meeting any of the criteria for either *moderate* or *high* PA.

It has to be taken into consideration that bouts of activity lasting less than 10' were not counted following IPAQ regulations. Moreover, it recommended that activity bouts greater than 3 hours be truncated.

- **Processing Speed**: described as *high* or *low*. It was measured with the Symbol Digit Test (SDT) of the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV). The task involved a sheet of paper upon which a table of paired digits and symbols was displayed. Below the table, there were rows of paired boxes. In the upper box, a digit was displayed and the participant's task was to fill in the blank lower box with the appropriate symbol from the table. See *Annex 3*. The time limit of the task was 120 seconds, and then, the number of correctly completed symbols was measured. Participants were classified according to whether they were above or below the 75th percentile adjusted for age and educational level.

- **Age**: measured in years.

7.5.2. Dependent Variables

All dependent variables are quantitative continuous and were obtained through the post-processing of the images using the 'Medis Medical Imaging' platform.

Structural parameters

All variables were normalized by the body surface area (BSA).

- **Left ventricle mass (LVM)** (g/m^2): it is a measure of the amount of myocardium in the left ventricle's walls.

- **Left ventricle end-diastolic volume (LVEDV)** (ml/m²): volume of blood in the left ventricle at the end of diastole. It represents the maximum capacity of the left ventricle to hold blood at the end of the relaxation phase.
- **Left ventricle end-systolic volume (LVESV)** (ml/m²): volume of blood in the left ventricle at the end of systole. It represents the minimum volume of blood in the left ventricle after contraction.
- **Left ventricle mass-to-volume ratio (LV M/V)** (g/ml): ratio of the left ventricle mass to left ventricle end-diastolic volume.
- **Right ventricle end-diastolic volume (LVEDV)** (ml/m²): volume of blood in the right ventricle at the end of diastole.
- **Right ventricle end-systolic volume (RVESV)**(ml/m²): volume of blood remaining in the right ventricle at the end of systole.

Functional parameters

- **Left ventricle ejection fraction (LVEF)** (%): percentage of blood pumped out of the left ventricle during each heartbeat, calculated as: [(LVESV-LVEDV)/LVEDV]* 100
- **Left ventricle stroke volume (LVSV)** (ml/m²): volume of blood ejected from the left ventricle during each heartbeat, calculated as: LVEDS – LVEDV.
- **Left ventricle cardiac output (LVCO)** (l/(min*m²): volume of blood pumped by the left ventricle per minute, calculated as: (LVEDS – LVEDV)*Heart Rate
- **Left ventricle endocardial global longitudinal strain (LV EndoGLS)** (%): percentage of change in the length of the inner layer of the left ventricle's wall in the longitudinal direction during the cardiac cycle. See *Annex 4* for a visual representation.
- **Left ventricle endocardial global circumferential strain (LV EndoGCS)** (%): percentage of change in the circumference of the inner layer of the left ventricle's wall in the circumferential direction during the cardiac cycle. See *Annex 4* for a visual representation.
- **Left ventricle global radial strain (LV GRS)** (%): percentage of change in the thickness of the entire left ventricle's wall in the radial direction during the cardiac cycle. See *Annex 4* for a visual representation.

- **Right ventricle ejection fraction (RVEF)** (%): percentage of blood pumped out of the right ventricle during each heartbeat, calculated as: [(RVESV-LVEDV)/RVEDV]*100
- **Right ventricle stroke volume (RVSV)** (ml/m²): volume of blood ejected from the right ventricle during each heartbeat, calculated as: RVEDS – RVEDV.

The stroke volume of both ventricles as well as the left ventricle cardiac output were normalized by the BSA.

7.5.3. Co-variables

- **Age**: measured in years.

- **Sex**: defined as male or female.

- **HTA**: defined as yes or no. Self-reported.

- **DM**: defined as yes or no. Self-reported.

- **Dyslipidemia**: defined as yes or no. Self-reported.

7.6. STATISTICAL ANALYSIS

Analyzes were conducted using R[3] version 4.3.1. to examine relationships between variables. Descriptive tables compared males and females using chi-squared (χ^2) or Fisher's exact test when low cell counts in the comparison of categorical variables, expressed as number (%). T-tests or Welch's tests were utilized to compare sexes concerning continuous descriptive variables, expressed as mean (SD).

Categorical variables included 'moderate-low' and 'high' levels of physical activity, and 'high' and 'low' levels of processing speed. Comparisons of various structural and

[3] R Core Team (2023). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/ (34).

functional cardiac parameters between categories were performed using either Student's T-tests or Welch's tests, according to whether the homogeneity of the variances could be assumed or not.

Linear regression models were also performed to assess the relationship of physical activity and processing speed (both included as categorical) with the cardiac parameters in separate models. Models were fit for the overall sample and stratified by sex to check for potential different effects across sexes. Different adjusted models were done to control for potential confounders: *Model 1* adjusted by age, *Model 2* adjusted by age and sex, *Model 3* adjusted by age and CVRF, *Model 4* adjusted by age, sex, and CVRF. Cardiovascular risk factors included HTA, dyslipidemia and DM.

The relationship between aging and cardiac parameters, both of which were continuous variables, was assessed using linear regression models for the entire sample and stratified by sex. Adjusted models were done to control for potential confounders: *Model 1 adjusted* by sex, Model 2 adjusted by CVRF (including HTA, dyslipidemia and DM), Model 3 adjusted by sex and CVRF.

All structural variables and some functional variables including stroke volume and cardiac output were adjusted for Body Surface Area (BSA). Analyses with p-values less than 0.05 were considered statistically significant. Confidence intervals (CI) were computed at the 95% of confidence interval.

8. ETHICAL ASPECTS

The protocol for 'The Aging Imageomics Study' was approved by the Clinical Research Ethics Committee (CEIC) from Hospital Universitari Doctor Josep Trueta, on October 27th. See *Annex 5*.

This investigation adheres to the 64th Declaration of Helsinki signed by the World Medical Association in October 2013, ensuring alignment with human rights and ethical principles. Additionally, it respects the Principles of Biomedical Ethics of Beauchamp and Childress from 1970, last reviewed in 2009: autonomy, justice, beneficence, and non-maleficence.

Throughout the study, the values and personal choices of participants have been respected, informing them of their freedom to decline participation at any time. To ensure a clear understanding of the project, an informational sheet detailing the study protocol was provided and explained by a member of the team. Refer to *Annex 6*. Furthermore, participants were supplied with a contact number to address any additional concerns.

Signed informed consent was needed before enrolling in the study. Moreover, an additional sheet where individuals could choose to decline being informed about potential findings was made available. See *Annex 7*.

Researchers had no conflict of interest. The primary motivation behind researchers involvement was to generate scientific knowledge in order to improve the quality of life in the process of aging.

9. RESULTS

A total number of 2181 participants from the 'MARK' and 'MESGI50' studies were initially considered potential candidates for 'The Aging Imageomics Study'. However, the final sample ultimately consisted of 1030 participants. This reduction in the sample size was attributed to various factors, including deaths, unavailability for contact, failure to meet the inclusion criteria, and declines in participation.

Among the final pool, 233 subjects did not undergo the CMR or their images could not be synchronized with the electrocardiogram (ECG), and 30 individuals did not attend the second visit. Additionally, 21 individuals had missing information regarding physical activity (PA) or the Symbol Digit Test (SDT). As a result, the analyzed sample consisted of 746 participants (mean age, 66.85 ± 7.08 years; range, 50-98 years; 46% females), 44% from the 'MESGI50' and 56% from the 'MARK' study. These participants had analyzable CMR images as well as complete information about PA and processing speed. Notably, 218 participants of the final analyzed sample lacked data on the longitudinal and circumferential strain, and thus, results regarding these variables are only available for 528 participants. This limitation is attributed to the incorrect orientation of the heart in the long axis, which prevented the delineation of the left ventricle during the third step of the post-processing acquisition. *Figure 11* is a flowchart showing the process.

Table 1 provides a summary of the sociodemographic characteristics of the study population, stratified by sex. Educational level and working status were grouped into three categories. There were no significant differences regarding sex.

Table 2 presents cardiovascular risk factors stratified by sex. It includes hypertension (HTA), which was present in almost half of the study population (45.54%), systolic and diastolic blood pressure, as well as metabolic risk factors such as diabetes (DM), dyslipidemia, levels of total cholesterol, HDL and LDL cholesterol, and fasting triglycerides. More males had hypertension than females, and they also had higher values of diastolic blood pressure, with these differences being statistically significant. In contrast, parameters of cholesterol (total, HDL and LDL) were significantly higher in females. Other important variables such as smoking, level of PA, and adherence to the

Mediterranean diet are also presented, outlining sex differences in physical activity. Additionally, it provides insights into the prevalence of specific CV conditions and personal and family history of CVD. Few participants had been diagnosed with heart failure (1,22%) and atrial fibrillation (1,76%).

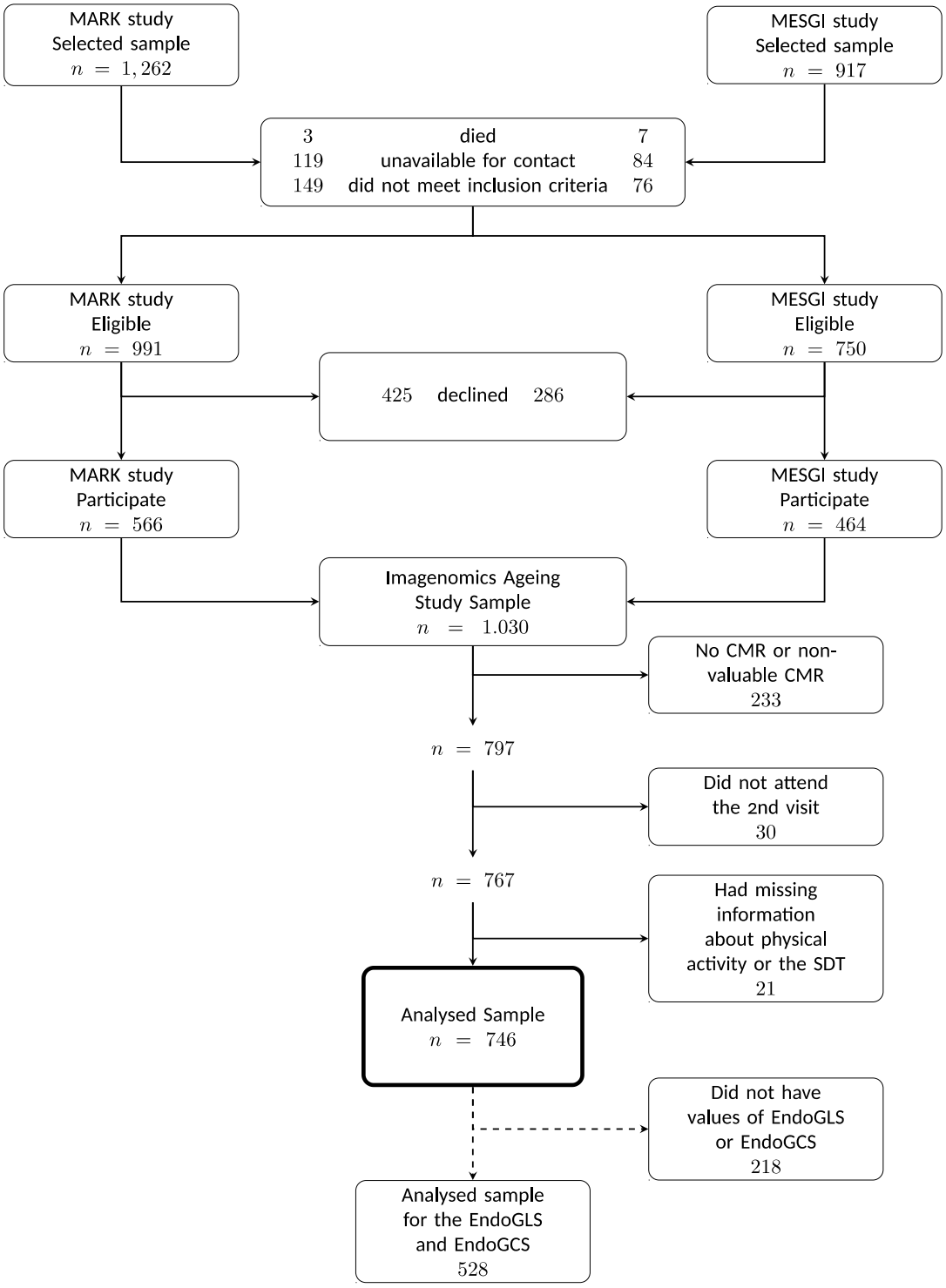

Figure 11. Flowchart of the study.

Table 1. Sociodemographic characteristics of the study population

Variables	Category	Total sample	Female	Male
N, mean (SD)		746	341	405
Age (years), mean (SD)		66.86 (7.06)	66.19 (7.31)	67.43 (6.79)
Education level, n (%)	Up to primary	420 (56.76)	200 (58.82)	220 (55.00)
	Secondary	235 (31.76)	104 (30.59)	131 (32.75)
	University	85 (11.49)	36 (10.59)	49 (12.25)
Working status, n (%)	Retired	527 (71.22)	230 (67.85)	297 (74.06)
	Employed	173 (23.38)	84 (24.78)	89 (22.19)
	Unemployed/sick	40 (5.41)	25 (7.37)	15 (3.74)

Table 2. Cardiovascular risk factors and medical history of the study population

Cardiovascular risk factors	Category	Total sample	Female	Male
Hypertension, n (%)		337 (45.54)	139 (40.88)	198 (49.50)*
Systolic blood pressure (mmHg), mean (SD)		147.98 (19.11)	148.90 (20.77)	147.21 (17.58)
Diastolic blood pressure (mmHg), mean (SD)		89.23 (9.75)	87.75 (9.74)	90.48 (9.60)*
Diabetes, n (%)		156 (21.02)	68 (19.94)	88 (21.95)
Dyslipidemia, n (%)		202 (27.30)	84 (24.71)	118 (29.50)
Total cholesterol (mg/dL), mean (SD)		198.01 (34.56)	206.06 (32.54)	191.25 (34.79)*
HDL cholesterol (mg/dL), mean (SD)		53.37 (16.06)	58.83 (17.07)	48.80 (13.59)*
LDL cholesterol (mg/dL), mean (SD)		120.80 (31.12)	123.69 (30.26)	118.34 (31.66)*
Fasting triglycerides (mg/dL), mean (SD)		121.67 (74.43)	117.95 (60.40)	124.80 (84.37)
Smoke, n (%)		119 (16.15)	51 (15.18)	68 (16.96)
Physical activity levels, n (%)	High	368 (49.33)	143 (41.94)	225 (55.56)*
	Moderate	318 (42.63)	166 (48.68)	152 (37.53)
	Low	60 (8.04)	32 (9.38)	28 (6.91)
Mediterranean diet adherence, n (%)	High	235 (31.67)	110 (32.45)	125 (31.02)
	Moderate	445 (59.97)	203 (59.88)	242 (60.05)
	Low	62 (8.36)	26 (7.67)	36 (8.93)
Medical history of CVD				
Heart failure, n (%)	Yes	9 (1.22)	4 (1.19)	5 (1.25)
Atrial fibrillation, n (%)	Yes	13 (1.76)	7 (2.08)	6 (1.50)
Personal history cardiovascular disease, n (%)	Yes	119 (16.10)	51 (15.13)	68 (16.92)
Family history cardiovascular disease, n (%)	Yes	281 (38.55)	148 (44.71)	133 (33.42)*

(*) Significant differences regarding females and males (p-value <0,05)

Descriptive cardiac parameters, organized into structural and systolic functional variables, are shown in Table 3 and Table 4. Both tables are stratified by sex, and p-values were calculated to assess the presence of statistically significant differences between sexes. In all variables means were higher in males and significantly different from females. Notably, strains including GRS and EndoGLS, were the only parameters that did not show sex-based differences. It's worth noting that all variables fall within the normal range, consistent with a non-disease population.

Table 3. Left ventricle (LV) and right ventricle (RV) *structural* variables

Structural variables	**Total sample**	**Female**	**Male**	**p-value**
LV Mass (g/m²)	45.77 (8.87)	42.73 (7.62)	48.34 (9.03)	**p<0.001**
LV End-Diastolic Volume (ml/m²)	62.38 (14.58)	59.46 (13.32)	64.85 (15.15)	**p<0.001**
LV End-Systolic Volume (ml/m²)	23.22 (9.32)	21.59 (8.83)	24.60 (9.51)	**p<0.001**
LV Mass/Volume Ratio (g/m²)	0.75 (0.15)	0.74 (0.13)	0.77 (0.17)	**0.003**
RV End-Diastolic Volume (ml/m²)	62.24 (15.94)	55.88 (12.21)	67.60 (16.73)	**p<0.001**
RV End-Systolic Volume (ml/m²)	25.61 (9.03)	21.57 (6.77)	29.02 (9.30)	**p<0.001**

Data are expressed as mean (SD)
All variables are adjusted for Body Surface Area.
P-value indicates differences between men and women.

Table 4. Left ventricle (LV) and right ventricle (RV) *functional* variables

Functional variables		**Total sample**	**Female**	**Male**	**p-value**
LV Ejection Fraction (%)		63.41 (9.26)	64.40 (8.86)	62.58 (9.51)	**0.007**
LV Stroke Volume* (ml/m²)		39.16 (9.33)	37.87 (8.21)	40.25 (10.05)	**p<0.001**
LV Cardiac Output* (l/(min*m²))		2.68 (0.64)	2.60 (0.57)	2.74 (0.68)	**0.002**
LV Endocardial Global Longitudinal Strain (%)		-18.42 (5.75)	-18.91 (5.86)	-17.96 (5.62)	0.058
	Missings, n (%)	218 (29.22)	85 (24.93)	133 (32.84)	
LV Endocardial Global Circumferential Strain (%)		-25.60 (10.77)	-26.60 (10.34)	-24.66 (11.10)	**0.038**
	Missings, n (%)	218 (29.22)	85 (24.93)	133 (32.84)	
LV Global Radial Strain (%)		68.18 (41.04)	66.23 (30.14)	69.83 (48.33)	0.233
RV Ejection Fraction (%)		58.81 (10.28)	61.19 (9.81)	56.80 (10.25)	**p<0.001**
RV Stroke Volume (ml/m²)*		36.63 (11.08)	34.31 (9.47)	38.59 (11.95)	**p<0.001**

Data are expressed as mean (SD)
(*) Variables adjusted for Body Surface Area.
P-value indicates differences between men and women.

9.1. PHYSICAL ACTIVITY

Table 5 presents the differences between the 'moderate-low' and 'high' physical activity levels. It is worth noting that the number of participants and the mean age were similar in both groups. However, there were notable differences in terms of sex distribution. The mean of the METs-minute per week in the 'moderate-low' group was 1540.34 and the in the 'high' group was 7804.11. The number of participants with hypertension, diabetes and dyslipidemia was similar in both groups.

The relationship between the level of PA and different structural variables of the heart is included in Table 6. In all variables, means were lower in the 'moderate-low' activity group, except for the LV mass-to-volume ratio, which showed no differences. Significant differences were observed for LVM, LVEDV, RVEDV and RVESV. Conversely, LVESV and LV M/V ratio were not significant.

Regarding cardiac functional variables only the LVSV, LVCO, and LV EndoGCS variables were positively associated with physical exercise, with lower values in participants from the 'moderate-low' group. The LV EndoGCS was the functional variable exhibiting the most significant relationship (p-value 0,026). Contrary to the structural parameters, the right ventricle showed no significant differences in functional variables. See Table 7.

Linear regression models were also performed to assess the relationship of the variables. In Table 8, unadjusted results are presented for the overall sample and stratified by sex. Notably, when stratified by sex, most parameters lost their statistical significance. The only exceptions were a significant increase of 2.64% in the LV EndoGCS among women in the 'high' PA group, and a modest increase of 0.14 (l/(min*m^2) in LVCO among men in the 'high' PA group.

In Table 9, linear regression models were adjusted into different models, but no meaningful changes were observed when adjusting by age and CVRF (HTA, dyslipidemia and DM) in comparison to the unadjusted model. However, once results were adjusted for sex, all variables, except for RVEDV and RVESV, lost their significance.

Table 5. Description of the participants in the 'moderate-low' and 'high' groups of physical activity

Variable description	Category	Total sample	Moderate-Low	High	p-value
Participants, n		746	378	368	
Sex, n (%)	Female	341 (45.71)	198 (52.38)	143 (38.86)	**p<0.001**
	Male	405 (54.29)	180 (47.62)	225 (61.14)	
Age, mean (SD)		66.86 (7.06)	66.91 (7.52)	66.81 (6.55)	0.844
Total physical activity (mets-minutes/week), mean (SD)		4,630.24 (4,289.78)	1,540.34 (856.73)	7,804.11 (4,082.58)	**p<0.001**
Hypertension, n (%)		337 (45.54)	179 (47.61)	158 (43.41)	0.283
Dyslipidemia		202 (27.30)	100 (26.60)	102 (28.02)	0.724
Diabetes		156 (21.02)	79 (20.90)	77 (21.15)	1.000

Table 6. Cardiac *structural* variables categorized by the level of physical activity

Structural variables	Total sample	Moderate-Low	High	p-value
Participants	746	378	368	
LVM (g/m²)	45.77 (8.87)	45.02 (8.67)	46.55 (9.01)	**0.019**
LVEDV (ml/m²)	62.38 (14.58)	61.22 (14.02)	63.58 (15.06)	**0.028**
LVESV (ml/m²)	23.22 (9.32)	22.73 (9.01)	23.73 (9.61)	0.145
LV M/V ratio (g/ml)	0.75 (0.15)	0.76 (0.15)	0.75 (0.15)	0.806
RVEDV (ml/m²)	62.24 (15.94)	60.39 (15.46)	64.15 (16.21)	**0.001**
RVESV (ml/m²)	25.61 (9.03)	24.47 (9.01)	26.79 (8.92)	**p<0.001**

Data are expressed as mean (SD)

All variables are adjusted for Body Surface Area

Table 7. Cardiac *functional* variables categorized by the level of physical activity

Functional variables	Total sample	Moderate-Low	High	p-value
LVEF (%)	63.41 (9.26)	63.48 (9.33)	63.33 (9.19)	0.827
LVSV* (ml/m²)	39.16 (9.33)	38.49 (9.13)	39.85 (9.49)	**0.047**
LVCO* (l/(min*m²))	2.68 (0.64)	2.63 (0.62)	2.72 (0.65)	**0.044**
LV EndoGLS (%)	-18.42 (5.75)	-18.65 (5.50)	-18.19 (5.98)	0.361
LV EndoGCS (%)	-25.60 (10.77)	-26.66 (10.18)	-24.58 (11.24)	**0.026**
LV GRS (%)	68.18 (41.04)	68.14 (31.53)	68.23 (48.97)	0.975
RVEF (%)	58.81 (10.28)	59.48 (10.85)	58.11 (9.62)	0.070
RVSV (ml/m²)*	36.63 (11.08)	35.92 (11.03)	37.36 (11.11)	0.075

Data are expressed as mean (SD)

(*) Variables adjusted for Body Surface Area

Table 8. Coefficients of linear regression models assessing the association between categories of physical activity and cardiac variables

Structural variables	**Total**	**Females**	**Males**
LVM* (g/m²)	**1.53 (0.26,2.80) [0.019]**	-0.15 (-1.80,1.50) [0.860]	1.55 (-0.22,3.33) [0.085]
LVEDV* (ml/m²)	**2.35 (0.26,4.44) [0.028]**	0.79 (-2.09,3.66) [0.591]	2.37 (-0.60,5.34) [0.118]
LVESV* (ml/m²)	0.99 (-0.34,2.33) [0.145]	0.63 (-1.28,2.53) [0.519]	0.58 (-1.29,2.45) [0.545]
LV M/V ratio* (g/ml)	-0.00 (-0.02,0.02) [0.806]	-0.01 (-0.04,0.02) [0.399]	-0.00 (-0.04,0.03) [0.855]
RVEDV* (ml/m²)	**3.76 (1.49,6.04) [0.001]**	1.16 (-1.48,3.79) [0.388]	3.10 (-0.18,6.38) [0.064]
RVESV* (ml/m²)	**2.32 (1.03,3.61) [p<0.001]**	0.99 (-0.47,2.45) [0.182]	1.62 (-0.20,3.45) [0.081]
Functional variables			
LVEF (%)	-0.15 (-1.48,1.18) [0.827]	-0.66 (-2.58,1.25) [0.497]	0.73 (-1.14,2.60) [0.442]
LVSV* (ml/m²)	**1.36 (0.02,2.70) [0.047]**	0.16 (-1.62,1.94) [0.859]	1.80 (-0.17,3.77) [0.074]
LVCO* (l/(min*m²))	**0.09 (0.00,0.19) [0.044]**	0.00 (-0.12,0.13) [0.967]	**0.14 (0.00,0.27) [0.044]**
LV EndoGLS (%)	0.46 (-0.53,1.44) [0.361]	0.15 (-1.31,1.62) [0.837]	0.44 (-0.92,1.81) [0.524]
LV EndoGCS (%)	**2.08 (0.24,3.91) [0.027]**	**2.64 (0.08,5.21) [0.043]**	0.99 (-1.71,3.69) [0.472]
LV GRS (%)	0.09 (-5.81,6.00) [0.975]	-3.24 (-9.75,3.26) [0.327]	1.96 (-7.55,11.47) [0.686]
RVEF (%)	-1.36 (-2.84,0.11) [0.070]	-0.87 (-2.99,1.25) [0.420]	-0.71 (-2.73,1.30) [0.486]
RVSV (ml/m²)*	1.44 (-0.15,3.03) [0.075]	0.17 (-1.88,2.21) [0.873]	1.48 (-0.87,3.82) [0.217]

Data are expressed as coefficients (95% confidence interval) [p-value]

(*) Variables adjusted for Body Surface Area

Table 9. Coefficients of linear regression models assessing the association between categories of physical activity and cardiac variables

Structural variables	Model 1	Model 2	Model 3	Model 4
LVM* (g/m²)	**1.53 (0.26,2.80) [0.018]**	0.78 (-0.44,2.00) [0.210]	**1.66 (0.40,2.93) [0.010]**	0.54 (-0.70,1.77) [0.395]
LVEDV* (ml/m²)	**2.33 (0.25,4.42) [0.028]**	1.60 (-0.47,3.67) [0.131]	**2.50 (0.38,4.62) [0.021]**	1.23 (-0.91,3.38) [0.259]
LVESV* (ml/m²)	0.99 (-0.35,2.33) [0.147]	0.58 (-0.76,1.91) [0.396]	1.08 (-0.28,2.44) [0.119]	0.40 (-0.98,1.79) [0.569]
LV M/V ratio* (g/ml)	-0.00 (-0.02,0.02) [0.827]	-0.01 (-0.03,0.02) [0.564]	-0.00 (-0.02,0.02) [0.845]	-0.007 (-0.029,0.016) [0.552]
RVEDV* (ml/m²)	**3.74 (1.47,6.01) [0.001]**	**2.15 (0.01,4.28) [0.049]**	**4.20 (1.93,6.47) [p<0.001]**	**2.19 (0.00,4.38) [0.050]**
RVESV* (ml/m²)	**2.32 (1.03,3.60) [p<0.001]**	**1.31 (0.12,2.50) [0.031]**	**2.64 (1.37,3.91) [p<0.001]**	**1.51 (0.31,2.70) [0.014]**
Functional variables				
LVEF (%)	-0.15 (-1.48,1.19) [0.831]	0.11 (-1.23,1.45) [0.871]	-0.17 (-1.51,1.16) [0.797]	0.20 (-1.16,1.57) [0.768]
LVSV* (ml/m²)	**1.35 (0.01,2.68) [0.048]**	1.02 (-0.32,2.36) [0.135]	**1.42 (0.08,2.77) [0.039]**	0.83 (-0.54,2.20) [0.233]
LVCO* (l/(min*m²))	**0.09 (0.00,0.19) [0.045]**	0.07 (-0.02,0.17) [0.112]	**0.10 (0.01,0.19) [0.036]**	0.06 (-0.03,0.15) [0.209]
LV EndoGLS (%)	0.46 (-0.52,1.44) [0.358]	0.31 (-0.68,1.31) [0.537]	0.50 (-0.50,1.50) [0.325]	0.23 (-0.79,1.25) [0.657]
LV EndoGCS (%)	**2.08 (0.24,3.91) [0.027]**	1.80 (-0.07,3.66) [0.059]	**2.20 (0.34,4.06) [0.021]**	1.51 (-0.40,3.41) [0.121]
LV GRS (%)	0.06 (-5.84,5.96) [0.985]	-0.50 (-6.45,5.45) [0.868]	-0.89 (-6.87,5.09) [0.771]	-1.12 (-7.06,4.82) [0.710]
RVEF (%)	-1.37 (-2.85,0.10) [0.067]	-0.80 (-2.26,0.65) [0.279]	**-1.57 (-3.06,-0.09) [0.038]**	-1.07 (-2.56,0.42) [0.159]
RVSV (ml/m²)*	1.43 (-0.16,3.01) [0.077]	0.83 (-0.74,2.40) [0.298]	1.56 (-0.04,3.17) [0.056]	0.69 (-0.94,2.32) [0.407]

Model 1: adjusted by age; **Model 2**: adjusted by age and sex; **Model 3**: adjusted by age and CVRF (HTA, dyslipidemia, DM); **Model 4**: adjusted by age, sex and CVRF (HTA, dyslipidemia, DM).

Data are expressed as coefficients (95% confidence interval) [p-value]

(*) Variables adjusted for Body Surface Area.

9.2. PROCESSING SPEED

Table 10 and 11 display the relationship between the level of processing speed, categorized as 'low' and 'high' and cardiac structural and functional changes. No significant associations were observed with any cardiac variable.

Furthermore, Table 12 presents unadjusted coefficients from linear regression models, both for the overall sample and stratified by sex. However, no significant relationships were identified in the analysis.

Linear regression models were adjusted by age, by age and sex, by age and CVRF (HTA, dyslipidemia and DM), and by age, sex and CVRF. However, as there were no meaningful changes compared with the unadjusted model, the results presented in this section are unadjusted and stratified by sex. To see adjusted results refer to *Annex 8*.

Table 10. Relationship between cardiac *structural* variables and level of processing speed

Structural variables	Total sample	Low	High	p-value
Participants	746	459	287	
LVM (g/m²)	45.77 (8.87)	45.82 (9.24)	45.69 (8.24)	0.848
LVED (ml/m²)	62.38 (14.58)	62.52 (14.94)	62.17 (14.02)	0.754
LVESV (ml/m²)	23.22 (9.32)	23.24 (9.41)	23.20 (9.18)	0.953
LV M/V ratio (g/ml)	0.75 (0.15)	0.75 (0.16)	0.75 (0.15)	0.964
RVEDV (ml/m²)	62.24 (15.94)	62.32 (15.93)	62.13 (15.97)	0.879
RVESV (ml/m²)	25.61 (9.03)	25.57 (9.17)	25.68 (8.82)	0.863

Data are expressed as mean (SD)

All variables are adjusted for Body Surface Area

Table 11. Relationship between cardiac *functional* variables and level of processing speed

Variable description	Total sample	Low	High	p-value
LVEF (%)	63.41 (9.26)	63.43 (9.21)	63.38 (9.36)	0.948
LVSV* (ml/m²)	39.16 (9.33)	39.28 (9.50)	38.98 (9.06)	0.668
LVCO* (l/(min*m²))	2.68 (0.64)	2.68 (0.65)	2.67 (0.62)	0.854
LV EndoGLS (%)	-18.42 (5.75)	-18.40 (5.84)	-18.44 (5.60)	0.942
LV EndoGCS (%)	-25.60 (10.77)	-25.45 (11.06)	-25.88 (10.25)	0.655
LV GRS (%)	68.18 (41.04)	66.87 (44.82)	70.28 (34.11)	0.269
RVEF (%)	58.81 (10.28)	58.93 (10.33)	58.60 (10.21)	0.668
RVSV (ml/m²)*	36.63 (11.08)	36.75 (11.17)	36.45 (10.95)	0.720

Data are expressed as mean (SD)

(*) Variables adjusted for Body Surface Area

Table 12. Coefficients of linear regression models assessing the association between categories of processing speed and cardiac variables

Structural variables	**Total**	**Females**	**Males**
LVM* (g/m²)	-0.13 (-1.44,1.18) [0.848]	-0.56 (-2.27,1.15) [0.518]	-0.54 (-2.33,1.25) [0.553]
LVEDV* (ml/m²)	-0.34 (-2.50,1.81) [0.754]	-2.59 (-5.56,0.39) [0.088]	0.69 (-2.32,3.69) [0.652]
LVESV* (ml/m²)	-0.04 (-1.42,1.34) [0.953]	-0.93 (-2.90,1.05) [0.357]	0.25 (-1.64,2.13) [0.795]
LV M/V ratio* (g/ml)	0.00 (-0.02,0.02) [0.964]	0.03 (-0.00,0.06) [0.085]	-0.02 (-0.06,0.01) [0.154]
RVEDV* (ml/m²)	-0.18 (-2.54,2.17) [0.879]	-1.91 (-4.64,0.82) [0.169]	-0.40 (-3.72,2.92) [0.814]
RVESV* (ml/m²)	0.12 (-1.22,1.45) [0.863]	-0.43 (-1.95,1.08) [0.573]	-0.45 (-2.29,1.40) [0.633]
Functional variables			
LVEF (%)	-0.05 (-1.41,1.32) [0.948]	0.05 (-1.93,2.04) [0.959]	0.12 (-1.77,2.01) [0.900]
LVSV* (ml/m²)	-0.30 (-1.68,1.08) [0.668]	-1.66 (-3.49,0.17) [0.076]	0.44 (-1.55,2.43) [0.664]
LVCO* (l/(min*m²))	-0.01 (-0.10,0.09) [0.854]	-0.10 (-0.22,0.03) [0.136]	0.04 (-0.09,0.18) [0.553]
LV EndoGLS (%)	-0.04 (-1.07,0.99) [0.942]	-0.01 (-1.56,1.54) [0.987]	-0.19 (-1.57,1.18) [0.781]
LV EndoGCS (%)	-0.44 (-2.36,1.49) [0.655]	-1.11 (-3.84,1.62) [0.424]	-0.14 (-2.86,2.58) [0.921]
LV GRS (%)	3.42 (-2.64,9.48) [0.269]	1.87 (-4.89,8.62) [0.587]	4.18 (-5.39,13.76) [0.391]
RVEF (%)	-0.33 (-1.85,1.19) [0.668]	-0.73 (-2.93,1.46) [0.512]	0.57 (-1.46,2.60) [0.583]
RVSV (ml/m²)*	-0.30 (-1.94,1.34) [0.720]	-1.48 (-3.59,0.64) [0.171]	0.05 (-2.32,2.42) [0.967]

Data are expressed as coefficients (95% confidence interval) [p-value]

(*) Variables adjusted for Body Surface Area

9.3. CARDIAC AGING

A comprehensive overview of the relationship between age and various cardiac parameters is detailed in Table 13. Among the structural variables, significant inverse associations with the LV and RV end-diastolic volumes were observed. For each year of increasing age, these volumes decreased by approximately -0,17 ml/m² and -0.20 ml/m², respectively. The LV M/V ratio, on the other hand, exhibited significant change with age, with a coefficient of 0.003 g/ml. No age-related associations with LVM or systolic volumes for both LV and RV were found. Moving on to functional variables, age displayed a significant inverse relationship with LVSV, LVCO, and RVSV. Ejection fraction for both ventricles, as well as strain measurements, remained unrelated to age.

The table also exhibits this relationship stratified by sex. In males, all variables retained their statistical significance, and even the RVESV exhibited significant change with age, showing a coefficient of -0.15ml/m^2. For females, only the LV M/V ratio, RVEDV and RVSV maintained statistical significance, losing it for LVEDV, LVSV and LVCO.

Linear regression models were separately adjusted by sex and age, as well as together. However, no significant changes were observed compared to the unadjusted model, except for the appearance of statistically significant decrease of the RVESV when adjusting for sex. The results presented in this section are unadjusted and stratified by sex. To see adjusted results refer to *Annex 8*.

Table 13. Coefficients of linear regression models assessing the association between age and cardiac variables

Structural variables	**Total**	**Females**	**Males**
LVM* (g/m²)	0.03 (-0.06,0.12) [0.500]	0.04 (-0.07,0.15) [0.442]	-0.05 (-0.18,0.08) [0.454]
LVEDV* (ml/m²)	**-0.17 (-0.32,-0.02) [0.022]**	-0.15 (-0.34,0.05) [0.134]	**-0.27 (-0.48,-0.05) [0.016]**
LVESV* (ml/m²)	-0.06 (-0.15,0.04) [0.234]	-0.07 (-0.20,0.06) [0.266]	-0.08 (-0.22,0.06) [0.248]
LV M/V ratio* (g/ml)	**0.003 (0.002,0.005) [p<0.001]**	**0.003 (0.001,0.005) [0.003]**	**0.003 (0.001,0.006) [0.009]**
RVEDV* (ml/m²)	**-0.20 (-0.36,-0.03) [0.018]**	**-0.20 (-0.38,-0.03) [0.025]**	**-0.34 (-0.58,-0.10) [0.006]**
RVESV* (ml/m²)	-0.04 (-0.13,0.05) [0.373]	-0.02 (-0.12,0.07) [0.631]	**-0.15 (-0.28,-0.02) [0.026]**
Functional variables			
LVEF (%)	0.03 (-0.07,0.12) [0.577]	0.07 (-0.06,0.20) [0.276]	0.01 (-0.13,0.14) [0.933]
LVSV* (ml/m²)	**-0.12 (-0.21,-0.02) [0.017]**	-0.08 (-0.19,0.04) [0.218]	**-0.19 (-0.33,-0.04) [0.011]**
LVCO* (l/(min*m²))	**-0.01 (-0.01,-0.00) [0.034]**	-0.00 (-0.01,0.00) [0.376]	**-0.01 (-0.02,-0.00) [0.016]**
LV EndoGLS (%)	0.05 (-0.03,0.12) [0.217]	0.03 (-0.07,0.14) [0.529]	0.04 (-0.06,0.15) [0.397]
LV EndoGCS (%)	0.02 (-0.12,0.16) [0.788]	-0.02 (-0.20,0.17) [0.840]	0.03 (-0.18,0.23) [0.794]
LV GRS (%)	-0.35 (-0.76,0.07) [0.103]	-0.08 (-0.52,0.36) [0.737]	-0.66 (-1.36,0.03) [0.061]
RVEF (%)	-0.10 (-0.20,0.01) [0.073]	-0.14 (-0.28,0.01) [0.059]	-0.00 (-0.15,0.15) [0.972]
RVSV (ml/m²)*	**-0.15 (-0.27,-0.04) [0.007]**	**-0.18 (-0.32,-0.04) [0.011]**	**-0.19 (-0.36,-0.01) [0.034]**

Coefficients represent change in the dependent variable per 1-year increase in age.

Data are expressed as coefficients (95% confidence interval) [p-value]

(*) Variables adjusted for Body Surface Area

10. DISCUSSION OF RESULTS

In the context of our research, we evaluated physical activity, processing speed, and aging and its association between cardiac structural and functional parameters in a non-athletic population aged ≥50 years.

10.1. PHYSICAL ACTIVITY

In our study, initial analyses suggested a potential association between various structural and functional cardiac variables and the level of physical activity. After adjusting for age and CVRF, this association remained robust. However, once the models were adjusted by sex, most variables lost their statistical significance. The only exceptions were for the RVEDV and RVESV, both of which showed a significant increase in the high physical activity group compared to the 'moderate-low' group.

Unadjusted sex-stratified results sustained an increase in the LV EndoGCS (2,64 %) in females with high levels of physical activity. In males, a subtle increase in LVCO was statistically significant, although the magnitude was modest (0.14 (l/(min*m²)). Possible factors influencing these sex-specific associations warrant further investigation. Surprisingly, RVEDV and RVESV were not statistically significant in sex-stratified results possibly due to limitations in statistical power.

Collectively, these findings suggest a general lack of association between 'high' and 'moderate-low' levels of PA concerning the left ventricle, while there is an association between the right ventricle structural variables.

In the existing literature, there is a study within the 'MESA' (12) that assessed various levels of physical activity and their impact on the cardiac structure and function of the left ventricle. Exercise was also evaluated using METs, and cardiac variables were assessed by CMR. However, in contrast to our study, they used a semiquantitative questionnaire called Typical Week Physical Activity Survey (TWPAS), which only took into account intentional exercise. Results revealed significant changes in the LVM, LVEDV, LVESV and LVSV, with stronger associations observed in males. However, it is

worth noting that the magnitude of these variables was minimal, so they did not represent a substantial impact from a physiological perspective. The largest coefficient comparing physical activity groups was for the LVEDV at 4.18 ml/m^2 more than the lower groups, representing an increase of only 2%. The 'MESA' did not find any significant differences in terms of the LV M/V ratio, LVEF and LVCO.

Although results from 'MESA' are not directly comparable, and values are not stratified by sex, the study features informative sex-stratified graphs. These revealed that approximately the magnitude of change in LVEDV in both men and women resembled our study (being 0.79 in women and 2.37 in men), contrary to the LVM, whose values were much lower in our study both for males and females. The pattern of the LV M/V ratio was similar in both studies, with no sex-based differences (coefficient of 0.01 g/ml). When considering LVSV, the increase in our results was consistent with those of males in the 'MESA', but not in females. Overall, despite the lack of statistically significant results for all these variables, coefficients in our study also presented greater magnitude in males. However, it is important to emphasize that the magnitude of changes at the physiological level is minimal.

It should be noted that contrary to the 'MESA', our study measured not only intentional activities but also casual walking. Although the percentage of METs representing casual walking was not analyzed, since our population's mean age is 66 years we can assume it is a significant portion of the calculated METs. Thus, differences between these studies could arise due to the requirement of a higher level of intentional physical activity to achieve significant cardiac changes. Moreover, it's worth considering that the 'MESA' had 4.992 participants, which is seven times larger than our study's population, so they had greater statistical power to detect smaller, yet significant changes.

Notably, our study distinguished itself by analyzing left ventricle strains, encompassing EndoGCS, EndoGLS, and GRS. These variables allowed us to explore more precisely systolic function, even though we only found one association in females. In this case, for those engaged in higher levels of PA, LV EndoGCS was notably 2.64% higher, indicating improved cardiac contraction compared to those engaged in 'moderate-low' levels of physical activity.

In another separate investigation conducted within the 'MESA' (35), researchers examined the relationship between intentional physical activity and the structure and function of the right ventricle. Characteristics resembled the left ventricle study but with a sample size of 1876 participants. They evaluated RVEDV, RVSV and RVEF, revealing significant associations for the first two variables. Results were adjusted by age, sex and CVRF. Notably, our research mirrored the 'MESA' in revealing a substantial increase in RVEDV (2,19 ml/m^2) within the high physical activity group, even though the significance of this increase hovered on the edge of statistical significance. Likewise, both studies found RVEF not significant. Differently from the 'MESA', our study did not find significant changes for the RVSV. Additionally, we analyzed the RVESV, which was statistically significant, with a coefficient of 1.51 ml/m^2 more in the high physical activity group.

The existing literature only features these studies with similar goals and characteristics. More research is needed to provide a deeper understanding of the extent of structural and functional cardiac changes at different levels of physical activity. It would be intriguing to investigate whether the cardiac changes appear when comparing populations of a wider age range, including individuals under 50 years. Additionally, exploring a broader spectrum of METS could enhance the knowledge of this relationship. On the other hand, future research may need to consider that the beneficial effects of physical activity may not be directly tied to structural and functional cardiac changes but also due to the contribution of a more favorable cardiovascular risk profile.

10.2. PROCESSING SPEED

In the present study, none of the cardiac structural or functional variables were found to be associated with processing speed levels.

Other studies such as the cross-sectional 'Framingham Heart Study' (18) evaluated the inverse relationship with CMR in the absence of heart failure. They stratified LVEF and examined its impact on various cognitive tests, including the 'Trail Making Test', which is considered to evaluate executive functions and processing speed. Surprisingly, higher

LVEF levels (≥73.2%) were associated with poorer mean cognitive performance compared with the referent range (62-73.2%), while lower levels (<62%) showed no such association. These results are somehow controversial, since patients with heart failure and lower levels of LVEF have been associated with an increased risk of dementia (17), as well as a reduction in processing speed measures (36), but not the opposite way.

Another relevant study within the 'MESA' (19), examined processing speed using the Symbol Digit Test in a large population without clinically recognized CVD, similar to our study. They found that LVM significantly differed from the test outcome, showing an inverse relationship with a coefficient of -0.105 g/m^2. Thus, a lower level of processing speed was associated with greater LVM. The LV M/V ratio was also examined, and while it was considered significant, it exhibited a very weak association with a coefficient of -0.001 g/ml and a confidence interval that nearly included zero (-0.612,-0.000). Consequently, even though it seems their structural parameters differed from ours, their low magnitudes suggest that a larger sample size might have been required to establish a similar relationship. Moreover, it is important to note that these minor changes do not represent a noteworthy discovery despite the statistical significance. Additionally, in the 'MESA', systolic functional parameters including LVEF, LVSV, and LV circumferential strain were not significantly different, aligning with our findings. It is worth noting that it is unclear how the outcome of the SDT was measured, which might differ from our approach.

These two studies are the only ones in the literature that measure cognitive function with processing speed tests and that involve a substantial number of participants (1114 and 4999 respectively). Moreover, both studies employed CMR for assessing cardiac parameters, which has proven to be the most accurate method (28).

Our study also assessed structural and functional cardiac parameters not studied in previous literature. It included variables like LVEDV, LVESV, LVCO, and various functional variables such as EndoGLS, EndoGCR, and GRS. Moreover, we extended our investigation to the right ventricle, exploring volumes, ejection fraction, and stroke volume. None of these parameters demonstrated an association.

In conclusion, we did not find a significant association between processing speed and cardiac structural and functional variables, but there are still numerous other cognitive skills yet to be explored. In addition, while studying the magnitude of individual cognitive abilities is valuable, aging is a complex process, and so it may be also relevant to investigate cognition as a holistic capacity.

10.3. CARDIAC AGING

Some age-related cardiac structural and functional changes were found in this study. Even after adjusting for sex and CVRF, these associations remained robust. As age increased, all variables decreased except for the LV M/V ratio, which increased by 0.003 g/ml per year. Notably, when results were stratified by sex, differences emerged. Males exhibited a significant decrease in the LVEDV, RVEDV, LVSV, LVCO and RVSV, along with an increase in the LV M/V ratio. Moreover, males presented a statistically significant decrease in the RVESV, which was only observed when the sample was stratified by sex, and when the models were adjusted by sex. In contrast, females only showed a significant decrease in the RVEDV and RVSV, with an increase in the LV M/V ratio. Differences between sexes might be attributed to variations in cardiac aging between sexes or could be the result of limitations in statistical power.

It's worth noting that findings of the overall sample regarding LVEDV, LVM and the LV M/V ratio align with a study conducted within the 'MESA' (20). However, our study did not identify significant changes in the LVESV. In terms of functional variables, the significant decrease of the LVSV also aligns with the 'MESA' with approximately the same magnitude, with a reduction of -0,13ml/m^2 each year.

On the other hand, our study revealed no age-related changes in the LVEF, contrary to the 'MESA' which there was an increase of 0,09% each year. They explain it due to the progressive decline in the LV volumes, particularly the LVESV, a variable that did not show a significant decrease in our study. The enhanced LVEF contrasts with trends seen in other studies, where this parameter is not influenced by age (10,22).

Notably, LVCO and strains were not analyzed in the 'MESA'. Our study found a significant decrease in the LVCO, but the magnitude of the coefficient was very modest (-0.01 l/(min*m^2) each year of age), so it represents little change. It is important to highlight the lack of age-related changes regarding strains, which supports the idea of the preserved systolic function seen in our study since strains are considered to be more sensitive than LVEF (26).

A systematic review and meta-analysis which comprised studies of at least a sample size of ≥50 subjects and with healthy ≥18 years old participants found no statistical differences towards LVESV, LVM and LVEF, but significant differences regarding LVEDV, which mirrored our study (21).

Our results identified distinct sex-specific patterns of age-related structural and functional changes in the heart. Notably, left ventricular changes were predominantly observed in males, which could be partly attributed to the fact that males had higher baseline values across these variables compared to females, potentially amplifying the impact of age-related changes. However, it is important to take into account that our study had a slightly larger number of male participants (405 males compared to 341 females), which might have contributed to the increased statistical power in this group.

11. CONCLUSIONS

Main conclusions

- In individuals aged ≥50 years, a higher level of physical activity was not found to be associated with increased **left ventricle mass**, **volumes** or **mass-to-volume ratio**.

- In individuals aged ≥50 years, a higher level of processing speed was not found to be associated with increased **left ventricle mass**, **volumes** or **mass-to-volume ratio**.

- In individuals aged ≥50 years, increasing age was not found to be associated with changes in the **left ventricle mass** or **left ventricle end-systolic volume**. However, a reduction in the **left ventricle end-diastolic** volume was found to be associated in males and an increase in the **left ventricle mass-to-volume ratio** was found to be associated in both sexes.

Secondary conclusions

- In individuals aged ≥50 years, a higher level of physical activity was not found to be associated with increased **left ventricle ejection fraction** or **stroke volume**. However, an increase in the **left ventricle global endocardial circumferential strain** was found to be associated in females and an increase in the **left ventricle cardiac output** was found to be associated in males.

- In individuals aged ≥50 years, a higher level of physical activity was found to be associated with increased **right ventricle volumes** but no association with increased **right ventricle ejection fraction** or **stroke volume** was found**.**

- In individuals aged ≥50 years, a higher level of processing speed was not found to be associated with increased **left ventricle ejection fraction**, **stroke volume**, **cardiac output** or **strains**.

- In individuals aged ≥50 years, a higher level of processing speed was not found to be associated with increased **right ventricle volumes**, **ejection fraction** or **stroke volume.**

- In individuals aged ≥50 years, increasing age was not found to be associated with changes in **left ventricle ejection fraction** or **strains**. However, in males, a reduction in **left ventricle stroke volume** and **cardiac output** was found.

- In individuals aged ≥50 years, increasing age was found to be associated with structural changes in the **right ventricle**. **End-diastolic volume** decreased in both sexes, while **end-systolic volume** only decreased in males. **Right ventricle ejection fraction** remained stable, but increasing age was found to be associated with a reduction in **stroke volume.**

12. STRENGTHS AND LIMITATIONS

Our research had several strengths that enhanced the robustness of our results. It benefited from a substantial local community-based cohort, comprising a total sample size of 746 participants. Notably, it employed CMR, recognized as the most accurate and reliable technique for assessing cardiac structure and function ensuring the highest quality of data and precision in our results. Additionally, the study was conducted using a systematic methodology and rigorous data collection techniques. It incorporated well-defined variables and tests that reduced ambiguity.

On the other hand, there were also limitations. Participants were recruited from two cohorts, one of which included participants with low to moderate cardiovascular risk which could have potentially influenced cardiac variables. However, to mitigate this bias, results were adjusted by CVRF. Furthermore, adjusted results were not different from those unadjusted. Moreover, although CMR was used, 233 acquisitions were not well synchronized, preventing the evaluation of those participants. They were random losses, so results should not have been influenced. It is also worth noting that there is no international consensus on a correct method for describing PA levels derived from self-report questionnaires. Comparisons between different methods can be problematic. The scoring method used in this study was the IPAQ, but it is designed for adults between 16 and 69 years of age. The mean age of our sample was 66.85 with an age range of 50-98 years. Although the questionnaire would not be recommended due to the age of our participants, it was chosen for its relatively short duration, as participants were required to complete multiple tests.

In terms of data analyses, adjusted CVRF models need to take into consideration that hypertension, dyslipidemia, and diabetes were self-reported variables. However, adjusted results were not different from those unadjusted. Furthermore, our study is cross-sectional and observational, hence, we are unable to establish causal connections between variables, only association. Lastly, this research aimed to explore relationships in a sample representing the province of Girona, which may limit its external validity.

13. REFERENCES

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14. ANNEXES

14.1. ANNEX 1 – Magnetic Resonance Imaging Acquisition Protocol

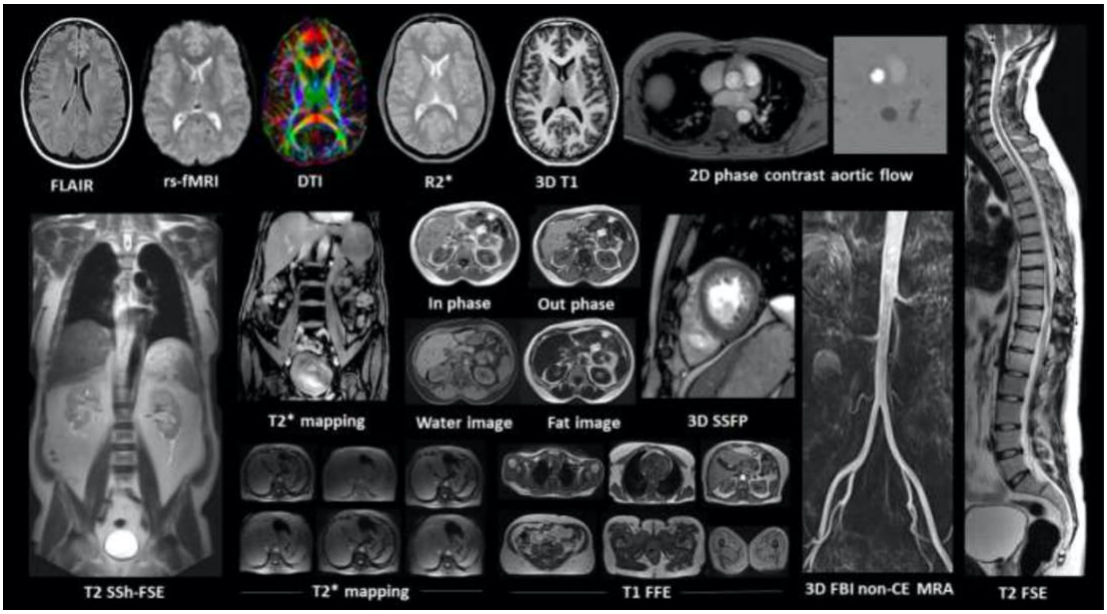


Figure 1. Magnetic resonance imaging acquisition protocol.
Abbreviations: DTI, diffusion tensor imaging; FLAIR, fluid attenuation inversion recovery; rsfMRI, resting-state functional magnetic resonance imaging; SSFP, steady-state free precession; SSh-FSE: single-shot fast spin echo; TSE, turbo spin echo.
Extracted from (37).

14.2. ANNEX 2 - International Physical Activity Questionnaire (IPAQ)

CUESTIONARIO INTERNACIONAL DE ACTIVIDAD FÍSICA (IPAQ)

Piense en todas las actividades **VIGOROSAS** que usted realizó en los **últimos 7 días.** Las actividades físicas intensas se refieren a aquellas que implican un esfuerzo físico intenso y que lo hacen respirar mucha más intensamente que lo normal. Piense **sólo** en aquellas actividades físicas que realizó durante por lo menos **10 minutos** seguidos.	
1. Durante los últimos 7 días ¿En cuántos realizo actividades físicas vigorosas tales como levantar pesos pesados, cavar, hacer ejercicios aeróbicos o andar rápido en bicicleta?	☐ Días por semana ☐ Ninguna actividad física intensa (vaya a la pregunta 3)
2. Habitualmente, ¿Cuánto tiempo en total dedicó a una actividad física intensa en uno de esos días? (ejemplo: si practicó 20 minutos marque 0 h y 20 min)	☐ Horas por día ☐ Minutos por día ☐ No sabe/no está seguro
Piense en todas las actividades **MODERADAS** que usted realizó en los **últimos 7 días.** Las actividades moderadas son aquellas que requieren un esfuerzo físico moderado que lo hace respirar algo más intensamente que lo normal. Piense solo en aquellas actividades que realizó durante por lo menos 10 minutos seguidos.	
3. Durante los últimos 7 días, ¿En cuántos días hizo actividades físicas moderadas como transportar pesos livianos, andar en bicicleta a velocidad regular o jugar a dobles en tenis? **No** incluya caminar.	☐ Días por semana ☐ Ninguna actividad física intensa (vaya a la pregunta 5)
4. Habitualmente, ¿Cuánto tiempo en total dedicó a una actividad física moderada en uno de esos días? (ejemplo: si practicó 20 minutos marque 0 h y 20 min)	☐ Horas por día ☐ Minutos por día ☐ No sabe/no está seguro
Piense en el tiempo que usted dedicó a **CAMINAR** en los **últimos 7 días**. Esto incluye caminar en el trabajo o en la casa, para trasladarse de un lugar a otro, o cualquier otra caminata que usted podría hacer solamente para la recreación, el deporte, el ejercicio o el ocio.	
5. Durante los últimos 7 días, ¿En cuántos caminó por lo menos 10 minutos seguidos?	☐ Días por semana ☐ Ninguna actividad física intensa (vaya a la pregunta 7)
6. Habitualmente, ¿Cuánto tiempo en total dedicó a caminar en uno de esos días?	☐ Horas por día ☐ Minutos por día ☐ No sabe/no está seguro

La ultima pregunta es acerca del tiempo que pasó usted **SENTADO** durante los días hábiles de los **últimos 7 dias.** Esto incluye el tiempo dedicado al trabajo, en la casa, en una clase, y durante el tiempo libre. Puede incluir el tiempo que paso sentado ante un escritorio, leyendo, viajando en autobús, o sentado o recostado mirando tele.	
7. Habitualmente, ¿Cuánto tiempo pasó sentado durante un día hábil?	☐ Horas por día ☐ Minutos por día ☐ No sabe/no está seguro

Valor del test:

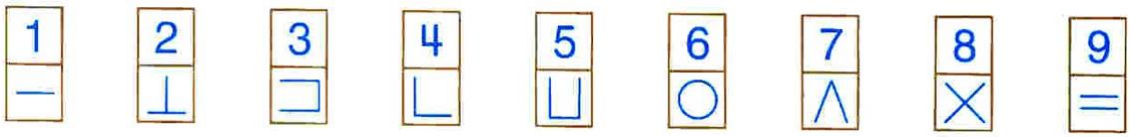
1. Actividad física **vigorosa**: 8 MET x minutos x días por semana
2. Actividad física **moderada**: 4 MET x minutos x días por semana
3. **Caminata**: 3,3 x minutos x días por semana.

Ejemplo: 8 MET x 30 minutos x 5 días = 1200 MET (**ACTIVIDAD FÍSICA INTENSA**)

A continuación sume los tres valores obtenidos:

TOTAL= Actividad física vigorosa + Actividad física Moderada + caminata

14.3. ANNEX 3 – Symbol Digit Test (WAIS-IV)



Ejemplos

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4

5	6	3	1	4	1	5	4	2	7	6	3	5	7	2	8	5	4	6	3

7	2	8	1	9	5	8	4	7	3	6	2	5	1	9	2	8	3	7	4

6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1	7

9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

2	7	3	6	5	1	9	8	4	5	7	3	1	4	8	7	9	1	4	5

7	1	8	2	9	3	6	7	2	8	5	2	3	1	4	8	4	2	7	6

14.4. ANNEX 4 – Schematic Representation of Strains

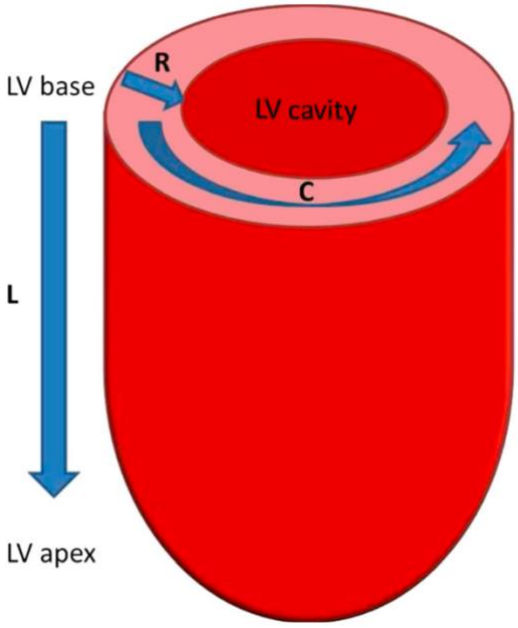


Figure 2. Schematic picture representing the left ventricle (LV) and the myocardial deformation directions. ***L*** longitudinal shortening, ***C*** circumferential shortening, ***R*** radial thickening.

Extracted from (26).

14.5. ANNEX 5 – Approval of the Research Ethics Committee

Hospital Universitari de Girona
Doctor Josep Trueta

Avinguda de França s/n.
17007 Girona
Telèfon 972 940 200
www.gencat.net/ics/trueta

Marta Riera Juncà, Secretària del Comitè d'Ètica d'Investigació CEI GIRONA, amb domicili a l'Hospital Universitari de Girona Dr. Josep Trueta Avinguda de França s/n 17007 Girona

CERTIFICA

Que el Comitè d'Ètica d'Investigació CEI GIRONA, segons consta en l'acta de la reunió celebrada el dia 24/10/2017 ha avaluat el projecte: **Imagenoma de l'envelliment: Estudi observacional poblacional per al desenvolupament de biomarcadors d'imatge corporal integral basats en ressonància magnètica en individus de 50 anys d'edat o més i la seva relació amb factors de l'esfera biopsicosocial, cardiovascular, metabolòmica, lipidòmica, microbiòmica i altres factors associats a l'envelliment. Cod SLT002-16/00250.** Protocol v. 01:01/09/17 QRD v01:01/09/17, FIP i CI v2:28/09/17 i FIP i CI obtenció mostra directe Biobanc col IME v1:set 17 v en català i castellà, FIP i CI projecte amb final Biobanc col IME v1:set 17 v en català i castellà amb el Dr. JOSEP PUIG ALCÁNTARA com a investigador principal.

Que els documents s'ajusten a les normes ètiques essencials i per tant, ha decidit la seva aprovació.

I, perquè consti, expedeixo aquest certificat.

Hospital Universitari de Girona
Doctor Josep Trueta
Comitè Ètic
d'investigació Clínica
Institut Català de la Salut

Girona, a 27 d'octubre de 2017

55002196

Generalitat de Catalunya
Departament de Salut

Institut Català de la Salut

14.6. ANNEX 6 – Information Sheet for the participant

FULL D'INFORMACIÓ AL PARTICIPANT DE L'ESTUDI
"IMAGENOMA DE L'ENVELLIMENT"

Benvolguda/Benvolgut,

Agraïm novament la seva col·laboració en l'estudi MESGI50 (Maduresa i Envelliment Satisfactori a Girona) que realitzem a diversos municipis de les comarques gironines i en el qual vostè hi participa des de l'any 2013. Aquest estudi està contribuint a millorar els coneixements que tenim sobre quines són i com canvien les circumstàncies vitals de les persones a partir dels 50 anys.

Els investigadors d'aquest estudi estem molt interessants en conèixer l'estat de salut dels participants i l'efecte que diverses malalties poden provocar durant el procés d'envelliment i en la qualitat de vida de les persones. Per aquest motiu s'ha constituït un grup de recerca que incorpora investigadors de l'Institut d'Investigació Biomèdica de Girona, de l'Institut de Recerca Biomèdica de Lleida, de l'Hospital Universitari Dr. Josep Trueta de Girona, de l'Institut d'Assistència Sanitària, de la Universitat de Girona i de la Universitat Pompeu Fabra de Barcelona per fer un MESGI50 encara més complert que incorpori diverses proves mèdiques, el **+MESGI50** i hem dissenyat un projecte de recerca que s'anomena **IMAGENOMA DE L'ENVELLIMENT**. El grup està composat per 44 investigadors de diferents especialitat com la imatge mèdica, la cardiologia, la endocrinologia, la neurologia, l'atenció primària, la microbiologia, la neuropsicologia, la bioestadística i la nutrició entre d'altres.

Abans que decideixi si participa en aquest estudi o no, és important que conegui quins són els objectius de l'estudi i què implica la seva participació. Si us plau, faci servir el temps que necessiti per a llegir tota la informació amb deteniment abans de prendre una decisió.

Quina és la finalitat de l'estudi?
L'estudi IMAGENOMA DE L'ENVELLIMENT vol desenvolupar marcadors d'imatge corporal basats en ressonància magnètica (que és una prova mèdica que utilitza un potent imant i ones de ràdio per poder visualitzar amb detall estructures internes del nostre cos) i conèixer la relació que hi ha amb altres marcadors de salut, com per exemple, els resultats d'una analítica de sang, el resultat d'un electrocardiograma o la seva capacitat de memòria entre molts altres marcadors de salut.

Per què és important aquest estudi?

Els resultats d'aquest estudi poden ajudar a conèixer millor el procés d'envelliment biològic del nostre cos i la seva relació amb moltes malalties freqüents en aquesta etapa de la vida com la hipertensió arterial, la diabetis o la malaltia d'Alzheimer entre d'altres. En la mesura en que l'estudi analitzarà molta informació sobre l'estil de vida i la salut això permetrà poder identificar factors de risc i desenvolupar recomanacions per promoure un procés d'envelliment satisfactori.

Per què em conviden a participar?

El convidem a participar perquè vostè ja forma part d'un estudi sobre la Maduresa i l'Envelliment Satisfactori a Girona, l'estudi MESGI i en l'entrevista que hem fet aquest any en el seu domicili ens va expressar el seu interès en participar.

Haig de participar obligatòriament?

No, en absolut. La seva participació és totalment voluntària i en qualsevol moment pot deixar de participar en l'estudi sense haver d'explicar-ne els motius.

En què consistirà la meva participació?

Si decideix participar se li programaran dues visites al Parc Hospitalari Martí i Julià de Salt on es troben les instal·lacions i aparells necessaris per fer les proves d'aquest estudi. En la **primera visita** se li farà la ressonància magnètica de cos sencer, una ecografia de les arteries del coll i un estudi de la composició corporal. Al finalitzar aquestes proves se l'informarà sobre el procediment de recollida de mostres biològiques de la segona visita, se li facilitarà un pot per recollir una mostra de femta, un pot per recollir una mostra d'orina i uns senzills qüestionaris que s'hauran d'entregar a la segona visita. A la **segona visita** haurà de venir en dejú per tal de fer una extracció sanguínia i haurà d'entregar el pot amb la mostra de femta i el pot amb la mostra d'orina per tal de cedir i formalitzar la donació de les mostres al Biobanc de l'Institut d'Investigació Biomèdica de Girona per futures investigacions. Previ a l'entrada de la mostra de sang al Biobanc, es farà una determinació dels paràmetres bioquímics més freqüents. També haurà d'entregar els qüestionaris de la primera visita. A continuació se li realitzarà un electrocardiograma, una exploració física que inclourà mesures de pressió i rigidesa arterial i un conjunt de proves per avaluar el seu estat d'ànim i diferents funcions mentals com la memòria, l'atenció o la capacitat visual i perceptiva.

Com s'utilitzaran les meves dades en aquest estudi?

Participant en aquest estudi realitzaria una contribució de gran valor per a la investigació científica. Les dades obtingudes de tots els participants només s'utilitzaran per a fins d'investigació científica. A la llarga, els resultats seran publicats en revistes científiques i presentats en congressos científics. Evidentment, les publicacions i presentacions mai contindran el nom o una altra informació que permeti identificar les persones que hi ha

participat. L'ús comercial d'aquestes dades està estrictament prohibit i no es vendran mai ni les mostres ni els resultats.

A la base de dades del projecte IMAGENOMA DE L'ENVELLIMENT no hi apareixerà ni el nom ni cap altre dada de caràcter personal que el pugui identificar. Les dades que es registrin seran codificades en una base de dades que mantindrà la confidencialitat de la informació de tots els participants. A cada registre individual se li assignarà un codi, de manera que no serà possible conèixer la identitat de cap dels participants.

Totes les dades que generi aquest estudi seran estrictament confidencials i només hi tindran accés els investigadors, les autoritat sanitàries, els membres del Comitè Ètic d'Investigació Clínica i el personal autoritzat per garantir la qualitat i l'anàlisi de les dades, tal com obliga la Llei Orgànica 15/1999 de 13 de desembre, de Protecció de dades de caràcter personal. Totes les dades seran processades, analitzades i guardades a l'Institut d'Investigació Biomèdica de Girona amb domicili a Carrer del Dr. Castany, s/n, 17190 de Salt i a l'Institut de Recerca Biomèdica de Lleida amb domicili a Av. Alcalde Rovira Roure, 80, 25198 de Lleida. Les mostres de sang, femta i orina recollides seran processades i custodiades al Biobanc IDIBGi per futures investigacions. Vostè podrà exercir en qualsevol moment els seus drets d'accés, rectificació, cancel·lació i oposició, així com obtenir informació sobre l'ús de les seves mostres i dades associades, dirigint-se a:

Dr. Josep Puig
Institut de Diagnòstic per la Imatge.
Institut d'Investigació Biomèdica de Girona.
Hospital Universitari Dr. Josep Trueta de Girona. Av de França s/n; 17007 Girona
Tel: 972 486 020 / Fax: 972 486 085

Quins riscos i beneficis tindré si participo?

La ressonància magnètica no representa cap risc per a la seva salut. Tanmateix, si vostè porta un marcapassos, implants a l'oïda interna (coclears), articulacions artificials recentment implantades o algun tipus especial de vàlvula cardíaca no podrà fer-se la prova. Abans de fer la ressonància magnètica els investigadors li faran un seguit de preguntes per garantir la seva seguretat en la realització de la ressonància magnètica. Els riscos associats a la punxada per a la realització de l'extracció de sang són els mateixos que els que podria experimentar per una analítica sol·licitada pel seu metge de família. En general, l'extracció de sang s'associa a riscos petits, encara que podria causar una mica de dolor, un petit hematoma per on entra l'agulla o ansietat davant les agulles. Les inflamacions o la lesió dels nervis o del sistema vascular només succeeixen en casos extremadament rars. Es prendran precaucions per a evitar aquests

inconvenients per part dels professionals sanitaris de l'estudi. La recollida de la mostra de femta i orina no suposarà cap risc afegit per a vostè.

Un benefici important pel fet de participar en aquest estudi és que a vostè se li farà una extensa bateria de proves mèdiques i en el cas que es detecti alguna anomalia que requereixi una atenció mèdica específica vostè serà informat i derivat als dispositius sanitaris oportuns (metge especialista en medicina familiar i comunitària o metge especialista hospitalari). En el cas de que no volgués ser informat dels resultats de les proves mèdiques haurà d'especificar-ho en el full de sol·licitud de rebuig a ser informat dels resultats de les exploracions mèdiques.

Quines avantatges i inconvenients tindré si participo?

Si decideix participar en l'estudi se li proporcionarà un informe complert amb els resultats de la prova de ressonància magnètica on es detallarà l'estat de diferents parts del seu cos com el cervell, el cor, el fetge, la arteria aorta, la columna vertebral i les articulacions. També se li farà arribar al seu domicili els resultats de l'analítica de sang i l'electrocardiograma perquè vostè ho pugui compartir amb el seu metge de família si ho considera convenient. Així mateix, d'acord amb els resultats obtinguts, rebrà un conjunt de recomanacions per afavorir el seu estat de salut. Tots els resultats de les proves mèdiques li facin no tindran cap cost econòmic per a vostè, però tampoc rebrà cap compensació econòmica per la seva participació.

El principal inconvenient de participar en aquest estudi és que haurà de desplaçar-se en dues ocasions al Parc Hospitalari Martí i Julià de Salt per tal que els tècnics i professionals de l'estudi fi facin les proves, recullin les mostres biològiques i li facin un conjunt de preguntes i tests per conèixer el seu estat de salut. La durada prevista de cada visita és de una hora i l' interval entre la primera i segona visita serà de uns 15 dies aproximadament (els gestors del l'estudi s'ajustaran a la seva disponibilitat per programar les visites). La primera visita la podrà fer o bé al matí o bé a la tarda. Tanmateix, la segona visita es farà pel matí, vostè haurà de venir en dejú per tal de fer l'extracció de sang i proporcionar una mostra de femta en el pot especial que se li proporcionarà en la primera visita. Està previst també habilitar alguns caps de setmana per facilitar les visites de les persones que per compromisos laborals o familiars tinguin dificultats per desplaçar-se entre setmana.

Qui ha revisat aquest estudi?

Aquest document ha estat revisat i aprovat pel Comitè Ètic d'Investigació Clínica de l'Hospital Universitari Dr. Josep Trueta. Aquest comitè té la responsabilitat de garantir que els estudis acompleixin les normes vigents i els protocols de bona pràctica clínica i ètica.

Qui finança aquest estudi?

Aquest estudi està finançat per una beca competitiva del Pla Estratègic de Recerca i Innovació en Salut (2016-2020) del Departament de Salut de la Generalitat de Catalunya amb l'objectiu de generar nou coneixement que tingui una repercussió directa en la millora de la salut dels ciutadans.

A qui puc dirigir-me per demanar més informació?

Per a més informació, pot posar-se en contacte amb l'investigador principal de l'estudi MESGI50 o bé amb l'investigador principal del projecte IMAGENOMA DE L'ENVELLIMENT. No dubti a consultar-l'hi si ho considera necessari. Si us plau, pregunti tots els dubtes que tingui i prengui's el temps necessari per decidir si vol participar en aquest estudi.

Dr. Josep Puig. Institut de Diagnòstic per la Imatge Institut d'Investigació Biomèdica de Girona Hospital Universitari Dr. Josep Trueta de Girona Av de França s/n; 17007 Girona Tel: 972 486 020 / Fax: 972 486 085	Dr. Josep Garre-Olmo Institut d'Assistència Sanitària Institut d'Investigació Biomèdica de Girona Edifici Mancomunitat 1 C/ Dr Castany s/n 17190 Salt Tel: 972 182 600 / Fax: 972 486 085

Una vegada més, li agraïm molt l'atenció que ens ha dispensat.

14.7. ANNEX 7

14.7.1. Informed consent sheet

FORMULARI DE CONSENTIMENT INFORMAT AL PARTICIPANT DE L'ESTUDI "IMAGENOMA DE L'ENVELLIMENT"

Jo, _____
(Nom i cognoms)

He llegit el full d'informació que m'ha lliurat.

He pogut fer preguntes sobre l'estudi 'IMAGENOMA DE L'ENVELLIMENT'.

He rebut suficient informació sobre l'estudi.

He parlat amb Josep Puig o col·laborador, amb telèfon de contacte 972486020 i declaro que:

- Comprenc que la meva participació és voluntària
- Comprenc que puc retirar-me de l'estudi quan vulgui sense haver de donar explicacions
- Presto lliurement la meva conformitat per participar en l'estudi

Consenteixo expressament a participar en l'estudi i entenc que amb la meva participació

Consenteixo expressament en el tractament de les meves dades personals i de salut.

I manifesto que les dades facilitades per l'estudi són exactes i veraces

A _____(lloc) , a _____(dia) de _____(mes) de _____(any)

Data _____ Firma del participant _____

Data _____ Nom i firma de l'informador _____

14.7.2. Refusal to be informed of the results

REBUIG A SER INFORMAT DELS RESULTATS DE L'EXPLORACIÓ DE RM REALITZADA DE L'ESTUDI "IMAGENOMA DE L'ENVELLIMENT"

Jo, _____
(Nom i cognoms)

He llegit el full d'informació que se m'ha lliurat i he signat el consentiment a participar en l'estudi.

He rebut suficient informació sobre l'estudi i he pogut fer preguntes sobre l'estudi.

Consenteixo expressament a participar en l'estudi i entenc que amb la meva participació.

Consenteixo expressament el tractament de les meves dades personals i de salut.

Declaro que;

Tot i la meva participació en l'estudi NO vull ser informat dels resultats obtinguts en l'exploració de ressonància magnètica realitzada.

A_____(lloc), a _____(dia) de _____(mes) de_____(any)

Data_____Firma del participant_____

Data_____Nom i Firma de l'informador _____

14.8. ANNEX 8 – Supplementary tables

14.8.1. Processing Speed

Table 1. Coefficients of linear regression models assessing the association between categories of processing speed and cardiac variables

Structural variables	Model 1	Model 2	Model 3	Model 4
LVM* (g/m²)	-0.14 (-1.45,1.17) [0.834]	-0.55 (-1.80,0.70) [0.388]	-0.08 (-1.39,1.23) [0.904]	-0.51 (-1.76,0.74) [0.420]
LVEDV* (ml/m²)	-0.28 (-2.43,1.87) [0.800]	-0.69 (-2.81,1.43) [0.523]	-0.41 (-2.59,1.78) [0.713]	-0.86 (-3.02,1.29) [0.430]
LVESV* (ml/m²)	-0.02 (-1.40,1.36) [0.978]	-0.25 (-1.61,1.12) [0.724]	-0.04 (-1.44,1.36) [0.954]	-0.29 (-1.67,1.09) [0.681]
LV M/V ratio* (g/ml)	-0.00 (-0.02,0.02) [0.950]	-0.00 (-0.03,0.02) [0.805]	0.00 (-0.02,0.02) [0.913]	-0.00 (-0.02,0.02) [0.947]
RVEDV* (ml/m²)	-0.11 (-2.46,2.24) [0.929]	-0.98 (-3.17,1.20) [0.376]	-0.24 (-2.60,2.11) [0.838]	-1.20 (-3.39,0.98) [0.279]
RVESV* (ml/m²)	0.13 (-1.20,1.47) [0.845]	-0.42 (-1.63,0.80) [0.503]	0.11 (-1.21,1.43) [0.873]	-0.49 (-1.69,0.71) [0.423]
Functional variables				
LVEF (%)	-0.06 (-1.43,1.31) [0.936]	0.08 (-1.29,1.45) [0.909]	-0.07 (-1.45,1.30) [0.917]	0.08 (-1.29,1.45) [0.912]
LVSV* (ml/m²)	-0.26 (-1.63,1.12) [0.714]	-0.44 (-1.81,0.92) [0.524]	-0.37 (-1.76,1.02) [0.604]	-0.57 (-1.95,0.81) [0.415]
LVCO* (l/(min*m²))	-0.01 (-0.10,0.09) [0.899]	-0.02 (-0.11,0.08) [0.719]	-0.01 (-0.11,0.08) [0.759]	-0.03 (-0.12,0.07) [0.575]
LV EndoGLS (%)	-0.05 (-1.07,0.98) [0.927]	-0.11 (-1.14,0.91) [0.827]	0.03 (-1.01,1.07) [0.957]	-0.04 (-1.08,1.00) [0.939]
LV EndoGCS (%)	-0.44 (-2.37,1.49) [0.653]	-0.59 (-2.51,1.34) [0.549]	-0.26 (-2.21,1.69) [0.792]	-0.43 (-2.38,1.52) [0.663]
LV GRS (%)	3.55 (-2.50,9.61) [0.250]	3.28 (-2.79,9.35) [0.290]	3.78 (-2.36,9.92) [0.228]	3.49 (-2.67,9.65) [0.266]
RVEF (%)	-0.30 (-1.81,1.22) [0.703]	0.02 (-1.47,1.51) [0.983]	-0.34 (-1.87,1.19) [0.660]	-0.00 (-1.50,1.50) [0.998]
RVSV (ml/m²)*	-0.24 (-1.87,1.39) [0.773]	-0.57 (-2.17,1.03) [0.487]	-0.35 (-2.00,1.30) [0.676]	-0.71 (-2.34,0.91) [0.388]

Model 1: adjusted by age; **Model 2**: adjusted by age and sex; **Model 3**: adjusted by age and CVRF (HTA, dyslipidemia, DM); **Model 4**: adjusted by age, sex and CVRF (HTA, dyslipidemia, DM).

Data are expressed as coefficients (95% confidence interval) [p-value]

(*) Variables adjusted for Body Surface Area.

Table 2. Coefficients of linear regression models assessing the association between age and cardiac variables

Structural variables	**Model 1**	**Model 2**	**Model 3**
LVM* (g/m²)	-0.00 (-0.09,0.08) [0.934]	-0.01 (-0.10,0.08) [0.814]	-0.04 (-0.12,0.05) [0.433]
LVEDV* (ml/m²)	**-0.21 (-0.35,-0.06) [0.005]**	**-0.18 (-0.33,-0.02) [0.025]**	**-0.20 (-0.36,-0.05) [0.009]**
LVESV* (ml/m²)	-0.08 (-0.17,0.02) [0.110]	-0.05 (-0.15,0.05) [0.316]	-0.06 (-0.16,0.03) [0.196]
LV M/V ratio* (g/ml)	**0.003 (0.002,0.005) [p<0.001]**	**0.003 (0.001,0.004) [0.001]**	**0.003 (0.001,0.004) [0.002]**
RVEDV* (ml/m²)	**-0.27 (-0.42,-0.12) [p<0.001]**	**-0.23 (-0.40,-0.06) [0.007]**	**-0.29 (-0.44,-0.13) [p<0.001]**
RVESV* (ml/m²)	**-0.09 (-0.17,-0.00) [0.039]**	-0.05 (-0.15,0.04) [0.283]	-0.09 (-0.17,0.00) [0.051]
Functional variables			
LVEF (%)	0.04 (-0.06,0.13) [0.425]	0.01 (-0.09,0.11) [0.855]	0.02 (-0.08,0.11) [0.723]
LVSV* (ml/m²)	**-0.13 (-0.23,-0.04) [0.006]**	**-0.13 (-0.23,-0.03) [0.012]**	**-0.14 (-0.24,-0.04) [0.006]**
LVCO* (l/(min*m²))	**-0.01 (-0.01,-0.00) [0.016]**	**-0.01 (-0.01,-0.00) [0.026]**	**-0.01 (-0.02,-0.00) [0.015]**
LV EndoGLS (%)	0.04 (-0.03,0.11) [0.298]	0.05 (-0.03,0.12) [0.221]	0.04 (-0.03,0.12) [0.276]
LV EndoGCS (%)	0.00 (-0.13,0.14) [0.959]	0.04 (-0.10,0.18) [0.561]	0.03 (-0.11,0.17) [0.681]
LV GRS (%)	-0.37 (-0.79,0.05) [0.082]	-0.33 (-0.77,0.10) [0.134]	-0.35 (-0.79,0.09) [0.115]
RVEF (%)	-0.07 (-0.17,0.03) [0.187]	-0.10 (-0.21,0.01) [0.068]	-0.08 (-0.19,0.02) [0.131]
RVSV (ml/m²)*	**-0.18 (-0.29,-0.07) [0.001]**	**-0.18 (-0.30,-0.06) [0.003]**	**-0.20 (-0.32,-0.08) [p<0.001]**

Model 1: adjusted by sex; **Model 2**: adjusted by CVRF (HTA, dyslipidemia, DM); **Model 3**: adjusted by sex and CVRF (HTA, dyslipidemia, DM).

Coefficients represent change in the dependent variable per 1-year increase in age.

Data are expressed as coefficients (95% confidence interval) [p-value]

(*) Variables adjusted for Body Surface Area.