HEART RATE VARIABILITY IN CLINICAL POPULATIONS: METHODOLOGICAL ASPECTS AND EFFECTS OF EXERCISE INTERVENTIONS

INTERNATIONAL DOCTORAL THESIS | **ELENA MARTINEZ ROSALES**

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Variabilidad de la frecuencia cardiaca en poblaciones clínicas: aspectos metodológicos y efectos del ejercicio físico

PROGRAMA DE DOCTORADO EN CIENCIAS MÉDICAS
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FACULTAD DE CIENCIAS DE LA EDUCACIÓN

ELENA MARTINEZ ROSALES

Mayo 2023

A mi madre y a mi padre.

«Somos la suma de nuestras experiencias y emociones. Pero, sobre todo, somos la suma de los que hacemos con ellas en cada instante»

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CERTIFICA:

Que la Tesis Doctoral titulada "**Heart rate variability in clinical populations: methodological aspects and effects of exercise interventions**" que presenta Dña. **Elena Martinez Rosales** al superior juicio del Tribunal que designe la Universidad de Almería, ha sido realizada bajo mi dirección durante los años 2019-2023, siendo expresión de la capacidad técnica e interpretativa de su autor en condiciones tan aventajadas que lo hacen merecedor del Título de Doctor por la Universidad de Almería, siempre y cuando así lo considere el citado Tribunal.

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Alberto Soriano Maldonado

En Almería, 10 Abril 2023

El doctorando Dña. Elena Martínez Rosales y los directores de la tesis D. Enrique García Artero y D. Alberto Soriano Maldonado:

Garantizamos, al firmar esta Tesis Doctoral, que el trabajo ha sido realizado por el doctorando bajo la dirección de los directores de la tesis y hasta donde nuestro conocimiento alcanza, en la realización del trabajo, se han respetado los derechos de otros autores al ser citados, cuando se han utilizado sus resultados o publicaciones.

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La doctoranda Elena Martínez Rosales ha realizado la presente Tesis Doctoral Internacional como beneficiaria de un contrato predoctoral para la Formación de Profesorado Universitario (FPU) del Ministerio de Ciencia, Innovación y Universidades (código: FPU18/01107), por Resolución de 12 de junio de 2019 de la Secretaría General de Universidades.

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Research projects and funding

The present doctoral Thesis was carried out in the context of two independent research projects, the EFIBAR (Ejercicio FÍsico tras cirugía BARiátrica) and the EJERCITALES (Efectos de un programa de eJERCIcio físico sobre la arTeriosclerosis subclínica y la inflAmación de pacientes con Lupus Eritematoso Sistémico) projects.

EFIBAR

The EFIBAR project was funded by the following organizations:

- Spanish Ministry of Economy and Competitiveness (MINECO), Plan Nacional de I+D+i call RETOS2016 (DEP2016-74926-R)
- Spanish Ministry of Science, Innovation and Universities (FPU18/01107)
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The EJERCITALES project was funded by the following organizations:

- Fundación para la Investigación Biosanitaria de Andalucía Oriental (PI-0525-2016 and PIER-0223-20)
- Ilustre Colegio Oficial de Médicos de Granada (Premios de Investigación 2017)
- Spanish Ministry of Education (FPU15/00002)

PILOT STUDY ON HEART RATE VARIABILITY

Finally, this International Doctoral Thesis also includes data from a non-funded pilot study on heart rate variability parameters conducted at the Andres Bello University, Chile.

ABSTRACT

“Good things, when short, are twice as good.”

- Tom Stoppard

Abstract (English)

Heart rate variability (HRV) is a noninvasive and sensitive measure of the autonomic nervous system function. Autonomic dysfunction, specifically, increased sympathetic and decreased parasympathetic activity, is common in autoimmune rheumatic diseases and people with obesity. Exercise is considered as a potential intervention to increase HRV and regulate the autonomic nervous system.

The aims of this international doctoral thesis were: i) to investigate how the selection of filters and different 5-minute segments using Kubios Premium software affects HRV parameters in patients with severe obesity and healthy participants (**Study I**); ii) to analyze the effect of a 12-week aerobic exercise program on HRV-derived parameters in women with systemic lupus erythematosus (SLE); and the associations of HRV-derived parameters with inflammatory markers and patient-reported outcomes (**Study II**); and iii) to determine the effect of a 16-week concurrent exercise program immediately after bariatric surgery on HRV-derived parameters, blood pressure, and cardiac structure and function in participants with severe obesity awaiting bariatric surgery **(Study III)**. To answer these aims, three studies were conducted in the context of two main projects: the EFIBAR and EJERCITALES trials and a cohort study.

Project I (Study I & III) included 80 participants with severe/morbid obesity who were evaluated before bariatric surgery, 4 months, and 12 months after the surgery. Participants were randomized to a control group (n=40) or an exercise group (n=40) who would perform a 16-week concurrent exercise program immediately after bariatric surgery. The variables measure were heart rate variability using a heart rate monitor (V800), arterial stiffness and blood pressure using Mobil-O-graph, and echocardiographic parameters using standard procedure.

Project II (Study II) in a combined cross-sectional and interventional study approach, 55 women with SLE were assigned to either aerobic exercise (n = 26) or usual care (n = 29) in a non-randomized trial. HRV was assessed using a heart rate monitor during 10 min, inflammatory and oxidative stress markers using standard procedures, psychological stress (Perceived Stress Scale), sleep quality (Pittsburg Sleep Quality Index), fatigue (Multidimensional Fatigue Inventory), depressive symptoms (Beck Depression Inventory), and quality of life (SF-36) were also assessed.

Project III (Study I) included 23 women awaiting bariatric surgery who were evaluated in follow-up measures 1 and 3 months after the surgery. From this project, only HRV baseline data was collected after measuring HRV for 10 minutes in a supine position.

The main findings of this Thesis were: i) filter selection during signal processing and body position during data collection significantly impact HRV-derived parameters in participants with severe obesity. These results have important implications for the accurate interpretation and clinical application of HRV data in research and practice. II) In women with systemic lupus erythematosus, reduced HRV signal regularity was related to increases in C-reactive protein and oxidative stress markers such as myeloperoxidase. However, a 12-week aerobic exercise program did not change HRV parameters compared to a control group in women affected by systemic lupus erythematosus. III) A 16-week supervised exercise program that started immediately after bariatric surgery did not significantly improve HRV or arterial stiffness parameters compared with a usual-care control group that followed international guidelines following bariatric surgery. However, the exercise intervention produced a significant reduction of systolic blood pressure and pulse pressure at 4 months compared to the control group and a reduction in left atrial diameter at 12 months.

The present international Doctoral Thesis provides and expands the knowledge on how HRV data processing and collection using Kubios software affects HRV parameters in participants with severe obesity. However, the results did not show improvements in HRV-derived parameters after the exercise programs in clinical populations. Further research is needed to better understand exercise's potential effects on HRV-derived parameters in these populations.

Resumen (Español)

La variabilidad de la frecuencia cardiaca (VFC) es un marcador no invasivo y sensible de la función del sistema nervioso autónomo. La disfunción autonómica, en concreto, el aumento de la actividad simpática y la disminución de la actividad parasimpática es frecuente en las enfermedades reumáticas autoinmunes y en las personas con obesidad severa. El ejercicio se considera una intervención potencial para aumentar la VFC y regular el sistema nervioso autónomo.

Los principales objetivos de la presente tesis doctoral son: i) investigar cómo la selección de filtros y diferentes segmentos de 5 minutos utilizando el software Kubios Premium afecta a los parámetros de VFC en pacientes con obesidad severa y participantes sanos (**Estudio I**); ii) analizar el efecto de un programa de ejercicio aeróbico de 12 semanas sobre los parámetros derivados de la VFC en mujeres con lupus eritematoso sistémico (LES); y las asociaciones de los parámetros derivados de la VFC con los marcadores inflamatorios y los parámetros auto-reportados por los pacientes (**Estudio II**); y iii) determinar el efecto de un programa de ejercicio concurrente de 16 semanas inmediatamente después de la cirugía bariátrica sobre los parámetros derivados de la VFC, la presión arterial y la estructura y función cardiacas en participantes con obesidad grave que fueron operados de cirugía bariátrica (**Estudio III**). Para responder a estos objetivos, se realizaron tres estudios en el contexto de dos proyectos principales: los ensayos EFIBAR y EJERCITALES y un estudio de cohortes.

El Proyecto I (Estudios I y III) incluyó a 80 participantes con obesidad severa/mórbida que fueron evaluados antes de la cirugía bariátrica, 4 meses y 12 meses después de la cirugía. Los participantes fueron asignados aleatoriamente a un grupo de control (n=40) o a un grupo de ejercicio (n=40) que realizaría un programa de ejercicio simultáneo de 16 semanas inmediatamente después de la cirugía bariátrica. Las variables medidas fueron la variabilidad de la frecuencia cardiaca mediante un pulsómetro (V800), la rigidez y la presión arterial mediante Mobil-O-graph, y los parámetros ecocardiográficos mediante un procedimiento estándar.

Proyecto II (Estudio II) en un enfoque combinado de estudio transversal y de intervención, 55 mujeres con LES fueron asignadas a ejercicio aeróbico (n = 26) o a atención habitual (n = 29) en un ensayo no aleatorizado. Se evaluó la VFC mediante un pulsómetro durante 10 minutos, los marcadores de estrés inflamatorio y oxidativo mediante procedimientos estándar, el estrés psicológico (Perceived Stress Scale), la calidad del sueño (Pittsburg Sleep Quality Index), la fatiga (Multidimensional Fatigue

Inventory), la sintomatología depresiva (Beck Depression Inventory) y la calidad de vida (SF-36).

Los principales hallazgos de esta Tesis fueron: i) la selección del filtro durante el procesamiento de la señal y la posición del cuerpo durante la recogida de datos afectan significativamente a los parámetros derivados de la VFC en participantes con obesidad grave. Estos resultados tienen importantes implicaciones para la interpretación precisa y la aplicación clínica de los datos de VFC. II) En mujeres con lupus eritematoso sistémico, la reducción de la regularidad de la señal de VFC se relacionó con aumentos de la proteína C reactiva y marcadores de estrés oxidativo como la mieloperoxidasa. Sin embargo, un programa de ejercicio aeróbico de 12 semanas no modificó los parámetros de la VFC en comparación con un grupo de control en mujeres afectadas por lupus eritematoso sistémico. III) Un programa de ejercicio supervisado de 16 semanas que comenzó inmediatamente después de la cirugía bariátrica no mejoró significativamente la VFC ni los parámetros de rigidez arterial en comparación con un grupo de control de atención habitual que siguió las directrices internacionales tras la cirugía bariátrica. Sin embargo, la intervención de ejercicio produjo una reducción significativa de la presión arterial sistólica y la presión del pulso a los 4 meses en comparación con el grupo de control y una reducción del diámetro de la aurícula izquierda a los 12 meses.

La presente tesis internacional proporciona y amplia los conocimientos sobre cómo el procesamiento y la recogida de datos de VFC mediante el software Kubios afecta estos parámetros en participantes con obesidad severa. Sin embargo, los resultados no mostraron mejoras en los parámetros derivados de la VFC tras los programas de ejercicio en las poblaciones clínicas estudiadas. Se necesitan más estudios para comprender mejor los efectos potenciales del ejercicio sobre los parámetros derivados de la VFC en estas poblaciones.

Abbreviations

ANS: Autonomic Nervous System

HRV: Heart Rate Variability

MPO: Myeloperoxidase

SDNN: Standard Deviation NN intervals

RMSSD: Root Mean Square Standard Deviation

ECG: Electrocardiogram

HF: High Frequency

LF: Low Frequency

VLF: Very Low Frequency

SampEn: Sample Entropy

DFA-a1: Detrended fluctuation analysis

BMI: Body Mass Index

SA: Sinoatrial

AV: Atrioventricular

LA: Left atrium

TNF-α: tumor necrosis factor α

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

HR: Heart Rate

SD1: standard deviation—poincaré plot crosswise

SD2: standard deviation—poincaré plot lengthwise

LV: Left Ventricle

FFT: Fast Fourier Transform

AR: Autoregressive Modelling

CVD: Cardiovascular Disease

CERT: Consensus on Exercise Reporting Template

HRR: Heart Rate Reserve

SF-36: 36-item Short-Form Health Survey

BDI-II: Beck Depression Inventory-second edition

PSS: Perceived Stress Scale

MFI: Multidimensional Fatigue Inventory

hsCRP: High-sensitivity CRP

IL-6: Interleukin 6

PNS: Parasympathetic Nervous System

SLE: Systemic Lupus Erythematosus

SNS: Sympathetic Nervous System

PREFACE

“If you have knowledge, let others light their candles at it.”

- Margaret Fuller

A brief history of Heart Rate Variability

Ludwick Fleck argued in 1935 that relating results to a single scientist is inappropriate because scientific progress is a collective work[1].It is especially true in a complex concept like **heart rate variability** (HRV), in which emerging ideas and discussions have allowed specific methods to help with its interpretation and use in the last 150 years, even though the concept of heart rate variability is ancient.

As early as 300 BC, the Chinese physician Bian Que (ca. 407 – ca. 310 BC) used pulse diagnosis when describing the "four diagnostic methods" of Traditional Chinese Medicine [2]. Western medicine historians typically credit Herophilus (ca. 335 - ca. 280 BC) as the first person to measure heart rate because he demonstrated the rhythmic pulsing of arteries. Galen of Pergamon (ca. 129 - ca. 216 AD) often referenced Herophilus's concept in his extensive writings (he wrote more than 18 books on the topic) on pulse measurement for predicting illnesses [3].

It wouldn't be until the golden age of physiology in the eighteenth century when the study of the autonomic control model described as a continuum of parasympathetic activation on one side and sympathetic activation on the other was finally pushed by Cannon (1871-1945), using the **homeostasis** term defined by Claude Bernard (1813-1878) [4]. The creation of this model allowed different physicians to use HRV in the clinical setting. To be highlighted, in 1963, Hon & Lee [5] noticed that a reduction in the variability of the heart in fetuses was related to afflictions later detected at birth. A couple of years later, Wolf [6] established the relationship between the state of the nervous system and heart rate variability.

Nevertheless, the most crucial milestone came in 1987 when Klieger demonstrated the role of HRV in predicting **mortality** in patients who had suffered a myocardial infarction [7]. It marks the turning point in which HRV became a popular research topic. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology published a manual to establish the minimum technical requirements, definitions, and recommendations for developing time and frequency domain spectral analysis and how to conduct clinical trials and patient scans with HRV [8].

When the Task Force was developing the guidelines for measuring HRV, their instructions were focused on electrocardiograms as the gold standard instrument to measure HRV. Although very accurate, the electrocardiogram had several limitations (i.e., difficulty in using it outside of the clinical setting, expensive) that made it difficult for several researchers. In 1977, finish professor Seppo Säynäjäkangas (who

later created the Polar Electro company) invented the first portable heart rate monitor. Through the evolution and development of technology, today, most smartwatches and even phone apps can measure HRV.

Nowadays, more than 98.000 studies about HRV have been published according to Pubmed (**Figure 1)**, and these figures are increasing yearly. In the last decade, not only is HRV a critical risk assessment tool in the clinical setting, but it has also become an essential tool for monitoring and diagnosing performance in sports and physical activities.

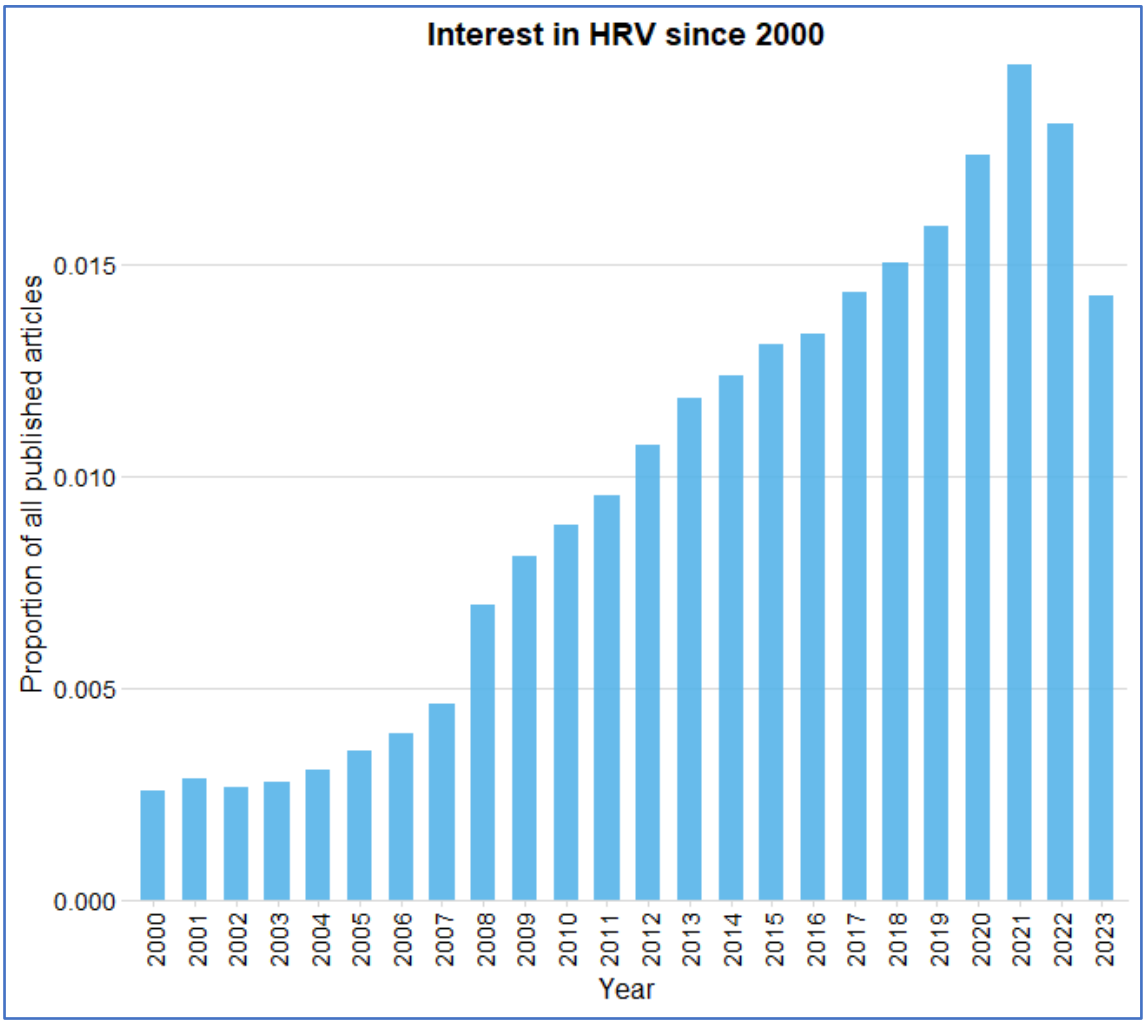


Figure 1. Number of articles published in Pubmed using heart rate variability as part of the title (figure created using the europepmc package in R).

Key terms

Heart rate variability → Variation of the time intervals between beat-to-beat. It can be measured differently, e.g., with an electrocardiogram (ECG), pulse waves, or similar methods. In practice, the most convenient and accurate method is to measure

the distance between QRS complexes (**Figure 2**) in milliseconds (ms) and, more specifically, the R-R interval.

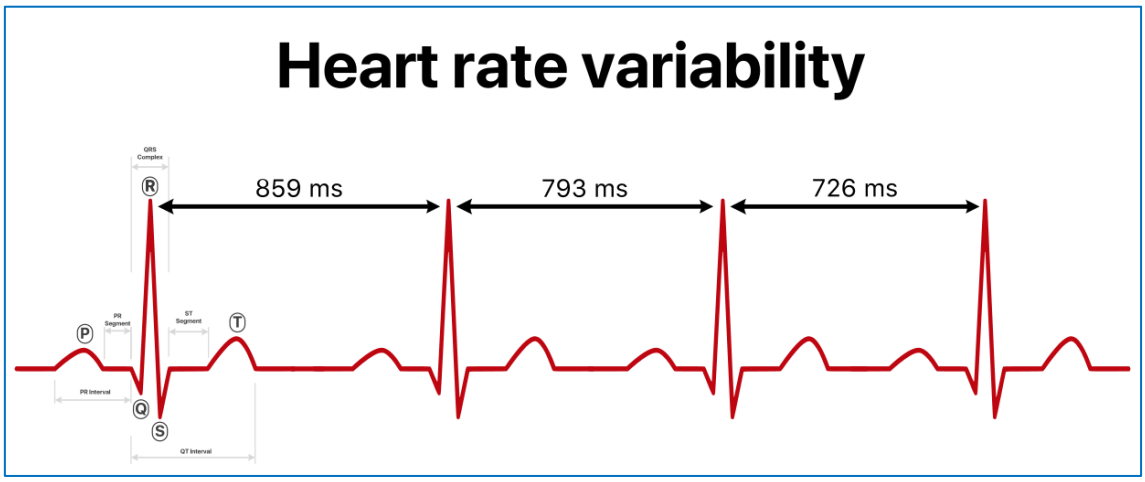


Figure 2. Heart rate variability visualized with R-R interval changes ***(modified from YitzhakNat**, https://commons.wikimedia.org/w/index.php?curid=121207798)*

Artifacts ⟶ Interference (anomalous) signals from sources other than the electrophysiological structures studied. These artifact signals may originate from light sources, monitor equipment problems, utility frequencies, or undesirable electrical physiological signals. These artifacts may obscure, distort, or completely change the underlying electrophysiological signal.

Homeostasis ⟶ A self-regulating process by which biological systems maintain stability while adjusting to changing internal or external conditions. This concept explains how an organism can maintain constant internal conditions that allow it to adapt and survive in the face of a changing and often hostile external environment. The disruption of homeostatic mechanisms leads to disease, and effective therapy must be directed toward re-establishing these homeostatic conditions [9].

Time domain ⟶ Time domain methods employ either statistical or geometric approaches to analyze the variability of time measures. These parameters tend to be very sensitive to artifacts or have a particular grade of arbitrariness.

In this section, I will highlight the parameters often appearing in this thesis book. However, the reader should know that more parameters can be calculated using time domain analysis.

- ***SDNN [ms]:*** the standard deviation (SD) of the normal-to-normal (NN) interval (the interval between adjacent normal QRS complexes), also called the R-R

interval. It is a global index of HRV and is the standard deviation of all normal QRS distances.

- ***pNN50 [%]:*** The number of pairs of adjacent normal R-R intervals that differ by more than 50ms divided by the total number of normal R-R intervals × 100.
- ***RMSSD [ms]:*** the square root of the mean squared differences between adjacent normal R-R intervals.

Frequency domain → Describes the periodic oscillations of the heart rate signal, broken down into different frequencies and amplitudes. The spectral power for a given frequency can then be quantified by determining the area under the curve within a specified frequency range. The two most common spectral analysis approaches are fast Fourier transform analysis (FFT) and autoregressive (AR) modeling, with the former being the most often used. For shorter duration recordings (2–5 min), three peaks are usually identified: very low frequency (VLF) <0.04 Hz, low frequency (LF), 0.04–0.15 Hz, and high frequency (HF) 0.15–0.4 Hz.

- ***Very Low Frequency [ms2]:*** Important determinant of physical activity and possibly reflects sympathetic activity, although its origin is very controversial. It can be used for both long and short measurements, and its frequency is between 0.003–0.004Hz.
- ***Low Frequency [ms2]:*** Modulated by both the parasympathetic and sympathetic systems. It primarily reflects the modulation of baroreceptors during heart rate in spontaneous blood pressure changes of the efferent sympathetic and vagus mechanisms.
- ***High Frequency [ms2]:*** It is usually interpreted as a marker of vagal modulation and is mediated by respiration, thus dependent on the respiratory pattern.

Non-Linear Methods → Different from linear methods because they are related to the complexity, unpredictability, and fractality of the signal. While linear methods assess the magnitude of the variability, non-linear methods evaluate the signal's quality, scaling, and correlation properties. These procedures have opened new possibilities in HRV research, and numerous parameters are computed daily. However, as mentioned before, here we only present those used in this thesis.

- ***Detrended fluctuation analysis (DFA-1):*** Measures the timely changes of the heart rate variability and especially the regulation quality, determining how the individual control systems work together. Values above 1 mean more stability and indicate compensations processes within the individual control

systems, while values below 0.8 indicate a hindered cooperation of the control systems.

- ***Sample Entropy:*** Meant to quantify the regularity of a time series; it is an estimate for predictability in finding matches in a short-time series. Its value is between 0 and 2, with 0 representing a sinus curve and 2 representing chaos (unpredictable behavior).

INTRODUCTION

“Do not wait until the conditions are perfect to begin.”

- Alan Cohen

The heart

The heart is a muscular organ that pumps blood throughout the body and is divided into four chambers. Blood enters the right atrium, is pumped into the right ventricle, and then is sent to the lungs for oxygenation. Oxygenated blood returns to the left atrium, is pumped into the left ventricle and then is sent to the rest of the body. This process is regulated by electrical impulses generated by the sinoatrial (SA) and atrioventricular (AV) nodes [10].

The SA node, a specialized group of cells located in the heart's right atrium, plays a critical role in maintaining normal heart rhythm. It is known as the "natural pacemaker" because it sets the pace for the heart's rhythmic contractions, generating electrical impulses that initiate each heartbeat [11]. When the SA node fires an electrical impulse, it spreads throughout the right atria, causing them to contract and pump blood into the ventricles. The electrical impulse then reaches the atrioventricular (AV) node (also located in the right atrium), which serves as a gateway for the impulse to reach the ventricles and cause them to contract [10]. The electrical changes in the heart muscle are depolarization (contraction of the heart) and repolarization (resting state) [10,11].

These two processes are part of the normal cardiac cycle and are reflected on an electrocardiogram (ECG), a diagnostic test that records the electrical activity of the heart, such as the P wave, QRS complex, and T wave [12]. Very briefly, the P wave represents the depolarization of the atria; the QRS complex represents the depolarization of the ventricles; and the T wave represents the repolarization of the ventricles, which return to their resting state after contraction (**Figure 3**).

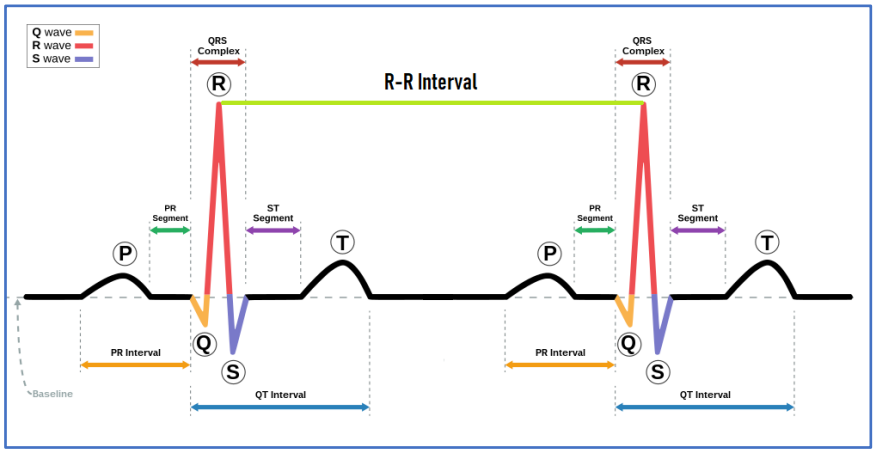


Figure 3. The electrical signal of the heart (modified from YitzhakNat, https://commons.wikimedia.org/w/index.php?curid=121207798)

Therefore, the P wave, QRS complex, and T wave provide essential information about the electrical activity and function of the heart. Abnormalities in their shape or duration can indicate various types of heart conditions. Since we have established that the electrical signal starts in the SA, what modulates it?

The Autonomic Nervous System

The Autonomic Nervous System (ANS) is a division of the nervous system that controls the body's automatic functions, such as heart rate, blood pressure, digestion, and respiration. The ANS has two branches: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) [4].

The SNS is often referred to as the "fight or flight" response, as it prepares the body for stressful conditions (i.e., increases heart rate, blood pressure, and respiration rate). In contrast, the PNS is referred to as the "rest" response (i.e., slowing heart rate and lowering blood pressure) [10]. The two branches of the ANS work in balance to regulate the body's functions and maintain homeostasis [9].

Regarding the heart, the sympathetic and parasympathetic nervous systems are antagonists [10]. The vagus nerve (under the PNS) acts upon the SA node to initiate a conduction system, while the SNS targets the AV node for the forceful contraction of heart chambers. Hence, sympathetic activation alters the inhibitory function of the vagus nerve and increases heart rate, while parasympathetic activates vagal inhibition and results in low heart rate [13]. Empirical research has demonstrated an association between elevated vagal tone, improved cardiac health, and decreased incidence of cardiovascular disease [14]. Several factors can influence the ANS, including environmental stimuli, hormonal signals, inflammation, emotions, metabolic states, aging, and exercise [15].

The relationship between inflammation and the ANS is complex and interdependent [16]. Inflammation is a response by the body's immune system to harmful stimuli, such as infection, injury, or tissue damage. While it can be seen as a protective mechanism, studies have shown that chronic inflammation can cause changes in the activity of the vagus nerve and oxidative stress which can further impair the function of the ANS [17,18]. Obesity has been associated with chronic low-grade inflammation. Excess fat tissue, particularly abdominal fat, can release pro-inflammatory cytokines and other signaling molecules that stimulate an inflammatory response [19]. Therefore, the ANS is shifted towards a sympathetic dominant state.

There are several mechanisms that can reduce inflammation. Exercise has been shown to have a positive effect on inflammation [20]. Regular physical activity has been found to reduce levels of pro-inflammatory cytokines and increase levels of anti-inflammatory cytokines in the body [21]. The anti-inflammatory effect of exercise is thought to be due to an increase in the production of hormones such as endorphins and adrenaline, which help to suppress inflammation [22]. Additionally, exercise has been shown to improve the functioning of the immune system, which may help to reduce the risk of inflammation [23]. To better understand the impact of inflammation on ANS function, it is crucial to study populations with conditions that have been linked to chronic inflammation, such as people with severe/morbid obesity and systemic lupus erythematosus. Therefore, investigating the effect of exercise on ANS function in these populations are needed in order to evaluate the potential of exercise as an intervention to improve ANS function and reduce the risk of chronic inflammation. So, how can we measure or evaluate whether there are changes in the ANS after exercise?

Heart Rate Variability

Heart Rate Variability (HRV) refers to the beat-to-beat change in the heart rate over time [3]. HRV has been widely used to assess peripheral physiological adaptations of complex brain and behavioral processes analysis [24] and is an important diagnostic and risk assessment tool for cardiac morbidity and mortality [25]. It has emerged as a valuable tool for understanding the connection between the autonomic nervous system, lifestyle factors, and overall health [26]. Higher HRV has been associated with better health and lower risk of disease, whereas lower HRV has been linked to poor health outcomes, including cardiovascular disease, diabetes, and depression [27]. Moreover, HRV has been found to be associated with patient-reported outcomes (PROs) in different clinical populations.[28,29] PROs are subjective measures of a patient's health status, such as symptoms, function, quality of life, and satisfaction with care. Studies have reported that lower HRV is associated with worse PROs in conditions such as cardiac surgery,[30] cancer,[31] chronic pain[28] and even in asymptomatic adults. Therefore, HRV monitoring can provide valuable information on a patient's subjective experience of their health, which can inform clinical decision-making and improve patient care.

Exercise is associated with improved heart rate variability (HRV), indicating better autonomic nervous system function and cardiovascular health.[32] Exercise improves HRV through multiple mechanisms. One way is by causing changes in the autonomic nervous system, resulting in a shift towards parasympathetic dominance and improved balance between the sympathetic and parasympathetic nervous systems.[33]

Furthermore, exercise can improve cardiovascular fitness and reduce inflammation which have been associated with higher HRV.[34,35] The extent to which HRV is improved may depend on factors such as exercise type, intensity, and duration.[36,37] Overall, regular physical activity is an effective approach for improving HRV and promoting overall health and well-being.

Methodological aspects

Due to its ease of use, non-invasive nature, and large amount of commercial equipment available to measure R-R intervals, there has been an increase in popularity in the use of HRV to assess autonomic cardiac function, especially using short-term recordings [38]. Researchers and clinicians can obtain different HRV metrics depending on the approaches used to analyze the variability of time measures, which relies on algorithms with certain assumptions (i.e., a higher amount of data points or more sensitivity to artifacts) and are divided in time, frequency domain and non-linear methods [4].

Time-domain values are obtained by traditional descriptive methods and usually comprise the standard deviation of NN intervals (SDNN), a global index of HRV, and RMSSD, the square root of the mean squared differences between adjacent normal R-R intervals. Frequency domain (power spectrum density) analysis describes the periodic oscillations of heart rate signals, which are composed of different frequencies and amplitudes and provide information about their intensity in the sinus rhythm signal of the heart [8]. The two most common spectral analysis approaches are fast Fourier transform analysis (FFT) and autoregressive (AR) modeling, with the former being the most often established. High frequency (HF) power is generally interpreted as a marker of vagal modulation and is respiration mediated, while low frequency (LF) power generally reflects the activity of the baroreflex in response to vasomotor tone [39]. Lastly, non-linear methods evaluate the biosignal's quality, scaling (changes in amplitude or frequency), and correlation properties (how the signal is related to other signals or stimuli). Sample entropy has been suggested as a promising algorithm for clinical value as it is meant to quantify the regularity of a time series [40].

According to the Task Force of Cardiology, it is imperative to process the heart rate signal to avoid the presence of artifacts that can contaminate R-R interval recordings[8]. Artifacts in R-R interval recordings can result in substantial distortions. A single heart period artifact can lead to errors larger than typical effect sizes [41], and it can lead to over-or under-estimate HRV-derived parameters [42]. Moreover, several studies argued that metrics calculated from segments of different lengths should not be compared [43]. Although the validity of some HRV parameters from ultra-short recordings has been

demonstrated [44], this methodology is not applicable for frequency and non-linear parameters in which segment lengths must be of at least 256 points.

Although different software are available to process R-R intervals raw data [45], Kubios software [46] is still one of the most frequently used in HRV data processing. It presents two methods for correcting artifacts and ectopic beats: i) threshold-based correction and ii) automatic correction [46]. The threshold-based correction (TBC) compares every R-R interval value against a local average, the median filtering of the total time series. Suppose an R-R interval differs from the local average more than a specified threshold value (i.e., low [0.35sec], medium [0.25sec], strong [0.15sec]). In that case, that interval is identified as an artifact and is marked for correction. Meanwhile, the automatic correction detects artifacts by applying a time-varying threshold based on the differences between successive RR intervals [47]. However, deciding which filter and/or time segment to analyze is left to the evaluator's subjectivity.

Several studies have evaluated the effects of different methodologies applying Kubios software when processing HRV data. Aranda et al. [48] found that when applying TBC filters in a sample of professional athletes, only the Very Strong filter affected HRV metrics. However, Alcantara et al. [49] found that TBC filters affected HRV metrics in three cohorts: overweight/obese children, young and middle-aged adults. A later study by the same authors found that TBC influenced the association between cardiovascular risk factors and HRV [50]. Cilhoroz et al. [51] were the only ones to compare TBC and automatic correction with manual correction, finding that manual correction was superior to TBC and automatic correction when detecting artifacts that could affect HRV metrics. Finally, when looking into segment selection, Ribeiro et al. [52] found no differences in HRV metrics when comparing the 256 highest stability points and the last 5 minutes of a recording in a sample of adults with aortic stenosis and physically active adults. Conversely, Miranda-Dantas et al. [53] found discrepancies in the Very Low frequency parameter (VLF) when studying different time intervals (i.e., 0-5 min, 2.5-7.5 min, and 5-10 min) in healthy adults. To our knowledge, no previous study has studied the effect that different Kubios and segment selections could have on HRV metrics and its effects on participants from a clinical population. Therefore, **Study I** of this Doctoral thesis will focus on studying the different configurations of filters and segment selection in a population of people with severe/morbid obesity compared to people with a healthy BMI.

Heart Rate Variability and Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multifactorial etiology that predominantly affects women [54]. In recent years, the diagnosis and treatment of SLE has significantly improved [55], and deaths due to lupus manifestation have decreased [56]. However, cardiovascular disease (CVD) mortality remains one of the leading causes of death in SLE patients [57,58].

Autonomic dysfunction is common in autoimmune rheumatic diseases [59], and specifically, increased sympathetic and decreased parasympathetic activity are reported by several studies in patients with SLE [60-62]. In this sense, patients with SLE have shown abnormal HRV, a surrogate marker of cardiac ANS dysfunction [62], which may predispose to the onset of fatal arrhythmias in these patients [63].

Exercise is a potential intervention that significantly increases cardiorespiratory fitness [64,65], improves cardiovascular function and PROs (i.e., fatigue, depression, etc.) [66] in patients with SLE. Although exercise has shown to decrease cardiovascular morbidity and mortality in the general population [67], its benefits in SLE population are understudied to the extent that exercise hardly appear in the EULAR guidelines for the management of this chronic disease [68]. Benatti and Pedersen [21] suggested that one of the mechanisms by which exercise might benefit the cardiovascular system in patients with rheumatic diseases is through direct or indirect anti-inflammatory effects. Based on the effects of exercise in the general population [69] and other chronic conditions [70,71], it might be hypothesized that exercise (and particularly aerobic exercise) could also increase HRV and thus regulate the ANS in women with SLE. Although there have been some studies evaluating HRV after an exercise stress test in this population [72,73], to the best of our knowledge, no prior research has evaluated the effects of an aerobic exercise program on HRV in women with SLE. We hope that the **Study II** included in this thesis helps to better understand HRV in this population after an exercise intervention.

Heart Rate Variability and bariatric surgery

The World Obesity Federation estimates that by 2030, nearly one billion people worldwide will suffer from obesity, with at least 111 million people having a BMI ≥ 40 kg/m2 [74]. Obesity is associated with type 2 diabetes, dyslipidemia, hypertension, cancer, infertility, and cardiovascular disease (CVD) [75,76], as well as a deteriorated quality of life and mental health [77]. Excessive accumulation of adipose tissue affects negatively the cardiovascular and nervous systems [78].

People with severe obesity have the sensitivity of the adrenergic receptors compromised, producing an autonomic imbalance where the vagal tone is reduced, and the sympathetic activity is increased[18]. In addition, the autonomic dysfunction is linked to increased diastolic dysfunction, ventricular hypertrophy, and cardiac remodeling[78]. In this sense, individuals with obesity have reduced cardiac and baroreceptor reflexes, which contributes to increased blood pressure and reduced heart rate variability.

Bariatric surgery has been proposed as an effective [79] and safe method for weight loss [80]. Different reviews have shown improvements in cardiac structure and function [81,82], HRV [83,84], blood pressure [85] and arterial stiffness[86]. When combined with lifestyle modifications such as exercise, greater health benefits have been observed compared to bariatric surgery alone [87,88] , given that exercise is associated with anti-atherosclerotic (i.e., decrease blood pressure, adiposity, and inflammation), anti-arrhythmic (i.e., decrease resting heart rate, and increase HRV) and anti-ischemic effects, which all together lower the risk for adverse health outcomes [89].

Several studies have investigated possible adaptations in HRV after exercise interventions on participants who have undergone bariatric surgery [90–92]. All studies had a duration of less than 12 weeks, usually started 3 months after the surgery and differ significantly in the type and volume of exercise prescribed (i.e.: whole-body electrostimulation, aerobic training or concurrent training). Furthermore, the data collection and processing varied widely (i.e.: from 24 hours to short-term recordings). It shouldn't be surprising then that results on HRV parameters are not consistent. This could be due to different exercise configurations, small sample sizes, and the timing or duration of the interventions prescribed in this population. To date, it still unknown whether an exercise intervention started immediately after bariatric surgery could improve HRV parameters. Autonomic behavior in people with obesity is characterized by sympathetic activation and vagal withdrawal[13]. From a preventive and therapeutic point of view, understanding the scenario of autonomic dysfunction and its possible fluctuations is of clinical importance because the changes produced by obesity in the autonomic nervous system play an important role in developing and progressing cardiovascular complications in this population [93]. This is the background for which **Study III** was conceptualized for this Doctoral thesis.

AIMS

General Aim

The overall aim of this Doctoral Thesis was to examine the influence of data collection and processing decisions on segment and type of filter to analyze raw heart rate variability signals to obtain HRV parameters and to study the effects of different exercise interventions on these parameters in clinical populations.

Specific Aims

Study I – Data collection and data processing of HRV signal

1. To investigate how the selection of filters and different 5-minute segments using Kubios Premium software affects HRV parameters in patients with severe obesity and healthy participants.
2. To compare to examine potential methodological modifications (e.g., positioning, breathing) in collecting HRV parameters in people with severe obesity.

Study II – Non-randomized controlled trial on women with SLE

1. To cross-sectionally explore the associations of HRV-derived parameters with inflammatory markers and patient-reported outcomes (PROs)
2. To analyze the effect of a 12-week aerobic exercise program on HRV-derived parameters in women with SLE.

Study III – Randomized Controlled Trial on patients awaiting bariatric surgery.

1. To determine the effect of a 16-week concurrent exercise program immediately after bariatric surgery on HRV-derived parameters, blood pressure, and cardiac structure and function in participants with severe obesity awaiting bariatric surgery.

METHODS

“Science is organized knowledge.”

- Herbert Spencer

Research projects

This International Doctoral Thesis is derived from the EFIBAR project, the EJERCITALES project, and a pilot study.

The EFIBAR project (Studies I & III)

Study design

The EFIBAR project is a parallel-group RCT (NCT03497546) investigating the effects of a 16-week supervised exercise program initiated immediately after bariatric surgery over one year on weight loss, body composition, cardiometabolic risk, physical fitness, and quality of life in patients with severe/extreme obesity (**Figure 4**) [94].

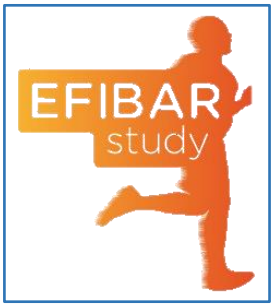


Figure 4. EFIBAR logo

The recruitment process occurred through the Bariatric Surgery Units of Torrecárdenas University Hospital and Hospital Mediterráneo, located in Almería (Spain), between May 1, 2018, and September 13, 2021. A total of 80 participants were targeted upon statistical power analysis based on the project's primary outcome (i.e., % of total weight loss [%TWL]). The assessments and intervention were carried out as the participant entered the study, with the last follow-up assessment for participant number 80 performed on September 2022. The EFIBAR project was approved by the Ethics Committee of the Torrecárdenas University Hospital (case No 76/2016). **Study I** uses the EFIBAR project's baseline data, while Study III examines pre-vs. post-intervention results following the RCT design.

Inclusion and exclusion criteria, randomization, and blinding

Eligible participants were: (i) adults between 18 and 60 years old; (ii) body mass index ≥40 or 35 kg/m^2 with comorbidities; (iii) acceptable surgical risk (defined by the anesthetist's approval); (iv) obesity maintained for at least five years; (v) failure of previous treatments; (vi) signed informed consent for surgical treatment; (vii) do not present contraindications for supervised physical exercise; (viii) residing in Almería capital or a willingness/predisposition to move and attend training sessions (if assigned to the exercise group). Participants were excluded from participating in the study if they presented: (i) severe psychiatric disorders such as schizophrenia, personality disorders, eating disorders, untreated depression, or suicidal tendencies; (ii) neurological disorders that may interfere with physical exercise; (iii) adrenal or thyroid pathology that may be the cause of obesity; (iv) rampant addiction to alcohol or drugs.

After the surgery, participants were randomly assigned to the intervention or control group. The randomized sequence was generated using computer-generated block randomization and concealed from the researchers using sealed and opaque envelopes numbered sequentially. A nurse, who was not involved in the measurements or intervention, opened an envelope in front of the participants without any research team member present. Given the nature of the intervention, participants were aware of group assignments after randomization. However, the research personnel responsible for data collection and analysis were blinded to group assignments at the follow-up visits (4 and 12 months after the surgery). A detailed description of the data collection process followed in this study is in **Figure 5**.

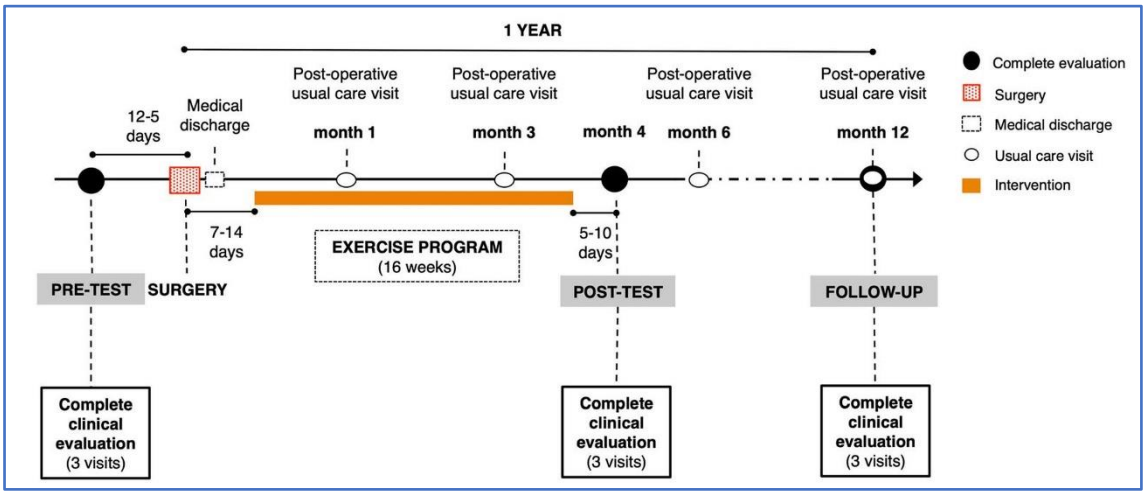
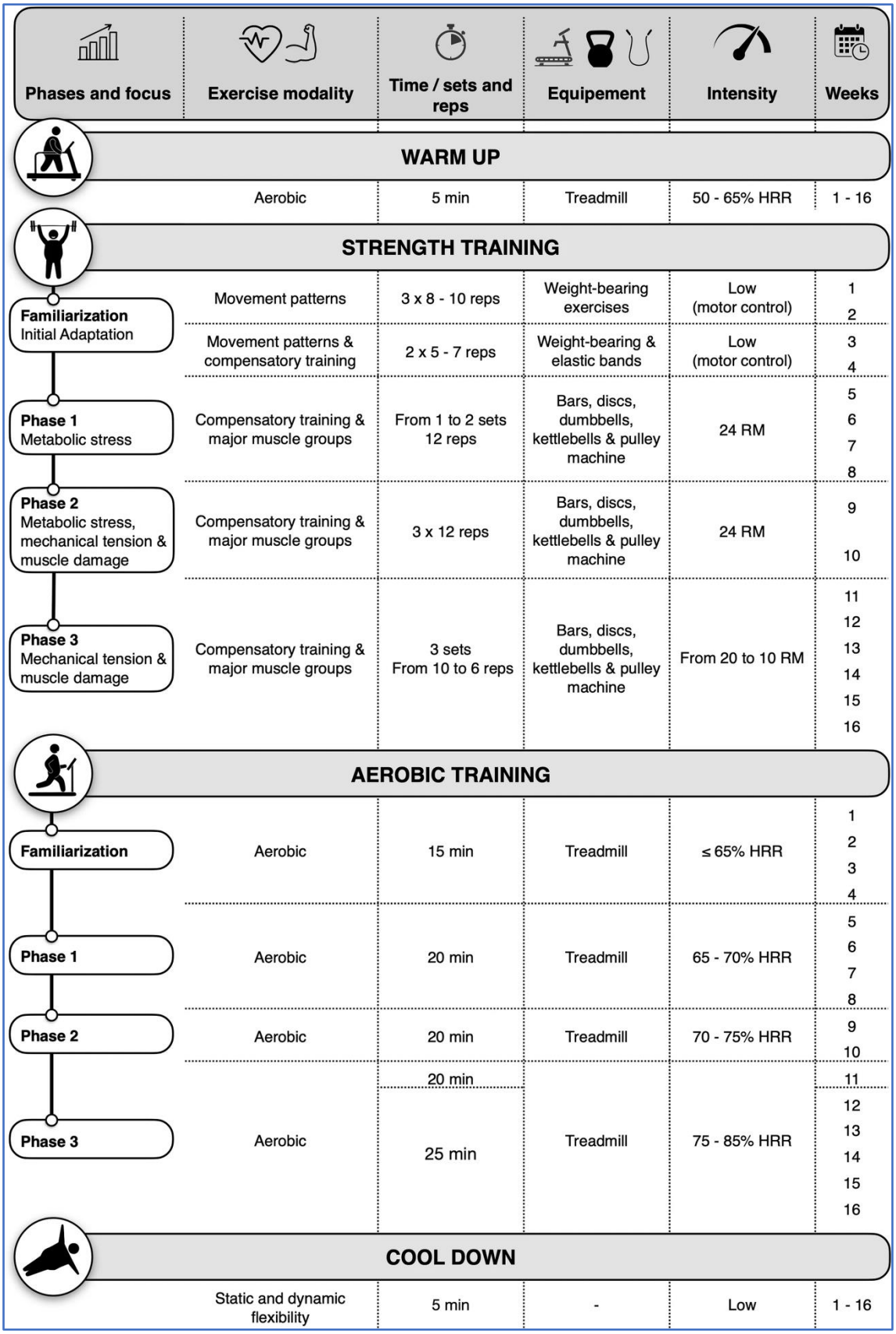


Figure 5. Data collection diagram of the EFIBAR study *(previously published in Artero, EG et* al [94]*)*

Exercise intervention

The EFIBAR exercise intervention has been reported following the CERT guidelines [95]. Very briefly, the program begins 7–14 days after surgery, exercising three times a week over 16 weeks, using 60-min sessions that include (i) warm-up, (ii) compensatory training (i.e., core stability and stabilizer muscle exercises), (iii) strength training, (iv) aerobic training, and (v) cool down. A detailed overview of the exercise intervention is provided in **Figure 6**. The intervention is performed individually and supervised, with a 1:1 ratio. Attendance, punctuality, training HR, rate of perceived exertion, mood, adverse events, and extra physical activity, among others, are recorded for each training session. Although no dietary intervention was conducted, all participants (both in the control and experimental group) received written counseling on the benefits of a healthy diet and regular physical activity during the reminder visits at months 1,3,4,6,9 and 12 after surgery.



Phases and focus	Exercise modality	Time / sets and reps	Equipement	Intensity	Weeks
WARM UP					
	Aerobic	5 min	Treadmill	50 - 65% HRR	1 - 16
STRENGTH TRAINING					
Familiarization Initial Adaptation	Movement patterns	3 x 8 - 10 reps	Weight-bearing exercises	Low (motor control)	1 2
	Movement patterns & compensatory training	2 x 5 - 7 reps	Weight-bearing & elastic bands	Low (motor control)	3 4
Phase 1 Metabolic stress	Compensatory training & major muscle groups	From 1 to 2 sets 12 reps	Bars, discs, dumbbells, kettlebells & pulley machine	24 RM	5 6 7 8
Phase 2 Metabolic stress, mechanical tension & muscle damage	Compensatory training & major muscle groups	3 x 12 reps	Bars, discs, dumbbells, kettlebells & pulley machine	24 RM	9 10
Phase 3 Mechanical tension & muscle damage	Compensatory training & major muscle groups	3 sets From 10 to 6 reps	Bars, discs, dumbbells, kettlebells & pulley machine	From 20 to 10 RM	11 12 13 14 15 16
AEROBIC TRAINING					
Familiarization	Aerobic	15 min	Treadmill	≤ 65% HRR	1 2 3 4
Phase 1	Aerobic	20 min	Treadmill	65 - 70% HRR	5 6 7 8
Phase 2	Aerobic	20 min	Treadmill	70 - 75% HRR	9 10
Phase 3	Aerobic	20 min 25 min	Treadmill	75 - 85% HRR	11 12 13 14 15 16
COOL DOWN					
	Static and dynamic flexibility	5 min	-	Low	1 - 16

Figure 6. Overview of the EFIBAR training program (previously published in Artero et al. [94]; for more details, see Villa-Gonzalez et al. [95])

Outcome Measures

A brief description of the measures from the EFIBAR project used in this Thesis is presented in this paragraph. More details about the rest of the evaluations that comprise EFIBAR are described elsewhere [94].

Bariatric Surgery

In this study, laparoscopic surgery is used to apply three distinct techniques: sleeve gastrectomy (SG), gastric bypass (GB), and one anastomosis gastric bypass (OAGB). The choice of technique for each participant is made by a team of endocrinologists, nutritionists, psychologists, and surgeons with consideration of several factors, such as the patient's BMI, age, comorbidities, and other relevant criteria.

Heart Rate Variability

Participants wore a **Polar V800** telemetry heart-rate monitor (Polar Electro Oy, Kempele, Finland). Heart rhythm was recorded for 10 minutes at a sampling frequency of 1000 Hz, with the patient seated for over 10 minutes between 8:30 AM and 11:30 AM in a quiet, temperature-controlled room (22–24°C). The raw signal data was downloaded from Polar Flow (https://flow.polar.com) as a ".txt" file which was later imported to Kubios Premium software (v.3.2, Heart Rate Analysis, University of Eastern Finland) to process the raw HRV data. The R-R intervals series were detrended using the smoothness prior method with alpha set at 500 with an interpolation rate set at 4 Hz. The time domain HRV variables analyzed were the standard deviation of all R-R intervals (SDNN), root mean square of successive differences in R-R intervals (RMSSD) and percentage of consecutive R-R intervals that differ by more than 50 ms (pNN50). The frequency domain analysis was computed using the fast Fourier transform (FFT), and the measures included: low frequency (LF: 0.04-0.15 Hz) power, high frequency (HF: 0.15-0.4 Hz) power, LF to HF power ratio (LF/HF) and very low frequency (VLF: 0-0.04 Hz). Nonlinear parameters included standard deviation 1 (SD1) and standard deviation 2 (SD2) from Poincaré Plot, sample entropy and detrended fluctuation analysis-alpha 1 (DFA-1).

Blood pressure outcomes

Blood pressure outcomes were assessed using the Mobil-O-Graph® oscillometry-based pulse analysis monitor (IEM GmbH, Stolberg, Germany). This device is reliable [96] in measuring brachial and central blood pressure [both systolic (SBP) and diastolic (DBP)], as well as arterial stiffness through pulse wave velocity (PVW), the elevation of which is an early marker of arteriosclerosis, and augmentation index at 75% of HR. Three readings were recorded with the participant resting quietly in a sitting position for 10

min, the cuff placed on the upper left arm around the brachial artery, and the palm facing upwards. The mean of the three recordings was used in the analysis.

Echocardiography variables

Transthoracic echocardiography was performed following a standardized protocol using a PHILIPS HD15 ultrasound machine and a PHILIPS Affiniti 50 (Philips Medical Systems, Bothell, USA). A segmental analysis was performed to assure segmental anatomy and to exclude a congenital heart defect in accordance with the Guidelines of the American Society of Echocardiography [97].

Left and right ventricular end-diastolic wall thickness and end-diastolic dimensions were obtained from the parasternal short-axis view at the level of the papillary muscles using M-mode. The left atrial diameter was determined from M-mode echocardiographic images using a leading-edge-to-leading-edge method, measuring the maximal distance between the posterior aortic root wall and the posterior LA wall at end-systole. The ejection fraction was measured by the biplane-modified Simpson method. For diastolic function, pulsed Doppler measurements of mitral and tricuspid inflow were performed in the apical four-chamber view. The sample volume was positioned between the tips of the mitral leaflets within $\pm 15^{\circ}$ of the central volume stream. Five consecutive cardiac cycles were recorded from every approach.

Three trained cardiologists performed this assessment at the Cardiology Unit in Torrecárdenas Hospital. Only baseline and post-12 months data were collected from all participants.

Anthropometry and body composition

Electric bioimpedance (InBody 270, Biospace Co., USA; Lookin'Body 120 software) was used to measure fat mass (FM, kg), fat-free mass (FFM, kg), and percentage of body fat (%BF). Height was measured using a portable system (SECA 213, Hamburg, Germany) with the patient shoeless in a standing position. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Control variables and other parameters

Participants were asked a series of questions that, although not part of the intervention itself, may influence the results of the studies presented in this thesis: (1) sex, age, educational level, marital status, occupational status, and income level; (2) personal history of obesity (obesity duration), cardiovascular disease, hypertension, smoke, obstructive sleep apnea (OSA), type 2 diabetes, and medication use.

The EJERCITALES project (Study II)

Study design

The EJERCITALES project is a non-randomized controlled trial (NCT03107442) investigating the effects of a 12-week aerobic exercise program on arterial stiffness, inflammation, and cardiorespiratory fitness (**Figure 7**) [65].

The recruitment process took place through the Systemic Autoimmune Diseases Unit of the "Virgen de las Nieves" and "San Cecilio" University Hospitals in Granada (Spain), starting on April 12, 2017. A total of 60 participants were targeted after power calculations for this project's primary outcome (i.e., PWV). The EJERCITALES project was approved by the Ethics Committee of the Granada (case No 10/2016). **Study II** uses the data from this project. To answer aim 1, we cross-sectionally used the participants' baseline data before they were included in the exercise or control group.

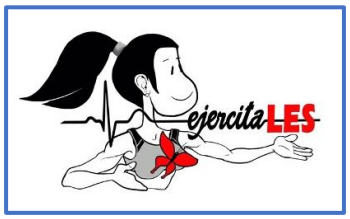


Figure 7. EJERCITALES logo.

Inclusion and exclusion criteria, randomization, and blinding

This study included women diagnosed with SLE according to the American College of Rheumatology criteria, a follow-up of ≥ 12 months, clinical and treatment stability during the previous six months, and not performing regular exercise (defined as ≥ 60 min/week of structured exercise). Exclusion criteria were: to have been under biological treatment in the previous six months or to need a prednisone dose of >10 mg/day; a background of CVD in the previous year; to present contraindications to performing physical activity; other associated rheumatic conditions; pregnancy; active acute or chronic infection; neoplasms; acute renal failure; cardiac or pulmonary involvement; body mass index (BMI) >35; or not being able to read, understand, and sign written informed consent.

Randomization was impossible as many participants lived far away and could not attend the exercise sessions in case of being randomized to exercise. Therefore, participants from the city of Granada were in the exercise group, and participants living outside Granada were in the control group. To minimize potential selection bias, groups were matched by age (±2 years), BMI (±1 kg/m2), and SLEDAI (±1 unit). The data analyzer was blinded to the patient allocation.

Exercise intervention

The patients assigned to exercise performed two 75-minute sessions per week for 12 weeks (i.e., 24 sessions) in an equipped room at "Virgen de las Nieves" Hospital under

the supervision of both exercise professionals and residents from the Internal Medicine Department. All sessions were performed in groups of a maximum of five persons (depending on the patients 'schedule preferences), and attendance was registered daily. All sessions began with a warm-up comprising 3–4 min of activation on the treadmill at about 35–40% of the heart rate reserve (HRR) plus 3–4 min of active stretching of major muscle groups and ended with a cool-down phase of static stretching of major muscle groups and relaxation. Exercise was prescribed individually to represent moderate-to-vigorous intensity, with training intensity ranging from 40% to 75% of each patient's HRR. The maximum heart rate (HRmax) was estimated with the formula by Tanaka et al. [98] (HRmax= 208−(0.7×age)). Only continuous exercise was performed during the first half of the program (6 weeks). From week 8, continuous and interval sessions were alternated. At week 12, the patients performed only interval training sessions, followed by some minutes of rest for hydration. The exercise intensity progressions had to be slightly modified since several patients perceived a 5% HRR increase as heavy and difficult-to-follow. Therefore, exercise intensity increased by 2.5% instead of 5% in some weeks. A more detailed description of the exercise intervention following the CERT guidelines can be found elsewhere [65] and in **Figure 8**.

Month	Week	Weekly MVPA (min)	Session (No.)	Training Type	Total Session Time (min)	Estimated Session Time at Target Intensity (min)	Intensity (% HRR)		Series/Workout
1	1	90	1	Continuous	55	≈40	35–45		7,5′ Warm-up + 15′ 35–45% + 3′ rec + 10′ 35–45% + 3′ rec + 10′ 35–45% + 7,5′ Cool down
			2	Continuous	65	≈50	35–45		7,5′ Warm-up + 2 × (15′ 35–45%/3′ rec) + 15′ 35–45% + 7,5′ Cool down
	2	105	3	Continuous	65	≈50	40–50		7,5′ Warm-up + 20′ 40–50% + 3′ rec + 15′ 40–50% + 3′ rec + 10′ 40–50% + 7,5′ Cool down
			4	Continuous	75	≈60	40–50		7,5′ Warm-up + 2 × (20′ 40–50%/3′ rec) + 15′ 40–50% + 7,5′ Cool down
	3	130	5	Continuous	75	≈60	45–55		7,5′ Warm-up + 25′ 45–55% + 3′ rec + 20′ 45–55% + 3′ rec + 10′ 45–55% + 7,5′ Cool down
			6	Continuous	85	≈70	45–55		7,5′ Warm-up + 2 × (25′ 45–55%/3′ rec) + 15′ 45–55% + 7,5′ Cool down
	4	145	7	Continuous	85	≈70	45–55		7,5′ Warm-up + 30′ 45–55% + 3′ rec + 25′ 45–55% + 3′ rec + 10′ 45–55% + 7,5′ Cool down
			8	Continuous	90	≈75	45–55		7,5′ Warm-up + 1 × (40′ 45–55%/3′ rec) + 30′ 45–55% + 7,5′ Cool down
							Interval lower bound	Interval higher bound	
2	5	150	9	Continuous	90	≈75	50–60		7,5′ Warm-up + 30′ 50–60% + 2.5′ rec + 25′ 50–60% + 2.5′ rec + 15′ 50–60% + 7,5′ Cool down
			10	Continuous	90	≈75	50–60		7,5′ Warm-up + 1 × (40′ 50–60%/5′ rec) + 30′ 50–60% + 7,5′ Cool down
	6	150	11	Continuous	90	≈75	55–60		7,5′ Warm-up + 1 × (40′ 55–60%/5′ rec) + 30′ 55–60% + 7,5′ Cool down
			12	Interval	90	≈75	50–55	60–65	7,5′ Warm-up + 1 × (25′ 50–55%+10′ 60–65%+5′ rec) + 1 × (25′ 50–55%+10′ 60–65%) + 7,5′ Cool down
	7	150	13	Continuous	90	≈75	57.5–62.5		7,5′ Warm-up + 1 × (45′ 57.7–62.5%/5′ rec) + 25′ 57.5–62.5% + 7,5′ Cool down
			14	Interval	90	≈75	52.5–57.5	60–65	7,5′ Warm-up + 1 × (20′ 52.5–57.5%+15′ 60–65%+5′ rec) + 1 × (20′ 52.5–57.5%+15′ 60–65%) + 7,5′ Cool down
	8	150	15	Continuous	90	≈75	55–60		7,5′ Warm-up + 1 × (40′ 55–60%/5′ rec) + 30′ 55–60% + 7,5′ Cool down
			16	Interval	90	≈75	50–55	60–65	7,5′ Warm-up + 1 × (30′ 55–60%+5′ 60–65%+5′ rec) + 1 × (30′ 55–60%+5′ 60–65%) + 7,5′ Cool down
							Interval lower bound	Interval higher bound	
3	9	150	17	Interval	90	≈75	55–60	65–70	7,5′ Warm-up + 2 × (15′ 55–60%+3′ 65–70%) + 5′ rec + 15′ 55–60% + 3′ 65–70% + 12′ 55–60% + 3′ 65–70% + 7,5′ Cool down
			18	Interval	90	≈75	55–60	65–70	7,5′ Warm-up + 2 × (15′ 55–60%+3′ 65–70%) + 5′ rec + 15′ 55–60% + 3′ 65–70% + 12′ 55–60% + 3′ 65–70% + 7,5′ Cool down
	10	150	19	Interval	90	≈75	57.5–62.5	65–70	7,5′ Warm-up + 3 × (11′ 57.5–62.5% + 3′ 65–70%) + 5′ rec + 2 × (11′ 57.5–62.5% + 3′ 65–70%) + 7,5′ Cool down
			20	Interval	90	≈75	57.5–62.5	70–75	7,5′ Warm-up + 3 × (11′ 57.5–62.5% + 3′ 70–75%) + 5′ rec + 2 × (11′ 57.5–62.5% + 3′ 70–75%) + 7,5′ Cool down
	11	150	21	Interval	90	≈75	60–65	70–75	7,5′ Warm-up + 2 × (15′ 60–65%+3′ 70–75%) + 5′ rec + 15′ 60–65% + 3′ 70–75% + 12′ 60–65% + 3′ 70–75% + 7,5′ Cool down
			22	Interval	90	≈75	60–65	70–75	7,5′ Warm-up + 2 × (15′ 60–65%+3′ 70–75%) + 5′ rec + 15′ 60–65% + 3′ 70–75% + 12′ 60–65% + 3′ 70–75% + 7,5′ Cool down
	12	150	23	Interval	90	≈75	60–65	70–75	7,5′ Warm-up + 5 × (5′ 60–65%+3′ 70–75%) + 5′ rec + 2 × (11′ 60–65%+3′ 70–75%) + 7,5′ Cool down
			24	Interval	90	≈75	60–65	70–75	7,5′ Warm-up + 5 × (5′ 60–65%+3′ 70–75%) + 5′ rec + 3 × (6′ 60–65%+4′ 70–75%) + 7,5′ Cool down

Figure 8. Overview of the training program of the EJERCITALES study (previously published in Soriano-Maldonado et al. [65])

Outcomes Measures

A brief description of the measures from the EJERCITALES project used in this thesis is presented in the following paragraph. More details about the evaluations comprising EJERCITALES are described elsewhere [65,66].

Heart Rate Variability

Participants wore a **Polar V800** telemetry heart-rate monitor (Polar Electro Oy, Kempele, Finland). Heart rhythm was recorded for 10 minutes at a sampling frequency of 1000 Hz, after 5 minutes of resting, with the patient seated for over 10 minutes between 4:00 PM and 7:00 PM in a quiet, temperature-controlled room (22–24°C). The R-R intervals series were detrended using the prior smoothness method with alpha set at 500 and an interpolation rate set at 4 Hz. After visual inspection for any premature contractions or ectopic beats in the recording; the evaluator manually selected a 5-min period. Kubios filters were applied accordingly based on inter-individual variability, and if the sample presented more than 5% of interpolated R-R intervals, it was discarded following the manufacturer's recommendation.

Inflammatory and oxidative stress markers

Blood samples were collected from the participants while fasting early in the morning. Serum high-sensitivity CRP was assessed by the ARCHITECT systems (MULTIGENT CRP Vario assay); the limit of quantitation was 0.2 mg/L, and the upper limit for normal serum was 5 mg/L (coefficient of variation <6%). Interleukin 6, TNF-α, and myeloperoxidase (MPO; as a marker of oxidative stress) were measured in plasma. Serum was initially separated by centrifugation and stored at −70◦C. Bioserum concentrations of IL-6/TNF-α (pg/mL) and MPO (ng/mL) were measured by an immunoradiometric assay using commercial kits (MILLIPLEX MAP Kit Human High Sensitivity T Cell Magnetic Bead Panel (HSTMAG-28SK) and Human Cardiovascular Disease Magnetic Bead Panel 2 (HCVD2MAG-67K)), Millipore) following the manufacturer's instructions. Quantitative data were obtained by using the Luminex-200 system (Luminex Corporation, Austin, TX, USA), and data analysis was performed on XPonent 3.1 software (Austin, TX, USA). The detection limits were 0.73 pg/mL for IL-6, 0.43 pg/mL for TNF- α, and 0.024 ng/mL for MPO.

Patient-Reported Outcomes

In this project, participants completed questionnaires about psychological stress, fatigue, sleep quality, depressive symptoms, and health-related quality of life. Psychological stress was measured with the Perceived Stress Scale (PSS), a 14-item self-report global measure designed to assess the degree to which situations in one's

life are appraised as stressful [99]. According to how patients felt during the last month, each item is rated from 0 (never) to 4 (very often). The PSS provides a single overall score (0–56), where a higher score represents more significant perceived stress. Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI) [100], which includes 5 subscales of fatigue severity: general, physical, and mental fatigue, as well as reduced activity and reduced motivation. Each subscale consists of four items ranging from 4 to 20, with higher scores indicating greater fatigue on that subscale. Depressive symptomatology was assessed through the Beck Depression Inventory-second edition (BDI-II) [101], where according to how patients felt during the past two weeks, each depressive symptom is rated from 0 (not present) to 3 (severe). The BDI-II provides an overall score (0–63), where a higher score indicates greater depressive symptomatology. The Spanish version of the 36-item Short-Form Health Survey (SF-36) assessed the quality of life of the participants. It assesses eight health dimensions that define two global domains: the physical and mental component scales (PCS and MCS, respectively) [102]. Lastly, disease activity was assessed through the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI, range 0–105, where a higher score indicates a higher degree of disease activity) [103]. More information about how the questionnaires were computed and administered can be found elsewhere [66].

Pilot study (Study I)

Study design

This analytical observational cohort study aimed to describe the short-term changes in HRV parameters before and after sleeve gastrectomy surgery [104]. Participants eligible for sleeve gastrectomy surgery, a type of bariatric surgery in which about 80% of the stomach is removed, were recruited over two years (2015 and 2016). All procedures followed the standards in the 1964 Helsinki declaration and its later amendments, and all patients signed informed consent. The sample size for this study was determined using an alpha error of 5% and a statistical power of 90% based on previously reported data for high-frequency (HF) power [105]. It was deemed that 17 patients were needed for this study. Participants with arrhythmias, severe CVD, chronic renal failure, chronic obstructive pulmonary disease, a smoking habit, using beta blockers, postmenopausal status, or who had undergone previous bariatric surgery were excluded. Participants were assessed 7-14 days before surgery and months 1 and 3 after the procedure. A total of 23 women with obesity (BMI≥30 kg/m^2) were included in the anthropometric and HRV parameters assessment.

Outcomes Measures

Heart Rate Variability

All assessments were performed in the morning to avoid variations in the circadian rhythm. The duration of RR intervals was recorded using a **Polar RS800CX** telemetry heart rate monitor (Polar Electro Oy, Kempele, Finland). After resting in the supine position for 5 min, the heart rate RR intervals were continuously recorded for 10 min in the same position in a quiet, temperature-controlled room (22–24 °C) while breathing at a controlled rate (14 breaths per minute) using a metronome. The time domain, frequency domain, and nonlinear analysis of HRV were determined from the 5-min resting RR record with the lowest average heart rate using Kubios Premium Software (3.0.2 version). A detailed description of the parameters analyzed can be found in Ibacache et al. [104] **Study I** uses the baseline data from this study.

Anthropometry

Body mass index (BMI) and waist circumference (at the level of the iliac crests) were determined using a DETECTO 439 balance scale and a Rosscraft anthropometric tape, respectively.

Statistical Analysis

Summary statistics are presented as means (standard deviations; SD) unless otherwise indicated. Data normality was examined using the Kolmogorov-Smirnoff test, visual histograms, and Q-Q plots. Those variables that did not follow a normal distribution were log-transformed (i.e., HRV parameters). **Study I** and **III** were analyzed with R statistical software (version 4.2.1), while **Study II** was analyzed with SPSS v.22 (IBM SPSS Statistics for Windows, Armonk, NY, IBM, Corp). Statistical significance was set at $p<0.05$.

Analyses conducted for Study I

Descriptive data are presented as mean (standard deviation; SD). Linear mixed-effect methods were conducted using the `lmer` package. The interaction of filter and segment for the HRV derived parameters was assessed using linear mixed-effects models, with filter and segments along their interaction included as predictors in the model. Estimations were performed using the restricted maximum likelihood method, adjusting for within-participant clustering from the repeated-measures design. The residuals and normal probability plots were conducted to evaluate the model fit and a likelihood ratio test comparing the full model to a null model without the predictors. Post hoc pairwise comparisons using Tukey correction for multiple comparisons were conducted when significance was found. To account for the influence of artifacts on HRV parameters, a linear model assessing its influence according to group, filter, and segment was performed. A similar analysis was performed to control for the possible differences in collecting HRV data (sitting vs. lying down, normal respiration vs. controlled respiration) in participants with obesity, which was divided in subsamples in accordance to the methodology employed in the EFIBAR and Chilean studies. Additional analyses excluded the raw values when no filter was applied to HRV parameters and with a subsample of participants with normal BMI matched by age.

Analyses conducted for Study II

Normality was tested using visual inspection of histograms and Q-Q plots. As HRV-derived parameters were non-normally distributed, their descriptive analysis was presented using the median and interquartile range, while a non-parametric test was used for the primary analysis. Between-group baseline characteristics were compared with the Student t-test (when normally distributed), Kruskal–Wallis test (when non-normally distributed) for continuous variables, and the Chi-square test for categorical variables. To explore the associations of HRV with inflammatory and oxidative stress markers (hsCRP, IL-6, TNF-α, and MPO) and PROs (aim 1), scatter plots and Spearman's bivariate correlations were used as preliminary analyses to understand raw

associations. Subsequently, quantile regression models were built, including the above HRV parameters as dependent variables and each inflammatory marker as independent variables in regression models, along with age, heart rate, and disease duration as relevant factors that might confound the association of interest. This exact procedure was followed with PROs. Other variables included in the regression model were SLEDAI, systemic damage index (SDI), and smoking. However, neither of these variables affected the regression coefficients; therefore, they were not included. Inflammatory markers (hsCRP, IL-6 and TNF-α) and MPO were winsorized to the highest value due to the presence of outliers.

To assess the effects of the exercise intervention (aim 2), the between group differences in the change from baseline in HRV-derived parameters were assessed through quantile regression with baseline values, heart rate, and age as covariables. As we aimed at assessing efficacy, the primary analyses were defined as per-protocol, where patients from the exercise group were included if attendance to the exercise sessions was ≥75%. We additionally performed sensitivity analyses, including (i) participants with attendance ≥90%; and (ii) baseline observation carried forward (BOCF).

Further variables derived from statistical analyses.

The inter-individual variability of the patients in response to the intervention was analyzed by categorizing participants from each group as responders, non-responders, or adverse responders using the typical error measurement (TE). The TE was calculated using the equation $TE=SDdiff/\sqrt{2}$, where SDdiff is the standard deviation of the difference scores observed between the 2 repeats of each measurement[106]. A responder was defined as an individual who demonstrated an increase (in favor of beneficial changes), an adverse responder was defined as an individual who demonstrated a decrease, and a non-responder was defined as an individual who failed to demonstrate an increase or decrease that was>2 times the TE away from 0. A change more than 2 times the TE means that this response is an actual physiological adaptation beyond what might be expected to result from technical and/or biological variability.

Analyses conducted in Study III

A prespecified sample size of 40 individuals per group was obtained from a power calculation based on the primary study outcome. Because the training effects of the variables included in this study were exploratory, no power calculation related to these outcomes was performed. Data normality was examined using the Kolmogorov-Smirnoff test, visual histograms, and Q-Q plots. Those variables that did not follow a normal

distribution were log-transformed (i.e., HRV parameters). Extreme outliers in the echocardiographic variables were winsordized to the lowest 5% and highest 95% values. Baseline characteristics with normal or non-normal distribution were reported as mean, SD, median, and interquartile range, respectively. Between-group baseline characteristics were compared with the student t-test (when normally distributed), Kruskal-Wallis (when non-normally distributed), and the Chi-square test for categorical variables.

Intervention effects on outcomes were assessed using linear mixed-effects models, with individual measures of growth being modeled as the function of the randomization group, assessment time (baseline, 4 months, and 12 months), and the interaction between group and time. Estimations were performed using the restricted maximum likelihood method, adjusting for within-participant clustering from the repeated-measures design. The model assumed that missing values were missing at random; therefore, all values presented in the tables are modeled-based estimates.

All analyses were performed using a per-protocol approach restricted to participants with valid outcome measures (control or exercise groups) who adhered to the pre-specified [95] attendance rate of at least 80% of planned sessions (only for the exercise group). Additionally, an intention-to-treat approach (including all participants as initially randomized) was used as sensitivity analysis.

RESULTS

"Science is the process that take us from confusion to understanding."

- Brian Greene

STUDY I

Heart rate variability assessment in people with obesity: influence of artifact correction, filters, and segment selection.

Results

A total of 75 participants, 60 participants with a BMI > 30 kg/m^2 and 15 participants matched by sex and age with a normal BMI, were included in this study (**Table 1**).

Table 1. Baseline characteristics of participants included in Study I.

Variables	Severe obesity (n=60)	Healthy BMI (n= 15)
Sex, n (%women)	47 (78%)	11 (73%)
Age (years)	40.9 (11.1)	42.7 (11.8)
Weight (kg)	114.9 (27.6)	63.9 (9.3)
Height (cm)	164.1 (8.3)	168.9 (10.9)
BMI (kg/m^2)	42.3 (8.6)	22.3 (1.9)

Data presented as mean (SD). BMI, body mass index.

The percentage of artifacts corrected in the HRV measurements when using Kubios filters in the different 5-min segments for each group are shown in **Table 2**. In **Figure 9**, a graphical representation of the percentage of artifacts corrected for each duration segment according to low, medium, strong and automatic filter are presented for each group of participants.

Table 2. Percentage of beats corrected in people with obesity and normal BMI.

Beats corrected in people with obesity (%)								
Filters	**0-5 min**		**2:30-7:30 min**		**5-10 min**		**Minimum Heart Rate**	
	Mean (SD)	**(Min - Max)**	**Mean (SD)**	**(Min - Max)**	**Mean (SD)**	**(Min - Max)**	**Mean (SD)**	**(Min - Max)**
No filter	0.0 (0.0)	(0.0 - 0.0)	0.0 (0.0)	(0.0 - 0.0)	0.0 (0.0)	(0.0 - 0.0)	0.0 (0.0)	(0.0 - 0.0)
Low	0.7 (1.8)	(0.0 - 10.8)	0.8 (2.1)	(0.0 - 9.6)	0.6 (2.0)	(0.0 - 11.7)	0.6 (1.9)	(0.0 - 9.6)
Medium	1.1 (3.2)	(0.0 - 20.4)	1.4 (3.8)	(0.0 - 19.3)	0.9 (3.1)	(0.0 - 19.7)	1.0 (3.1)	(0.0 - 19.4)
Strong	2.6 (6.5)	(0.0 - 41.3)	3.4 (7.5)	(0.0 - 41.4)	2.3 (6.5)	(0.0 - 42.0)	2.5 (6.5)	(0.0 - 41.1)

Automatic	0.7 (0.9)	(0.0 - 6.6)	0.4 (1.0)	(0.0 - 6.8)	0.5 (1.2)	(0.0 - 6.8)	0.5 (1.2)	(0.0 - 7.7)

Beats corrected in people with a normal BMI (%)

Filters	0-5 min		2:30-7:30 min		5-10 min		Minimum Heart Rate	
	Mean (SD)	(Min - Max)	Mean (SD)	(Min - Max)	Mean (SD)	(Min - Max)	Mean (SD)	(Min - Max)
No filter	0.0 (0.0)	(0.0 - 0.0)	0.0 (0.0)	(0.0 - 0.0)	0.0 (0.0)	(0.0 - 0.0)	0.0 (0.0)	(0.0 - 0.0)
Low	0.6 (1.2)	(0.0 - 3.8)	0.5 (0.8)	(0.0 - 2.4)	0.3 (0.7)	(0.0 - 2.4)	0.3 (0.7)	(0.0 - 2.7)
Medium	0.7 (1.4)	(0.0 - 5.3)	0.5 (0.8)	(0.0 - 2.5)	0.3 (0.6)	(0.0 - 2.4)	0.3 (0.7)	(0.0 - 2.7)
Strong	1.5 (2.0)	(0.0 - 8.0)	0.9 (0.9)	(0.0 - 2.4)	0.6 (0.9)	(0.0 - 2.6)	0.7 (1.0)	(0.0 - 2.8)
Automatic	1.0 (1.2)	(0.0 - 4.2)	0.6 (0.9)	(0.0 - 2.7)	0.5 (0.9)	(0.0 - 3.6)	0.5 (0.9)	(0.0 - 3.6)

Data presented as mean of beats corrected (SD), minimum and maximum

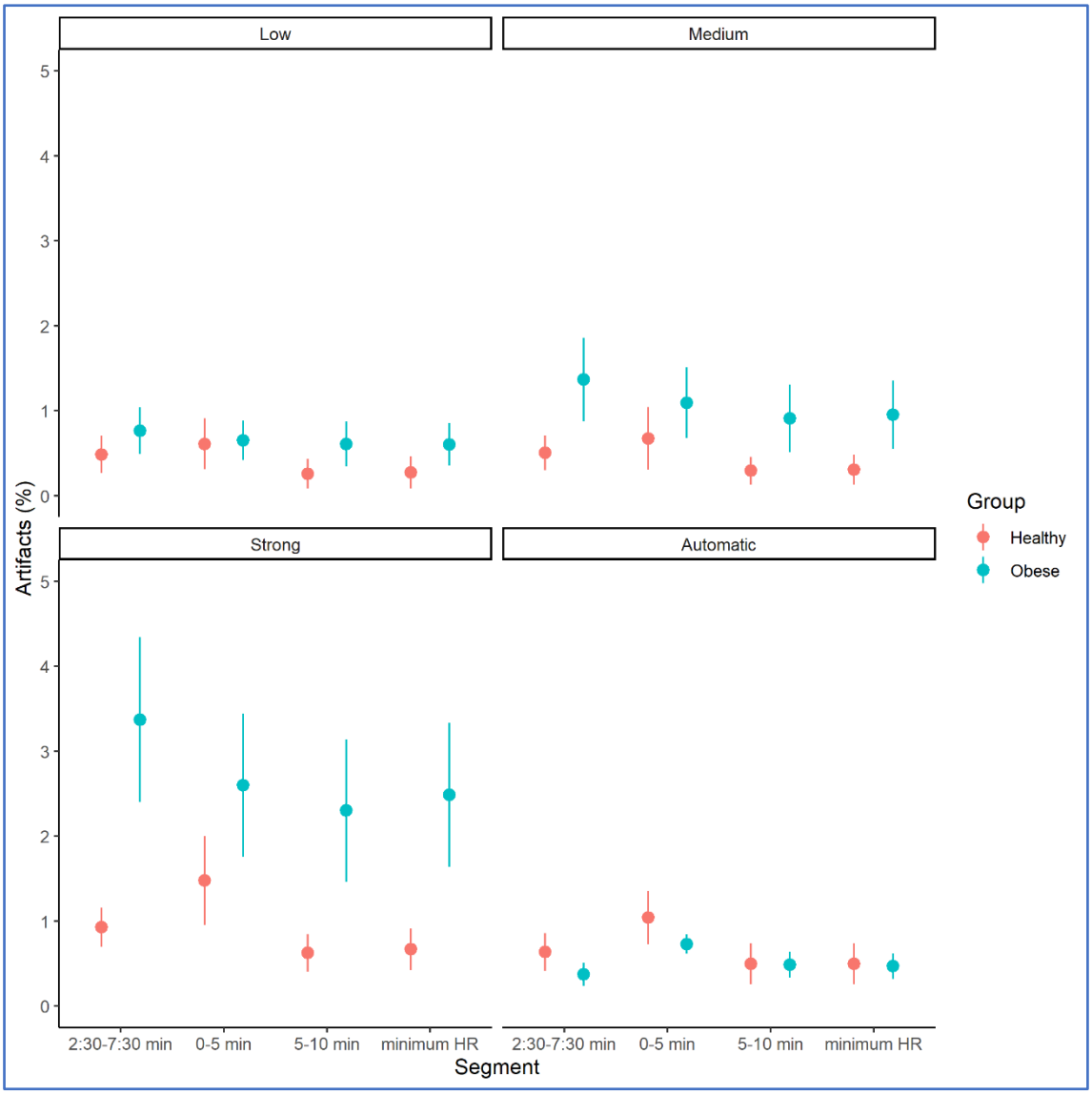


Figure 9. Percentage of artifacts corrected (5% threshold as recommended by Kubios manual) for each duration segment according to low, medium, strong and automatic filter are presented for people with obesity and normal BMI.

There was no significant differences between the percentage of artifacts presented in the signal across filters, segments, and groups. However, there was a significant difference in the percentage of artifacts according to the type of filter applied ($F(8.09)$, $p < 0.001$) and by filter according to the group of participants ($F(3.61)$, $p = 0.012$). Specifically, normal BMI participants did not present differences between the presence of artifacts when applying different filters; while people with obesity presented a higher percentage of artifacts present in the signal when applying the strong filter against the low, medium, and automatic filters (all $p<0.001$, **Figure 10**). Furthermore, the strong filter differed significantly between people with obesity and normal BMI (mean difference = -1.658, $p = 0.0208$; **Figure 10**).

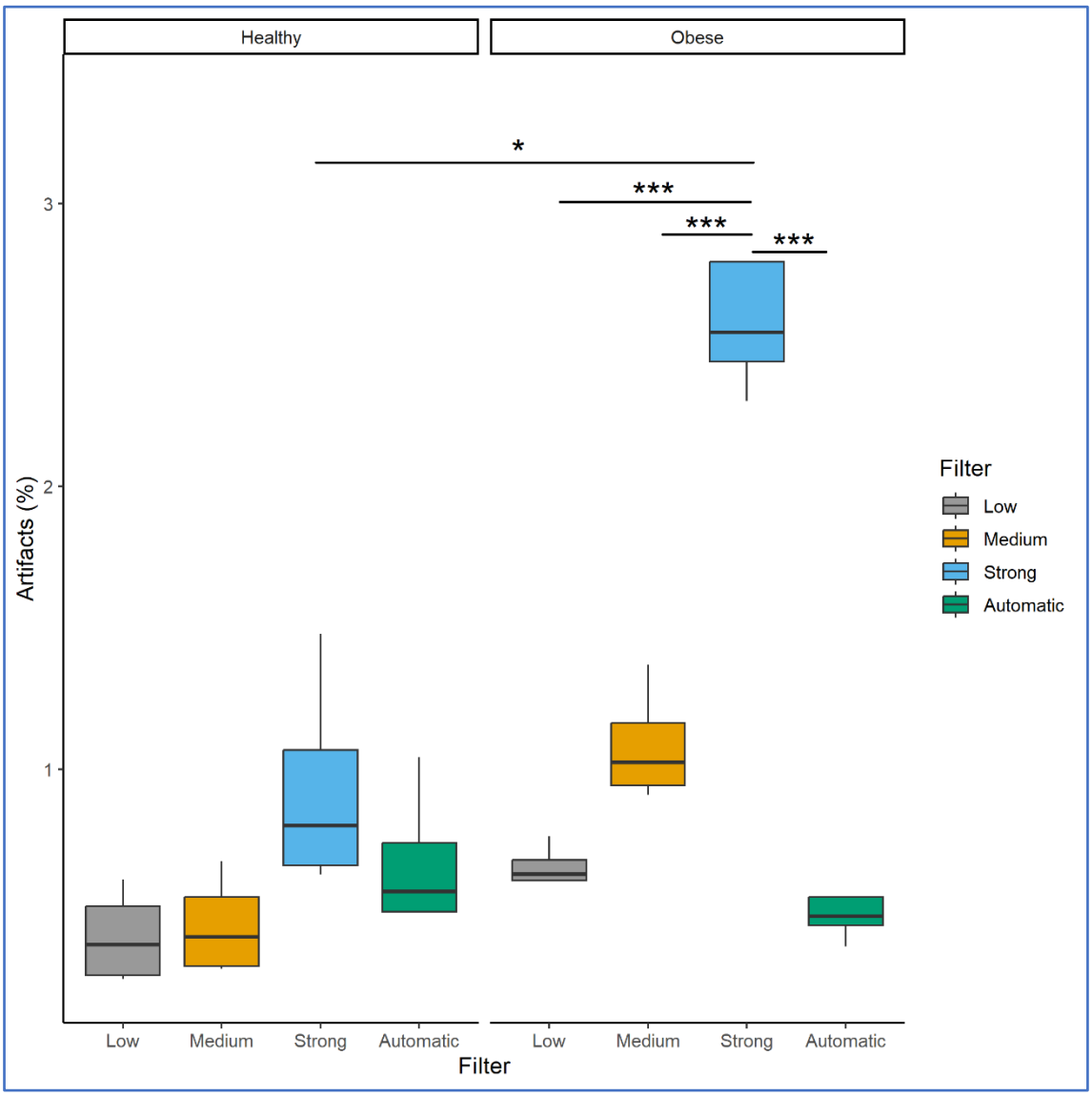


Figure 10. Percentage of artifacts corrected according to filter selection and group of participants. *, p<0.05; **, p<0.01; ***, p<0.001.

When assessing whether the position and respiration while collecting the data influenced HRV parameters in people with obesity, only SDNN (mean difference = 12.2 ms^2, 95% CI [1.8 to 22.6]; p<0.022), RMSSD (mean difference = 18.3 ms^2, 95% CI [5.0 to 31.6]; p<0.001) and HF (mean difference = 1.6, 95% CI [0.9 to 2.2]; p<0.001, **Figure 11**) values were significantly lower in participants who were lying down and had their respiration controlled by a metronome compared to participants who were sitting down following their normal pattern of respiration.

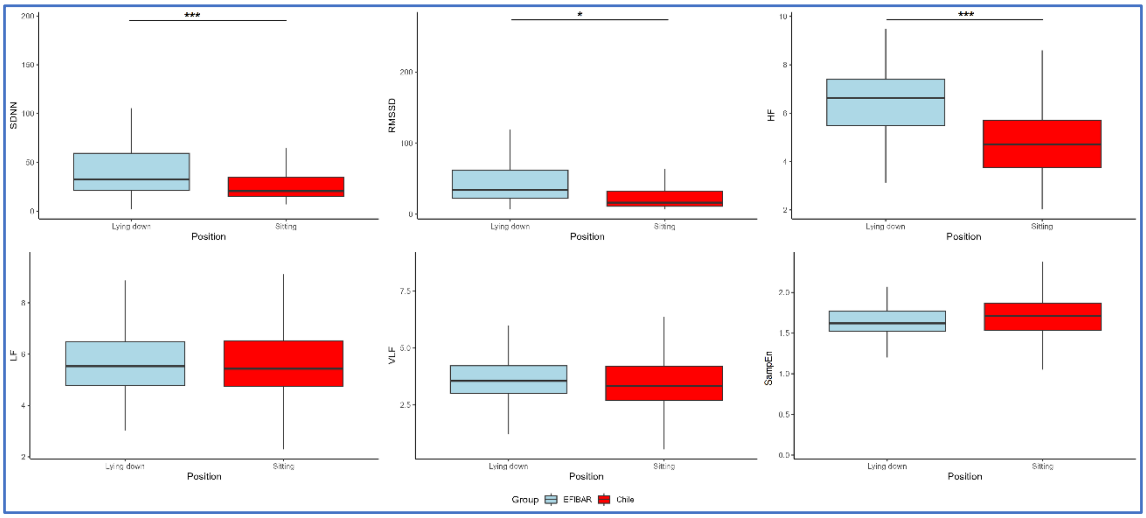


Figure 11. Effect of assessment position and respiration on HRV parameters. EFIBAR participants (n=37) were evaluated seated and with normal pattern of respiration while Chile participants (n=23) were evaluated lying down and their respiration was controlled. *, p<0.05; **, p<0.01; ***, p<0.001.

Time domain parameters

SDNN had higher values in the 0-5 min, 2:30-7:30 min, and 5-10 min segments when no filter (raw) was applied against the low, medium, strong, and automatic filter (all p<0.001, **Figure 12A**). Raw SDNN values in the 5-10 min segment were significantly higher than in the 2:30-7:30 min (mean difference = -45.4 ms^2, 95% confidence interval (CI) [-80.2 to -10.6]; p=0.0045), and the min HR (mean difference = -61.8 ms^2, 95% CI [-27.0 to -96.6]; p<0.001). The same happened to RMSSD, where the values were lower when using filters (all p<0.001, **Figure 12B**). Raw RMSSD values were significantly lower in the minimum HR segment compared to the 0-5 min (mean difference = 36.9 ms2; 95% CI [2.0 to 71.0]; p=0.0279) and 5-10 min segments (mean difference = 49.9 ms2, 95% CI [15.8 to 84.0], p<0.001). Surprisingly, there wasn't any statistical difference between the rest of the filters and no applying any type of filter in SDNN and RMSSD for the minimum HR segment.

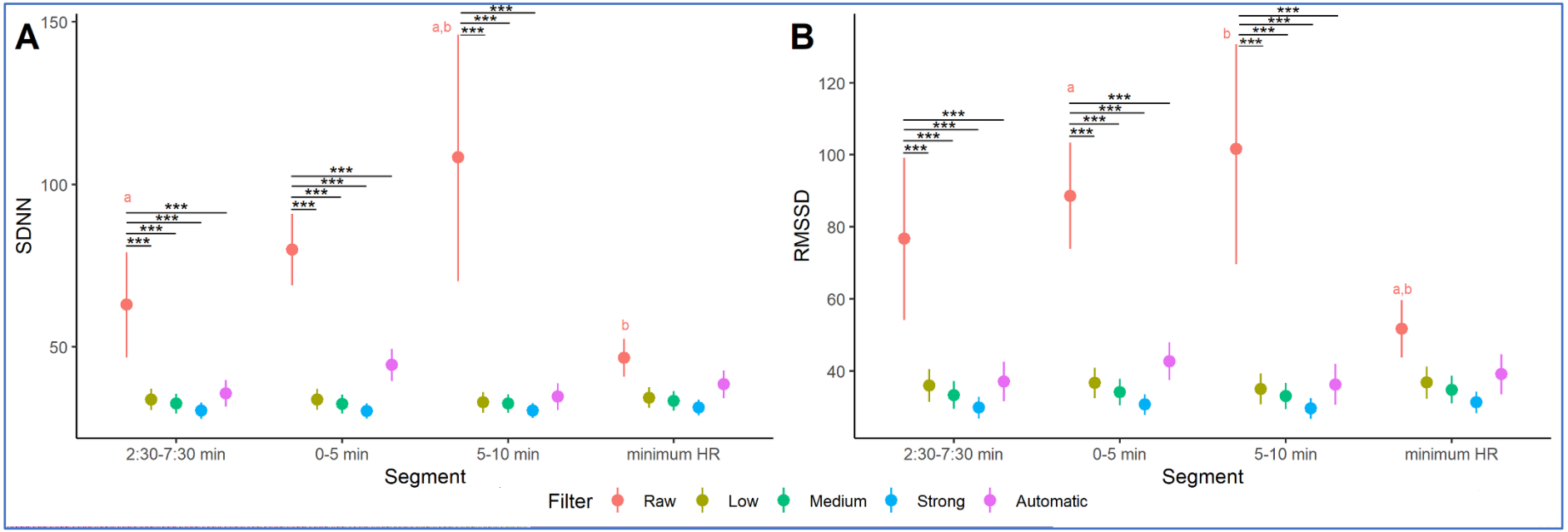


Figure 12. Interaction of filter and segments selection on time domain parameters (SDNN & RMSSD) of participants with obesity. *, p<0.05; **, p<0.01; ***, p<0.001. Letters indicate differences between the same filter in different segments.

In the sensitivity analysis where the none filter (raw) was excluded, the SDNN value was significantly higher when the automatic filter was applied compared to the low (mean difference = 10.6 ms^2, 95% CI [18.1 to 3.0], p<0.01), medium (mean difference = 12.1 ms^2, 95%CI [19.6 to 4.5], p<0.01), and strong filter (mean difference = 14.2 ms^2, 95% CI [21.7 to 6.6],p<0.01, **Figure 13A**) during the 0-5 min segment. Furthermore, when using the automatic filter, the raw SDNN value in the 0-5 segment was significantly higher than the raw values in the 2:30-7:30 min (mean difference= 8.7, 95% CI [16.3 to 1.2], p=0.015) and 5-10 min segments (mean difference= 9.7, 95% CI [2.2 to 17.3], p<0.01, **Figure 13A**). Regarding RMSSD, only in comparing the automatic and strong filters in the 0-5 min segment was the value significantly higher (mean difference = 12.0 ms^2, 95% CI [21.4 to 2.5]; p<0.01, **Figure 13B**).

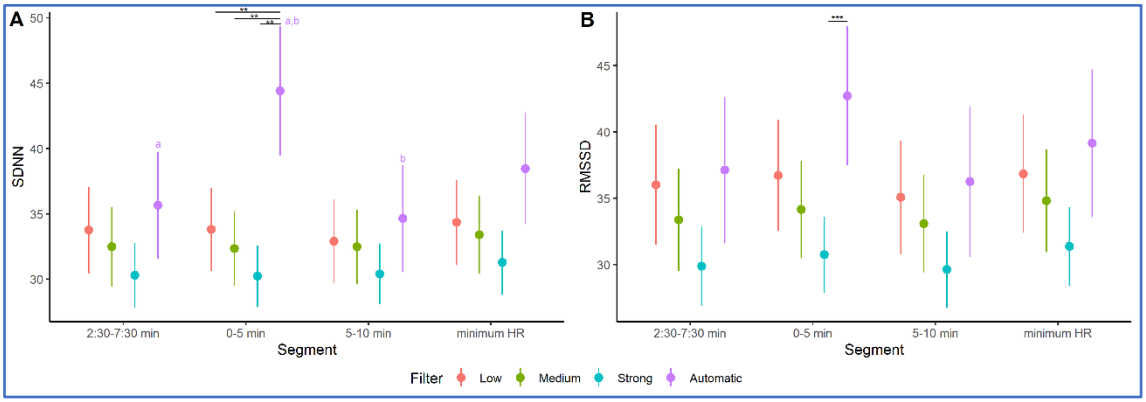


Figure 13. Interaction of filter (excluding raw values) and segments selection on time domain parameters (SDNN & RMSSD) of participants with obesity. Letters indicate differences between the same filter in different segments.

In further sensitivity analysis, when applying the same analysis to a subsample of participants with normal BMI matched by age, only in the 2:30-7:30 min and 0-5 min segments raw values of SDNN and RMSSD when no applying any filter was significantly higher than when applying filters (all p<0.05, **Figure 14A**).

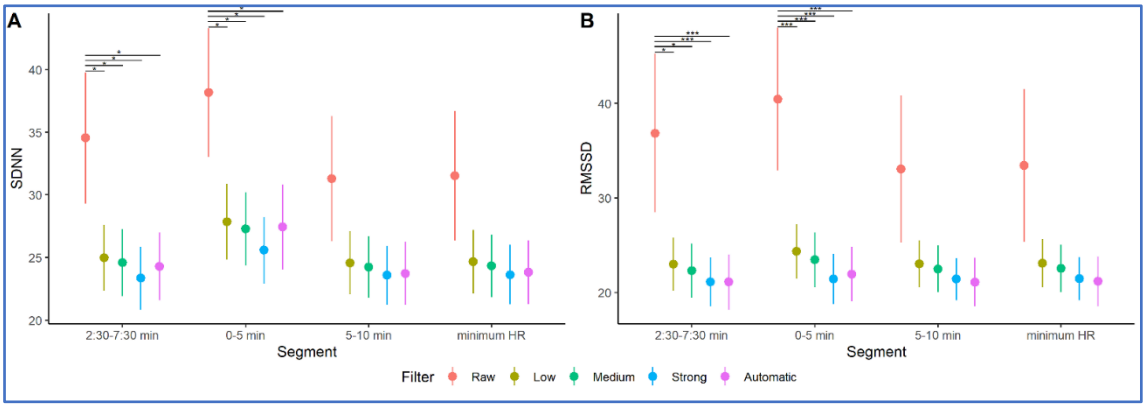


Figure 14. Interaction of filter and segments selection on time domain parameters (SDNN & RMSSD) of participants with normal BMI. * , p<0.05; **, p<0.01; ***, p<0.001.

No differences between raw values were found when comparing different segments. Lastly, when excluding the raw filter, results showed that SDNN's automatic filter value was significantly higher than the values from the 5-10 min (mean difference = 3.7 ms^2, 95% CI [0.1 to 7.3]; p=0.039) and min HR segments (mean difference = 3.6 ms^2, 95% CI [0.0 to 7.2]; p=0.047, **Figure 15A**).

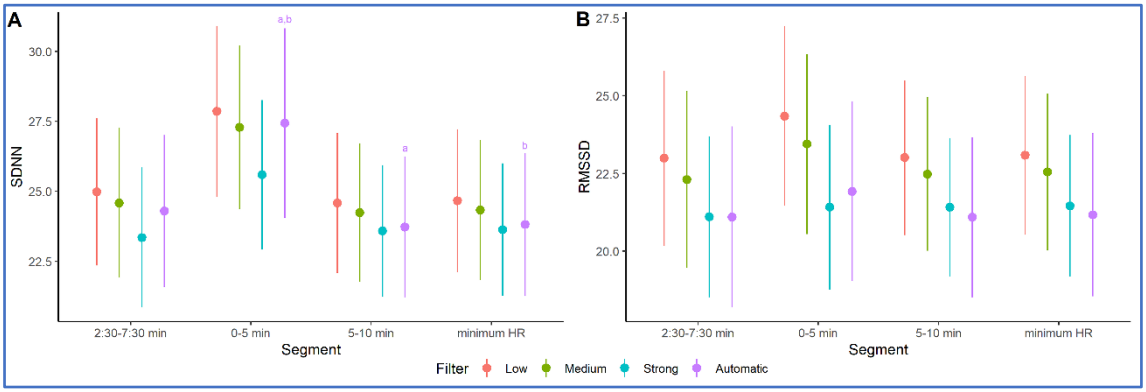


Figure 15. Interaction of filter and segments selection on time domain parameters (SDNN & RMSSD) of participants with normal BMI. *, p<0.05; **, p<0.01; ***, p<0.001. Letters indicate differences between the same filter in different segments.

Frequency domain parameters

HF values were lower when applying the low, medium, strong, and automatic filter compared to the none filter (raw) in the 5-10 min (all p<0.01) and minimum HR segments (all p<0.05, **Table 3**).

Table 3. Descriptive HRV parameters values according to filter and segment selection in participant with obesity.

	Filters					
Parameters	**Raw**	**Low**	**Medium**	**Strong**	**Automatic**	***Segment***
SDNN, ms	79.9 (84.6)	33.8 (24.6)	32.3 (22.3)	30.2 (18.2)	44.4 (38.3)	0-5 min
	63.0 (125.5)	33.8 (25.7)	32.5 (23.4)	30.3 (19.2)	35.6 (31.6)	2:30-7:30 min
	108.4 (295.4)	32.9 (24.6)	32.5 (22.0)	30.4 (18.1)	34.7 (31.7)	5-10 min
	46.6 (45.4)	34.4 (25.1)	33.4 (23.1)	31.3 (18.9)	38.5 (33.0)	minimum HR
RMSSD, ms	88.7 (113.9)	36.7 (32.5)	34.2 (28.5)	30.7 (22.3)	42.7 (40.5)	0-5 min
	76.7 (174.5)	36.0 (34.7)	33.4 (29.9)	29.9 (23.1)	37.1 (42.4)	2:30-7:30 min
	101.7 (248.2)	35.1 (33.2)	33.1 (28.4)	29.6 (22.2)	36.3 (44.0)	5-10 min
	51.7 (61.7)	36.9 (34.5)	34.8 (29.9)	31.4 (23.2)	39.2 (43.1)	minimum HR
HF, log	5.6 (1.8)	5.5 (1.7)	5.5 (1.6)	5.4 (1.5)	5.5 (1.7)	0-5 min
	5.7 (2.0)	5.4 (1.8)	5.4 (1.7)	5.3 (1.6)	5.3 (1.7)	2:30-7:30 min
	6.2 (2.6)	5.5 (1.7)	5.5 (1.6)	5.4 (1.5)	5.5 (1.7)	5-10 min
	6.1 (2.5)	5.6 (1.7)	5.6 (1.6)	5.5 (1.5)	5.6 (1.7)	minimum HR
LF, log	5.7 (1.3)	5.5 (1.2)	5.5 (1.2)	5.5 (1.1)	5.5 (1.3)	0-5 min
	5.8 (1.7)	5.5 (1.1)	5.5 (1.1)	5.5 (1.1)	5.5 (1.3)	2:30-7:30 min

	6.4 (2.7)	5.7 (1.2)	5.7 (1.2)	5.7 (1.1)	5.7 (1.2)	5-10 min
	6.4 (2.7)	5.7 (1.2)	5.7 (1.2)	5.7 (1.2)	5.6 (1.2)	minimum HR
VLF, log	3.7 (1.2)	3.5 (1.2)	3.4 (1.1)	3.4 (1.1)	3.5 (1.2)	0-5 min
	3.8 (1.9)	3.5 (1.3)	3.5 (1.3)	3.5 (1.3)	3.6 (1.5)	2:30-7:30 min
	4.3 (2.8)	3.7 (1.3)	3.7 (1.3)	3.6 (1.3)	3.6 (1.3)	5-10 min
	4.4 (2.8)	3.7 (1.3)	3.6 (1.3)	3.6 (1.3)	3.7 (1.4)	minimum HR
SampEn	1.2 (0.6)	1.7 (0.3)	1.7 (0.3)	1.7 (0.2)	1.6 (0.5)	0-5 min
	1.5 (0.4)	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	1.7 (0.3)	2:30-7:30 min
	1.5 (0.5)	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	5-10 min
	1.4 (0.6)	1.7 (0.3)	1.7 (0.2)	1.7 (0.2)	1.7 (0.4)	minimum HR

Abbreviations: SDNN, standard deviation NN intervals; RMSSD, root square means of standard deviation; HF, high frequency; LF, low frequency; VLF, very low frequency; SampEn, sample entropy; min, minutes.

Raw HF values in the 5-10 min segment were significantly higher than in the 2:30-7:30 min (mean difference = 0.5, 95% CI [0.9 to 0.1]; p=0.048), and 0-5 min segments (mean difference = 0.6, 95% CI [1.0 to 0.1]; p=0.0122), while the min HR was also significantly higher than the 0-5 min segment (mean difference = 0.5, 95% CI [1.0 to 0.1]; p=0.030, **Figure 16C**). Regarding LF, values were lower when applying the low, medium, strong, and automatic filter compared to the none filter (raw) in the 5-10 min and minimum HR segments (all p<0.01, **Figure 16D**). Raw LF values in the 5-10 min segment were significantly higher than in the 2:30-7:30 min (mean difference = 0.6, 95% CI [1.1 to 0.1]; p<0.001), and 0-5 min segments (mean difference = 0.7, 95% CI [1.2 to 0.3]; p=0.013), while the min HR was also significantly higher than the 0-5 min (mean difference = 0.7, 95% CI [1.1 to 0.2]; p=<0.001) and 2:30-7:30 min segments (mean difference = 0.5, 95% CI [1.0 to 0.1]; p=<0.001, **Figure 16D**). Lastly, VLF values were higher when no filter was applied than other filters in the 5-10 min and min HR segments (all p<0.01, **Figure 16E**). Raw VLF values in the min HR segment were significantly higher than in the 2:30-7:30 min (mean difference = 0.5, 95% CI [1.0 to 0.1]; p<0.05) and 0-5 min segments (mean difference = 0.7, 95% CI [1.2 to 0.2]; p<0.01), while the 5-10 was also significantly higher than the 0-5 min (mean difference = 0.6, 95% CI [1.1 to 0.1]; p<0.01, **Figure 16E**).

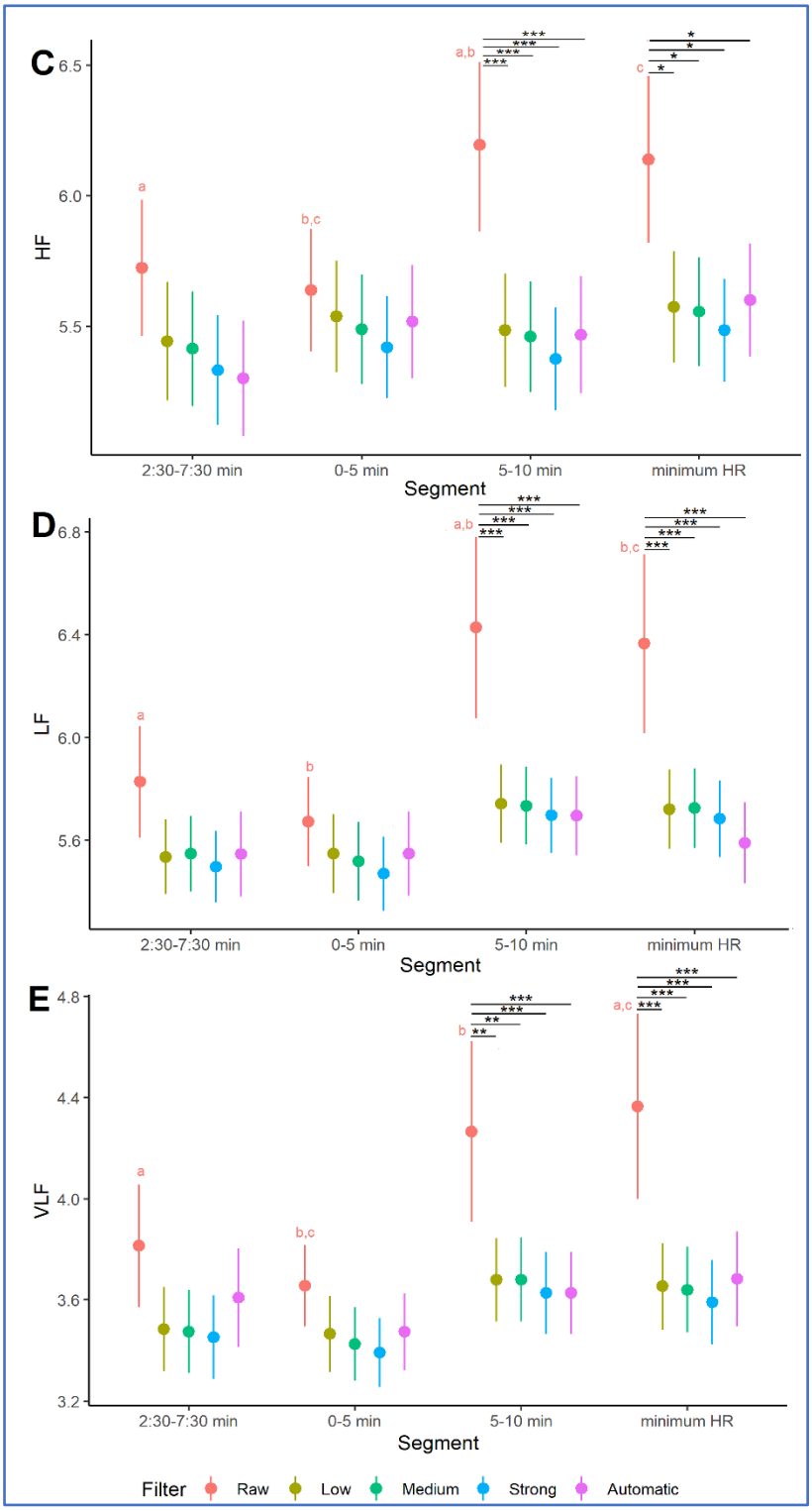


Figure 16. Interaction of filter and segments selection on frequency domain parameters (HF, LF, VLF [log transform]) of participants with obesity. *, p<0.05; **, p<0.01; ***, p<0.001. Letters indicate differences between the same filter in different segments.

Sensitivity analysis revealed that when the none filter (raw values) was excluded from the analysis in people with obesity, no frequency parameter values were affected by filter or segment selection (**Figure 17C, 17D & 17E**).

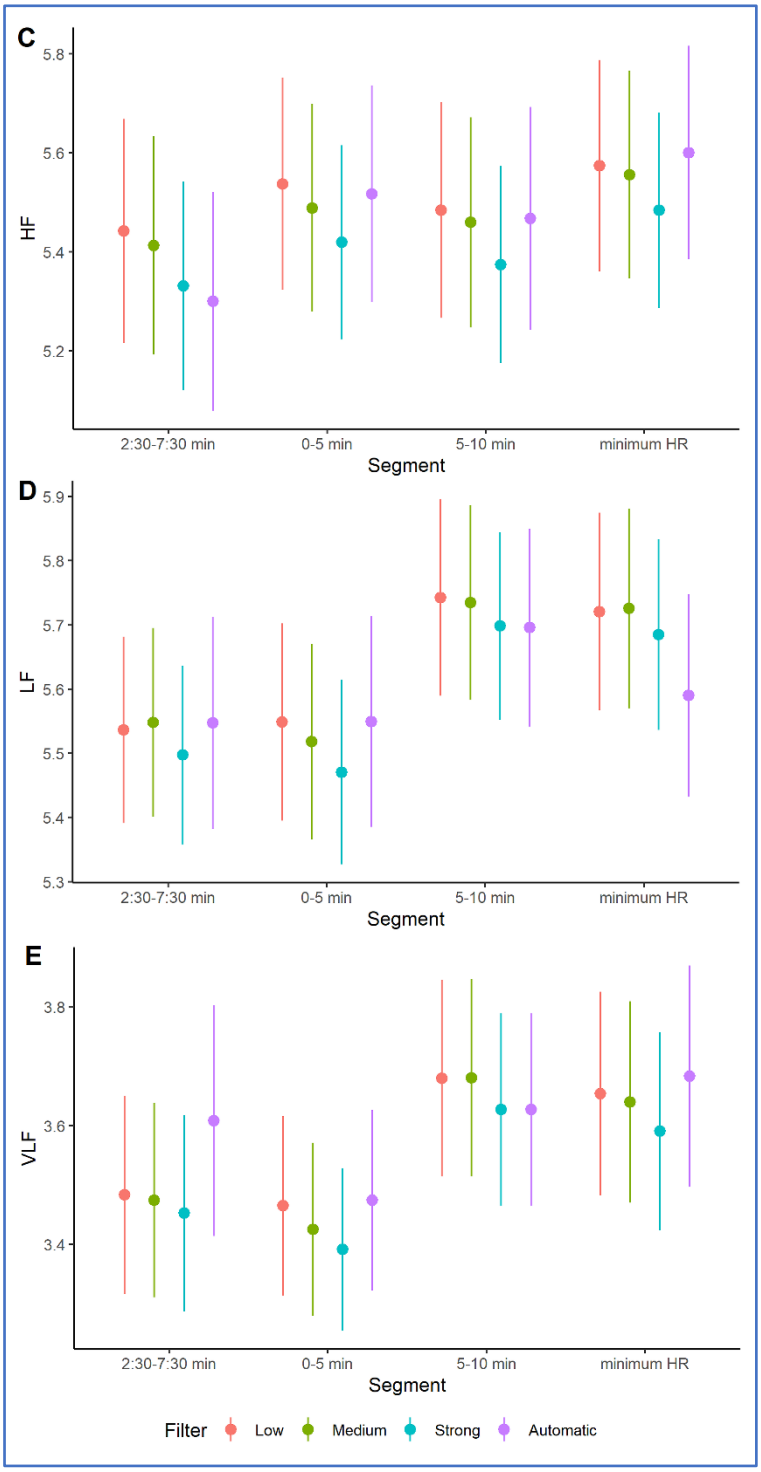


Figure 17. Interaction of filter (excluding raw values) and segments selection on frequency domain parameters (HF, LF, VLF [log transform]) of participants with obesity. *, p<0.05; **, p<0.01; ***, p<0.001.

In people with normal BMI, HF values were significantly higher when no filter was applied in the 2:30-7:30 min segment compared to the rest of the filters (all p<0.01, **Figure 18C**) and in the 0-5 min segment between none filter (raw) and strong filter (mean difference = 0.8, 95% CI [0.1 to 1.7], p = 0.025, **Figure 18C**). This also happened

in the LF parameter, where the raw value was significantly higher than the strong filter (mean difference = 0.6, 95% CI [0.0 to 1.2], p=0.035, **Figure 18D**) in the 2:30-7:30 min segment. In the VLF parameter, no differences were found.

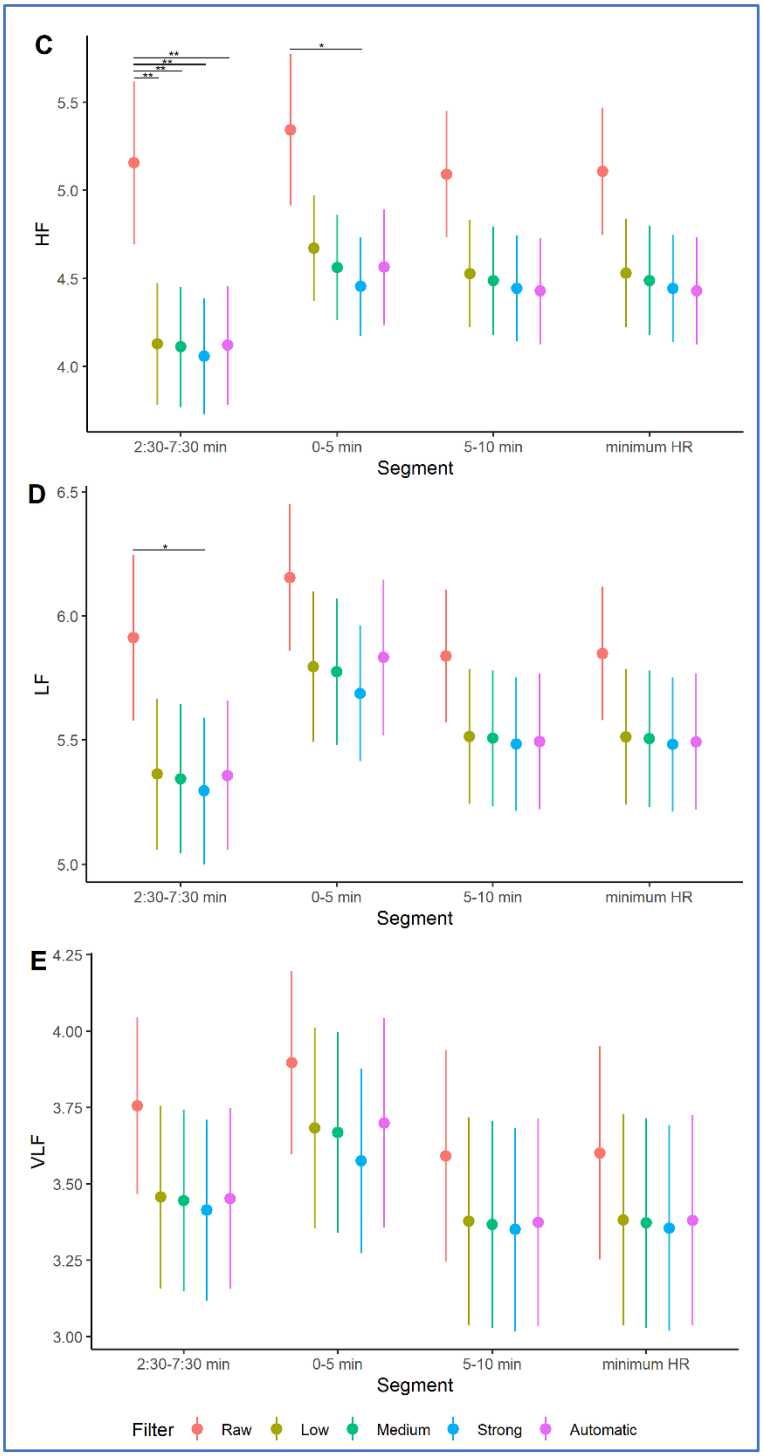


Figure 18. Interaction of filter and segments selection on frequency domain parameters (HF, LF, VLF [log transform]) of participants with normal BMI. *, p<0.05; **, p<0.01; ***, p<0.001.

In further sensitivity analysis in this subsample, when excluding the none filter (raw) values, there was a significant difference between the low filter HF values between the 2:30-7:30 min and the 0-5 min segments (mean difference = –0.5, 95% CI [–1.0 to –0.1], p=0.020, **Figure 19C**). For the LF parameter, there were differences between the 2:30-7:30 min and 0-5 min segments when comparing different types of filters. Specifically, the low filter (mean difference= –0.4, 95% CI [–0.8 to –0.1], p = 0.048, **Figure 19D**), medium filter (mean difference= –0.4, 95% CI [–0.9 to –0.1], p = 0.048, **Figure 19D**) and automatic filter (mean difference= –0.5, 95% CI [–0.9 to –0.1], p = 0.023, **Figure 19E**). Sensitivity analysis did not show significant differences for the VLF parameter in the subsample of people with normal BMI.

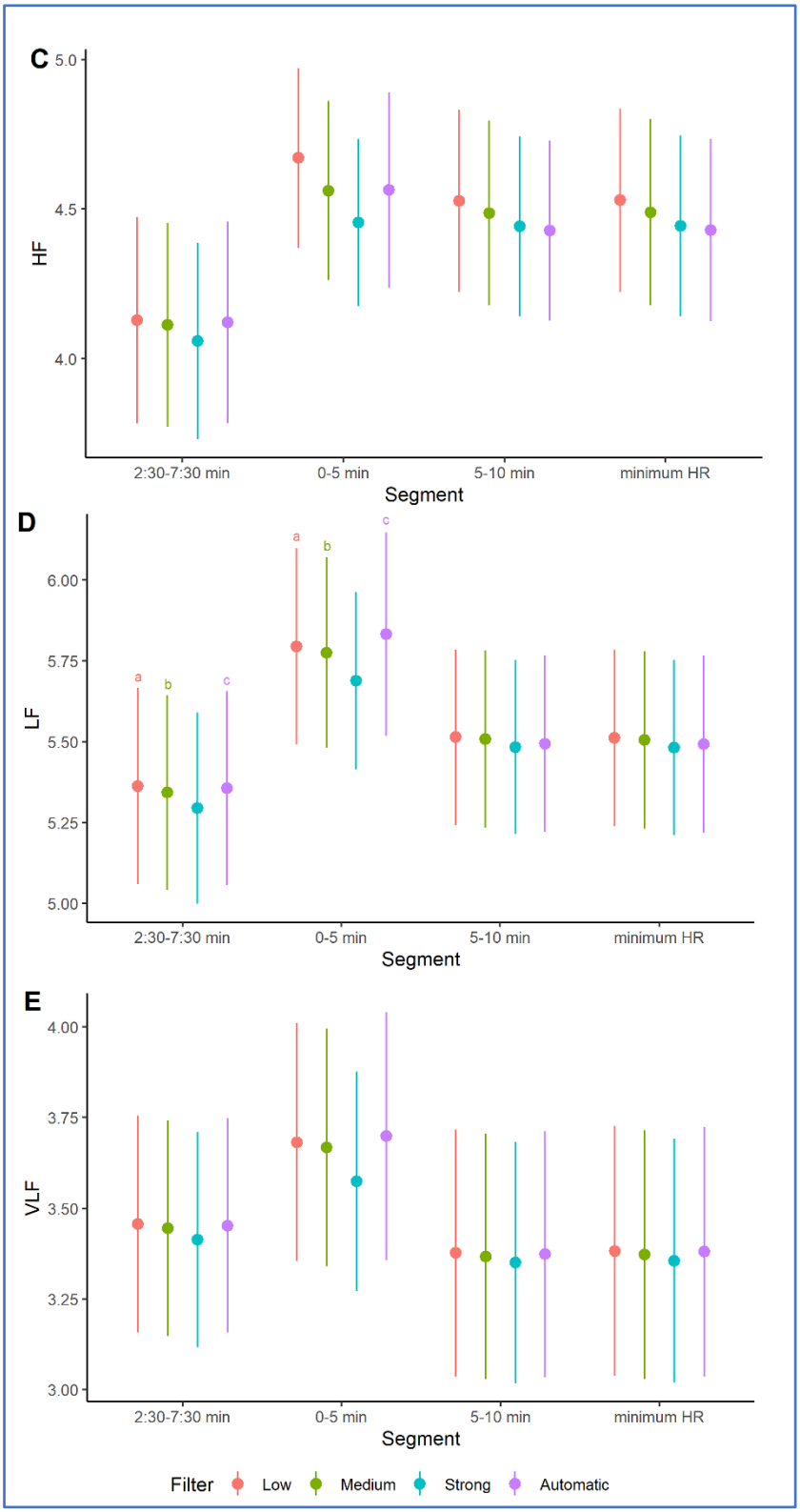


Figure 19. Interaction of filter (excluding raw values) and segments selection on frequency domain parameters (HF, LF, VLF [log transform]) of participants with normal BMI. *, p<0.05; **, p<0.01; ***, p<0.001. Letters indicate differences between the same filters.

Non-linear parameters

Finally, SampEn had higher values when low, medium, strong, and automatic filters were applied compared to the none filter (raw) in each segment (all p<0.01, **Figure 20F**). Furthermore, in the 0-5 min segment, the SampEn value from the automatic filter is significantly lower than the medium and strong filters (all p<0.05, **Figure 20F**). Raw SampEn values in the 0-5 min segment were significantly lower than in the 2:30-7:30 min (mean difference = -0.3, 95% CI [-0.2 to -0.4]; p<0.01), 5-10 min (mean difference = -0.3, 95% CI [-0.4 to -0.1]; p<0.01) and min HR segments (mean difference = -0.2, 95% CI [-0.3 to -0.1]; p<0.01, **Figure 20F**).

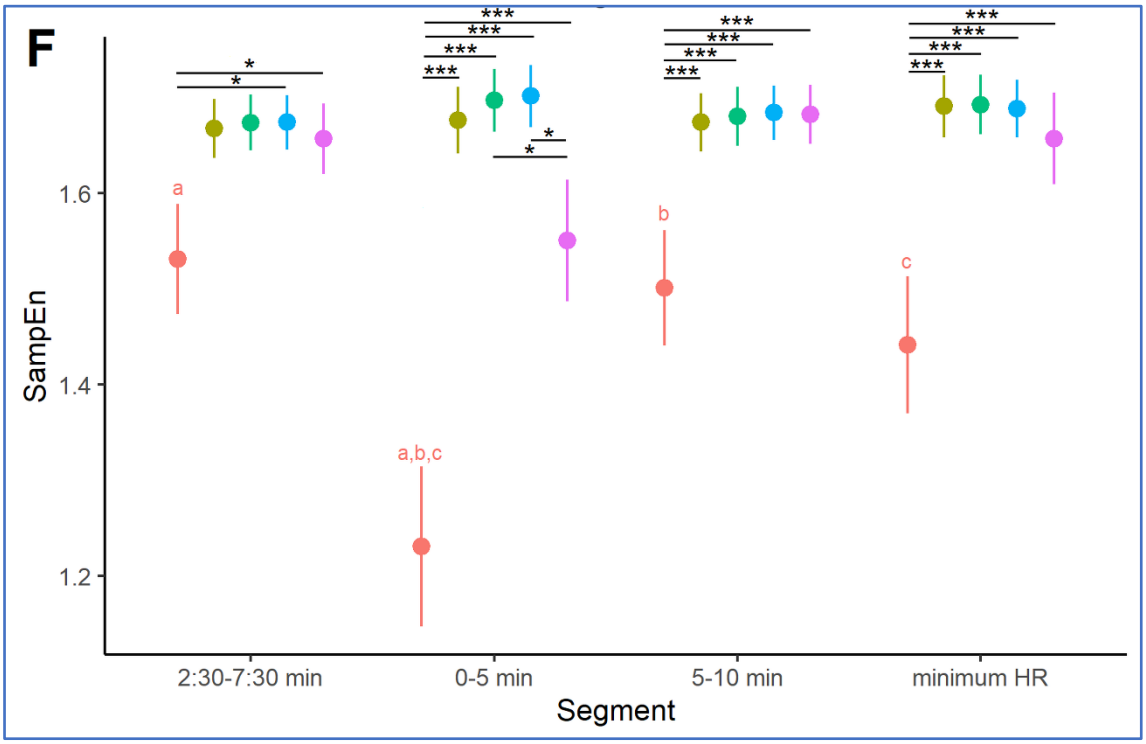


Figure 20. Interaction of filter and segments selection on non-linear methods parameter of participants with obesity. *, p<0.05; **, p<0.01; ***, p<0.001. Letters indicate differences between the same filter in different segments.

In sensitivity analysis where the none filter (raw) was excluded in people with obesity, the SampEn values were significantly lower in the 0-5 min segment compared to the rest of the filters for that same segment (all p<0.01, **Figure 21F**). Furthermore, the automatic filter values in the 0-5 min segment were significantly lower when compared to the automatic filter values of the 2:30-7:30 min (mean difference= -0.1, 95% CI [-0.1 to -0.2], p < 0.01, **Figure 21F**), the 5-10 min (mean difference= -0.1, 95% CI [-0.2 to -0.1], p < 0.01, **Figure 21F**) and min HR segments (mean difference= -0.1, 95% CI [-0.2 to -0.1], p < 0.01, **Figure 21F**).

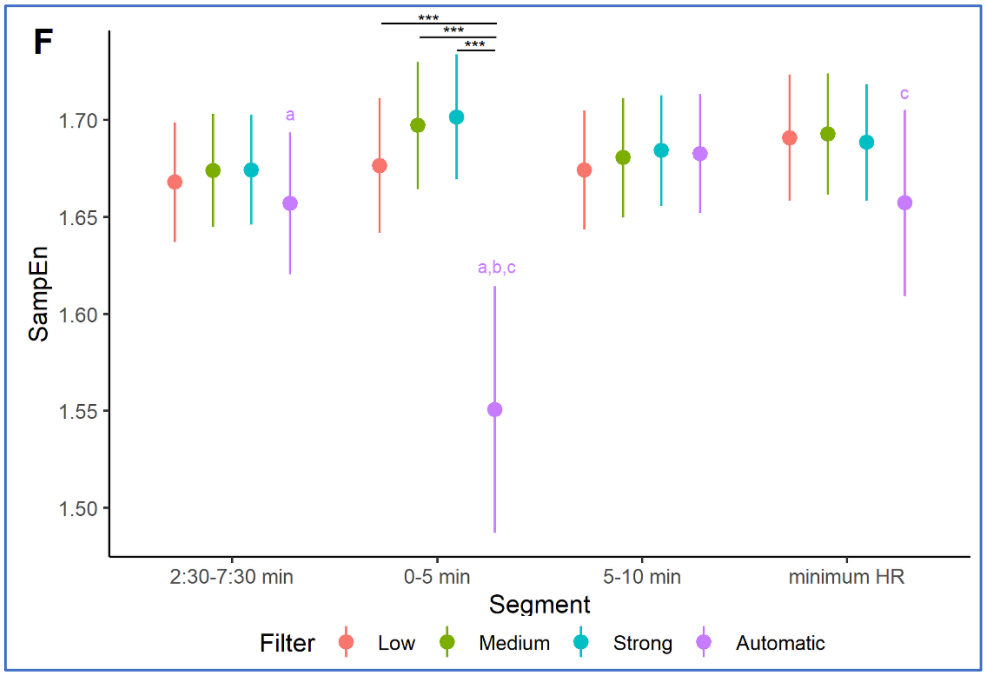


Figure 21. Interaction of filter (excluding raw values) and segments selection on non-linear methods parameter of participants with obesity. *, p<0.05; **, p<0.01; ***, p<0.001. Letters indicate differences between the same filter in different segments.

When studying the subsample of normal BMI, in the 0-5 min segment, the SampEn value from the none filter (raw) was significantly lower than the rest of the filters (all p<0.05, **Figure 22F**).

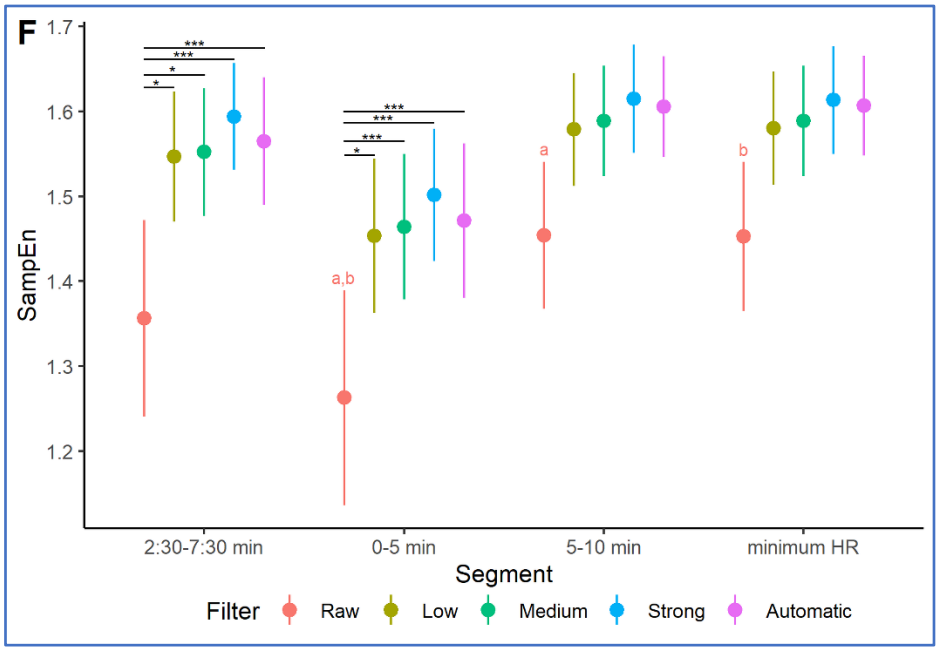


Figure 22. Interaction of filter and segments selection on non-linear methods parameters of participants with normal BMI. *, p<0.05; **, p<0.01; ***, p<0.001. Letters indicate differences between the same filter in different segments.

Moreover, when excluding the none filter values (raw) from the analysis in this subsample, there were significant differences between filters for the different segments. Specifically, the 0-5 min segment low filter had a significantly lower SampEn value than the low filter in the 2:30-7:30 min (mean difference = -0.1, 95%CI [-0.0 to -0.1], p=0.043, **Figure 23F**), the 5-10 min (mean difference = -0.1, 95%CI [-0.2 to -0.0], p=0.002, **Figure 23F**) and the min HR segments (mean difference = -0.1, 95%CI [-0.2 to -0.1], p=0.002, **Figure 23F**). This also applied to the strong and automatic filters (all p<0.05, **Figure 23F**). Surprisingly, the SampEn value when applying the medium filter was only significantly lower in the 0-5 min segment compared to the 5-10 min (mean difference = -0.1, 95%CI [-0.2 to -0.1], p=0.002, **Figure 23F**) and min HR segments (mean difference = -0.0, 95%CI [-0.1 to -0.0], p=0.002, **Figure 23F**).

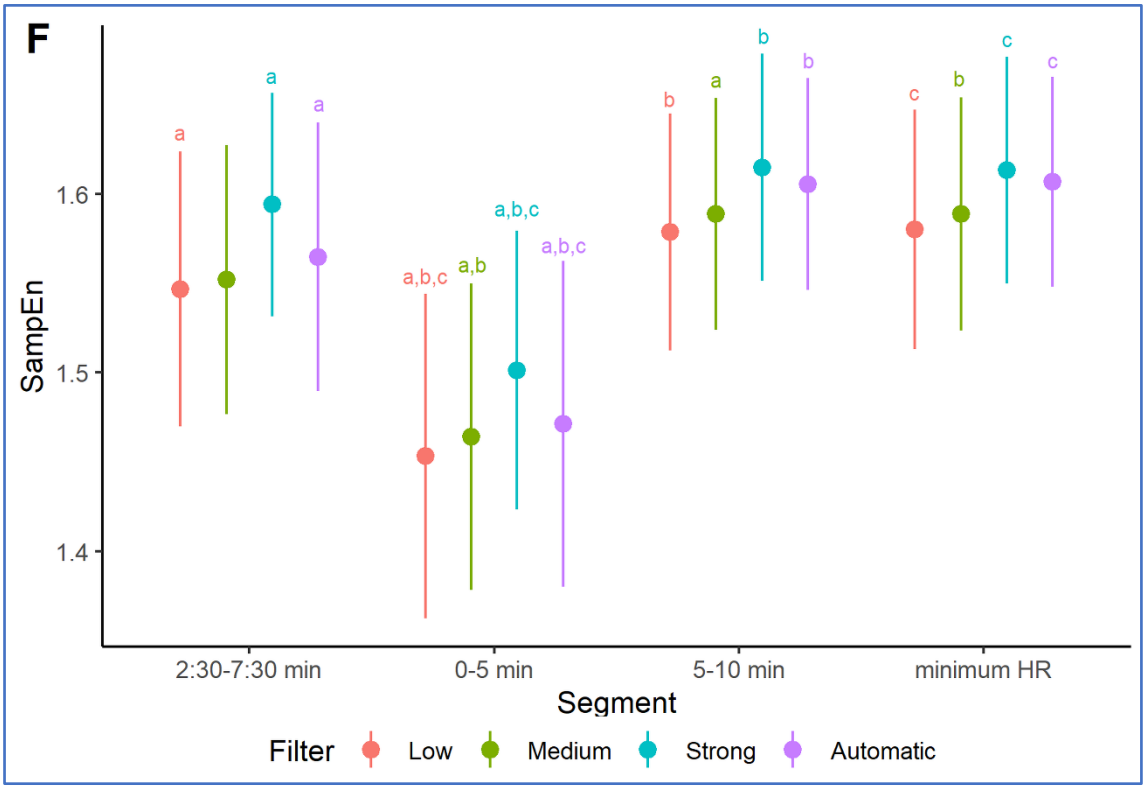


Figure 23. Interaction of filter (excluding raw values) and segments selection on non-linear methods parameters of participants with normal BMI. *, p<0.05; **, p<0.01; ***, p<0.001. Letters indicate differences between the same filter in different segments.

STUDY II

Heart Rate Variability in Women with Systemic Lupus Erythematosus: Association with Health-Related Parameters and Effects of Aerobic Exercise

Results

The flowchart of the study participants throughout the trial is presented in **Figure 24.** A total of 58 patients completed the baseline assessment and were included in aim 1 analysis (n = 55).

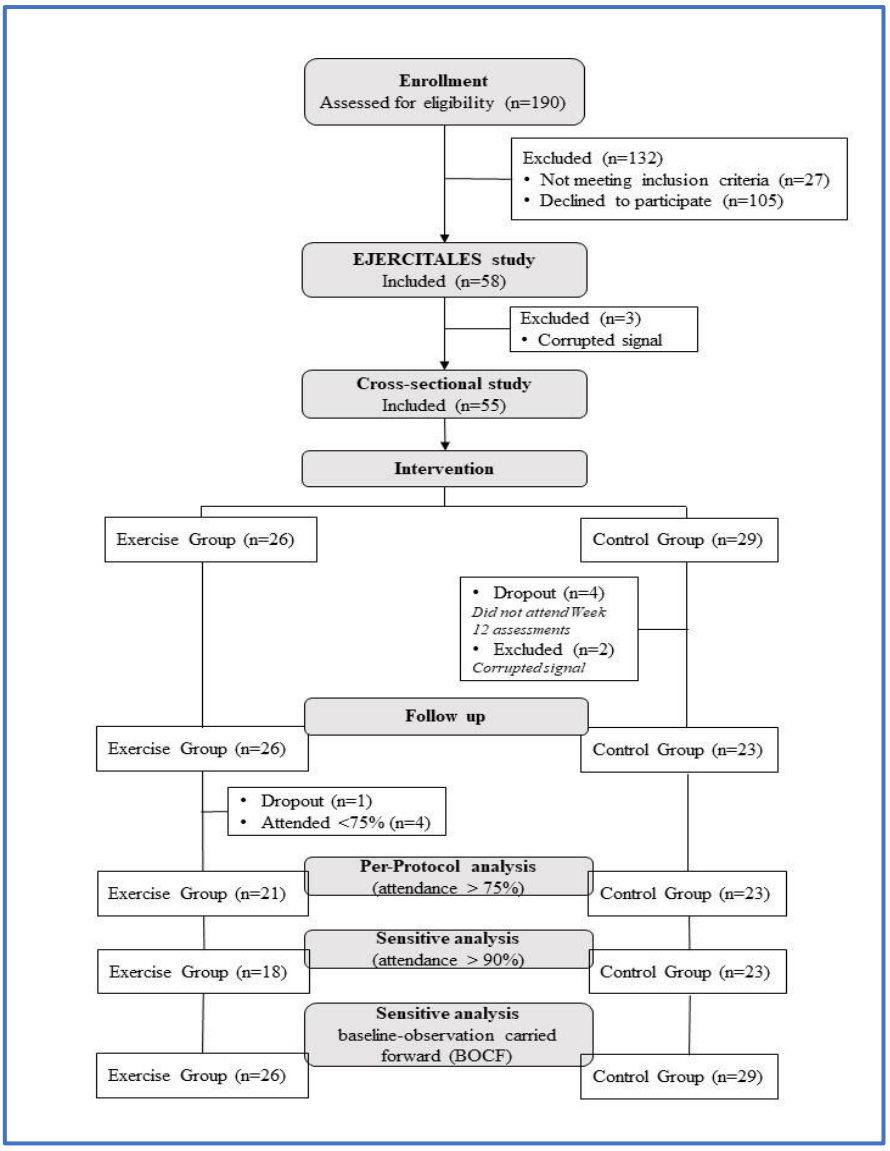


Figure 24. Flowchart diagram of study participants in Study II.

For aim 2, participants were assigned to either the exercise group (n = 26) or the control group (n = 32). At baseline (**Tables 4 and 5**), the control group showed a higher IL-6 levels (median difference 3.10 pg/mL; p = 0.018), lower score in the physical component summary of the SF-36 (mean difference −4.9 units; p = 0.034), and higher punctuation in depressive symptoms (mean difference 9.0 units; p = 0.011) than the exercise group.

Table 4. Baseline characteristics of the EJERCITALES participants.

	All (*n* = 55)	**Exercise (*n* = 26)**	**Control (*n* = 29)**	***p***
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Age, years	43.5 (14.0)	42.9 (15.1)	43.9 (13.3)	0.808
BMI, kg/m^2	25.4 (4.8)	25.9 (3.4)	25.0 (5.8)	0.491
SBP, mm/Hg	117.5 (10.3)	116.8 (9.9)	118.1 (10.6)	0.653
DBP, mm/Hg	75.3 (9.4)	75.5 (8.7)	75.1 (10.01)	0.843
MBP, mm/Hg	94.6 (8.7)	94.5 (8.3)	94.7 (9.2)	0.937
Mean HR, bpm	76.70 (10.71)	79.11 (9.76)	74.54 (11.23)	0.112
hsCRP, mg/L (median, IQR)	1.6 (2.6–6.5)	2.2 (1.9–7.6)	1.2 (1.5–7.1)	0.218
IL-6, pg/mL (median, IQR)	10.5 (9.4–12.3)	8.2 (7.1–11.7)	11.3 (10.3–14.0)	0.018
TNF-α, pg/mL (median, IQR)	15.6 (15.7–19.8)	16.5 (15.4–21.1)	14.8 (14.3–20.4)	0.385
MPO, ng/mL (median, IQR)	69.6 (79.1–119.6)	60.1 (62.4–126.9)	75.7 (76.3–130.9)	0.385
Smoke (%)	23.6	15.4	31.0	0.237
Menopause (%)	38.2	38.5	37.9	0.968
Dyslipidemia (%)	16.4	19.2	13.8	0.586
Statins (%)	16.4	23.1	10.3	0.203
Immunosuppressants (%)	45.5	46.1	44.8	0.921
Current corticosteroid intake (mg/day)	3.86 (5.1)	4.08 (6.1)	3.70 (4.2)	0.789
Disease duration, years	15.1 (10.1)	14.54 (10.4)	15.6 (9.9)	0.704
Total PA, min/week	94.8 (92.6)	97.5 (95.9)	92.4 (91.1)	0.660
SLEDAI	0.16 (0.764)	0.04 (0.196)	0.28 (1.0)	0.254
SDI	0.42 (1.1)	0.19 (0.63)	0.62 (1.3)	0.145
Psychological Stress (PSS; 0–56; median, IQR)	31.0 (28.9–32.1)	30.0 (27.7–31.6)	31.0 (28.7–33.9)	0.303

Depressive symptoms (BDI-II; 0–63)	12.8 (9.2)	8.0 (6.4–12.7)	17.0 (12.2–19.3)	0.011
Fatigue (MFI-S; 0–20)				
General Fatigue (median, IQR)	15.0 (12.9–15.1)	14.5 (12.1–15.3)	16.0 (12.5–15.9)	0.498
Physical fatigue	12.8 (4.7)	12.4 (4.8)	13.1 (4.7)	0.577
Reduced Activity (median, IQR)	10.0 (8.7–11.5)	8.0 (7.8–11.5)	11.0 (8.4–12.6)	0.741
Reduced Motivation	9.4 (3.7)	8.5 (3.4)	10.1 (3.9)	0.112
Mental Fatigue	12.2 (2.8)	12.04 (3.0)	12.3 (2.6)	0.720
Health-related QoL (SF-36) *				
Physical Component Summary	43.0 (8.2)	45.5 (8.5)	40.6 (7.8)	0.034
Mental Component Summary	44.9 (11.0)	47.5 (11.7)	40.4 (11.0)	0.106

* For SF-36 domains total sample size was n = 45 due to missing data. Values are the mean (standard deviation; SD), unless otherwise indicated. BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; mg, milligrams; MBP, mean blood pressure; MPO, myeloperoxidase; PA, physical activity; SBP, systolic blood pressure; SDI, systemic damage index; SLEDAI, systemic lupus erythematosus disease activity index; TNF-α, tumor necrosis factor alpha.

Table 5. Baseline heart rate variability (HRV) derived parameters of the study participants.

	All (*n* = 55)	**Exercise (*n* = 26)**	**Control (*n* = 29)**	***p***
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
SDNN, ms	19.59 (13.30–25.80)	15.87 (11.34–25.24)	21.42 (14.55–26.36)	0.376
RMSSD, ms	16.20 (11.55–25.07)	14.82 (8.86–24.86)	17.33 (13.61–26.75)	0.292
pNN50 (%)	0.57 (0.21–3.17)	0.42 (0.22–2.78)	0.70 (0.22–3.48)	0.715
LF, ms^2	164.12 (76.51–340.51)	157.23 (76.51–345.26)	198.18 (76.51–345.26)	0.607
HF, ms^2	97.20 (39.31–299.42)	93.65 (29.92–334.81)	100.37 (59.40–216.69)	0.607
LFHF	1.57 (0.93–2.81)	1.31 (0.83–3.29)	1.82 (1.08–2.55)	0.980
SD1, ms	11.48 (8.18–17.75)	10.49 (6.27–17.60)	12.27 (9.64–17.60)	0.292
SD2, ms	25.30 (15.54–30.46)	20.86 (18.28–30.42)	25.80 (18.29–30.42)	0.423
SampEn, au	1.70 (1.55–1.83)	1.70 (1.60–1.82)	1.70 (1.51–1.83)	0.692

Values are the median (IQR, interquartile range). HF, high frequency power in absolute value; LF, low frequency power in absolute value; pNN50, percentage of successive normal sinus RR intervals more than 50 ms; RMSSD, root mean square successive difference; SampEn, sample entropy; ms. milliseconds: SD1, standard deviation—poincaré plot crosswise; SD2, standard deviation—poincaré plot lengthwise; SDNN, standard deviation of NN intervals

Associations of HRV with Inflammatory, Oxidative Stress Markers, and PROs (Aim 1)

The raw association of the HRV parameters with inflammatory markers and PROs is presented in abbreviated form in **Table 6** (and **Figure 25** for more details). SampEn was inversely correlated with hsCRP and MPO ($r = -0.35$, $p < 0.01$ and $r = -0.32$, $p < 0.05$, respectively). LFHF ratio was positively correlated with IL-6 ($r = 0.32$, $p < 0.05$). There was no association of any time-domain derived parameter with inflammatory markers. Regarding PROs, LFHF ratio was positively correlated with the Physical Fatigue dimension of the MFI ($r = 0.30$, $p < 0.05$). There were no other significant correlations.

Table 6. Spearman's correlations between HRV derived parameters, inflammatory markers, and PROs (n = 55).

		hsCRP	IL-6	TNF - α	MPO	SLEDAI	SDI	PSS	BDI	MFI-General Fatigue	MFI-Physical Fatigue	MFI-Reduce Activity	MFI-Reduce Motivation	MFI-Mental Fatigue	SF-36 Physical Component	SF-36 Mental Component
SDNN	r_s	-0.05	-0.11	-0.21	0.04	-0.21	-0.14	0.16	-0.11	0.05	-0.14	-0.10	-0.08	-0.06	-0.03	-0.01
	95% CI	-0.32 to 0.21	-0.37 to 0.16	-0.45 to 0.05	-0.23 to 0.30	-0.45 to 0.06	-0.39 to 0.13	-0.11 to 0.41	-0.37 to 0.16	-0.21 to 0.32	-0.39 to 0.13	-0.36 to 0.17	-0.34 to 0.19	-0.32 to 0.21	-0.31 to 0.27	-0.30 to 0.28
	p	0.69	0.41	0.12	0.76	0.13	0.32	0.24	0.42	0.69	0.32	0.46	0.56	0.68	0.87	0.96
RMSDD	r_s	-0.09	-0.14	-0.17	-0.01	-0.19	-0.03	0.04	-0.04	0.06	-0.09	0.03	0.03	0.04	0.05	-0.05
	95% CI	-0.35 to 0.18	-0.39 to 0.13	-0.42 to 0.10	-0.28 to 0.25	-0.43 to 0.08	-0.29 to 0.24	-0.23 to 0.30	-0.31 to 0.22	-0.20 to 0.32	-0.34 to 0.18	-0.24 to 0.29	-0.24 to 0.29	-0.23 to 0.30	-0.25 to 0.33	-0.34 to 0.24
	p	0.52	0.30	0.21	0.93	0.17	0.82	0.78	0.75	0.64	0.53	0.83	0.83	0.79	0.75	0.73
pNN50	r_s	-0.06	-0.14	-0.17	0.05	-0.09	-0.06	0.16	-0.06	0.10	-0.09	0.05	-0.02	0.04	0.07	-0.04
	95% CI	-0.32 to 0.21	-0.39 to 0.13	-0.42 to 0.10	-0.22 to 0.31	-0.43 to 0.08	-0.32 to 0.21	-0.11 to 0.41	-0.32 to 0.21	-0.17 to 0.36	-0.34 to 0.18	-0.22 to 0.31	-0.28 to 0.25	-0.23 to 0.30	-0.22 to 0.35	-0.32 to 0.26
	p	0.66	0.31	0.21	0.71	0.17	0.66	0.24	0.66	0.47	0.53	0.72	0.90	0.78	0.64	0.81
LF	r_s	-0.03	-0.08	-0.23	0.06	-0.16	-0.17	0.17	-0.13	0.10	-0.08	-0.10	-0.13	-0.05	-0.03	0.01
	95% CI	-0.30 to 0.23	-0.34 to 0.19	-0.46 to 0.04	-0.21 to 0.32	-0.41 to 0.11	-0.42 to 0.10	-0.10 to 0.42	-0.38 to 0.14	-0.17 to 0.36	-0.33 to 0.19	-0.35 to 0.17	-0.38 to 0.14	-0.31 to 0.22	-0.32 to 0.26	-0.28 to 0.30
	p	0.81	0.56	0.10	0.66	0.24	0.21	0.20	0.35	0.45	0.58	0.49	0.35	0.71	0.84	0.95
HF	r_s	-0.07	-0.20	-0.23	-0.08	-0.26	-0.15	0.05	-0.14	-0.05	-0.25	-0.13	-0.13	-0.03	0.03	-0.07
	95% CI	-0.33 to 0.20	-0.44 to 0.07	-0.47 to 0.03	-0.34 to 0.19	-0.52 to 0.03	-0.40 to 0.12	-0.21 to 0.31	-0.39 to 0.13	-0.31 to 0.22	-0.49 to 0.01	-0.38 to 0.14	-0.38 to 0.14	-0.29 to 0.24	-0.27 to 0.31	-0.12 to 0.44
	p	0.60	0.15	0.09	0.58	0.06	0.28	0.70	0.31	0.72	0.06	0.34	0.34	0.86	0.86	0.25
LFHF	r_s	0.05	0.32*	0.17	0.20	0.17	0.03	0.08	0.12	0.14	0.30*	0.10	-0.03	-0.05	-0.11	0.17
	95% CI	-0.21 to 0.31	0.06 to 0.54	-0.10 to 0.42	-0.07 to 0.44	-0.10 to 0.42	-0.24 to 0.29	-0.19 to 0.34	-0.15 to 0.37	-0.13 to 0.39	0.04 to 0.52	-0.17 to 0.35	-0.29 to 0.24	-0.31 to 0.22	-0.39 to 0.18	-0.12 to 0.44
	p	0.70	0.02	0.21	0.15	0.22	0.84	0.55	0.38	0.32	0.03	0.48	0.84	0.70	0.46	0.25
SD1	r_s	-0.09	-0.14	-0.17	-0.01	-0.19	-0.03	0.04	-0.04	0.06	0.03	0.03	0.03	0.04	0.05	-0.05
	95% CI	-0.35 to 0.18	-0.39 to 0.13	-0.42 to 0.10	-0.28 to 0.25	-0.43 to 0.08	-0.29 to 0.24	-0.23 to 0.30	-0.31 to 0.22	-0.20 to 0.32	-0.24 to 0.29	-0.24 to 0.29	-0.24 to 0.29	-0.23 to 0.30	-0.25 to 0.33	-0.34 to 0.24
	p	0.52	0.30	0.21	0.93	0.17	0.82	0.78	0.75	0.64	0.83	0.83	0.83	0.79	0.75	0.73
SD2	r_s	-0.03	-0.09	-0.21	0.09	-0.20	-0.17	0.18	-0.14	0.06	-0.14	-0.15	-0.12	-0.09	-0.05	0.00

	95% CI	-0.29 to 0.24	-0.34 to 0.13	-0.45 to 0.06	-0.18 to 0.25	-0.44 to 0.07	-0.41 to 0.10	-0.09 to 0.42	-0.39 to 0.13	-0.20 to 0.32	-0.39 to 0.13	-0.40 to 0.12	-0.37 to 0.15	-0.34 to 0.18	-0.34 to 0.24	-0.29 to 0.29
	p	0.85	0.53	0.13	0.53	0.14	0.22	0.20	0.32	0.64	0.31	0.29	0.38	0.53	0.73	0.98
SampEn	r_s	-0.35**	-0.16	-0.16	-0.32*	-0.03	0.05	-0.19	0.15	0.05	0.04	0.20	0.20	0.23	0.24	0.14
	95% CI	-0.56 to-0.10	-0.41 to 0.11	-0.18 to 0.34	-0.54 to -0.06	-0.29 to 0.24	-0.22 to 0.31	-0.44 to 0.08	-0.12 to 0.40	-0.22 to 0.31	-0.23 to 0.30	-0.07 to 0.44	-0.07 to 0.44	-0.04 to 0.47	-0.06 to 0.48	-0.15 to 0.42
	p	0.01	0.25	0.53	0.02	0.84	0.71	0.16	0.28	0.73	0.79	0.15	0.14	0.09	0.05	0.35

Notes: *p<0.05; **p<0.01.

r_s, spearman's rho; 95% CI, confidence intervals; BDI, Beck depression inventory; HF, high frequency power; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; LF, low frequency power; MFI, multidimension fatigue inventory; MPO, myeloperoxidase; pNN50, percentage of successive normal sinus RR intervals more than 50 ms; PSS, perceived stress scale; RMSSD, root mean square successive difference; SampEn, sample entropy; ms. milliseconds; SD1, standard deviation – poincaré plot crosswise; SD2, standard deviation – poincaré plot lengthwise; SDI, systemic damage index; SDNN, standard deviation of NN intervals; SF-36, short form health survey; SLEDAI, systemic lupus erythematosus disease activity index; TNF-α, tumor necrosis factor alpha.

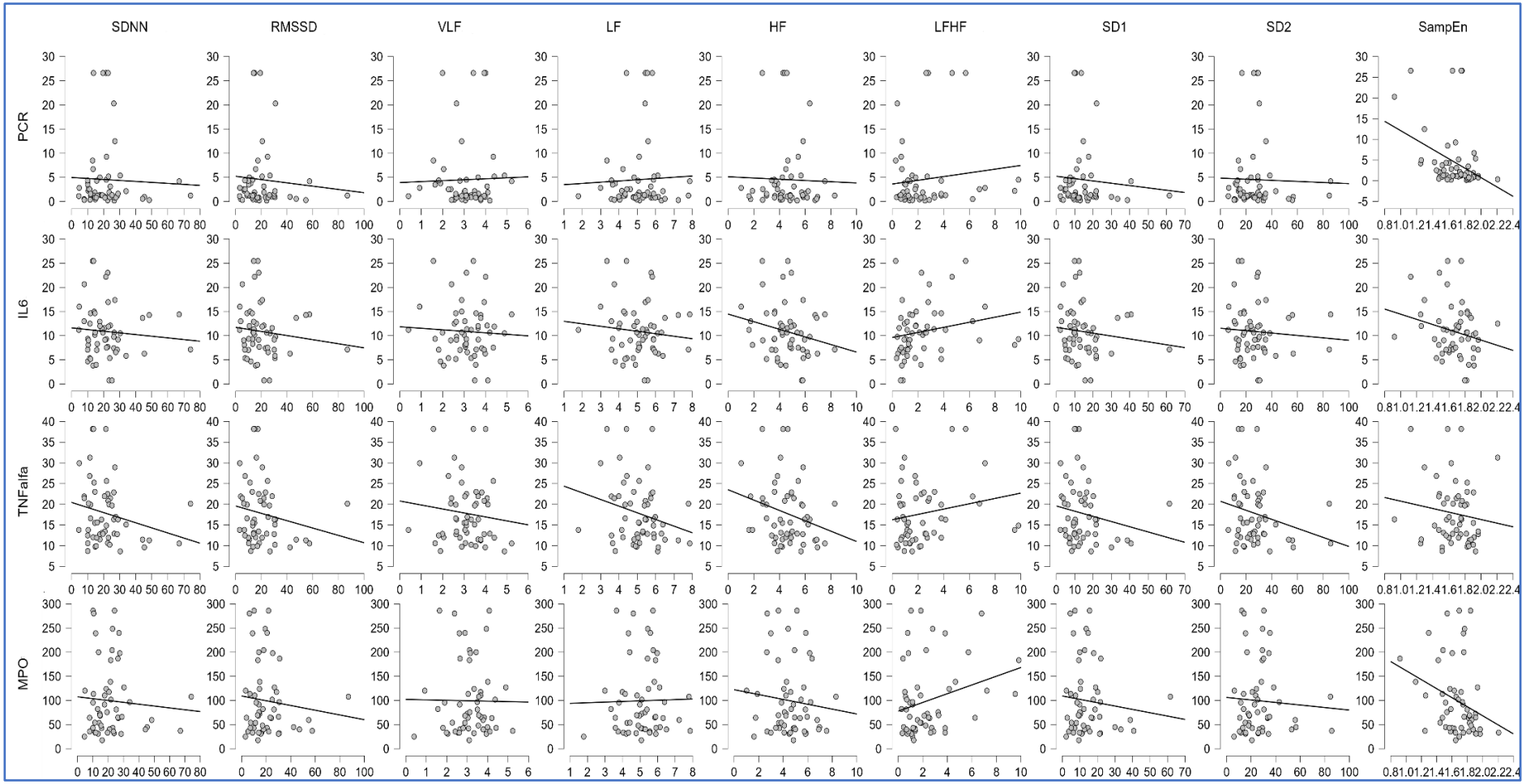


Figure 25. Correlations between HRV derived parameters and inflammatory markers (N=55).

The quantile regression models evaluating the association between HRV parameters, inflammatory markers, and PROs are presented in **Table 7** adjusted by age, heart rate and disease duration. Only significant correlations were explored. LFHF ratio was associated with the physical fatigue dimension of the MFI (unstandardized coefficient (B) = 0.89; 95% confidence interval (CI) 0.15 to 1.62; p = 0.019) but there was no association with IL-6 (B = 0.48; 95% CI −0.31 to 1.27; p > 0.05). SampEn was inversely associated with hsCRP (B = −4.82; 95% CI −8.62 to −1.03; p = 0.014) and MPO (B = −106.51; 95% CI −182.54 to −30.50; p = 0.007). We did not find associations of HRV derived parameters with SLEDAI or SDI.

Table 7. Quantile regression analysis evaluating the association between specific components of heart rate variability, inflammatory markers, and PROs in women with systemic lupus erythematosus (n = 55).

	B	SE	CI 95%		*p*
LFHF					
IL-6	0.48	0.39	−0.31	1.27	0.231
MFI-Physical Fatigue	0.89	0.37	0.15	1.62	0.019
SampEn					
hsCRP	−4.82	1.89	−8.62	−1.03	0.014
MPO	−106.51	37.85	−182.54	−30.50	0.007

hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6, LFHF, low frequency to high frequency ratio; MFI, multidimensional fatigue inventory; MPO, myeloperoxidase; SampEn, sample entropy; adjusted by age, heart rate and disease duration.

Effects of the Exercise Intervention on HRV-Derived Parameters (Aim 2)

The HRV signals from 5 participants from the control group were excluded due to excessive interpolated beats (>5%). Full HRV data at baseline and week 12 was obtained from 44 participants (21 exercise and 23 control). The primary analyses revealed no significant between-group differences between changes in HRV derived parameters (**Table 8**) in all domains, and these results were consistent in sensitivity analyses in which participants from the exercise group were included only when attendance of the exercise sessions was ≥90% (**Tables 9**) and in BOCF analyses (**Table 10**).

Table 8.Per-protocol (primary) analyses assessing the effects of 12-week progressive aerobic exercise on HRV derived parameters in women with SLE (participants in the exercise group were included if attendance was ≥75%).

Change from Baseline at Week 12	Exercise (*n* = 21)	Control (*n* = 23)	Median Difference (95% CI)	*p*
	Median (SE)	Median (SE)		
SDNN	2.70 (2.36)	4.18 (2.91)	−1.48 (−12.00 to 6.37)	0.539
RMSSD	2.03 (3.52)	2.75 (4.33)	−0.72 (−12.05 to 9.74)	0.831
pNN50	0.21 (1.93)	0.28 (2.96)	−0.07 (−5.87 to 6.16)	0.960
LF (ms)	2.50 (81.86)	−22.31 (57.00)	24.81 (−142.07 to 169.88)	0.858
HF (ms)	4.76 (98.31)	6.91 (73.40)	−2.15 (−140.79 to 129.24)	0.932
LFHF	−0.12 (1.30)	0.05 (1.01)	−0.17 (−01.45 to 2.30)	0.652
SD1	1.44 (2.49)	1.95 (3.07)	−0.51 (−8.53 to 6.90)	0.831
SD2	3.10 (2.51)	5.22 (3.04)	−2.45 (−11.91 to 6.33)	0.539
SampEn	0.02 (0.07)	0.01 (0.08)	0.01 (−0.31 to 0.23)	0.741

The analyses were adjusted for baseline values, mean heart rate, and age. Values are the median (standard error). HF, high frequency power in absolute value; LF, low frequency power in absolute value; pNN50, percentage of successive normal sinus RR intervals more than 50 ms; RMSSD, root mean square successive difference; SampEn, sample entropy; ms. milliseconds; SD1, standard deviation—poincaré plot crosswise; SD2, standard deviation—poincaré plot lengthwise; SDNN, standard deviation of NN intervals

Table 9. Sensitivity analyses assessing the effects of 12-week progressive aerobic exercise on HRV derived parameters in women with systemic lupus erythematosus (participants in the exercise group were included if attendance ≥90%).

Change from baseline at Week 12	Exercise (n = 18)	Control (n = 23)	***Median Difference (95% CI)***	***p***
	Median (SE)	Median (SE)		
SDNN	5.00 (2.64)	4.18 (2.91)	0.82 (-11.08 to 8.20)	0.763
RMSSD	3.67 (4.04)	2.75 (4.33)	0.92 (-14.51 to 12.00)	0.849
pNN50	0.47 (2.19)	0.28 (2.96)	0.19 (-7.93 to 7.78)	0.984
LF (ms)	2.52 (95.49)	-22.31 (57.00)	24.83 (-277.80 to 153.10)	0.561
HF (ms)	10.71 (115.16)	6.91 (73.40)	3.80 (-232.84 to 163.18)	0.723
LFHF	-0.01 (1.47)	0.05 (1.01)	-0.06 (-1.55 to 2.39)	0.670
SD1	2.60 (2.86)	1.95 (3.07)	0.65 (-10.27 to 8.50)	0.850

SD2	4.11 (2.77)	5.22 (3.04)	-1.11 (-12.49 to 6.80)	0.554
SampEn	0.02 (0.08)	0.01 (0.08)	0.01 (-0.25 to 0.37)	0.675

The analyses were adjusted for baseline values, mean heart rate and age. Values are the median (standard error). SDNN, standard deviation of NN intervals; RMSSD, root mean square successive difference; pNN50, percentage of successive normal sinus RR intervals more than 50 ms; LF, low frequency power in absolute value; HF, high frequency power in absolute value; LF/HF, ratio low/high frequency; SD1, standard deviation – poincaré plot crosswise; SD2, standard deviation – poincaré plot lengthwise. SampEn, sample entropy; ms. milliseconds; bpm, beats per minute

Table 10. Sensitivity analyses using baseline-observation carried forward imputation assessing the effects of 12-week progressive aerobic exercise on HRV derived parameters in women with systemic lupus erythematosus.

Change from baseline at Week 12	Exercise (n = 26)	Control (n = 29)	***Mean Difference (95% CI)***	***p***
	Median (SE)	Median (SE)		
SDNN	3.79 (2.00)	0.00 (2.30)	3.79 (-11.59 to 3.27)	0.266
RMSSD	4.70 (2.97)	0.00 (3.44)	4.70 (-10.35 to 8.84)	0.875
pNN50	0.40 (1.75)	0.00 (2.34)	0.40 (-3.39 to 2.00)	0.607
LF (ms)	9.19 (68.53)	0.00 (45.05)	9.19 (-145.40 to 109.40)	0.778
HF (ms)	10.71 (81.25)	0.00 (57.95)	10.71 (-137.69 to 119.44)	0.887
LFHF	0.08 (1.04)	0.00 (0.81)	0.08 (-0.78 to 1.61)	0.491
SD1	3.33 (2.10)	0.00 (2.43)	3.33 (-7.33 to 6.26)	0.875
SD2	3.30 (2.14)	0.00 (2.40)	3.30 (-10.53 to 2.68)	0.238
SampEn	0.02 (0.06)	0.00 (0.06)	0.02 (-0.19 to 0.22)	0.883

The analyses were adjusted for baseline values, mean heart rate and age. Values are the median (standard error). SDNN, standard deviation of NN intervals; RMSSD, root mean square successive difference; pNN50, percentage of successive normal sinus RR intervals more than 50 ms; LF, low frequency power in absolute value; HF, high frequency power in absolute value; LF/HF, ratio low/high frequency; SD1, standard deviation – poincaré plot crosswise; SD2, standard deviation – poincaré plot lengthwise. SampEn, sample entropy; ms. milliseconds; bpm, beats per minute

Regarding responders, non-responders, and adverse responders, in the control group we observed significant differences in RMSSD between responders against non-responders and adverse responders (p = 0.37 and p = 0.002, respectively) and between

non-responder and adverse responder (p = 0.37). In the exercise group, there was a significant difference in RMSSD between responders and non-responders (p = 0.001) **Figure 26**.

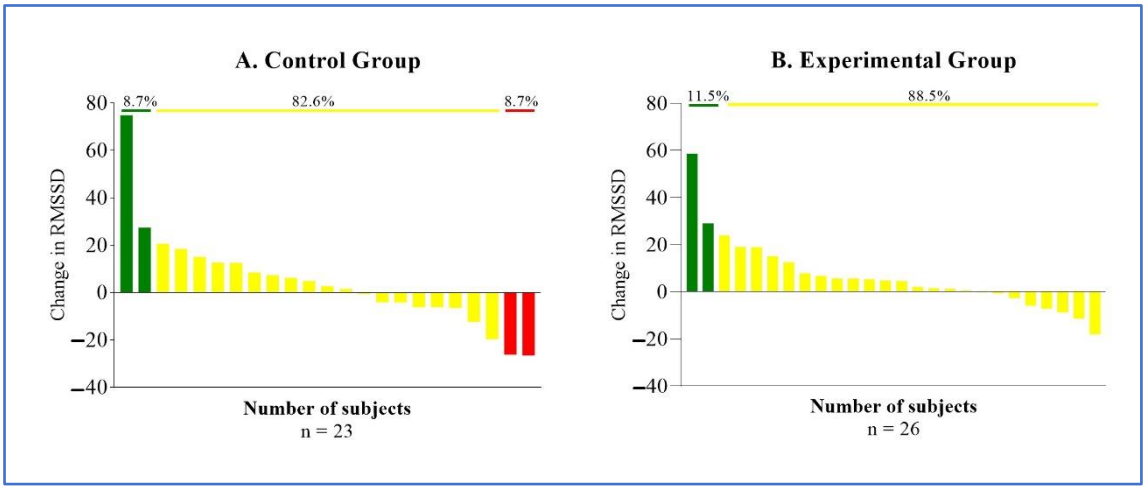


Figure 26. Responders (green line), non-responders (yellow line), and adverse responders (red line) on RMSSD endpoints. RMSSD; root mean square successive difference.

STUDY III

Impact of a 16-week concurrent exercise program on Heart Rate Variability, Arterial Stiffness, and Cardiac Structure and Function following Bariatric Surgery: Secondary Outcomes from the EFIBAR Randomized Trial

The flowchart of the study participants through the trial is presented in **Figure 27**. A total of 80 participants were enrolled and randomized to the control group (n=40) or the intervention group (n=40). Overall, 5 participants (6.25%; 3 from the control group and 2 from the intervention group) were unavailable for the 4-month follow-up due to health issues unrelated to the surgery or intervention. No serious adverse events occurred during the study intervention or evaluations.

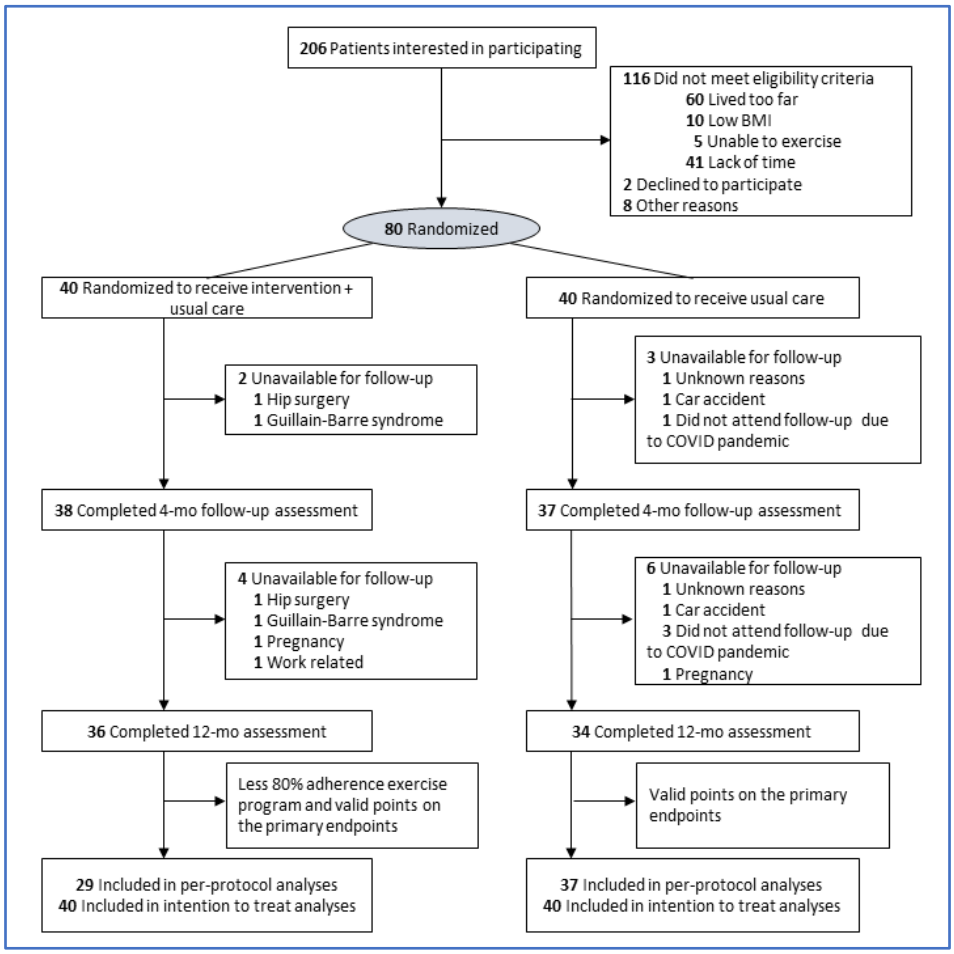


Figure 27. Flowchart of the study participants throughout the EFIBAR study.

A total of 66 participants were finally included in the per-protocol analysis. At baseline, these participants were on average 40.9 (9.9) year-old, weighted 127.8 (19.5)

kg, and mean body fat percentage and BMI were 65.5 (12.7) and 46.9 (6.4), respectively. 49 of them (73.1%) were women. Sociodemographic and clinical characteristics at baseline were well balanced between groups, both in the per-protocol approach (**Table 11**) and the ITT analyses (**Table 12**).

Table 11. Baseline descriptive characteristics of the study participants included in the per-protocol analyses.

	All (n = 66)	Control (n = 37)	Experimental (n = 29)	p
Sex, n (%) women	49 (74.0%)	28 (76.0%)	21 (72.0%)	0.764
Age, years	40.9 ± 9.9	40.6 ± 9.5	41.2 ±10.6	0.809
Height, m	1.65 ± 0.1	1.66 ± 0.1	1.65 ± 0.1	0.859
Weight, kg	127.8 ± 19.5	128.6 ± 18.4	126.7 ± 21.1	0.917
BMI, kg/m^2	46.9 ± 6.4	47.0 ± 6.4	46.4 ± 6.6	0.712
BF, %	65.2 ± 12.7	65.9 ± 11.9	64.1 ± 13.9	0.572
SBP, mm/Hg	131.3 ± 14.7	129.6 ± 12.5	133.4 ± 17.1	0.325
DBP, mm/Hg	80.2 ± 9.7	80.1 ± 9.3	79.9 ± 10.2	0.937
RHR, bpm	77.4 ± 12.2	79.5 ± 12.2	74.7 ± 11.9	0.132
Smoke (%)	13 (20.0%)	8 (12.0%)	5 (8.0%)	0.618
Medical conditions				
Type 2 diabetes	6 (9.0%)	3 (8.0%)	3 (10.00%)	0.754
Dyslipidemia	11 (17.0%)	4 (6.0%)	7 (11.0%)	0.164
Hypertension	27 (41.0%)	19 (29.0%)	8 (12.0%)	0.051
Cardiovascular disease	12 (18.2%)	8 (12.0%)	4 (6.0%)	0.384
Other	46 (70.0%)	29 (44.0%)	17 (26.0%)	0.083
Medications				
Insulin	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Antihypertensive	14 (22.0%)	6 (9.0%)	8 (12.0%)	0.287
Heart Medication	4 (6.0%)	2 (3.0%)	2 (3.0%)	0.823
Type of bariatric surgery				0.726
Sleeve gastrectomy	4 (6.0%)	3 (8.0%)	1 (3.0%)	
Gastric bypass	2 (3.0%)	1 (3.0%)	1 (3.0%)	
One anastomosis gastric bypass	61 (91.0%)	33 (89.0%)	28 (93.0%)	

Values are shown as mean +/- SD or n (%). BMI, body mass index; BF%, body at percentage; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RHR, resting heart rate.

Table 12. Baseline descriptive characteristics of the study participants included in the intention-to-treat analyses.

	All (n = 80)	*Control (n = 40)*	*Experimental (n = 40)*	*p*
Sex, n (%) women	58 (73.0%)	30 (75.0%)	28 (70.0%)	0.617
Age, years	41.1 ± 9.8	40.9 ± 9.3	41.2 ± 10.3	0.901
Height, m	1.65 ± 8.8	1.65 ± 9.1	1.65 ± 8.5	0.807
Weight, kg	128.7 ± 21.4	129.5 ± 19.0	128.0 ± 23.8	0.731
BMI, kg/m^2	47.1 ± 6.8)	47.4 ± 6.9	46.8 ± 6.9	0.704
BF, %	65.9 ± 13.4	66.6 ± 12.3	65.1 ± 14.8	0.622
SBP, mm/Hg	131.4 ± 14.9	129.6 ± 13.2	133.2 ± 16.5	0.310
DBP, mm/Hg	80.6 ± 9.7	79.9 ± 9.2	81.2 ± 10.3	0.572
RHR, bpm	77.5 ± 12.1	78.8 ± 12.5	76.2 ± 11.7	0.372
Smoke (%)	17 (21.0%)	9 (23.0%)	8 (20.0%)	0.572
Medical conditions				
Type 2 diabetes	8 (10.0%)	3 (8.0%)	5 (13.0%)	0.456
Dyslipidemia	13 (16.0%)	5 (13.0%)	8 (20.0%)	0.390
Hypertension	33 (41.0%)	21 (53.0%)	12 (30.0%)	0.041
Cardiovascular disease	13 (16.5%)	9 (23.1%)	4 (10.0%)	0.206
Other	23 (28.7%)	9 (22.5%)	14 (35.0%)	0.323
Medications				
Insulin	6 (7.59%)	2 (5.1%)	4 (10.0%)	0.675
Antihypertensive	16 (18.0)	5 (13.0%)	9 (23.0%)	0.154
Heart Medication	6 (8.0%)	4 (10.0%)	2 (5.0%)	0.432
Type of bariatric surgery				0.335
Sleeve gastrectomy	5 (6.0%)	4 (10.0%)	1 (3.0%)	
Gastric bypass	3 (4.0%)	1 (3.0%)	2 (5.00%)	
One anastomosis gastric bypass	72 (90.0%)	35 (88.0%)	37 (93.0%)	

Values are shown as mean +/- SD or n (%). BMI, body mass index; BF%, body at percentage; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RHR, resting heart rate.

Effects of the Exercise Intervention on Heart Rate Variability

The between-groups comparisons for HRV parameters are presented in **Table 13**. There were no between-group differences on any HRV-derived parameters. These sensitivity analyses (ITT) confirmed these results in **Table 14**.

Table 13. Per-protocol (primary) analyses assessing the effects of 16-week exercise intervention on HRV derived parameters in participants who underwent bariatric surgery (participants in the exercise group were included if attendance was ≥80%).

End point	Control (n=37)	Experimental (n=29)	Mean difference between groups (95%CI)[a]
Heart Rate Variability			
HR, bpm (95% CI)			
Baseline	80.6 (76.9 to 84.3)	76.5 (72.4 to 80.6)	NA
Change at 4 mo	-14.4 (-9.8 to -18.9)	-13.7 (-8.5 to -18.9)	-0.8 (-5.1 to 6.5)
Change at 12 mo	-17.4 (-12.6 to -22.2)	-13.2 (-7.7 to -18.6)	-4.2 (-1.8 to 10.2)
RMSSD, ms (95% CI)			
Baseline	2.9 (2.7 to 3.1)	2.9 (2.7 to 3.2)	NA
Change at 4 mo	0.8 (0.5 to 1.2)	0.8 (0.5 to 1.1)	-0.0 (-0.4 to 0.3)
Change at 12 mo	1.0 (0.6 to 1.3)	0.7 (0.4 to 1.1)	-0.3 (-0.7 to 0.1)
SDNN, ms (95%CI)			
Baseline	3.1 (2.9 to 3.3)	3.0 (2.9 to 3.2)	NA
Change at 4 mo	0.6 (0.3 to 0.8)	0.6 (0.3 to 0.8)	0.0 (-0.3 to 0.3)
Change at 12 mo	0.6 (0.4 to 0.9)	0.5 (0.2 to 0.8)	-0.1 (-0.4 to 0.2)
HF, log (95%CI)			
Baseline	4.8 (4.3 to 5.2)	4.7 (4.2 to 5.2)	NA
Change at 4 mo	1.6 (0.9 to 2.2)	1.5 (0.8 to 2.2)	-0.1 (-0.8 to 0.7)
Change at 12 mo	1.9 (1.2 to 2.5)	1.4 (0.7 to 2.1)	-0.5 (-1.3 to 0.3)
LF, log (95%CI)			
Baseline	5.7 (5.3 to 6.0)	5.3 (4.9 to 5.6)	NA
Change at 4 mo	0.7 (0.2 to 1.2)	0.9 (0.4 to 1.4)	0.2 (-0.4 to 0.8)
Change at 12 mo	0.7 (0.1 to 1.1)	0.7 (0.2 to 1.3)	0.0 (-0.6 to 0.7)
VLF, log (95%CI)			
Baseline	3.5 (3.2 to 3.9)	3.1 (2.7 to 3.5)	NA
Change at 4 mo	0.6 (0.0 to 1.0)	1.0 (0.4 to 1.5)	0.4 (-0.3 to 1.0)
Change at 12 mo	0.7 (0.1 to 1.2)	0.8 (0.3 to 1.5)	0.2 (-0.5 to 0.9)
SampEn,			
Baseline	1.6 (1.6 to 1.7)	1.7 (1.6 to 1.8)	NA
Change at 4 mo	0.1 (-0.0 to 0.2)	0.1 (-0.0 to 0.3)	0.1 (-0.1 to 0.2)
Change at 12 mo	0.1 (-0.1 to 0.2)	0.0 (-0.1 to 0.2)	-0.1 (-0.2 to 0.1)
DFA1,			
Baseline	1.2 (1.1 to 1.3)	1.1 (1.0 to 1.2)	NA
Change at 4 mo	-0.3 (-0.4 to -0.1)	-0.2 (-0.3 to -0.0)	0.1 (-0.1 to 0.3)
Change at 12 mo	-0.4 (-0.5 to -0.2)	-0.2 (-0.3 to -0.1)	0.2 (-0.0 to 0.4)

Abbreviations: HR, heart rate; RMSSD, root mean square standard deviation; SDNN, standard deviation N-N intervals; HF, high frequency; LF, low frequency; VLF, very low frequency; SampEn, sample entropy; DFA1, detrended fluctuation analysis alpha 1.

[a] Derived using the group x time interaction term from a linear mixed-effect model that included study group, time (baseline, 4 months and 12 months), and study group x time interaction term as fixed effects and participants as random effects.

Table 14. Intention-to-treat (secondary) analyses assessing the effects of 16-week exercise intervention on HRV derived parameters in participants who underwent bariatric surgery.

End point	Control (n=40)	Experimental (n=40)	Mean difference between groups (95%CI)
Heart Rate Variability			
HR, bpm (95% CI)			
Baseline	80.3 (76.7 to 83.8)	76.9 (73.4 to 80.4)	NA
Change at 4 mo	-14.3 (-20.1 to -9.4)	-10.9 (-16.0 to -8.8)	1.2 (-4.1 to 6.5)
Change at 12 mo	-17.3 (-20.6 to -11.1)	-13.9 (-15.5 to -8.3)	4.6 (-0.8 to 10.1)
RMSSD, ms (95% CI)			
Baseline	25.9 (15.2 to 36.6)	24.6 (14.1 to 35.2)	NA
Change at 4 mo	26.2 (2.0 to 49.5)	23.9 (11.4 to 32.5)	-2.2 (-21.7 to 17.2)
Change at 12 mo	27.5 (3.6 to 45.6)	16.3 (7.8 to 20.8)	-11.2 (-31.2 to 8.8)
SDNN, ms (95%CI)			
Baseline	26.8 (17.1 to 36.5)	24.6 (19.1 to 30.1)	NA
Change at 4 mo	18.7 (2.2 to 33.7)	17.3 (9.0 to 22.9)	-1.3 (-14.3 to 11.6)
Change at 12 mo	18.1 (1.4 to 30.4)	11.7 (5.6 to 15.5)	-6.3 (-19.7 to 7.0)
HF, log (95%CI)			
Baseline	4.6 (4.2 to 5.1)	4.6 (4.2 to 5.1)	NA
Change at 4 mo	1.7 (0.8 to 2.4)	1.6 (1.0 to 2.0)	-0.1 (-0.8 to 0.2)
Change at 12 mo	2.0 (1.2 to 2.5)	1.4 (0.9 to 1.9)	-0.6 (-1.3 to 0.2)
LF, log (95%CI)			
Baseline	5.6 (5.3 to 5.9)	5.2 (4.9 to 5.6)	NA
Change at 4 mo	0.7 (0.2 to 1.3)	1.0 (0.5 to 1.3)	0.3 (-0.3 to 0.8)
Change at 12 mo	0.6 (0.0 to 1.1)	0.8 (0.4 to 1.1)	0.1 (-0.5 to 0.6)
VLF, log (95%CI)			
Baseline	3.5 (3.2 to 3.9)	3.1 (2.8 to 3.5)	NA
Change at 4 mo	0.6 (0.1 to 1.0)	1.1 (0.5 to 1.4)	0.5 (-0.1 to 1.1)
Change at 12 mo	0.7 (0.0 to 1.1)	1.0 (0.3 to 1.3)	0.3 (-0.4 to 0.9)
SampEn,			
Baseline	1.6 (1.5 to 1.7)	1.7 (1.6 to 1.8)	NA
Change at 4 mo	0.1 (0.0 to 0.2)	0.1 (-0.0 to 0.2)	0.0 (-0.1 to 0.2)
Change at 12 mo	0.1 (-0.0 to 0.2)	0.0 (-0.1 to 0.2)	-0.1 (-0.2 to 0.1)
DFA1,			
Baseline	1.2 (1.1 to 1.3)	1.1 (1.0 to 1.2)	NA
Change at 4 mo	-0.3 (-0.4 to -0.1)	-0.2 (-0.3 to -0.0)	0.1 (-0.0 to 0.3)
Change at 12 mo	-0.4 (-0.5 to -0.2)	-0.2 (-0.3 to -0.1)	0.2 (0.0 to 0.3)

Abbreviations: HR, heart rate; RMSSD, root mean square standard deviation; SDNN, standard deviation N-N intervals; HF, high frequency; LF, low frequency; VLF, very low frequency; SampEn, sample entropy; DFA1, detrended fluctuation analysis alpha 1.

Effects of the Exercise Intervention on Blood Pressure and Arterial Stiffness

The between-group difference in blood pressure and arterial stiffness are presented in **Table 15**.

Table 15. Per-protocol (primary) analyses assessing the effects of 16-week exercise intervention on blood pressure and arterial stiffness parameters in participants who underwent bariatric surgery (participants in the exercise group were included if attendance was ≥80%).

End point	Control (n=37)	Experimental (n=29)	Mean difference between groups (95%CI) [a]
SBP, mmHg			
Baseline	130.0 (125.2 to 135.0)	133.0 (128.7 to 139.2)	NA
Change at 4 mo	-8.1 (-13.1 to -3.1)	-14.6 (-20.2 to -8.9)	-6.5 (-12.7 to -0.2)[b]
Change at 12 mo	-19.3 (-24.5 to -14.1)	-15.9 (-21.7 to -10.1)	3.4 (-3.0 to 9.9)
DBP, mmHg			
Baseline	80.6 (77.2 to 84.1)	80.0 (76.1 to 83.9)	NA
Change at 4 mo	-6.7 (-10.6 to -2.9)	-7.9 (-12.2 to -3.5)	-1.4 (-6.2 to 3.4)
Change at 12 mo	-12.3 (-16.3 to -8.3)	-9.2 (-13.7 to -4.7)	2.3 (-2.6 to 7.3)
MAP, mmHg			
Baseline	103.2 (99.4 to 107.0)	104.5 (100.1 to 108.8)	NA
Change at 4 mo	-7.3 (-11.4 to -3.2)	-10.9 (-15.6 to -6.3)	-3.6 (-8.8 to 1.5)
Change at 12 mo	-15.5 (-19.8 to -11.3)	-12.2 (-17.0 to -7.5)	3.3 (-2.0 to 8.6)
PWV, m/s			
Baseline	6.5 (6.2 to 6.9)	6.7 (6.3 to 7.0)	NA
Change at 4 mo	-0.3 (-0.4 to -0.1)	-0.4 (-0.6 to -0.3)	-0.2 (-0.4 to 0.0)
Change at 12 mo	-0.6 (-0.8 to -0.5)	-0.5 (-0.7 to -0.3)	0.1 (-0.1 to 0.4)
PP, mmHg			
Baseline	49.3 (46.4 to 52.3)	53.4 (50.1 to 56.7)	NA
Change at 4 mo	-1.2 (-2.1 to 4.5)	-6.7 (-10.4 to -2.9)	-5.5 (-9.7 to -1.3)[c]
Change at 12 mo	-7.0 (-10.5 to -3.5)	-6.6 (-10.5 to -2.8)	0.3 (-4.0 to 4.6)
Aix75, %			
Baseline	21.2 (17.4 to 25.0)	20.1 (15.8 to 24.4)	NA
Change at 4 mo	-5.6 (-11.1 to -0.0)	-7.6 (-13.9 to -1.3)	-2.0 (-9.0 to 4.9)
Change at 12 mo	-9.1 (-14.8 to -2.1)	0.1 (-6.3 to 6.5)	8.9 (1.8 to 16.2)[c]
Cardiac output, L/min			
Baseline	5.4 (5.2 to 5.7)	5.4 (5.1 to 5.7)	NA
Change at 4 mo	-0.2 (-0.5 to 0.1)	-0.3 (-0.6 to 0.1)	-0.1 (-0.5 to 0.4)
Change at 12 mo	-0.4 (-0.8 to -0.1)	-0.7 (-0.8 to -0.1)	-0.3 (-0.7 to 0.1)

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PWV, pulse wave velocity; PP, pulse pressure; Aix75, augmentation index at 75% heart rate.

[a] Derived using the group x time interaction term from a linear mixed-effect model that included study group, time (baseline, 4 months and 12 months), and study group x time interaction term as fixed effects and participants as random effects.

[b] $p<0.05$ for time x group interactions.

[c] $p= <0.01$ for time x group interactions.

Systolic blood pressure was significantly more reduced in the exercise group (mean change -14.6 mmHg, 95% CI -20.2 to -8.9) than the control group (mean change -8.1 mmHg, 95% CI -13.1 to -3.1) at 4 months (between-group difference -6.5 mmHg, 95% CI -12.7 to -0.2; p = 0.043, **Table 15**). Pulse pressure also was significantly more decreased in the exercise group (mean change -6.7 mmHg, 95% CI -10.4 to -2.9) than the control group (mean change -1.2 mmHg, 95% CI -2.1 to -4.5) at 4 months (between-group difference -5.5 mmHg, 95% CI -9.7 to -1.3; p = 0.010, **Table 15**). However, these difference between groups in systolic (between-group difference 3.4 mmHg, 95% CI -3.0 to 9.9) and pulse pressure (between-group difference 0.3 mmHg, 95% CI -4.0 to 4.6) disappeared at 12 months. Augmentation index at 75% HR was significantly lower in the control group (mean change -9.1%, 95% CI -14.8 to -2.1) than the exercise group (mean change 0.1%, 95% CI -6.3 to 6.5) at 12 months (between-group difference 8.9%, 95% CI 1.8 to 16.2, p value = 0.015, **Table 15**). There were no significant between-group differences in diastolic, mean blood pressure, pulse wave velocity and cardiac output. These sensitivity analyses (ITT) confirmed these results (**Table 16**).

Table 16. Intention-to-treat (secondary) analyses assessing the effects of 16-week exercise intervention on blood pressure and arterial stiffness parameters in participants who underwent bariatric surgery.

End point	Control (n=40)	Experimental (n=40)	Mean difference between groups (95%CI) [a]
SBP, mmHg			
Baseline	130.0 (125.4 to 134.5)	133.4 (128.8 to 138.0)	NA
Change at 4 mo	-8.1 (-12.6 to -3.3)	-14.5 (-18.8 to -9.4)	-6.4 (-12.4 to -0.5)[b]
Change at 12 mo	-19.3 (-24.9 to -16.4)	-16.7 (-22.5 to -12.0)	2.6 (-3.6 to 8.7)
DBP, mmHg			
Baseline	80.4 (77.1 to 83.7)	81.5 (78.2 to 84.8)	NA
Change at 4 mo	-6.6 (-10.7 to -2.9)	-8.5 (-10.9 to -5.3)	-1.9 (-6.5 to 2.6)
Change at 12 mo	-12.1 (-16.0 to -8.7)	-11.0 (-15.6 to -6.9)	1.1 (-3.6 to 5.8)
MAP, mmHg			
Baseline	103.1 (99.4 to 106.8)	104.9 (101.2 to 108.6)	NA
Change at 4 mo	-7.2 (-11.2 to -3.3)	-10.9 (-14.2 to -7.2)	-3.7 (-8.6 to 1.2)
Change at 12 mo	-15.5 (-20.0 to -12.4)	-13.2 (-17.7 to -8.8)	2.3 (-2.8 to 7.3)
PWV, m/s			
Baseline	6.6 (6.2 to 6.9)	6.7 (6.3 to 7.0)	NA
Change at 4 mo	-0.3 (-0.4 to -0.1)	-0.4 (-0.6 to -0.3)	-0.2 (-0.4 to 0.0)
Change at 12 mo	-0.6 (-0.8 to -0.5)	-0.5 (-0.7 to -0.3)	0.1 (-0.1 to 0.3)
PP, mmHg			
Baseline	49.6 (46.8 to 52.3)	51.9 (49.1 to 54.7)	NA
Change at 4 mo	-1.0 (-4.2 to 2.3)	-5.9 (-9.3 to -2.8)	-4.6 (-8.4 to -0.8)[c]
Change at 12 mo	-7.1 (-10.7 to -5.8)	-5.6 (-9.1 to -2.7)	1.5 (-2.4 to 5.4)
Aix75, %			
Baseline	21.8 (18.5 to 25.1)	19.8 (16.2 to 23.4)	NA
Change at 4 mo	-5.8 (-9.3 to -1.1)	-6.8 (-10.6 to -1.1)	-1.0 (-7.2 to 5.2)
Change at 12 mo	-9.3 (-14.8 to -2.2)	-0.1 (-5.7 to 5.7)	9.2 (2.8 to 15.6)[c]
Cardiac output, L/min			
Baseline	5.4 (5.2 to 5.6)	5.5 (5.2 to 5.7)	NA

Change at 4 mo	-0.2 (-0.5 to 0.0)	-0.3 (-0.8 to -0.0)	-0.2 (-0.6 to 0.2)
Change at 12 mo	-0.4 (-0.8 to -0.1)	-0.7 (-1.0 to -0.4)	-0.3 (-0.7 to 0.1)

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PWV, pulse wave velocity; PP, pulse pressure; Aix75, augmentation index at 75% heart rate.

[a] Derived using the group x time interaction term from a linear mixed-effect model that included study group, time (baseline, 4 months and 12 months), and study group x time interaction term as fixed effects and participants as random effects.

[b] p<0.05 for time x group interactions.

[c] *p*= <0.01 for time x group interactions.

Effects of the Exercise Intervention on Echocardiographic variables

Echocardiographic variables were obtained at baseline and 12 months and between-group differences are presented in **Table 17**.

Table 17. Per-protocol (primary) analyses assessing the effects of 16-week exercise intervention on echocardiographic parameters in participants who underwent bariatric surgery (participants in the exercise group were included if attendance was ≥80%).

End point	Control (n=37)	Expeimental (n=29)	Mean difference between groups (95%CI) [a]
LV morphology			
LV mass, g			
Baseline	164.0 (147.1 to 181.3)	172.2 (152.0 to 192.	NA
Change at 12 mo	18.2 (0.5 to 35.9)	-3.4 (-25.0 to 18.2)	21.6 (-5.9 to 49.2)
LV mass index, g/m^2			
Baseline	71.4 (64.4 to 78.3)	74.0 (65.5 to 82.5)	NA
Change at 12 mo	-7.2 (-15.7 to 1.4)	-18.6 (-29.0 to -8.2)	11.4 (-1.8 to 24.7)
Septum thickness, mm			
Baseline	10.9 (10.3 to 11.4)	9.8 (9.3 to 10.4)	NA
Change at 12 mo	1.0 (0.5 to 1.6)	0.8 (0.1 to 1.5)	0.2 (-0.6 to 1.1)
Posterior wall thickness, mm			
Baseline	10.3 (9.8 to 10.8)	10.3 (9.7 to 10.9)	NA
Change at 12 mo	1.1 (0.6 to 1.7)	0.6 (-0.1 to 1.4)	0.5 (-0.4 to 1.4)
LV end-systolic diameter, mm			
Baseline	29.1 (27.1 to 31.1)	29.3 (26.9 to 31.6)	NA
Change at 12 mo	-0.3 (-2.6 to 1.9)	-2.9 (-5.8 to -0.0)	2.6 (-1.0 to 6.2)
LV end-diastolic diameter, mm			
Baseline	46.4 (44.4 to 48.5)	47.7 (45.3 to 50.1)	NA
Change at 12 mo	-0.6 (-2.7 to 1.5)	-0.9 (-3.4 to 1.6)	0.3 (-2.9 to 3.5)
LV systolic function			
Ejection fraction, %			
Baseline	61.9 (59.6 to 64.1)	62.5 (59.8 to 65.1)	NA
Change at 12 mo	-2.7 (-5.9 to 0.6)	0.6 (-3.2 to 4.4)	-3.3 (-8.3 to 1.6)
LV diastolic function			
LA diameter, mm			
Baseline	37.2 (35.2 to 39.2)	35.9 (33.5 to 38.3)	NA
Change at 12 mo	2.3 (-0.1 to 4.6)	-2.2 (-5.0 to 0.6)	4.5 (0.9 to 8.1) [b]
E wave, cm/s			
Baseline	79.4 (73.8 to 85.1)	80.2 (73.5 to 86.9)	NA
Change at 12 mo	-7.5 (-14.4 to -0.7)	-3.3 (-11.4 to 4.8)	-4.2 (-14.7 to 6.3)

A wave, cm/s			
Baseline	72.2 (66.5 to 77.9)	74.1 (67.9 to 80.7)	NA
Change at 12 mo	9.9 (4.2 to 15.5)	5.6 (-1.1 to 12.3)	4.3 (-4.4 to 12.9)
E/A ratio,			
Baseline	1.1 (1.0 to 1.2)	1.1 (1.0 to 1.3)	NA
Change at 12 mo	-0.3 (-0.5 to -0.2)	-0.2 (-0.4 to -0.0)	-0.1 (-0.3 to 0.1)
E/e' index			
Baseline	7.0 (6.4 to 7.6)	6.4 (5.7 to 7.1)	NA
Change at 12 mo	0.7 (0.1 to 1.4)	-0.1 (-0.9 to 0.7)	0.9 (-0.1 to 1.9)
Deceleration time, ms			
Baseline	198.1 (180.0 to 216.3)	208.0 (186.5 to 229.3)	NA
Change at 12 mo	-9.0 (-35.2 to 17.1)	-0.8 (-31.4 to 29.8)	-8.2 (-48.1 to 31.6)

Abbreviations: LV, left ventricle; LA, left atrium.

[a] Derived using the group x time interaction term from a linear mixed-effect model that included study group, time (baseline and 12 months), and study group x time interaction term as fixed effects and participants as random effects.

[b] p=0.017 for time x study group interactions.

Left atrium diameter was significantly reduce in the exercise group (mean change -2.2 mm, 95% CI -5.0 to 0.6) than the control group (mean change 2.3 mm, 95% CI -0.1 to 4.6) at 12 months (between-group difference 4.5 mm, 95% CI 0.9 to 8.1; p value = 0.017, **Table 17**). There were no significant between-group differences in the rest of the echocardiographic parameters (**Figure 28**).

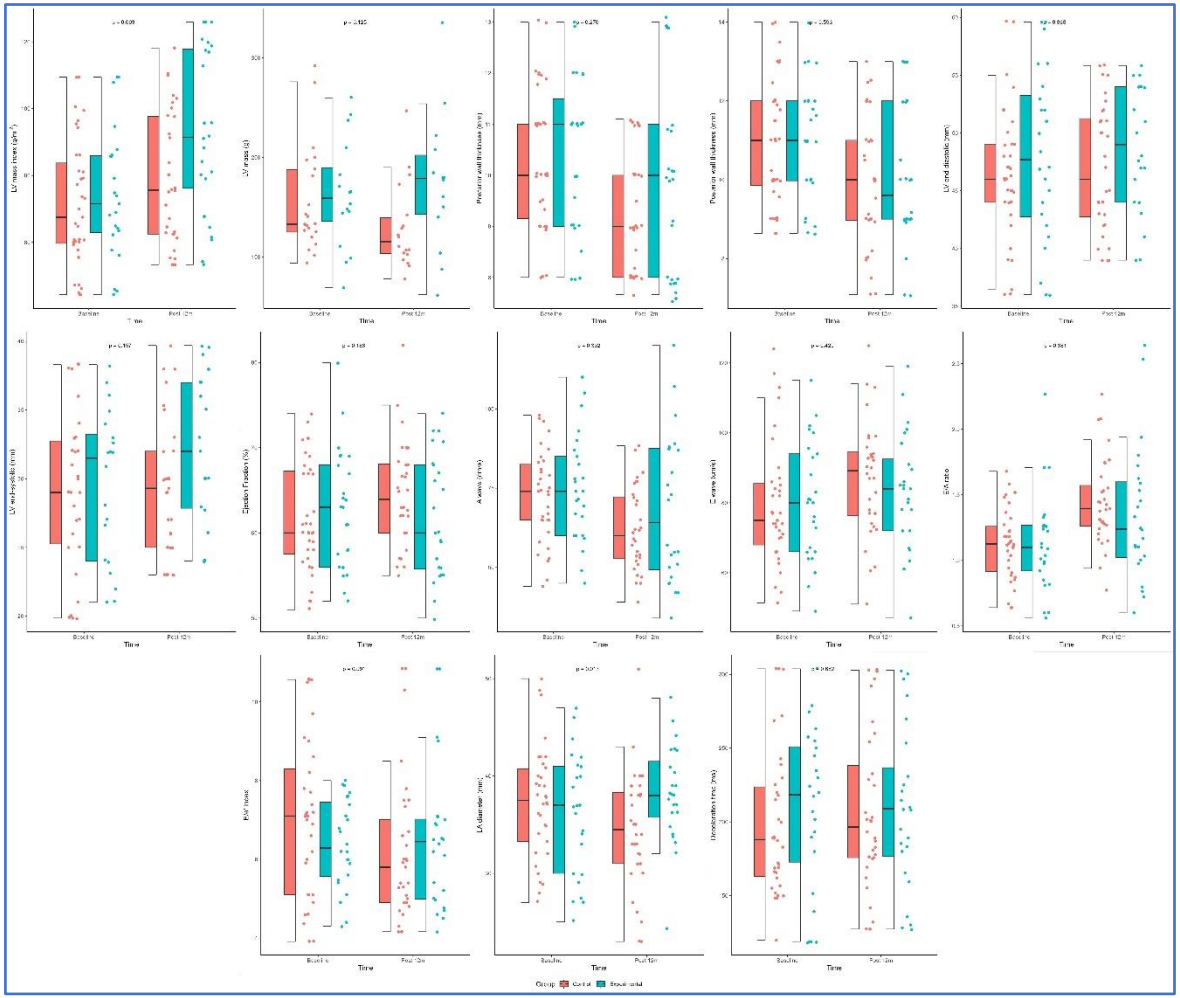


Figure 28. Graphical representation of the changes in the exercise and control group at baseline and 12 months in echocardiographic variables. Abbreviations: LV, left ventricle; LA, left atrium

These sensitivity analyses (ITT) confirmed these results in **Table 18.**

Table 18. Intention-to-treat (secondary) analyses assessing the effects of 16-week exercise intervention on echocardiographic parameters in participants who underwent bariatric surgery.

End point	Control (n=40)	Experimental (n=40)	Mean difference between groups (95%CI) [a]
LV morphology			
LV mass, g			
Baseline	165.7 (147.0 to 180.2)	174.8 (157.0 to 192.5)	NA
Change at 12 mo	17.9 (0.4 to 35.4)	-0.1 (-18.9 to 18.7)	18.0 (-7.3 to 43.4)
LV mass index, g/m^2			
Baseline	71.2 (64.6 to 77.8)	75.4 (68.3 to 82.6)	NA
Change at 12 mo	-7.25 (-15.6 to 1.08)	-16.5 (-25.4 to -7.7)	9.3 (-2.7 to 21.3)
Septum thickness, mm			
Baseline	9.8 (9.3 to 10.4)	10.2 (9.6 to 10.8)	NA
Change at 12 mo	1.0 (0.5 to 1.6)	0.9 (0.3 to 1.5)	0.1 (-0.7 to 0.9)
Posterior wall thickness, mm			
Baseline	10.3 (9.8 to 10.8)	10.5 (10.0 to 11.1)	NA
Change at 12 mo	1.4 (0.5 to 1.8)	0.8 (0.2 to 1.5)	0.3 (-0.6 to 1.2)
LV end-systolic diameter, mm			
Baseline	29.0 (27.2 to 30.9)	30.0 (27.9 to 32.0)	NA
Change at 12 mo	-0.4 (2.6 to 1.8)	-2.2 (-4.7 to 0.3)	1.8 (-1.5 to 5.1)
LV end-diastolic diameter, mm			
Baseline	46.4 (44.4 to 48.4)	47.2 (45.1 to 49.3)	NA
Change at 12 mo	-0.6 (-2.7 to 1.4)	-1.7 (-3.9 to 0.5)	1.0 (-1.8 to 4.0)
LV systolic function			
Ejection fraction, %			
Baseline	61.7 (59.6 to 63.9)	62.3 (60.1 to 64.6)	NA
Change at 12 mo	-2.8 (-6.0 to 0.3)	0.0 (-3.3 to 3.3)	1.1 (0.1 to 2.0)
LV diastolic function			
LA diameter, mm			
Baseline	37.3 (35.4 to 39.2)	36.2 (34.2 to 38.2)	NA
Change at 12 mo	2.3 (-0.0 to 4.7)	-1.7 (-4.1 to 0.7)	4.0 (0.7 to 7.4) [a]
E wave, cm/s			
Baseline	80.2 (74.7 to 85.6)	78.4 (72.7 to 84.2)	NA
Change at 12 mo	-7.0 (-13.8 to -0.2)	-6.2 (-13.2 to 0.9)	-0.8 (-10.5 to 8.8)
A wave, cm/s			
Baseline	73.1 (67.7 to 78.4)	72.0 (66.5 to 77.5)	NA
Change at 12 mo	10.3 (4.6 to 16.0)	5.0 (-0.9 to 10.9)	5.3 (-2.8 to 13.4)
E/A ratio,			

Baseline	1.1 (1.0 to 1.2)	1.1 (1.0 to 1.3)	NA
Change at 12 mo	-0.3 (-0.4 to -0.1)	-0.2 (-0.4 to -0.1)	-0.1 (-0.3 to 0.1)
E/e' index,			
Baseline	7.1 (6.5 to 7.6)	6.3 (5.7 to 6.9)	NA
Change at 12 mo	0.8 (0.1 to 1.5)	-0.3 (-1.0 to 0.4)	-0.3 (-1.1 to 0.5)
Deceleration time, ms			
Baseline	207.0 (189.0 to 225.2)	206.1 (188.0 to 224.1)	NA
Change at 12 mo	-9.0 (-33.7 to 15.7)	-1.5 (-27.0 to 24.1)	-7.5 (-42.7 to 27.6)

Abbreviations: LV, left ventricle; LA, left atrium.

[a] Derived using the group x time interaction term from a liner mixed-effect model that included study group, time (baseline and 12 months), and study group x time interaction term as fixed effects and participants as random effects.

DISCUSSION

“Never be afraid to sit awhile and think”

- Lorraine Hansberry

Summary of findings

The main findings of the present Doctoral Thesis suggest that: I) filters are essential to obtain HRV-derived parameters and that individuals with obesity exhibited a significantly higher percentage of artifacts when using the strong filter. Body position and respiration influence time domain and HF parameters in people with severe/morbid obesity; II) In women with systemic lupus erythematosus, sample entropy was inversely associated with hsCRP and MPO and low frequency and high frequency ratio was directly associated with physical fatigue. Additionally, 12 weeks of progressive aerobic training did not change HRV-derived parameters in comparison to a control group of participants that followed usual care; III) A concurrent exercise program of 16 weeks immediately after bariatric surgery did not change HRV and arterial stiffness parameters in comparison to a control group that followed the clinical recommendations after the surgery. However, a decrease in systolic and pulse pressure after the intervention in patients who participated in the exercise program compared to the control group at 4 months, although these differences disappeared at 12 months. Moreover, the left atrium diameter was significantly reduced in the exercise group compared to the control group at 12 months. Overall, these findings contribute to the growing body of literature on the potential clinical applications of HRV.

Discussion of main findings

Heart rate variability assessment in people with obesity: influence of artifact correction, filters, and segment selection (Study I)

The main findings of this study indicate that to obtain HRV derived parameters, it is essential to apply filters to the raw signal. Additionally, individuals with obesity showed a significantly higher percentage of artifacts when using the strong filter compared to the other filters. Moreover, the body position and respiration of participants influenced the SDNN, RMSSD, and HF values, which were significantly higher when participants were sitting down and not controlling their respiration. In addition, although the time and frequency domain parameters examined did not show any impact from segment selection, SampEn exhibited an interaction between filter and segment selection, with the 0–5-min segment showing lower values when using the automatic filter than the rest of the segments, indicating that this configuration could severely change the interpretation of this parameter for this clinical population.

Different studies have raised concerns about leaving unedited artifacts since it could introduce distortions and present a problem for the interpretation of HRV-derived

parameters;[107] especially in frequency parameters since the presence of artifacts increases power, and therefore their values, in all frequency bands [108]. However, the maximum allowed number for edited R-R intervals for HRV analysis has not been standardized, with editing numbers varying from 1 to 30% depending on different studies [2]. Kubios user's guide recommends less than 5% of interpolated RR intervals when analyzing results [47]. Based on our data, while there are not significant differences between healthy controls and people with obesity, the strong filter presented a higher number of artifacts than the rest of the filters, which could indicate that it should be applied with caution in this population since studies have shown that even a difference of 10 ms could indicate a reduction of almost 20% in the risk of mortality.[109,110]

According to Peltola [31], the more reliable strategy for data processing of artifacts is manual editing with visual verification of the RR intervals arguing that automatic correction systems can never replace this strategy. Similar findings were found in a recent study in which Kubios automatic correction methods were used in participants performing an incline running test using heart rate monitors (HRMs) [112]. The authors concluded that the automatic correction method was not recommended because it was not possible to determine with accuracy the source of artifacts in HRM signals while running. In our study, we did not use ECG tracing to verify whether "authentic" artifacts happened or not, so we cannot assure whether the differences between the strong filter and automatic filters were due to an excessive sensitivity by the strong filter or to the use of HRMs for assessments, which in fact could create an excess of artifacts. However, it should be noted that when excluding the raw values, the automatic filter corrected SampEn more than any filter. This difference could be significant because while the relationship between non-linear measurements and illness is complex, some non-linear domain parameters have demonstrated clinical relevance [108].

Lastly, our findings indicate that individuals with obesity demonstrated higher values in SDNN, RMSSD, and HF parameters while sitting and without controlling their respiration, as opposed to lying down and with controlled respiration. These results could indicate that the participants should lie down to obtain betters values in these parameters. However, individuals with severe obesity may experience compromised diaphragm efficiency and extrinsic airway compression when lying flat due to pressure exerted by the abdomen, leading to increased breathing, severe hypoxemia, and depressed cardiac output [113,114]. Therefore, it is recommended that individuals with severe obesity not be allowed to lie completely flat.

This study has limitations that must be acknowledged. First, the participants in the present analyses had severe / morbid obesity awaiting bariatric surgery (78% of women), so we cannot extrapolate our findings to the general population. Second, we used HRMs for RR interval data recording (Polar RS800CK and Polar V800), which - although validated- are not considered the gold standard. Third, the methodology for the assessment was not standardized (seated vs. supine, natural breathing vs. controlled breathing), although we tried to control for these differences through several analyses. Nevertheless, the study also has strengths that need to be highlighted. First, we used a relatively large sample of patients with severe/morbid obesity (n=60). Second, the HRV parameters were obtained from short-term recordings and in different (time, frequency, and non-linear) domains. Third, the impact of Kubios filters was tested in different 5-min segments providing practical applications that for non-linear methods parameters using the first five minutes should be used with caution.

After the publication of the first global standard of measurement [115], there have been several great contributions, such as new methodology standards [116], an evaluation and recapitulation of non-linear methods [117,] and a useful guideline on reporting HRV data [118]. However, HRV as a clinical tool is still under-recognized partly due to its difficulty in data processing and because there are no standardized recommendations about suitable editing methods for different HRV analyses [13]. It would be beneficial to agree on standard rules or guidelines of what kind of editing or filtering operations researchers should perform before processing HRV data so that results from different studies can be compared.

Heart Rate Variability in Women with Systemic Lupus Erythematosus: Association with Health-Related Parameters and Effects of Aerobic Exercise (Study II)

Our cross-sectional analyses revealed that, among the studied HRV-related variables, sample entropy was inversely associated with hsCRP and MPO and that low frequency and high frequency ratio was directly associated with physical fatigue in women with SLE. The secondary analyses of our clinical trial revealed that 12 weeks of progressive aerobic training did not change HRV-derived parameters in comparison to a control group of SLE patients who received recommendations for a healthy lifestyle.

Imbalance in the sympathetic and parasympathetic divisions of the ANS are associated with increased risk of inflammation [119] which could lead to higher cardiovascular risk [120]. In our study, we observed that higher values of hsCRP and MPO were associated with decreased regularity (SampleEn) but not with any other HRV parameter. Elevated

hsCRP and MPO levels have been shown to be increased in this population and associated with inflammation [121]. Several inflammatory pathways seem to be involved in the relationship with HRV. One of the possible explanations could be changes in the activity of the vagal system that modulates the inflammatory response significantly, which can be blocked or enhanced by transmitter substances (i.e., noradrenaline) or by pro-inflammatory cytokines [122]. A decrease in regularity (SampleEn) could be related to the idea proposed by Goldberger et al. [123], in which nonlinear complexity breaks down with aging and disease reducing the individual's adaptive capabilities. We also found a positive correlation between HRV and IL-6 but not with TNF- α. After adjusting the quantile regression model by age, heart rate, and disease duration we did not find an association between HRV and IL-6. However, it should be noted that both inflammatory markers and ANS have a circadian variation and that the explanatory power of correlating HRV activity and inflammation may be limited by the time frame of the analysis [124]. Given that our HRV data were collected in the afternoon and once at baseline and after the intervention, this could affect our conclusions about these associations.

Regarding PROs, we did not find in our sample associations between HRV and depression, stress or health-related quality of life as previously reported [125]. However, we observed an association between HRV and physical fatigue, as previous findings in other illnesses such as breast cancer [31]. According to Pagani et al. [126], slow autonomic responses to environmental demands or an imbalance between sympathetic and parasympathetic branches may contribute to reduced physical activity and increased fatigue. It is important to note that fatigue improvements have been described in SLE independently of changes in fitness levels and that fatigue is a multifaceted phenomenon that might be affected by different peripheral and central mechanisms [127]. However, we have observed reductions in general fatigue after our exercise intervention with cardiorespiratory fitness as a mediator [66], which could be related to better conditioning in these patients.

To the best of our knowledge, no prior research has evaluated the effects of aerobic exercise on HRV in women with SLE. Our results showed no differences in HRV between groups after an aerobic exercise program. However, as shown in **Figure 15**, some participants improved their RMSDD after the intervention and, compared to the control group, all participants slightly improved as well even if these differences were not significant. It is important to note that our sample size is small, and we had dropout patients in both groups, although our results were consistent across different sensitivity analyses. This show that, although our intervention improved CRF in these

patients[65], it was not as effective in other secondary parameters such as HRV. Therefore, a more effective or intense intervention program could have had improvements in HRV and other physiological parameters. In fact, HRV as a tool to guide daily training has shown to be superior (at increasing fitness and exercise performance) to other training conventional methods [128].

Impact of a 16-week concurrent exercise program on Heart Rate Variability, Arterial Stiffness, and Cardiac Structure and Function following Bariatric Surgery: Secondary Outcomes from the EFIBAR Randomized Trial (Study III)

The main findings of these secondary analyses from the EFIBAR trial indicate that a 16-week supervised concurrent exercise program started immediately after bariatric surgery did not improve HRV and cardiac function parameters. However, our results revealed a decrease in systolic and pulse pressure after the intervention in patients who participated in the exercise program compared with patients receiving only post-surgery usual care at 4 months, although these differences disappeared at 12 months. Moreover, the left atrium diameter was significantly reduced in the exercise group compared to the control group at 12 months.

Our exercise program had no significant effects on any of the HRV parameters studied. These results go in line with very recent studies. Ricci et al.[91] did not find changes in time, frequency, and non-linear domain parameters after six weeks of a whole-body electrostimulation program. Neither did Belzile et al. [92] in time and frequency domain parameters after a 12-week concurrent exercise program that started three months after the surgery. Only Castello et al. [90] found that the exercise group had greater improvements in RMSSD and SDNN than the control group after 16 weeks of an aerobic program performed between 50-70% HR_{peak}, although it should be noted that the final sample size was relatively small (n=10 for each group). Altogether it seems that the changes in the autonomic nervous system, whether increases or decreases are mainly dependent on weight gain and loss [83,129]. Indeed, it has been hypothesized that abdominal fat might provoke the metabolic alterations responsible for activating the sympathetic branch in people with obesity.

Our study revealed that participants who underwent the exercise intervention exhibited reduced systolic and pulse pressure at 4 months compared to the control group, despite prior studies suggesting otherwise.[91,92] However, these differences disappeared at the 12 months. While a recent meta-analysis indicated that combining an exercise intervention with bariatric surgery can improve blood pressure compared to bariatric surgery alone, the authors were unable to determine whether the

improvement was due to chronic effects of the exercise intervention or the sub-acute exercise hypotension effect, possibly caused by not reporting the timing of blood pressure assessments. [130] Our findings suggest that an exercise intervention of 16-weeks immediately following bariatric surgery does not result in chronic effects on blood pressure. Moreover, we did not find changes in different arterial stiffness parameters (i.e., pulse wave velocity [PWV]). However, this is not surprising since Petersen et al.[131] found that changes in PWV were correlated to changes in blood pressure in bariatric patients, even if the direction of the causality needed to be established. Although exercise has been suggested as a protective factor for endothelial function and inflammation in people undergoing bariatric surgery [132], the mechanism by which exercise reduces blood pressure has not yet been established, and it may differ according to the exercise program prescribed [27]. Therefore, we cannot exclude that a more intense and extended exercise program could have significantly improved these parameters.

To our knowledge, this is the first randomized controlled trial to investigate the impact of an exercise program on echocardiographic parameters in bariatric patients. Prior meta-analyses have established that weight loss from bariatric surgery decreases left ventricular mass (LVM) and enhances left ventricular (LV) function [133]. Our findings indicate that the exercise group experienced a reduction in left atrial (LA) diameter compared to the control group, but no changes were observed in other echocardiographic parameters. These results may have varying explanations.

Firstly, echocardiographic studies are vulnerable to subjectivity and reporting bias in interpreting echocardiograms, especially in people with obesity with limited acoustic windows and suboptimal data [97]. Secondly, Vest et al. [134] argue that it is not a direct hemodynamic (i.e., cardiac output) adaptation to weight loss but perhaps the altered metabolic profile that results in LVM regression regardless of changes in blood pressure. Studies like Nault et al. [135] would support this hypothesis, as they found differences in the metabolic profile of participants who underwent bariatric surgery compared to a non-treated group of participants with obesity, without differences in the echocardiographic parameters with increases in LA diameter. Lastly, we cannot discount the potential role of exercise in these results, since people exposed to exercise present cardiac chamber enlargement, with athletes presenting greater LVM than untrained subjects even when accounting for body size [136].

LIMITATIONS & STRENGTHS

“Humility is a peace that accepts one's strengths and limitations.”

- Tim Hiller

Limitations and strengths

Limitations

The findings of this Doctoral Thesis should be interpreted with caution due to several limitations.

The major limitation that all three studies have in common is using a heart rate monitor as the criterion by which HRV was measured instead of the gold standard (ECG). Both heart rate monitors used in this Doctoral thesis (Polar V800 and RS800CX) were previously validated in resting conditions [137,138] and during exercise [139,140] against an electrocardiogram, respectively. However, it should be noted that healthy young adults performed these validation studies raising concerns about the accuracy of heart rate monitors to detect non-sinus beats in special populations [38,141]. Another limitation is that most of the participants are women in their middle age, so we cannot completely generalize the findings from these studies to men or the general population in HRV. Mainly because different studies have demonstrated changes due to sex and age in HRV-derived parameters [142,143].

Regarding **Study II & III**, given the high intra-individual variations and the complex interactions influencing HRV, more variable measurements should have been collected to detect changes caused by the training program or due to the particularities of the populations studied. Furthermore, some statistical analyses performed may lack enough statistical power given the limited sample size since HRV was a secondary outcome in both studies.

Strengths

This Doctoral thesis has strengths that are worth mentioning. First, the methodology for analyzing HRV described in **Study I** was used in **Studies II & III** by the same evaluator and a detailed description of the data collection of HRV was presented. Second, both exercise interventions performed in **Study II & III** have been reported according to the CERT guidelines [144,] which allows transparency and replicability that has been traditionally lacking in exercise-based clinical trials. Third, attendance to both exercise programs were high even though **Study III** was severely affected by the COVID-19 pandemic. Lastly, the inclusion of non-linear parameters in these populations will grant clarity in further research about the behavior of these parameters after exercise programs.

FUTURE RESEARCH DIRECTIONS

"Victory comes from finding opportunities in problems"

- Sun Tzu

Future research directions

The possibilities of HRV in sport sciences and clinical populations is more exciting than ever:

As proven by **Study II**, non-linear parameters can give useful information about the complexity of the signal in relation to inflammatory markers in women with SLE. Longitudinal studies in this line are needed to understand further how the progression of the inflammation produced by the disease affects the ANS in this population. Furthermore, DFA-alpha1 has been recently discovered to provide information about the ventilatory threshold when performing a stress test [145].

In **Study I,** Kubios software was used to perform the analysis. Although user-friendly and popular among researchers and practitioners, it presents several limitations. Among them, it is not open source, and its more complete version is paid. Because it is commercial software, there are limitations about the settings at which the researcher can set up the data analysis, which lacks transparency. Considering that new parameters using non-linear methods are developed constantly, and machine learning is being applied [26], the need for open-source software is imperative for researchers.

This study also highlights the need for reporting guidelines/checklists of data collection and processing in HRV. Steps in this direction have been taken in different areas of science [146,147,] but due to the particularities found in sports sciences research, where the use of heart rate monitors, smartphones, and ultra-short recordings are more likely to be used to measure HRV, there is a need of a unique checklist which would allow better reporting of HRV in our field.

In **Study II & III,** the exercise intervention prescribed did not improve HRV parameters. Future research should study whether higher intensities and training frequency could have improved these parameters in these clinical populations. Moreover, HRV-monitoring training has been successful in increasing submaximal physiological parameters leading to fewer non-responders regarding performance in endurance training [148]. Whether this could be applied and be successful in clinical populations is yet to be demonstrated.

CONCLUSSIONS

“Finally, in conclusion, let me say just this.”

- Peter Sellers

Conclusions

The results of the present Doctoral Thesis suggest that:

1. The impact of different filters, segments, and body positions can affect HRV parameters in participants with severe obesity and in those with normal weight. People with severe obesity had a significantly higher percentage of artifacts with the strong filter than those with normal BMI. Body position and respiration influenced SDNN, RMSSD, and HF values, which were significantly higher in participants lying down with controlled respiration. Therefore, this study provides valuable insights into relevant methodological factors that can affect HRV and emphasizes the importance of applying filters and controlling body position and respiration when conducting HRV research.

2. In women with systemic lupus erythematosus with mild/inactive disease, higher plasma hsCRP and MPO concentrations are related to decreased regularity of the HRV signal, and physical fatigue seems to be related to HRV. Additionally, a 12 weeks of supervised progressive aerobic training program (75 min twice a week between 40% and 75% of the heart rate reserve) did not improve HRV-derived parameters compared to a usual care control group. Future studies are needed to evaluate the effect of different exercise configurations and doses on HRV and other cardiovascular risk factors in systemic lupus erythematosus.

3. A 16-week supervised exercise program that started immediately after bariatric surgery did not significantly improve HRV or arterial stiffness parameters compared with a usual-care control group that followed international guidelines following bariatric surgery. However, the exercise intervention produced a significant reduction of systolic blood pressure and pulse pressure at 4 months compared to the control group and a reduction in left atrial diameter at 12 months. Future studies with longer interventions and different exercise configurations are needed in this population.

Conclusiones

Los resultados de esta tesis Doctoral sugieren que:

1. El impacto de los distintos filtros, segmentos y posición corporal puede afectar a los parámetros de la VFC en los participantes con obesidad grave y en los que tienen un peso normal. Las personas con obesidad grave presentaron un porcentaje significativamente mayor de artefactos con el filtro fuerte en comparación con las personas con un IMC normal. La posición corporal y la respiración influyeron en los valores de SDNN, RMSSD y HF, que fueron significativamente mayores en los participantes que estaban tumbados con respiración controlada. Por lo tanto, este estudio proporciona información valiosa sobre los factores metodológicos relevantes que pueden afectar a la VFC y subraya la importancia de aplicar filtros y controlar la posición corporal y la respiración al realizar investigaciones sobre la VFC.

2. En mujeres con lupus eritematoso sistémico con enfermedad leve/inactiva, las concentraciones plasmáticas más elevadas de hsCRP y MPO están relacionadas con una menor regularidad de la señal de VFC, y la fatiga física parece estar relacionada con la VFC. Además, un programa de 12 semanas de entrenamiento aeróbico progresivo supervisado (75 min dos veces por semana entre el 40% y el 75% de la reserva de frecuencia cardiaca) no mejoró los parámetros derivados de la VFC en comparación con un grupo control. Se necesitan estudios para evaluar el efecto de diferentes configuraciones y dosis de ejercicio sobre la VFC y otros factores de riesgo cardiovascular en pacientes con lupus eritematoso sistémico.

3. Un programa de ejercicio supervisado de 16 semanas de duración que comenzó inmediatamente después de la cirugía bariátrica no produjo mejoras significativas en la VFC ni en los parámetros de rigidez arterial en comparación con un grupo control que recibió atención habitual que siguió las directrices internacionales tras cirugía bariátrica. Sin embargo, la intervención de ejercicio produjo una reducción significativa de la presión arterial sistólica y la presión del pulso a los 4 meses en comparación con el grupo control, y una reducción del diámetro de la aurícula izquierda a los 12 meses. Se necesitan estudios con intervenciones más prolongadas y diferentes configuraciones de ejercicio en esta población.

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CURRICULUM VITAE

“Give a man a fish and you feed him for a day. Teach him how to fish and you feed him for a lifetime.”

- Lao Tzu

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Academic experience and background

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1. American Heart Association, Member: 2020~.
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Publications in peer-reviewed journals

Journal publications derived from this Thesis

1. **Martínez-Rosales, E.**, Sola-Rodríguez, S., Vargas-Hitos, JA., Gavilán-Carrera, B., Rosales-Castillo, A., Hernández-Martínez, A., Artero, EG., Sabio, JM., Soriano-Maldonado, A. Heart Rate Variability in Women with Systemic Lupus Erythematosus: Association with Health-Related Parameters and Effects of Aerobic Exercise. *International Journal of Environmental Research and Public Health*. 2020; 17(24):9501. https://doi.org/10.3390/ijerph17249501
2. **Martínez-Rosales, E.,** Ibachache, P., Cano-Cappellacci, M., Aparicio-Gómez, JA., Aceituno-Cubero, J., Soriano-Maldonado, A., Artero, EG. Heart rate variability assessment in people with obesity: influence of artefact correction and segment selection. *In submission process*.

3. **Martínez-Rosales, E., et al.** Impact of a 16-week concurrent exercise program on Heart Rate Variability, Arterial Stiffness, and Cardiac Structure and Function following Bariatric Surgery: Secondary Outcomes from the EFIBAR Randomized Trial. *In preparation.*

Other journal publications as first author not included in this Thesis

4. **Martínez-Rosales, E.**, Hernández-Martínez, A., Sola-Rodríguez, S., Cornejo-Esteban, I., Soriano-Maldonado, A. Representation of women in sport sciences research, publications, and editorial leadership positions: are we moving forward?. *Journal of Science and Medicine in Sport*. 2021; https://doi.org/10.1016/j.jsams.2021.04.010
5. **Martínez-Rosales, E.**, Hernández-Martínez, A., Sola-Rodríguez, S., Cornejo-Esteban, I., Soriano-Maldonado, A. Reply to letter to the editor regarding "Representation of women in sport sciences research, publications, and editorial leadership positions: Are we moving forward?", *Journal of Science and Medicine in Sport*, Volume 24, Issue 11, 2021, Page 1099, https://doi.org/10.1016/j.jsams.2021.08.001

Co-authored journal publications

6. Hernández-Martínez A, **Martínez-Rosales E**, Alcaraz-Ibáñez M, Soriano-Maldonado A, Artero EG. Influence of Body Composition on Arterial Stiffness in Middle-Aged Adults: Healthy UAL Cross-Sectional Study. *Medicina*. 2019; 55(7):334. https://doi.org/10.3390/medicina55070334
7. Soriano-Maldonado A, Martínez-Forte S, Ferrer-Márquez M, **Martínez-Rosales, E.**, Hernández-Martínez, A., Carretero-Ruiz, A., Villa-González, E., Barranco-Ruiz, Y., Rodríguez-Pérez, M. A., Torrente-Sánchez, M. J., Carmona-Rodríguez, L., Soriano-Maldonado, P., Vargas-Hitos, J. A., Casimiro-Andújar, A. J., Artero, E. G., & Fernández-Alonso, A. M. Physical Exercise following bariatric surgery in women with Morbid obesity: Study protocol clinical trial (SPIRIT compliant). *Medicine* (Baltimore). 2020;99(12):e19427. https://doi.org/10.1097/MD.0000000000019427
8. Ibacache, P., Cárcamo, P., Miranda, C. Bottinelli, A., Guzmán, J., **Martínez-Rosales, E.**, Artero EG., Cano-Cappellacci, M. Improvements in Heart Rate Variability in Women with Obesity: Short-term Effects of Sleeve Gastrectomy. *Obesity Surgery*. 2020; 30, 4038-4045. https://doi.org/10.1007/s11695-020-04721-y

9. Carretero-Ruiz, A., **Martínez-Rosales, E.**, Cavero-Redondo, I., Álvarez-Bueno, C., Martínez-Vizcaíno, V., Navarro, C. G., ... & Artero, E. G. Impact of exercise training after bariatric surgery on cardiometabolic risk factors: a systematic review and meta-analysis of controlled trials. *Reviews in Endocrine and Metabolic Disorders*. 2021; 1-22.
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11. Artero EG, Ferrer-Márquez M, Torrente-Sánchez MJ, **Martínez-Rosales E**, Carretero-Ruiz A, Hernández-Martínez A, López-Sánchez L, Esteban-Simón A, Romero Del Rey A, Alcaraz-Ibáñez M, Rodríguez-Pérez MA, Villa-González E, Barranco-Ruiz Y, Martínez-Forte S, Castillo C, Gómez Navarro C, Aceituno Cubero J, Reyes Parrilla R, Aparicio Gómez JA, Femia P, Fernández-Alonso AM, Soriano-Maldonado A. Supervised exercise immediately after bariatric surgery: the study protocol of the EFIBAR randomized controlled trial. *OBES SURG* (2020).
12. Alcaraz-Ibáñez, M., Carrascosa-Ruiz, I., **Martínez-Rosales, E.,** & Burgueño, R. (2022). Influencia de los contenidos de meta sobre la intención de práctica de ejercicio físico en adolescentes: La importancia de aspirar a desarrollar habilidades. *Cultura, Ciencia y Deporte*, 17(52), 87-94. http://doi.org/10.12800/ccd.v17i52.1615
13. Burgueño, R; Chillón, P; Herrador-Colmenero, M; Villa-González, E; **Martínez-Rosales, E**; Alcaraz-Ibáñez, M; Sevil-Serrano, J. Basic Psychological Need Frustration Scale: Adaptation and validation to active commuting to school in Spanish children and adolescents. *Transportation research part F: traffic psychology and behaviour 91 (2022): 346-356*. https://doi.org/10.1016/j.trf.2022.10.010

Books and book chapters

1. Gallego Antonio, J., Alcaraz-Ibáñez, M., Aguilar-Parra, J. M., Cangas, A. J., **Martínez-Rosales, E.**, y Martínez-Morillas, E. (2018). Libro de Actas del VI Congreso Internacional de Deporte Inclusivo: Salud, desarrollo y bienestar personal. Almería: UAL Editorial. ISBN: 978-84-17261-00-9

Distinguished communications in conferences (n= 36)

Oral communications

1. **Martinez-Rosales, E.,** Hernandez-Martinez, A., Sola-Rodriguez, S., Esteban-Cornejo, I., Soriano-Maldonado, A. Female Leadership in Sport Sciences: Representation of Women in Publications and Editorial Board Positions. 26th Annual Congress of the European College of Sport Science (Virtual), 8th- 10th September 2021, ISBN 978-3-9818414-4-2.
2. **Martínez-Rosales, E.,** Hernández-Martínez, A., López-Sánchez, L., Rodríguez-Pérez MA, Soriano-Maldonado, A., Artero, E. Muscle quality in patients awaiting bariatric surgery: the EFIBAR project. 27th Annual Congress of the European College of Sport Science between 30 October - 2 September 2022 in Seville - Spain. Published in Book of Abstracts, ISBN 978-3-9818414-5-9, page 546.
3. **Martínez-Rosales, E.,** Hernández-Martínez, A., Alcaraz-Ibáñez, M., López-Sánchez, L., Díez-Fernández, D.M., Soriano-Maldonado, A., Artero, EG. Comparison of Heart Rate Variability, Physical Activity, And Fitness Parameters Between Healthy Women and Breast Cancer Survivors. American Heart Association (AHA) Scientific Sessions, Dallas, USA. 14th -16th November 2020.

Participation in research projects

2022-2023 *RESET Life: evaluation of a novel instrument for the management of chronic back pain at the workplace*

PI: A. Casimiro **Role:** research assistant **Funding:** 7.000 €

2022-2023 *Analysis and evaluation of the representation of women in publications and editorial boards between 2020 & 2022*

PI: A. Soriano-Maldonado **Role:** research assistant **Funding:** 6.000 €

2020-2021 *Creation of didactic materials for novel innovation in education*

PI: A. Soriano-Maldonado **Role:** research assistant **Funding:** 3.000 €

2018-2019 *Pilot Study Healthy UAL*

PI: EG. Artero **Role:** research assistant **Funding:** 7.000 €

2018-2022 *EMOVAR: Exercise after bariatric surgery in women with severe obesity: effects of ovarian function and mechanisms*

PI: A. Soriano-Maldonado **Role:** project manager **Funding:** 108.900 €

2018-2022 *EFIBAR: Exercise after bariatric surgery in the treatment of severe obesity*

PI: EG. Artero **Role:** research assistant **Funding:** 108.900 €

Teaching experience

2019-2020	Expressive and Rhythms Activities (22.5h)
	BSc in physical activity and sport sciences
	Sport, Multiculturality and social integrity (5h)
	BSc in social education
	Physical Activity Programs for Older Adults (16h)
	BSc in physical activity and sport sciences
	Practicum III (8h)
	BSc in education
2020-2021	Team Sports: Soccer and Volleyball (60h)
	BSc in physical activity and sport sciences
2021-2022	Team Sports: Handball and Basketball (37.5h)
	BSc in physical activity and sport sciences
	Motor skills, health, and development in infancy (17.5h)
	BSc in education
2022-2023	Physical activity, healthy habits, and quality of life (9 h)
	BSc in education
	Practicum (4h)
	BSc in physical activity and sport sciences

International stays

Research stays

27/08/2021-27/11/2021	Iowa State University
	Ames, IA (USA)
	Supervisor: PhD Duck-Chul Lee
17/07/2022-31/10/2022	Iowa State University
	Ames, IA (USA)
	Supervisor: PhD Duch-Chul Lee

Academic stays

01/08/2015-31/05/2016	St. Ambrose University Davenport, IA (USA)
01/08/2016-31/05/2017	Missouri Southern State University Jopli, MO (USA)

Invited lectures, seminars and workshops

15/03/2022 Why would I study Sport Sciences? Work options and research (2h)
Workshop at IES Algazul, Almeria (Spain)

24/09/2021 Representation of women in sport science: how, when, and why? (2h)
Open seminar at Iowa State University, Ames (USA)

15/03/2021 Work options and research in Sport Sciences and the role of women (2h)
Workshop at IES Carmen de Burgos, Almeria (Spain)

Funding obtained

2021-2022 *International mobility grant*
Funder: Ministry of Education, Culture and Sports **Funding:** 5.500 €

2020-2021 *International mobility grant*
Funder: Ministry of Education, Culture and Sports **Funding:** 5.500 €

2020-2021 *International mobility grant* ***(Rejected)***
Funder: Ministry of Education, Culture and Sports **Funding:** 5.500 €

2019-2023 *University Teachers Training (main grant for PhD studies from the Spanish Ministry)*
Funder: Ministry of Education, Culture and Sports **Funding:** 80.000 €

2018-2019 *Research assistant in the EFIBAR project (for MSc students)*
Funder: University of Almeria **Funding:** 30.000 €

2017-2018 *Starting research grant (for MSc students)*
Funder: Ministry of Education, Culture and Sports **Funding:** 1.800 €

Invited Journal Review (in alphabetical order)

- Complementary Therapies in Clinical Practice
- European Journal of Sport Science

- International Journal of Exercise and Psychology
- Journal of Cachexia, Sarcopenia and Muscle
- Occupational & Environmental Medicine
- Peer J
- Scientific Reports
- Seminars in Arthritis and Rheumatism
- Women & Health

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“Life before death.
Strength before weakness.
Journey before destination.”

- Brandon Sanderson

Lo primero que hago antes de leer una tesis es ir a la parte de agradecimientos. Ya sea al principio o al final, siempre la encuentras, siempre está ahí. Para mí es la parte más bonita de una tesis. Creo que es aquí, donde se refleja el verdadero proceso de lo que el doctorado ha significado para el doctorando y aquellos que lo han acompañado en el camino. Es también donde el doctorando le da su toque de personalidad (se oye su voz) a un documento (el de la tesis) que es impersonal y con una estructura rígida. Envidia me dan aquellos que son capaces de escribir los agradecimientos con un humor que te hacen esbozar una sonrisa (o soltar una carcajada), los que escriben tan bonito que te emocionan (sin tu conocer a nadie) o ¡las dos cosas! No tengo yo ese don, lo que si tengo es una sinceridad honesta y espero hacer justicia a todo el mundo que aparece en estas páginas.

Echando la vista atrás, no puedo si no expresar mi más profunda gratitud a todos los que me habéis acompañado en este viaje. Ha sido un largo y difícil camino de cuatro años, o cinco si has tenido la mala suerte de sufrir una pandemia. Lo que, en principio, por mi ingenuidad, parecía un camino recto y plano resultó ser por momentos un camino lleno de curvas, precipicios, barrizales, tropiezos y momentos de oscuridad en los que en determinadas situaciones he necesitado luz para ver hacia donde me dirigía. Han sido muchas las personas que, de manera directa o indirecta, me han apoyado y ayudado hasta llegar al destino final de este maravilloso viaje. Solo puedo daros las gracias una y mil veces.

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Gracias **Enrique**, por acercarte, durante las jornadas de Obesidad, a esa chica que acababa de llegar de E.E.U.U y no tenía muy claro en qué dirección ir y preguntarme si me iba a matricular en el máster de investigación ya que buscabas a alguien con mi perfil. Por decirme, echa esta beca de colaboración…y este contrato de técnico…y vamos a pedir la FPU. ¿Y te acuerdas lo que pasó? Que nos rechazaron (injustamente, por cierto). Todavía recuerdo tus palabras en esa llamada: "*En este mundo nos rechazan más veces que las que nos aceptan. Solo podemos aprender de esto, el año que viene la pedimos de nuevo*". Y así fue y así ha sido. Creo que pocas personas te

han podido generar más estrés en este tiempo que yo. Con llamadas a las 6:00 AM o las 23:30PM porque ha pasado algo con un participante o porque tengo que cambiar las horas de docencia porque me voy dos meses más tarde de lo previsto de estancia, me acaban de dar el visado y te estoy llamando desde el avión…Y nunca has dudado de lo que te planteaba o de las decisiones (acertadas o erróneas) que haya podido tomar en este tiempo. Gracias por decir con orgullo que yo he sido tu primera FPU. Espero haber estado a la altura de tus expectativas.

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GRACIAS a mi compañera de batallas

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la cuerda y rápidamente recibía un tirón de confirmación de que ahí estabas. Así hemos ido, entre risas y lágrimas, lágrimas y risas, apoyándonos mutuamente. Me he adelantado en el camino, pero no te preocupes que te espero para la próxima batalla.

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Chicos, tenemos pendiente un paintball y cervezas. Ahí lo dejo.

GRACIAS a los indestructibles del despacho 2.05 del Ed. Central

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Seguramente nunca hubiera estudiado CCAFD si no hubiera tenido la maravillosa experiencia de competir a voleibol. Durante mucho tiempo ha sido una parte fundamental de mi vida, con (no estoy exagerando) más de un tercio de las horas de mi vida dentro de un pabellón de voleibol. He conocido a gente de 10. Perdonad si no puedo mencionaros a todos en nombre. Gracias a mis compañeras de equipo y a los entrenadores. Por ayudarme a ir arrastrando libros y portátil por autobuses y aeropuertos de toda España, que han sido comprensivos cuando he tenido bajones de rendimiento en momentos concretos por el volumen de trabajo que afectaban luego al volley...En los días que llegaba reventada o estresada al entrenamiento, me decían: "*Jelen, olvídate de la tesis y el curro, vamos a entrenar y a disfrutar un rato*". Tengo esa espinita clavada de que, quizás, cuando más falta ha hecho que este, no he podido estar. Os pido perdón por no haber podido ayudaros esta temporada, intentaré resarcirme pronto.

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Al enano peludo, a **Chico** (que lo adoptamos el mismo año que comencé la tesis), al que le dan igual las horas de trabajo, reuniones o similares. Él tiene su horario y de ahí no lo mueve nadie. Porque ha aportado su granito de arena cuando venía al despacho a darme con el morro para obligarme a salir a darme un paseo. En retrospectiva, esos paseaos fueron un bien necesario para aclarar la mente.

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A mi **madre,** que si le preguntarais a qué me dedico no sabría muy bien deciros con exactitud qué es. Pero está aquí escuchándome hablar en inglés y probablemente le esté sonando todo a cuando nos ponemos a ver programas de cocina en inglés, están explicando y me pregunta *"¿Qué significa [imitación alejada de toda realidad de la pronunciación de dicha palabra con posibilidad de invención de nuevo idioma]?"*. Gracias por ponerme los pies en el suelo. Por no tomarme demasiado en serio. Por enfadarte más que yo cuando han venido mal dadas. Por ser los cimientos de la casa, porque ves las cosas con una claridad que ya quisiera yo. Por tu risa contagiosa. Eres única, una especie en peligro de extinción.

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me faltaba a mí, lo ponías tu contándome historias de cuando comenzaste el doctorado en Murcia. Siempre me has recordado que mi peor enemigo soy yo, que los limites me los pongo yo sin darme cuenta. Porque, aunque sé que llevas la procesión por dentro, hoy es un día de celebración.

¡Os quiero!

ANNEXES

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Article

Heart Rate Variability in Women with Systemic Lupus Erythematosus: Association with Health-Related Parameters and Effects of Aerobic Exercise

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Abstract: Abnormal heart rate variability (HRV) has been observed in patients with systemic lupus erythematosus (SLE). In a combined cross-sectional and interventional study approach, we investigated the association of HRV with inflammation and oxidative stress markers, patient-reported outcomes, and the effect of 12 weeks of aerobic exercise in HRV. Fifty-five women with SLE (mean age 43.5 ± 14.0 years) were assigned to either aerobic exercise (n = 26) or usual care (n = 29) in a non-randomized trial. HRV was assessed using a heart rate monitor during 10 min, inflammatory and oxidative stress markers were obtained, psychological stress (Perceived Stress Scale), sleep quality (Pittsburg Sleep Quality Index), fatigue (Multidimensional Fatigue Inventory), depressive symptoms (Beck Depression Inventory), and quality of life (36-item Short-Form Health Survey) were also assessed. Low frequency to high frequency power (LFHF) ratio was associated with physical fatigue (p = 0.019). Sample entropy was inversely associated with high-sensitivity C-reactive protein (p = 0.014) and myeloperoxidase (p = 0.007). There were no significant between-group differences in the changes in HRV derived parameters after the exercise intervention. High-sensitivity C-reactive protein and myeloperoxidase were negatively related to sample entropy and physical fatigue was positively related to LFHF ratio. However, an exercise intervention of 12 weeks of aerobic training did not produce any changes in HRV derived parameters in women with SLE in comparison to a control group.

Keywords: autonomic nervous system; exercise; inflammation; fatigue; rheumatic disease

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multifactorial etiology that predominantly affects women [1]. In recent years, the diagnosis and treatment of SLE has significantly improved [2], and deaths due to lupus manifestation have decreased [3]. However, cardiovascular disease (CVD) mortality remains one of the leading causes of death in SLE patients [4,5].

The importance of the autonomic nervous system (ANS) on cardiovascular health and prognosis has already been reported [6,7]. In fact, the ANS plays a key role in regulating immune responses to inflammatory stimuli [8]. Heart rate variability (HRV) is a noninvasive and sensitive measure of ANS function [9] and is defined as the physiological variation in the duration of intervals between sinus beats [10]. Autonomic dysfunction is common in autoimmune rheumatic diseases [11], and specifically, increased sympathetic and decreased parasympathetic activity as reported by several studies in patients with SLE [12–14]. In this sense, patients with SLE have shown abnormal HRV, a surrogate marker of cardiac ANS dysfunction [15], which may predispose to the onset of fatal arrhythmias in these patients [16]. Considering that HRV is inversely associated with inflammatory markers in healthy individuals and in patients with CVD [17], it is of clinical interest to: (i) understand the extent to which HRV might be associated to inflammatory markers and patient-reported outcomes (PROs) and (ii) whether HRV can be enhanced through interventions in women with SLE.

Exercise is a potential intervention that significantly increases cardiorespiratory fitness [18,19], improves cardiovascular function and PROs (i.e., fatigue, depression, etc.) [20] in patients with SLE. Although exercise has shown to decrease cardiovascular morbidity and mortality in the general population [21,22], its benefits in SLE population are understudied to the extent that exercise hardly appear in the EULAR guidelines for the management of this chronic disease [23]. Benatti and Pedersen [24] suggested that one of the mechanisms by which exercise might benefit the cardiovascular system in patients with rheumatic diseases is through direct or indirect anti-inflammatory effects. Based on the effects of exercise in the general population [25] and other chronic conditions [26,27], it might be hypothesized that exercise (and particularly aerobic exercise) could also increase HRV and thus regulate the ANS in women with SLE. Although there have been some studies evaluating HRV after an exercise stress test in this population [28,29], to the best of our knowledge, no prior research has evaluated the effects of an aerobic exercise program on HRV in women with SLE.

Therefore, the aims of this study are (1) to cross-sectionally explore the associations of HRV with inflammatory markers and PROs; and (2) to analyze the effect of a 12-week aerobic program in women with SLE on HRV derived parameters.

2. Materials and Methods

2.1. Study Design and Participants

This study included data of 58 women with SLE from a non-randomized controlled trial investigating the effects of a 12-week aerobic exercise program on arterial stiffness, inflammation, and cardiorespiratory fitness [19]. Participants were recruited from the Systemic Autoimmune Diseases Unit of the "Virgen de las Nieves" and "San Cecilio" University Hospitals (Granada, Spain). A comprehensive description of the inclusion and exclusion criteria can be found elsewhere [19]. The study was approved by the Research Ethics Committee of Granada (ref. No.: 10/2016) and registered at clinicaltrials.gov [NCT03107442] with HRV among the pre-established secondary outcomes. All participants signed written informed consent. The baseline data were used for the cross-sectional analyses of the present study.

2.2. Intervention

2.2.1. Exercise Group

The exercise program has been comprehensively described elsewhere [19] following the Consensus on Exercise Reporting Template (CERT) [30]. Participants assigned to the exercise group performed two 75-min sessions per week of moderate to vigorous intensity aerobic exercise on a treadmill (BH, Serie i.RC12 Dual, Vitoria-Gasteiz, Spain) for 12 weeks. All sessions began with a warm-up on the treadmill at about 35–40% of the heart rate reserve (HRR) plus 3–4 min of active stretching, while ending with a cool down of static stretching and relaxation. Exercise was prescribed with training

intensity progressively increasing in a range from 40% to 75% of each individual's HRR. In all sessions, heart rate was monitored with a Polar V800 (Polar Inc., Kempele, Finland).

Only continuous exercise was performed during the first half of the program. Continuous sessions comprised several bouts of exertion at constant intensity, followed by a couple of minutes of recovery. At 8 weeks, continuous and interval sessions were alternated, and at 12 weeks, the patients performed only interval training sessions, with periods of lower and higher intensity efforts followed by some minutes of rest for hydration. The progression in volume and/or intensity was undertaken by increasing the treadmill speed or inclination according to the perceived exertion of each patient. Lastly, the exercise intensity progressions had to be slightly modified since several patients perceived a 5% HRR intensity increase as very heavy and difficult-to-follow. Therefore, exercise intensity increased by 2.5% instead of 5% in some weeks.

2.2.2. Control Group

SLE patients assigned to the control (usual care) group received information about a healthy lifestyle, including physical activity guidelines and basic nutritional information.

2.3. Heart Rate Variability

Participants were requested not to drink caffeinated or alcoholic drinks, to fast for at least 3 h, and not to participate in physical activity 24 h before the assessment. R-R intervals were recorded with a Polar V800 (Polar Inc., Kempele, Finland), a validated instrument [31], placed at the sternum level. Participants were place in supine position in a quiet room (temperature 22–24 °C) between 4 p.m. and 7 p.m., and were instructed to breath normally, stay relaxed and not to speak or fidget during the assessment. HRV was recorded for 10 min, after a period of 5 min, at a sampling frequency of 1000 Hz. HRV raw data was analyzed with Kubios (HRV analysis, Finland). After visual inspection for any premature contractions or ectopic beats in the recording, a 5-min period was manually selected by the evaluator. Kubios filters were applied accordingly based on inter-individual variability and if the sample presented more than 5% of interpolated R-R intervals it was discarded as per manufacturer's recommendation [32].

The following HRV derived parameters were analyzed: the standard deviation of the average normal-to-normal (NN) interval (SDNN), the square root of the mean squared differences of successive NN intervals (RMSSD), and percentage of consecutive R-R intervals that differ by more than 50 ms (pNN50), low frequency power (LF: 0.04–0.15 Hz), high frequency power (HF: 0.15–0.4 Hz) and LF to HF power ratio (LFHF) indices (which were computed using the fast Fourier transform), Poincaré Plot were standard deviation 1 (SD1), represents short-term variability, and standard deviation 2 (SD2), the long-term variability (compared with SD1); and sample entropy (SampEn).

2.4. Patient-Reported Outcomes

Health-related quality of life was assessed using the short version of the Spanish version of the 36-item Short-Form Health Survey (SF-36) [33]. Depression was assessed through the Beck Depression Inventory-second edition (BDI-II) [34]. Psychological stress was measured with the Perceived Stress Scale (PSS) [35], and fatigue with the Multidimensional Fatigue Inventory (MFI) [36].

2.5. Inflammatory and Oxidative Stress Markers

Fasting blood samples for biochemical and immunological tests were collected and processed. High-sensitivity CRP (hsCRP), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) were measured as markers of inflammation, whereas myeloperoxidase (MPO) was determined as a marker of oxidative stress.

2.6. Other Measurements

Height was measured using a height gauge, weight with a bioimpedance device (InBody R20, Korea), and body mass index (BMI) was calculated (kg/m^2). Blood pressure was measured with Mobil-O-Graph® (IEM GmbH, Stolberg, Germany) [37]. Disease activity was assessed through the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) [38]. Physical activity was self-reported with the International Physical Activity Questionnaire [39]. All participants filled out a socio-demographic and clinical data questionnaire.

2.7. Classification of Responders, Non-Responders, and Adverse Responders

The inter-individual variability of the patients in the response to the intervention was analyzed by categorizing participants from each group as responders, non-responders or adverse responders using the typical error measurement (TE). The TE was calculated using the equation TE = SDdiff/$\sqrt{2}$, where SDdiff is the standard deviation of the difference scores observed between the 2 repeats of each measurement [40]. A responder was defined as an individual who demonstrated an increase (in favor of beneficial changes), an adverse responder was defined as an individual who demonstrated a decrease, and a non-responder was defined as an individual who failed to demonstrate an increase or decrease that was >2 times the TE away from 0. A change more than 2 times the TE means that this response is a true physiological adaptation beyond what might be expected to result from technical and/or biological variability [41].

2.8. Treatment Allocation and Blinding

Randomization was not possible as many participants lived far and were not able to attend the exercise sessions in case of being randomized to exercise. Therefore, participants from the city of Granada were included in the exercise group and participants living outside Granada were included in the control group. To minimize potential selection bias, we aimed to match the groups by age (±2 years), BMI (±1 kg/m^2), and SLEDAI (±1 unit). The data analyzer was blinded to the patient allocation.

2.9. Statistical Analysis

Normality was tested using visual inspection of histograms and Q-Q plots. As HRV-derived parameters were non-normally distributed, their descriptive analysis was presented using median and interquartile range, while non-parametric test was used for the main analysis. Between-group baseline characteristics were compared with the Student t-test (when normally distributed), Kruskal–Wallis test (when non-normally distributed) for continuous variables and the Chi-square test for categorical variables. To explore the associations of HRV with inflammatory and oxidative stress markers (hsCRP, IL-6, TNF-α and MPO) and PROs (aim 1), scatter plots and Spearman's bivariate correlations were used as preliminary analyses to understand raw associations. Subsequently, quantile regression models were built, including each of the above HRV parameters as dependent variables and each inflammatory marker as independent variables in regression models along with age, heart rate, and disease duration as relevant factors that might confound the association of interest. This same procedure was followed with PROs. Other variables included in the regression model were SLEDAI, systemic damage index (SDI), and smoking. However, neither of these variables affected the regression coefficients; therefore, they were not included. Inflammatory markers (hsCRP, IL-6 and TNF–α) and MPO were winsorized to the highest value due to the presence of outliers.

To assess the effects of the exercise intervention (aim 2), the between group differences in the change from baseline in HRV-derived parameters were assessed through quantile regression with baseline values, heart rate, and age as covariables. As we aimed at assessing efficacy, the primary analyses were defined as per-protocol, where patients from the exercise group were included if attendance to the exercise sessions was ≥75%. We additionally performed sensitivity analyses including (i) participants with attendance

≥90%; and (ii) baseline observation carried forward (BOCF). All the analyses were conducted with SPSS v.26 (IBM SPSS Statistics, Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

3. Results

The flowchart of the study participants throughout the trial is presented in Figure 1. A total of 58 patients completed the baseline assessment and were included in aim 1 analysis ($n = 55$).

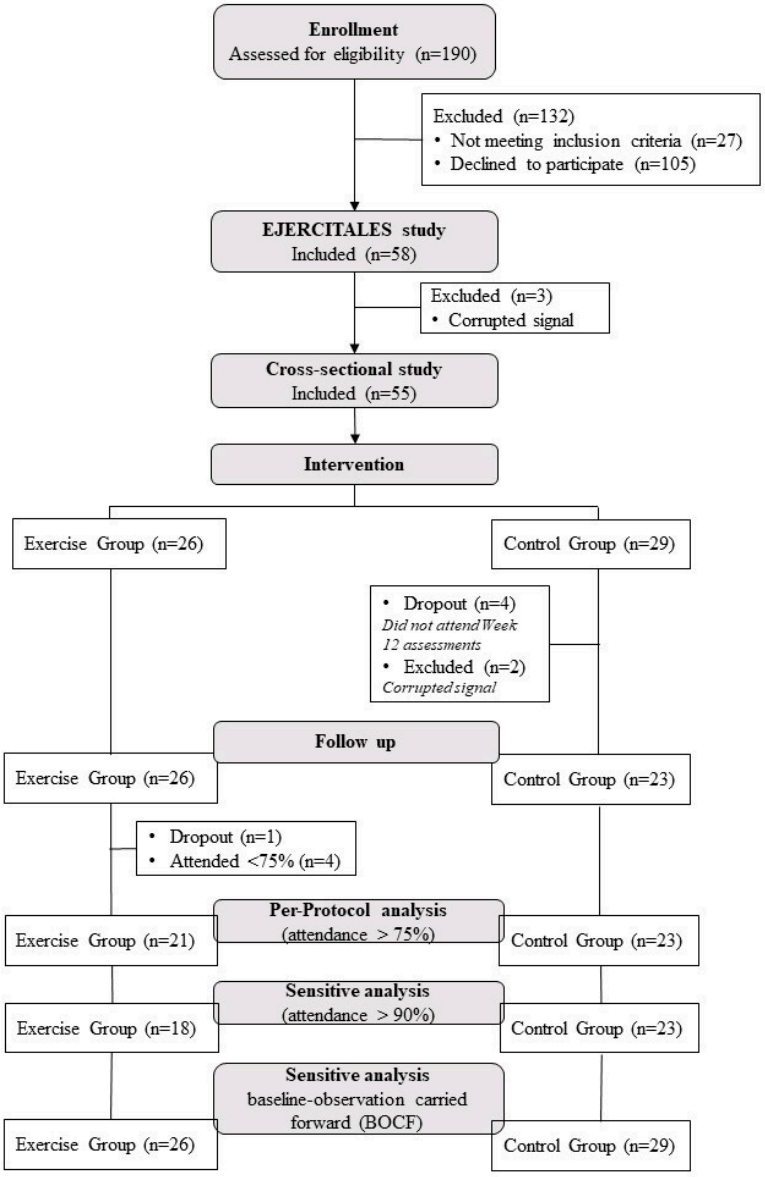

Figure 1. Flowchart of the study participants throughout the study.

For aim 2, participants were assigned to either the exercise group ($n = 26$) or the control group ($n = 32$). At baseline (Tables 1 and 2), the control group showed a higher IL-6 levels (median difference 3.10 pg/mL; $p = 0.018$), lower score in the physical component summary of the SF-36 (mean difference −4.9 units; $p = 0.034$), and higher punctuation in depressive symptoms (mean difference 9.0 units; $p = 0.011$) than the exercise group.

Table 1. Baseline characteristics of the study participants.

	All (n = 55)	Exercise (n = 26)	Control (n = 29)	p
	Mean (SD)	Mean (SD)	Mean (SD)	
Age, years	43.5 (14.0)	42.9 (15.1)	43.9 (13.3)	0.808
BMI, kg/m^2	25.4 (4.8)	25.9 (3.4)	25.0 (5.8)	0.491
SBP, mm/Hg	117.5 (10.3)	116.8 (9.9)	118.1 (10.6)	0.653
DBP, mm/Hg	75.3 (9.4)	75.5 (8.7)	75.1 (10.01)	0.843
MBP, mm/Hg	94.6 (8.7)	94.5 (8.3)	94.7 (9.2)	0.937
Mean HR, bpm	76.70 (10.71)	79.11 (9.76)	74.54 (11.23)	0.112
hsCRP, mg/L (median, IQR)	1.6 (2.6–6.5)	2.2 (1.9–7.6)	1.2 (1.5–7.1)	0.218
IL-6, pg/mL (median, IQR)	10.5 (9.4–12.3)	8.2 (7.1–11.7)	11.3 (10.3–14.0)	0.018
TNF-α, pg/mL (median, IQR)	15.6 (15.7–19.8)	16.5 (15.4–21.1)	14.8 (14.3–20.4)	0.385
MPO, ng/mL (median, IQR)	69.6 (79.1–119.6)	60.1 (62.4–126.9)	75.7 (76.3–130.9)	0.385
Smoke (%)	23.6	15.4	31.0	0.237
Menopause (%)	38.2	38.5	37.9	0.968
Dyslipidemia (%)	16.4	19.2	13.8	0.586
Statins (%)	16.4	23.1	10.3	0.203
Immunosuppressants (%)	45.5	46.1	44.8	0.921
Current corticosteroid intake (mg/day)	3.86 (5.1)	4.08 (6.1)	3.70 (4.2)	0.789
Disease duration, years	15.1 (10.1)	14.54 (10.4)	15.6 (9.9)	0.704
Total PA, min/week	94.8 (92.6)	97.5 (95.9)	92.4 (91.1)	0.660
SLEDAI	0.16 (0.764)	0.04 (0.196)	0.28 (1.0)	0.254
SDI	0.42 (1.1)	0.19 (0.63)	0.62 (1.3)	0.145
Psychological Stress (PSS; 0–56; median, IQR)	31.0 (28.9–32.1)	30.0 (27.7–31.6)	31.0 (28.7–33.9)	0.303
Depressive symptoms (BDI-II; 0–63)	12.8 (9.2)	8.0 (6.4–12.7)	17.0 (12.2–19.3)	0.011
Fatigue (MFI-S; 0–20)				
General Fatigue (median, IQR)	15.0 (12.9–15.1)	14.5 (12.1–15.3)	16.0 (12.5–15.9)	0.498
Physical fatigue	12.8 (4.7)	12.4 (4.8)	13.1 (4.7)	0.577
Reduced Activity (median, IQR)	10.0 (8.7–11.5)	8.0 (7.8–11.5)	11.0 (8.4–12.6)	0.741
Reduced Motivation	9.4 (3.7)	8.5 (3.4)	10.1 (3.9)	0.112
Mental Fatigue	12.2 (2.8)	12.04 (3.0)	12.3 (2.6)	0.720
Health-related quality of life (SF-36; 0–00) *				
Physical Component Summary	43.0 (8.2)	45.5 (8.5)	40.6 (7.8)	0.034
Mental Component Summary	44.9 (11.0)	47.5 (11.7)	40.4 (11.0)	0.106

* For SF-36 domains total sample size was n = 45 due to missing data. Values are the mean (standard deviation; SD), unless otherwise indicated. BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; mg, milligrams; MBP, mean blood pressure; MPO, myeloperoxidase; PA, physical activity; SBP, systolic blood pressure; SDI, systemic damage index; SLEDAI, systemic lupus erythematosus disease activity index; TNF-α, tumor necrosis factor alpha.

Table 2. Baseline heart rate variability (HRV) derived parameters of the study participants.

	All (n = 55)	Exercise (n = 26)	Control (n = 29)	p
	Median (IQR)	Median (IQR)	Median (IQR)	
SDNN, ms	19.59 (13.30–25.80)	15.87 (11.34–25.24)	21.42 (14.55–26.36)	0.376
RMSSD, ms	16.20 (11.55–25.07)	14.82 (8.86–24.86)	17.33 (13.61–26.75)	0.292
pNN50 (%)	0.57 (0.21–3.17)	0.42 (0.22–2.78)	0.70 (0.22–3.48)	0.715
LF, ms^2	164.12 (76.51–340.51)	157.23 (76.51–345.26)	198.18 (76.51–345.26)	0.607
HF, ms^2	97.20 (39.31–299.42)	93.65 (29.92–334.81)	100.37 (59.40–216.69)	0.607
LFHF	1.57 (0.93–2.81)	1.31 (0.83–3.29)	1.82 (1.08–2.55)	0.980
SD1, ms	11.48 (8.18–17.75)	10.49 (6.27–17.60)	12.27 (9.64–17.60)	0.292
SD2, ms	25.30 (15.54–30.46)	20.86 (18.28–30.42)	25.80 (18.29–30.42)	0.423
SampEn, au	1.70 (1.55–1.83)	1.70 (1.60–1.82)	1.70 (1.51–1.83)	0.692

Values are the median (IQR, interquartile range). HF, high frequency power in absolute value; LF, low frequency power in absolute value; pNN50, percentage of successive normal sinus RR intervals more than 50 ms; RMSSD, root mean square successive difference; SampEn, sample entropy; ms. milliseconds: SD1, standard deviation—poincaré plot crosswise; SD2, standard deviation—poincaré plot lengthwise; SDNN, standard deviation of NN intervals.

3.1. Associations of HRV with Inflammatory, Oxidative Stress Markers, and PROs (Aim 1)

The raw association of the HRV parameters with inflammatory markers and PROs is presented in abbreviated form in Table 3 (see Table S1 and Figure S1 for more details). SampEn was inversely correlated with hsCRP and MPO (r = −0.35, $p < 0.01$ and r = −0.32, $p < 0.05$, respectively). LFHF ratio was positively correlated with IL-6 (r = 0.32, $p < 0.05$). There was no association of any time-domain derived parameter with inflammatory markers. Regarding PROs, LFHF ratio was positively correlated with the Physical Fatigue dimension of the MFI (r = 0.30, $p < 0.05$). There were no other significant correlations.

Table 3. Spearman's correlations between HRV derived parameters, inflammatory markers, and PROs (n = 55).

	hsCRP	IL-6	TNF-α	MPO	SLEDAI	SDI	PSS	BDI	MFI-General Fatigue	MFI-Physical Fatigue	MFI-Reduce Activity	MFI-Reduce Motivation	MFI-Mental Fatigue	SF-36 Physical Component	SF-36 Mental Component
SDNN	−0.05	−0.11	−0.21	0.04	−0.21	−0.14	0.16	−0.11	0.05	−0.14	−0.10	−0.08	−0.06	−0.03	−0.01
RMSSD	−0.09	−0.14	−0.17	−0.01	−0.19	−0.03	0.04	−0.04	0.06	−0.09	0.03	0.03	0.04	0.05	−0.05
pNN50	−0.06	−0.14	−0.14	0.05	−0.09	−0.06	0.16	−0.06	0.10	−0.09	0.05	−0.02	0.04	0.07	−0.04
LF	−0.03	−0.08	−0.23	−0.08	−0.16	−0.17	0.17	−0.13	0.10	−0.08	−0.10	−0.13	−0.05	−0.03	0.01
HF	−0.07	−0.20	−0.23	−0.08	−0.25	−0.15	0.05	−0.14	−0.05	−0.25	−0.13	−0.03	−0.03	0.03	−0.07
LFHF	0.05	0.32 *	0.17	0.20	0.17	0.03	0.08	0.12	0.14	0.30 *	−0.13	−0.05	−0.05	−0.11	0.17
SD1	−0.09	−0.14	−0.17	−0.01	−0.19	−0.03	0.04	−0.04	0.06	−0.09	−0.03	0.04	0.04	0.05	−0.05
SD2	−0.03	−0.09	−0.21	0.09	−0.20	−0.17	0.18	−0.14	0.06	−0.14	0.03	−0.09	−0.09	−0.05	0.00
SampEn	−0.35 **	−0.16	−0.16	−0.32 *	−0.03	−0.05	−0.19	0.15	0.05	0.04	−0.12	0.23	0.23	0.14	0.14

Notes: * $p < 0.05$; ** $p < 0.01$. BDI, Beck depression inventory; HF, high frequency power; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; LF, low frequency power; MFI, multidimension fatigue inventory; MPO, myeloperoxidase; pNN50, percentage of successive normal sinus RR intervals more than 50 ms; PSS, perceived stress scale; RMSSD, root mean square successive difference; SampEn, sample entropy; ms. milliseconds; SD1, standard deviation—poincaré plot crosswise; SD2, standard deviation—poincaré plot lengthwise; SDI, systemic damage index; SDNN, standard deviation of NN intervals; SF-36, short form health survey; SLEDAI, systemic lupus erythematosus disease activity index; TNF-α, tumor necrosis factor alpha.

The quantile regression models evaluating the association between HRV parameters, inflammatory markers, and PROs are presented in Table 4 adjusted by age, heart rate and disease duration. Only significant correlations were explored. LFHF ratio was associated with the physical fatigue dimension of the MFI (unstandardized coefficient (B) = 0.89; 95% confidence interval (CI) 0.15 to 1.62; $p = 0.019$) but there was no association with IL-6 (B = 0.48; 95% CI −0.31 to 1.27; $p > 0.05$). SampEn was inversely associated with hsCRP (B = −4.82; 95% CI −8.62 to −1.03; $p = 0.014$) and MPO (B = −106.51; 95% CI −182.54 to −30.50; $p = 0.007$). We did not find associations of HRV derived parameters with SLEDAI or SDI.

Table 4. Quantile regression analysis evaluating the association between different components of heart rate variability, inflammatory markers, and PROs in women with systemic lupus erythematosus ($n = 55$).

	B	SE	CI 95%		p
LFHF					
IL-6	0.48	0.39	−0.31	1.27	0.231
MFI-Physical Fatigue	0.89	0.37	0.15	1.62	0.019
SampEn					
hsCRP	−4.82	1.89	−8.62	−1.03	0.014
MPO	−106.51	37.85	−182.54	−30.50	0.007

hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6, LFHF, low frequency to high frequency ratio; MFI, multidimensional fatigue inventory; MPO, myeloperoxidase; SampEn, sample entropy; adjusted by age, heart rate and disease duration.

3.2. Effects of the Exercise Intervention on HRV-Derived Parameters (Aim 2)

The HRV signals from 5 participants from the control group were excluded due to excessive interpolated beats (>5%). Full HRV data at baseline and week 12 was obtained from 44 participants (21 exercise and 23 control). The primary analyses revealed no significant between-group differences between changes in HRV derived parameters (Table 5) in all domains, and these results were consistent in sensitivity analyses in which participants from the exercise group were included only when attendance of the exercise sessions was ≥90% (Table S2) and in BOCF analyses (Table S3).

Table 5. Per-protocol (primary) analyses assessing the effects of 12-week progressive aerobic exercise on HRV derived parameters in women with systemic lupus erythematosus (participants in the exercise group were included if attendance was ≥75%).

Change from Baseline at Week 12	Exercise ($n = 21$)	Control ($n = 23$)	Median Difference (95% CI)	p
	Median (SE)	Median (SE)		
SDNN	2.70 (2.36)	4.18 (2.91)	−1.48 (−12.00 to 6.37)	0.539
RMSSD	2.03 (3.52)	2.75 (4.33)	−0.72 (−12.05 to 9.74)	0.831
pNN50	0.21 (1.93)	0.28 (2.96)	−0.07 (−5.87 to 6.16)	0.960
LF (ms)	2.50 (81.86)	−22.31 (57.00)	24.81 (−142.07 to 169.88)	0.858
HF (ms)	4.76 (98.31)	6.91 (73.40)	−2.15 (−140.79 to 129.24)	0.932
LFHF	−0.12 (1.30)	0.05 (1.01)	−0.17 (−01.45 to 2.30)	0.652
SD1	1.44 (2.49)	1.95 (3.07)	−0.51 (−8.53 to 6.90)	0.831
SD2	3.10 (2.51)	5.22 (3.04)	−2.45 (−11.91 to 6.33)	0.539
SampEn	0.02 (0.07)	0.01 (0.08)	0.01 (−0.31 to 0.23)	0.741

The analyses were adjusted for baseline values, mean heart rate, and age. Values are the median (standard error). HF, high frequency power in absolute value; LF, low frequency power in absolute value; pNN50, percentage of successive normal sinus RR intervals more than 50 ms; RMSSD, root mean square successive difference; SampEn, sample entropy; ms. milliseconds; SD1, standard deviation—poincaré plot crosswise; SD2, standard deviation—poincaré plot lengthwise; SDNN, standard deviation of NN intervals.

Regarding responders, non-responders, and adverse responders, in the control group we observed significant differences in RMSSD between responders against non-responders and adverse responders ($p = 0.37$ and $p = 0.002$, respectively) and between non-responder and adverse responder ($p = 0.37$). In the

exercise group, there was a significant difference in RMSSD between responders and non-responders ($p = 0.001$) Figure 2.

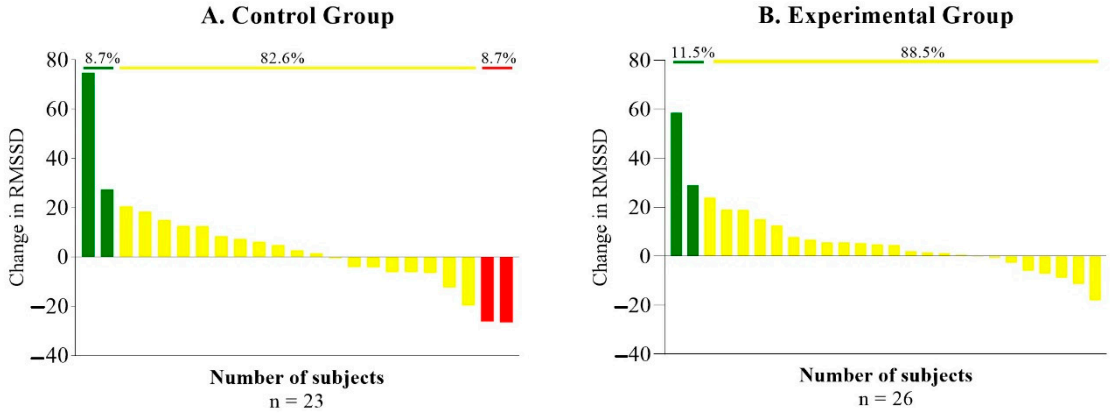

Figure 2. Responders (green line), non-responders (yellow line), and adverse responders (red line) on RMSSD endpoints. RMSSD; root mean square successive difference.

4. Discussion

Our cross-sectional analyses revealed that, among the studied HRV-related variables, sample entropy was inversely associated with hsCRP and MPO and that low frequency and high frequency ratio was directly associated with physical fatigue in women with SLE. The secondary analyses of our clinical trial revealed that 12 weeks of progressive aerobic training did not change HRV-derived parameters in comparison to a control group of SLE patients who received recommendations for a healthy lifestyle.

Imbalance in the sympathetic and parasympathetic divisions of the ANS are associated with increased risk of inflammation [8] which could lead to higher cardiovascular risk [41]. In our study, we observed that higher values of hsCRP and MPO were associated with decreased regularity (SampleEn) but not with any other HRV parameter. Elevated hsCRP and MPO levels have been shown to be increased in this population and associated with inflammation [42]. In addition, MPO and hsCRP accurately predicted cardiovascular mortality risk and risk assessment in coronary angiography patients [43]. Several inflammatory pathways seem to be involved in the relationship with HRV. One of the possible explanations could be changes in the activity of the vagal system that modulates the inflammatory response significantly, which can be blocked or enhanced by transmitter substances (i.e., noradrenaline) or by pro-inflammatory cytokines [44]. A decrease in regularity (SampleEn) could be related to the idea proposed by Goldberger et al. [45], in which nonlinear complexity breaks down with aging and disease reducing the individual's adaptive capabilities. We also found a positive correlation between HRV and IL-6 but not with TNF- α. After adjusting the quantile regression model by age, heart rate, and disease duration we did not find an association between HRV and IL-6. However, it should be noted that both inflammatory markers and ANS have a circadian variation and that the explanatory power of correlating HRV activity and inflammation may be limited by the time frame of the analysis [46]. Given that our HRV data were collected in the afternoon and once at baseline and after the intervention, this could affect our conclusions about these associations.

Regarding PROs, we did not find in our sample associations between HRV and depression, stress or health-related quality of life as previously reported [47]. However, we observed an association between HRV and physical fatigue, as previous findings in other illnesses such as breast cancer [48]. According to Pagani et al. [49], slow autonomic responses to environmental demands or an imbalance between sympathetic and parasympathetic branches may contribute to reduced physical activity, and increased fatigue. It is important to note that fatigue improvements have been described in SLE independently of changes in fitness levels and that fatigue is a multifaceted phenomenon that might be affected by different peripheral and central mechanisms [50]. However, we have observed reductions

in general fatigue after our exercise intervention with cardiorespiratory fitness as a mediator [20], which could be related to a better conditioning in these patients.

To the best of our knowledge, no prior research has evaluated the effects of aerobic exercise on HRV in women with SLE. Yorgun et al. [28] studied HRV during 24 h in SLE patients and controls after an exercise stress test finding a higher QT dispersion, along the lines of previous work by Rivera-López et al. [51], and impairments in the autonomic cardiac function in SLE patients compared to controls. A similar study was performed by Bienias et al. [29] controlling the effect of beta-blockers in one of the groups, concluding that impaired heart rate recovery was associated with disease duration and beta-blocker treatment. Our results showed no differences in HRV between groups after an aerobic exercise program. However, as shown in Figure 2, there are some participants that improved their RMSDD after the intervention and, compared to the control group, all participants slightly improved as well even if these differences were not significant. It is important to note that our sample size is small, and we had dropout patients in both groups, although our results were consistent across different sensitivity analyses (Tables S2 and S3). This show that, although our intervention improved CRF in these patients [19], it was not as effective in other secondary parameters such as HRV. Therefore, a more effective or intense intervention program could have had improvements in HRV and other physiological parameters. In fact, HRV as a tool to guide daily training has shown to be superior (at increasing fitness and exercise performance) to other training conventional methods [52].

This study has limitations. First, since our sample size was relatively small, and this study is exploratory and hypotheses-generating in nature, we did not perform corrections for multiple comparisons, which would likely eliminate all the observed associations. Future studies with larger samples should confirm or contrast these findings. Second, only women with mild/inactive disease were included. Therefore, the results are not generalizable to men or even women with medium–high disease. Third, this study comes from the secondary analysis of a non-randomized design, and, despite statistical adjustment, residual confounding cannot be discarded. Four, we did not have a group of healthy subjects performing the exercise program, which would have enabled us to compare the results. However, the study also has some strengths that must be highlighted. First, to our knowledge this is the most comprehensive study done about HRV in women with SLE. Second, we have shown how everyone responded individually to the exercise program based on their HRV.

5. Conclusions

Our study suggests that increases in hsCRP and MPO are related to decreased regularity, and that physical fatigue seems to be related to HRV in women with SLE. Additionally, 12 weeks of progressive aerobic training (75 min twice a week) did not produce any changes in HRV derived parameters compared to a usual care control group in women with mild/inactive disease. Future clinical trials with larger sample sizes and a different training program or with higher intensity are needed to enhance our understanding on how HRV could help monitor inflammation in this population; and how they respond to an exercise intervention using HRV as a guideline to prescribe training on a day-to-day basis.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/24/9501/s1, Figure S1: Correlations between HRV derived parameters and inflammatory markers ($n = 55$), Table S1: Spearman's correlations between HRV derived parameters, inflammatory markers, and PROs ($n = 55$), Table S2: Sensitivity analyses assessing the effects of 12-week progressive aerobic exercise on HRV derived parameters in women with systemic lupus erythematosus (participants in the exercise group were included if attendance ≥90%), Table S3: Sensitivity analyses using baseline-observation carried forward imputation assessing the effects of 12-week progressive aerobic exercise on HRV derived parameters in women with systemic lupus erythematosus.

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HEART RATE VARIABILITY IN CLINICAL POPULATIONS: METHODOLOGICAL ASPECTS AND EFFECTS OF EXERCISE INTERVENTIONS

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