Diploma Thesis

Two-Year Bi-Directional Associations Between Central Adiposity and Heart Rate Variability Among Pre-Adolescents

submitted by

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Keutschach, 18.01.2021

Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis I followed the "Guidelines of the Medical University of Graz on Good Scientific Practice".

Keutschach, 18.01.2021 *Lisa Maria Käfer, eh*

Preface

During my studies at the Medical University of Graz I established the foundation to appreciate the complexity of the human body and its physiological processes. The unsolved mystery of the autonomic nervous system and its assumed influence in nearly every homeostatic process going on within the body, has fascinated me since my freshman year. I am passionate about its potential to elucidate pathophysiological processes of adverse outcomes and to counteract diseases before they become chronic.

During my term abroad in Tromsø, Norway, I was able to emphasis my studies on public health. It was back then that I understood the importance of public health research and interventions. In the EC in Cape Town, South Africa, I learned to appreciate the value of communication. Research findings and public health strategies are worth nothing when people do not feel the need to get involved. In a rural hospital in St. Anthony, Canada, I realised that interventions need to be tailored to the environment where you plan to implement them. In Sydney and Wollongong, Australia, I had the pleasure to work with different professions and began to appreciate the value of a multidisciplinary team and different approaches. On the psychiatry ward in Heidelberg, Germany, I became aware of the fact that health is much more than the mere absence of disease. Back then, I became an advocate of mental health as it is fundamental to our perceived quality of life. In the children's hospital of Zurich, Switzerland, I understood that there is so much to learn from children. I began to appreciate their adaptability, resilience and potential to create our future. And eventually, during this very intense academic year in Montreal, Canada, I realised that focusing on the health of our offspring can lead the way to a healthier society.

I am committed to contribute to the development of diagnostic tools to help counteract excessive weight gains in children as obesity is much more than a simple physical makeup. The overarching goal is to convince children and their parents that it is worth investigating time and effort in their health before they are forced to make time for their illness.

In the course of my medical studies I travelled a lot to discover new perspectives and understand the bigger picture. The one thing I have learned from experiences and encounters along the way is to always *listen to your heart*. I therefore decided to devote my thesis to investigate in what we can learn from listening to our hearts.

Acknowledgements

I wish to thank all the people whose support was a milestone in the completion of this project.

I would like to express my sincere appreciation to my supervisor and mentor, Dr. Tracie A. Barnett, who has the substance of a genius. Somehow she always manages to ask the right questions. Her invaluable and tireless guidance proved monumental towards the success of this study. When the pandemic hit hard and I was a foreigner in a new country, she was always there for me and offered support that went far beyond the professional level. Her commitment is inspiring and there is so much more to learn from her.

Heart-felt thanks to the QUALIY research team led by Dr. Mélanie Henderson for their fruitful discussions and precious input over this academic year. I owe special thanks to Dr. Paul Poirier whose insight and expertise steered me through this research and allowed my studies to go the extra mile.

I wish to express my gratitude to Ao.Univ.-Prof. Mag. Dr. Dr. Erwin Petek, the Dean of Study Affairs, at the Medical University of Graz, and Dr.med.univ. Ingrid Lafer, who supported my academic endeavours and without whom this project would not have been realised. I would like to recognise the indispensable assistance of the international office team of the Medical University of Graz who gave me the opportunity and financial support to facilitate this research exchange.

From the bottom of my heart I would like to say big thank you to my friends and family without whom I would not have been able to complete this research, and without whom I would not have made it through my medical studies. To my dear friend, Johannes Blohberger, who has always reassured me and averted imminent mental breakdowns. To Katrin and Florian Käfer who have provided moral and emotional support throughout my life. To my grandfathers, Josef Käfer and Josef Woath, who I know, have struggled whenever I left home to see the world but who have provided me a home I still love to come back to. To my aunt, Brigitte Käfer, who has always encouraged me. To my aunt, Claudia Woath, who has always believed in me and tirelessly listened to my worries. And my biggest thanks to my parents, Sabine and Wolfgang Käfer, for all the support they have shown me along my way. Even when the road got tough, they never gave me any idea that I could not do whatever I wanted to do or be whomever I wanted to be.

Table of Content

Abbreviations

AndGyn	Android-to-Gynoid-Ratio
ANS	autonomic nervous system
BMI	body mass index
CDC	Centre for Disease Control and Prevention
CHU	Centre Hospitalier Universitaire
DXA	dual energy X-ray absorptiometry
HF	high frequencies (0.015-0.4 Hz)
HRV	heart rate variability
IBI	inter-beat interval (i.e. time period between two successive heartbeats)
IUCPQ	Institut universitaire de cardiologie et de pneumologie de Québec
LF	low frequencies (0.04-0.15 Hz)
MVPA	moderate to vigorous physical activity (min/day)
nu	normalized unit
QUALITY	Quebec Adipose and Lifestyle Investigation in Youth study
pNN50	proportion of RR intervals that differ by more than 50 ms from the previous interval (%)
PNS	parasympathetic nervous system
RMSSD	square root of the mean of the differences of the successive RR intervals (ms)
RSA	respiratory sinus arrhythmia
SDNN	standard deviation of the RR intervals (ms)
SNS	sympathetic nervous system
VLF	very low frequencies (0.0033-0.04 Hz)
WHO	World Health Organization
WHtR	Waist-to-Height-Ratio

Due to the large number of tables, we decided to enhance readability by colouring significant findings. Throughout this scientific treatise, statistically significant results displayed in tables are highlighted with a colour coding as follows:

- p values < 0.01 are coloured in dark grey,
- p values <0.05 are indicated by medium grey,
- p values < 0.1 are marked by a light grey colouring.

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Zusammenfassung

Kernfrage und Zielsetzung: Um besser zu verstehen, wie Beeinträchtigungen der Herzfrequenzvariabilität und die Entwicklung von pädiatrischem Übergewicht zusammenhängen, zielt diese Studie darauf ab, bidirektionale prospektive Assoziationen zwischen Stammfettsucht und Herzfrequenzvariabilitätsindizes zu untersuchen, die jeweils im Alter von 8-10 Jahren bzw. 10-12 Jahren erhoben wurden. Mit Hilfe eines Cross-Lagged-Panel-Designs beabsichtigen wir zu eruieren, inwieweit Fettleibigkeit die Ursache oder die Konsequenz von Veränderungen im kardialen autonomen Nervensystem ist.

Methoden: Die Daten stammen aus einer Kohortenstudie, bestehend aus Kindern mit erhöhtem Risiko für Fettleibigkeit. Die aktuelle Studie umfasst 406 Kinder, darunter sowohl Buben (n = 229) als auch Mädchen (n = 177), die aus Schulen in Quebec, Kanada, rekrutiert wurden. Zu Studienbeginn wurden 42% der Kinder im Alter von 8-10 Jahren (9,6 ± 0,9) als übergewichtig oder adipös eingestuft. Die Herzfrequenzvariabilität wurde mittels Kurzzeitmesssung erhoben; Parameter aus Zeit- und Frequenzbereichen wurden abgeleitet, die es ermöglichten, zwischen sympathischer und parasympathischer Aktivität zu differenzieren. Die Körperfettverteilung wurde mittels Dual-Röntgen-Absorptiometrie ermittelt und durch das Verhältnis zwischen androider und gynoider Fettmasse ausgedrückt. BMI z-score und Taille-zu-Größe-Verhältnis wurden in eigenständigen Modellen dargestellt, um deren klinische Relevanz zu ergründen. In bidirektionalen multiplen linearen Regressionsmodellen wurden relevante Einflussgrößen, wie Unterschiede im Körperfettanteil, Geschlecht, Alter, Sexualentwicklung und körperliche Aktivität berücksichtigt.

Ergebnisse: Positive Zusammenhänge zwischen Fettleibigkeit und LFnu und dem LF/HF-Verhältnis sowie negative Assoziationen zwischen Fettleibigkeit und HFnu wurden in beiden Wirkrichtungen beobachtet. Ergebnisse in Bezug auf LF waren inkonsistent. Kinder mit niedrigeren RMSSD- und pNN50-Werten im Alter von 8-10 Jahren zeigten eine signifikant höhere Fettleibigkeit im Alter von 10-12 Jahren. Die Ergebnisse waren über alle Messgrößen der Fettleibigkeit hinweg beständig.

Schlussfolgerung: Ein konsistentes sympathovagales Ungleichgewicht im Sinne einer sympathischen Dominanz in beide Wirkrichtungen untermauert die Hypothese, dass das autonome Nervensystem sowohl einen gewissen Beitrag an der Entstehung als auch an der Unterhaltung von Fettleibigkeit leistet. Kinder, die niedrigere parasympathisch gesteuerte Zeitbereichs-Parameter (d.h. RMSSD und pNN50) bei Studienbeginn aufwiesen, zeigten zwei Jahre später ein höheres Ausmaß an Fettleibigkeit, und hier insbesondere Stammfettsucht. Dies legt nahe, dass parasympathisch gesteuerte Herzfrequenzvariabilitätsindizes plausible Frühindikatoren für eine zukünftige Gewichtszunahme darstellen. Die Erkenntnisse unterstreichen das Potenzial der Überwachung der Herzfrequenzvariabilität als Risikobewertungsinstrument für pädiatrische Fettleibigkeit.

Abstract

Objective: In order to better understand how impairments in heart rate variability and the development of pediatric obesity are linked, this study investigated bi-directional prospective associations between central adiposity and heart rate variability indices at age 8-10 years and 10-12 years. By employing a cross-lagged panel design, we intended to examine the extent to which obesity is the cause or the consequence of changes in the cardiac autonomic nervous system.

Methods: Data originate from a cohort study on the development of metabolic disease in children at risk for obesity The present study comprises 406 children, including both boys (n = 229) and girls (n = 177) recruited from schools in Quebec, Canada. At baseline, 42% of the children aged 8-10 years (9.6 ± 0.9) were considered overweight or obese. Short-term heart rate variability acquisition was performed; time- and frequency-domain parameters were derived allowing us to differentiate between sympathetic and parasympathetic activity. Body fat distribution was determined through dual-energy X-ray absorptiometry and expressed by the ratio between android and gynoid fat mass. BMI z-score and Waist-to-Height-Ratio were incorporated in separate models to help elucidate their clinical relevance. Bi-directional multiple linear regression models were adjusted for body fat, sex, age, sexual maturity, and physical activity.

Results: Positive associations between adiposity and LFnu and LF/HF-Ratio as well as negative associations between adiposity and HFnu were observed in either direction. Results in regards of LF were inconsistent. Lower levels of RMSSD and pNN50 at age 8-10 years were significantly associated with greater adiposity at age 10-12 years. Findings were consistent across all adiposity measures.

Conclusion: A consistent sympathovagal imbalance in terms of a sympathetic predominance in either direction reinforces the idea of the autonomic nervous system being a meaningful contributor to both the emergence and maintenance of obesity. Children who presented with lower parasympathetically-driven time-domain parameters (i.e. RMSSD and pNN50) at baseline, exhibited greater adiposity, particularly central fat, two years later, suggesting that heart rate variability parameters are a conceivable early sign of future weight gain. These findings highlight the potential of heart rate variability surveillance as a risk assessment tool for pediatric obesity.

1 Introduction

Obesity has both direct and indirect effects on premature mortality and is considered a major risk factor for non-communicable diseases such as type 2 diabetes, cardiovascular diseases and musculoskeletal disorders (1). Many of the contributing factors are cumulative, a particularly worrisome realization given that the onset of obesity tends to be at an increasingly early age (1). Moreover, tracking of excess weight into adulthood is particularly evident in children with severe obesity and a strong family history (2, 3). As a consequence, paediatric obesity commonly leads to a prolonged exposure to obesity going hand in hand with increased morbidity and mortality in later life (4-6). On these grounds, paediatric obesity has emerged as one of the most pressing public health concerns worldwide, placing an enormous burden on future generations and on the health care system.

Compared to acutely threatening diseases such as infections and cancer, obesity may be viewed as a chronic condition that gradually impairs various processes in the body, leading to systemic alterations such as inflammation and toxicity. It is challenging to identify risk factors whose impacts are only observable years or even decades later. Moreover, the incremental effects of sustained obesity dampen any sense of urgency and minimize the perceived severity (7). At the same time, the slow development of obesity offers the possibility to recognise pathophysiological changes at an early stage, to observe them objectively and to develop efficient interventions to counteract.

In 2007, the UK Foresight (8) created an illustrative *obesity system map* (enclosed in the supplementary material) to visualise the complex systemic structure of obesity and its broad range of influencing factors and interactions. They defined 108 determinants, which represent a densely interwoven set of interdependencies in 7 thematic clusters. Energy balance is represented at the heart of the UK Foresight *obesity system map*. Technically speaking, obesity is the consequence of sustained energy imbalance with energy intake exceeding energy expenditure. It has become apparent over the past decade that the autonomic nervous system (ANS) plays a crucial role in regulating the energy balance (9). With its two branches, the sympathetic and the parasympathetic nervous system, the ANS directly influences both energy expenditure and energy intake. The ANS also exerts additional influence on other key variables such as appetite, psychological ambivalence

and dietary habits. In fact, it has even been proposed that alterations of the ANS may be the underlying pathway between obesity and adverse cardiovascular outcomes (10, 11). In general, the two divisions act antagonistically to maintain a dynamic homeostasis of vital functions that allows the body to adjust to physiological or physical fluctuations of daily life (12). In the cardiovascular system, the dynamic interplay leads to measurable fluctuations between intervals of consecutive heart beats, commonly known as heart rate variability (HRV) (13). Time- and frequency-domain analyses allow us to quantify and differentiate between sympathetic and parasympathetic cardiovascular activity (14). As a result, HRV has been widely studies as reliable marker of autonomic modulation in both adults (15) and children (16, 17).

Various studies in adults provide evidence that shifts in the dynamic cardiac ANS balance are associated with changes in energy balance and eating behaviours highlighting the key function of the ANS in the development of obesity. Low sympathetic activity is associated with excess weight gain (18-20); high sympathetic activity, on the other hand, seems to promote the maintenance of obesity (21-23). Low parasympathetic activity reduces the feeling of satiety and appetite control and thus leads to excessive food intake (24, 25). Reduced parasympathetic activity has also been characterised by increased impulsivity and decreased self-control (26). Accordingly, reduced parasympathetic activity may reinforce pathological eating behaviours such as binge eating and impede adherence to weight loss interventions (27). At the same time, evidence suggests that blunted parasympathetic activity in persons with obesity improves with weight loss (28-30) and after bariatric surgeries (31).

However, associations between cardiac autonomic functions and obesity are not only observed in adulthood. Children with obesity also demonstrate a measurable disruption of their normal ANS maturation. Compared to normal-weight peers, children with obesity appear to exhibit a sympathovagal imbalance, in terms of a sympathetic predominance, paired with lower overall HRV (32-34). Recently, HRV in children has gained attention as low parasympathetic activity has been associated with paediatric obesity (35-37) and cardiovascular morbidity (38, 39) and mortality (40-42). Low parasympathetic activity was also observed to be associated with higher food cravings and reduced food-related self-regulatory capacity in adolescents (26, 27). However, findings with respect to sympathetic activity are inconsistent, leading Rabbia et al. (43) and Nagai et al. (44) to postulate that the discrepant findings may be related to the duration of obesity.

While a relationship between paediatric obesity and HRV patterns has been established, the existing evidence comprises only cross-sectional studies in obese albeit healthy children. Synthesizing findings is challenging due to substantial heterogeneity in methodology and population characteristics. Hence the establishment of age-specific reference values and unfavourable HRV patterns is intricate. Nevertheless, fluctuating autonomic imbalances seem to be dependent on the duration of obesity. However, the temporality with respect to the onset of obesity, that is, the extent to which obesity is the cause or the consequence of changes in the ANS, remains unclear. Longitudinal designs are needed to investigate this relationship more thoroughly and in particular to understand how HRV changes over time and in relation to excess weight gain.

Form a physiological point of view both directions are plausible. In general, the majority of studies are based on the assumption that obesity impacts HRV. However, changes in HRV prior to the onset of obesity has never been looked and represent an intriguing concept. As the ANS plays a crucial role in the regulation of energy balance and eating behaviour, it is a plausible contributor and potentially a cause of both the emergence and maintenance of obesity. To date, HRV from cross-sectional studies established a solid understanding of the pathogenesis of abnormal ANS imbalances in children with obesity. Our aim is to contribute additional insight by investigating 2-year prospective associations between body weight parameters and the autonomic balance as measured by HRV.

With two data collections two years apart, we aim to examine the two possible cross-lagged relationships between the age of 8-10 (visit 1) and 10-12 (visit 2) (Figure 1.1).

i. It is believed that obesity impacts HRV and numerous studies confirmed this relation. We will check this broadly accepted assumption by investigating in the associations between adiposity at the age 8-10 years and HRV parameters at the age 10-12 years (cross-lagged relation 1).
ii. Existing literature also provides evidence making the ANS a plausible contributor to the emergence of obesity. Our study design will allow us to examine reverse relations to investigate the impact of HRV parameters at age 8-10 years on adiposity measures at age 10-12 years (cross-lagged relation 2). Up to now, potential ANS changes prior to excess weight gain have remained entirely unexplored. In previous studies, fluctuations in HRV parameters in normal-weight children were usually interpreted as a physiological range. By linking HRV values

to adiposity measures two years later, we endeavour to unmask HRV patterns that are indicative of future excess weight gain.

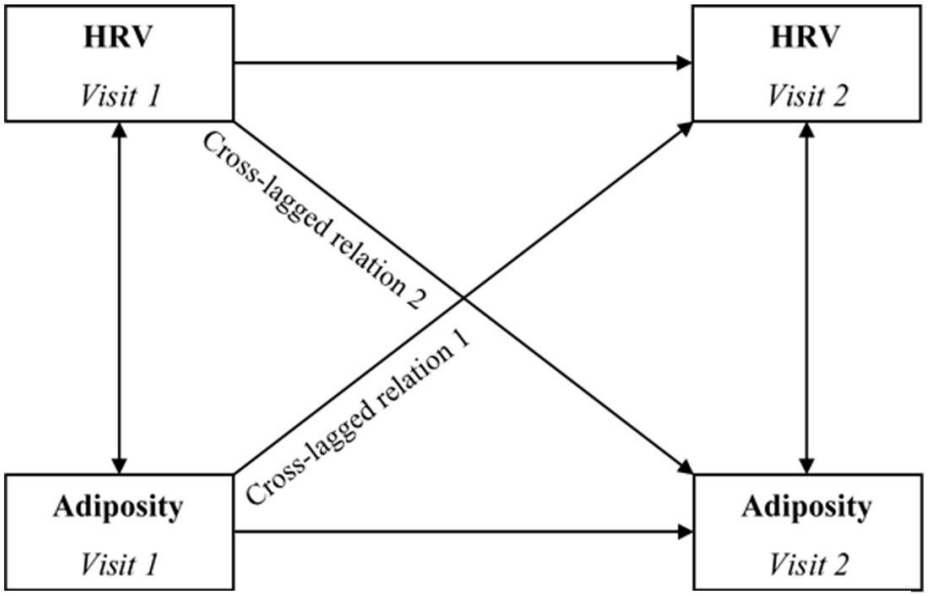


Figure 1.1 Cross-Lagged Panel Model: Our cross-lagged relation 1 hypothesizes that central adiposity at age 8-10 years leads to alterations in HRV parameters at age 10-12 years. Compared to this, our cross-lagged relation 2 suggests that HRV parameters at age 8-10 years lead to the development of central adiposity at age 10-12 years.

The scientific background and fundamentals of both HRV and adiposity assessment techniques will be discussed in the following sections.

1.1 Assessment of Heart Rate Variability

HRV is defined as the variation between successive heartbeats. On ECG recordings, the interval between two R wave peaks of the QRS complex (i.e. RR-interval) resembles the time period between two heartbeats. Hence differences in the RR intervals reflect inter-beat oscillations and can be utilized to derive HRV (45, 46).

Moreover, the standards set by Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology (14), provide guidance on time- and frequency-domain analysis, which allow us to differentiate between sympathetic and parasympathetic cardiovascular activity.

Pioneering research studying selective pharmaceutical blockage established the basis of today's distinction between sympathetic and parasympathetic contribution to autonomic control (47-49). The blockage of a single division provides insight in the functional extent of the unblocked branch. Although pharmaceutical blockages might be the most accurate approach to differentiate between the two branches, it is invasive, labour intense and associated with risks. The limited practicability makes it even harder to justify its application in children. Consequently, blockage approaches have not been applied in clinical practice and large scale studies. At the same time, various findings linking either increased sympathetic or reduced parasympathetic activity with adverse outcomes point to a need for objective and cost-effective measurement techniques. When it comes to cardiac autonomic activity, insights about the origin of different HRV parameters paired with their non-invasive and user-friendly acquisition, have been a major incentive for its development and practical use.

1.1.1 Physiological Basis of Heart Rate Variability

Under physiological conditions, the sinoatrial node is the exclusive pacemaker regulating heart rate (i.e. chronotropic effects). The sinoatrial node is innervated by the ANS, and both parasympathetic and sympathetic efferents elicit opposing chronotropic effects. Notably, these effects are not symmetrical as the activation of the two branches utilizes different biochemical pathways (50, 51).

Parasympathetic activation slows heart rate. The PNS releases acetylcholine which is characterized by a short latency of effect (<1 second) and a rapid metabolism and clearance (46, 52). This allows the PNS to exert cardiac autonomic control on a beat-to-beat basis.

Counteractively, sympathetic activation accelerates heart rate. Sympathetic chronotropic effects are initiated by the synaptic release of noradrenaline. Compared to acetylcholine, noradrenaline is resorbed and metabolized relatively slowly causing a delay of effect of approximately 5 seconds (52). Despite the slower onset, sympathetic stimulation results in a longer duration of action compared to parasympathetic effects.

Due to these functional differences in neurotransmitters, the two opposing branches of the ANS operate at different frequencies and variation in heart rate (46). This physiological concept forms the basis for the allocation of HRV indices to either sympathetic or parasympathetic activity.

1.1.2 Heart Rate Variability Indices

Standardized recording and guidelines on the derivation of time- and frequency-domain parameters have been established by the Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology (14) to provide a consistent approach and nomenclature. In this section the most relevant indices are presented. Along with a description of their derivation their interpretability and evidence for their clinical importance is outlined below.

1.1.2.1 Time-Domain Indices

Perhaps the simplest and most intuitive indices are time-domain measures. On the downside, they are susceptible to artefacts like supraventricular and ventricular beats. Careful pre-processing is required to remove extrasystolic beats and other inferences before analysis (53).

In general, time-domain indices quantify the amount of variability in inter-beat intervals (IBI). IBI is the time period between two successive heartbeats, sometimes also referred to as heart period (Figure 1.2). They can further be distinguished between RR intervals, which are IBIs between all successive heartbeats and normal-to-normal intervals (NN interval), which are only IBIs from which artifacts like ectopic beats have been removed (i.e. only heartbeats resulting from sinus node depolarization are included).

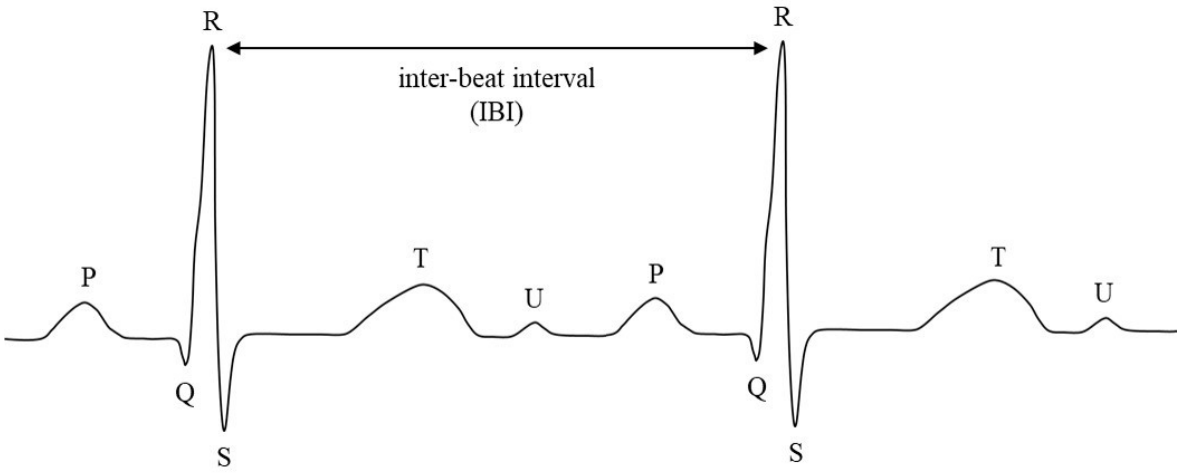


Figure 1.2 Standard ECG Components: In an ECG record, the P wave reflects atrial depolarization (i.e. atrial contraction) that initiates a heartbeat. The isoelectric PR segment represents the impulse conduction through the atrioventricular node leading to ventricular depolarization. Hence, the QRS complex reflects ventricular contraction. The isoelectric ST segment represents completed ventricular depolarization and the subsequent T wave reflects ventricular repolarization of contractile cells. The U wave is seen occasionally after the T wave, especially in children. Though its genesis remains elusive. Since the R waves shows the greatest amplitude within a heartbeat, it is usually used to derive cardiac chronotropic response. Inter-beat interval (IBI) is the time period between two successive heartbeats. Therefore IBIs represent the intervals between two consecutive R peaks. RR intervals are defined as intervals of all successive heartbeats, while NN intervals only comprise heartbeats resulting from sinus node depolarization (i.e. IBI from which artifacts like ectopic beats have been removed).

The Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology (14) described numerous time-domain indices including both statistical and geometric measures, but only the most common ones are presented herein. A detailed overview of all available parameters can be found elsewhere (54).

SDNN

Some indices are derived directly from the NN interval. The simplest and most common variable is the standard deviation of the NN interval (SDNN), and is typically measured in milliseconds. SDNN measures overall HRV; it is not appropriate to quantify change in SNS or PNS activity as both branches contribute to SDNN. SDNN is considered more accurate in long-term recordings. The Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology refer to SDNN as the "gold standard" for risk stratification in 24h recordings. SDNN has also been shown to predict both cardiovascular morbidity and mortality (55).

RMSSD and pNN50

Other indices are derived from differences between successive NN intervals, capturing beat-to-beat variability. Considering the faster kinetics of acetylcholine-mediated effects compared to those of noradrenaline discussed in section 1.1.1, it becomes apparent that the parasympathetic influence forms the basis for RMSSD and pNN50. Consequently, RMSSD and pNN50 are primary measures to estimate PNS activity. RMSSD is defined as the square root of the mean squared differences of successive NN intervals measured in milliseconds. First, each difference of successive NN intervals needs to be calculated and squared. The results are then averaged and the square root of the total is obtained. pNN50 describes the percentage of successive NN intervals that differ from each other by more than 50ms (Figure 1.3).

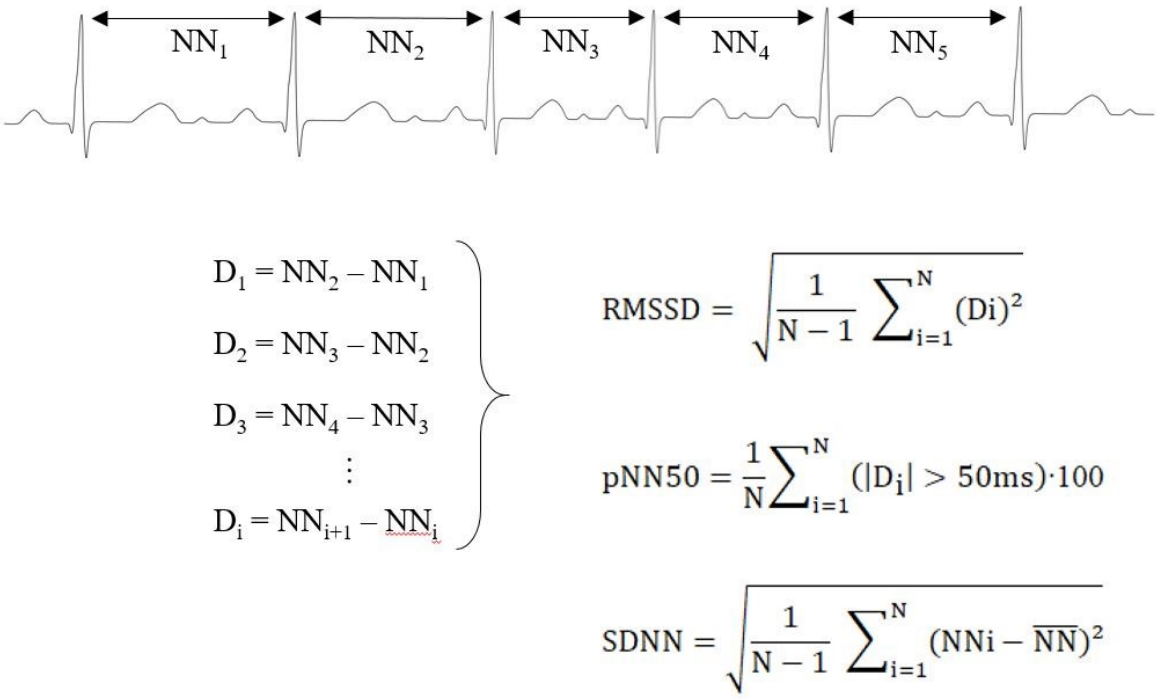


Figure 1.3 Time-Domain Indices: For the calculation of SDNN, the square root of the variance is measured. For the calculation of RMSSD and pNN50, the differences of successive NN intervals are obtained. To derive RMSSD, differences are squared, and averaged before the root square of the total is calculated. To derive pNN50, the percentage of differences greater than 50ms is calculated.

1.1.2.2 Frequency-Domain Indices

Frequency-domain indices are derived from periodic oscillations of the heart rate signal. Transformation processes like Fast Fourier Transformation analysis or autoregressive modeling decompose signals in discrete frequencies and quantify their amplitudes (Figure 1.4). The distribution of power (i.e. variability) expressed by a function of frequencies varies in relation to cardiac autonomic alterations. In 1966, the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (14) classified four distinguishable entities, providing standardized assessment of frequency-domain indices: ultra-low-frequency (ULF), very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF); all measured in milliseconds squared.

ULF

The lowest detectible frequencies are ultra-low-frequencies (≤ 0.003 Hz) and constitute of fluctuations of heart rate with a period from 5 minutes to 24 hours. Because of this it can only be assessed in 24h recordings (56). The long oscillation periods may implicate associations with slow-acting physiological processes and circadian rhythms (55).

VLF

Very-low frequencies comprise rhythms with periods between 25 and 300 seconds and therefore require at least 5 minutes of recordings. In 24h ECGs, VLF ranges between 0.003 and 0.04 Hz. However, in short-term recordings, it includes all frequencies ≤ 0.04 Hz because there is no defined ULF range. Although VLF can be assessed in short-term recordings, most findings related to VLF are only apparent in 24h observations. Recent evidence suggests that VLF is pivotal to health. 24h VLF correlates with inflammation markers (57) and while all 24h HRV parameters are associated with adverse outcomes and mortality, 24h VLF appears to be the strongest predictor (58-60). VLF has also been associated with thermoregulation (61) and kidney function (62). Parasympathetic blockage results in an almost complete abolishment of VLF while sympathetic blockage does not affect its power at all (63). This might indicate PNS contribution. However, VLF amplitude and oscillations also appear to be influenced by the SNS (55).

95% of the total HRV power comprises ULF and VLF components (64). Yet their physiological correlates are only vaguely understood.

LF

Low-frequencies (0.04-0.15 Hz) include rhythms with periods between 7 and 55 seconds. LF was previously called the baroreceptor band because it resembles fluctuations related to the regulation of blood pressure and vasomotor tone. Oscillations in the vasomotor tone, so called arterial Mayer waves, occur in synchrony with LF components (65, 66). These arterial Mayer waves are substantially attenuated or even completely eliminated by alpha adrenergic (i.e. SNS) blockage (52). Researchers therefore attributed arterial Mayer waves and LF oscillations to mere sympathetic modulation (67, 68). However, the exclusive sympathetic origin of both Mayer waves and LF components has been challenged by many (52, 69-71). For example, atropine administration (i.e. PNS blockage) reduced LF by 84%, clearly demonstrating PNS involvement (72). Some authors even suggest that all frequency-domain parameters are modulated by the PNS only (63, 71).

In 1981, Akselrod et al. (49) were the first to show that parasympathetic blockage eliminates HRV above 0.06 Hz and sympathetic blockage diminishes HRV around 0.04 Hz. They concluded that LF therefore reflects both SNS and PNS activity. Other researchers came to the same conclusion (73, 74) and over the years it became apparent that the SNS does not seem to produce oscillations above 0.10 Hz, whereas the PNS was observed to modulate rhythms down to 0.05 Hz (55).

Although there is ongoing debate about the origins of LF components, influences stemming from both ANS branches appear to be the most plausible. Notably, the SNS contribution of LF is fundamentally dependent on testing conditions (54). Therefore LF values should only be compared when measured under consistent settings.

HF

High frequencies (0.15-0.40 Hz) are also called respiratory band because they are affected by breathing from 9-24 bpm (55). Respiratory sinus arrhythmia (RSA) is a physiological rhythmic heart rate oscillation related to the respiratory frequency (75, 76). RSA is characterized by a shortening of the IBI with inspiration and a lengthening with expiration. In other words, the heart rate accelerates on inhales, and slows on exhales. Physiological mechanism causing RSA might include intrathoracic and arterial pressure alterations caused by breathing (52). The magnitude of RSA increases with increased tidal volume and decreased respiratory rate what might explain associations between HF and physical activity (75). Parasympathetic blockage virtually eliminates HF oscillations suggesting that

HF is mediated by the PNS only (49, 72). Parasympathetically-driven time-domain parameters such as RMSSD and pNN50 are highly correlated with HF and a reduction of all three of these is associated with increased morbidity (56, 77, 78).

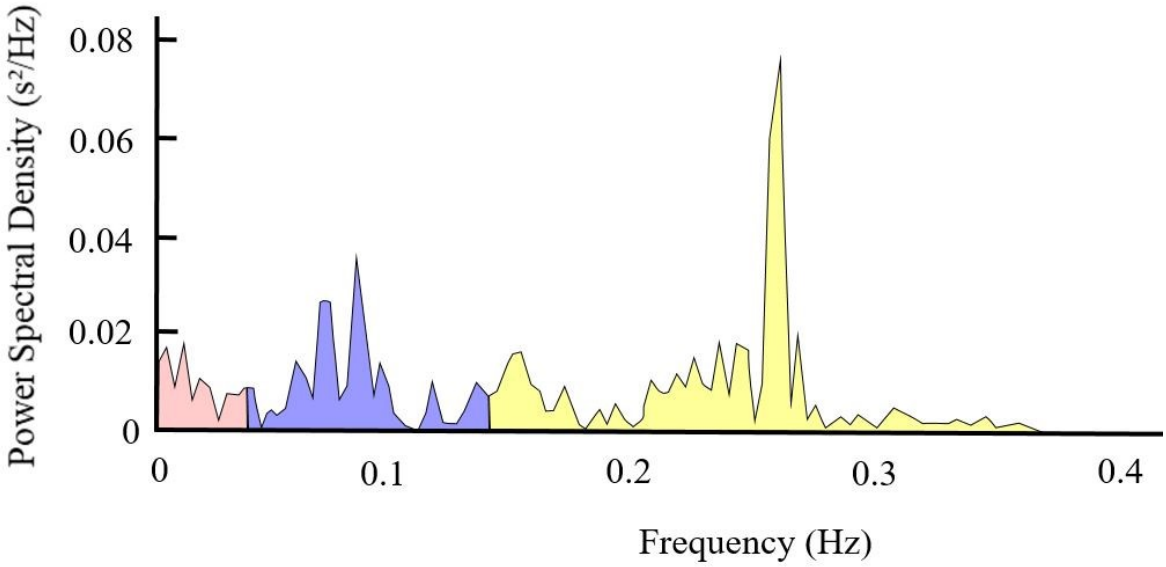


Figure 1.4 Short-Term Frequency-Domain Indices: Fast Fourier Transformation (FFT) decomposes signals in discrete frequencies and quantify their amplitudes (i.e. power spectral density). In short-term recordings, these frequencies are classified in three groups: very-low-frequency (VLF, ≤0.04 Hz; presented in light red), low-frequency (LF, 0.04 – 0.15 Hz, presented in light purple), and high-frequency (HF, 0.15 – 0.40 Hz, presented in light yellow).

LF/HF-Ratio and Normalized Units

Under the initial assumption that LF is generated by SNS activity and HF represents PNS activity, the ratio of LF to HF is considered to be an estimate of the relative balance between the two branches (67). According to this model, a low ratio indicates parasympathetic dominance. In contrast, high values reflect sympathetic supremacy. Similarly to vivid controversies regarding the origins of LF, the accuracy of the LF/HF-Ratio as a marker of sympathovagal balance is contested (55, 79).

Normalized units feature the relative value of either LF or HF in proportion to the sum of their power. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (14) approve normalized units as proxies for the balanced behaviour of SNS and PNS. Other authors support this view arguing that the computed normalized units are more robust to changes in total power (80-82). SNS activity usually decreases total HRV power, whereas PNS activity increases it.

Therefore absolute values might be misleading. Notably, this approach only holds under the premise of an inherent reciprocity of HRV; i.e. where LF and HF are inversely related, representing additive effects of SNS and PNS respectively. However, this approach is disputed, with some contesting the assumption of HRV as an independent continuum between SNS and PNS, arguing that this approach is merely a statistical artifact (70) or hat it neglects other regulatory mechanisms (71). Despite the ongoing controversy, both LF/HF-Ratio and normalized units are widely used as estimates for sympathovagal balance.

1.1.2.3 Non-Linear Measurements

While not considered for the current project, non-linear measurement methods may also be used to analyse HRV. They borrow techniques from fractal mathematics to analyse patterns of similarities of HRV over a given time period. A comprehensive explanation of these methods is provided elsewhere (54, 83).

1.1.3 Clinical Use of Heart Rate Variability

The prognostic potential of HRV assessments to identify high risk patients has not yet been fully exploited by clinicians. Scientific evidence suggests that HRV could be an applicable diagnostic tool for various mental (e.g., PTSD (84), depression (85, 86)) and physical (e.g., pain (87, 88), inflammation (89, 90), end-stage renal disease (91), cancer (92)) disorders. It has also been considered as a predictor of prognosis for acute care (e.g. sepsis (93), myocardial infaction (58, 94), stroke (95)).

In the early 1960s, obstetricians were the first to introduce HRV as a clinical tool (96). Acute alterations in fetal HRV were used as marker for foetal distress and predicted foetal hypoxia (97). Today, fetal heart rate monitoring before and during labour has become the standard of care in many countries, especially in high risk pregnancies (98).

In intensive care medicine, HRV diagnostics are increasingly tested for their use in life-threatening conditions including multiple organ dysfunction (60), sepsis (99) and trauma (64, 100).

More recently, the 2019 ESC guidelines in diabetes and prediabetes (101) emphasised the role of HRV as a marker of diabetic cardiovascular autonomic neuropathy after both Liao et al. (102) and Pop-Busui et al. (103) reported associations between low HRV and coronary artery disease. Shah et al. (104) extended these findings by reporting an

association between cardiac autonomic impairment and higher HbA(1c) levles. In their cohort of patients with diabetes, participants with symapthovagal imbalance had greater arterial stiffness compared to those with unremarkable cardiac autonomic activity.

Furthermore, scientific evidence strongly supports a relationship between the increased number of components of metabolic syndrome and low parasympathetic modulation in both adults (105) and children (42, 106, 107).

There is a large body of research that focuses on the cardiovascular system. Reduced HRV is increasingly recognized in patients suffering from cardiovasular conditions such as hypertension (108, 109), coronary artery disease (110) and heart failure (111).
The interplay between ANS imbalance and both cardiovasuclar and overall morbidity and mortality (112-115) makes HRV an appealing diagnostic tool for clinical evaluation and general risk stratification. Ultimately, establishing a solid scientific foundation for HRV and its interpretability could provide clinicians the confidence to incorporate its independent prognostic information in their clinical assessement. With emerging evidence suggesting a link between obesity and ANS abnormalities, the potential benefits of HRV surveillance to public health extend even further.

1.1.4 Normative Values for Heart Rate Variability

To date, uniformly accepted normative values do not exist. Current literature only provides a heterogeneous mixture of reference values. Using short-term HRV data from 21,438 healthy adults, reference values for SDNN, RMSSD, LF, HF and LF/HF-Ratio were generated and published in a systemic review (116). With respect to 24h recordings, some large-scale references exist for both time- (117) and frequency-domain measures (90). In addition, Umetani et al. (118) present some valuable insight from their 24h HRV data for 260 healthy participants ranging from 10 to 99 years of age.

Published reports of large-scale studies in children and adolescents are sparse and only available for short-term measures. Seppälä et al. (119) report normative values for 464 prepubertal children aged 6-8 years. Michels et al. (120) monitored HRV in 460 children between the age of 5-10 years and Sharma et al. (121) add references for adolescents drawn from a sample of 451 participants between 12-17 years. Galeev et al. (122) provide age-specific references for children aged 6-16 years. However, their 3,300 ECG recordings were only about 2 minutes long, compromising the interpretability of some measures.

Due to the susceptibility of HRV indices to varying measurement conditions, the establishment of reference values is challenging. Aspects like recording period length, time of day of recording, recording method, removal of artifacts, respiration, position, movements and recent physical activity should be factored in to draw meaningful conclusions (54). Subject characteristics like age, sex and heart rate also influence HRV measures. In a pediatric population, researchers face further obstacles, given that the developing body with its formative puberty-related changes can have substantial impacts on HRV.

1.2 Influential Covariates in a Pediatric Population

The discrepancy across ANS function studies among obese children is thought to arise largely from uncontrolled or poorly controlled confounding. An increasing body of scientific research and observational evidence shows that numerous physiological and lifestyle factors affect HRV parameters.

1.2.1 Age

HRV indices are a function of age, which reflects the maturation of the cardiac autonomic system. During the transition from childhood to adulthood the LF/HF-Ratio declines while RMSSD and SDNN increase with age (35). However, findings differ according to observed age groups. Michels et al. (120) reported significant parasympathetic increases and sympathetic decreases by age among children aged 5-10 years. On the other hand, Gąsior et al. (123) did not observe any correlations between age and HRV parameters among children aged 6-13 years.

Age-related alterations may be a consequence of physiological changes due to growth. Heart size in relation to body size positively correlates with age (124). Accordingly, there is an increase in stroke volume and left ventricular mass (125). These hemodynamic changes lead to a slowing of heart rate (i.e. a lengthening of the IBIs) (126). Respiratory rate is another example of physiological age-related changes that have an impact on HRV. It is known that the respiratory rate declines form birth to adolescence and thereby affecting LF and HF power (126, 127).

1.2.2 Sex

In 2016, a meta-analysis comprising 296,247 healthy participants revealed a relative vagal dominance in women and a relative SNS dominance in men. Independently of heart rate, female HRV recordings generally showed lower SDNN and LF power, but greater HF power. Gender differences in the sympathovagal balance are further reflected by a lower LF/HF-Ratio in women (54).

In children, there is an ongoing controversy on the influence of sex. No association was observed by Seppälä et al. (119) in a sample of 465 prepubertal children aged 6-8 years, or by Bobkowski et al. (128) in 100 healthy children aged 3-18 years. Others generally report lower values among girls. Notably, Silvetti et al. (129) who observed lower SDNN values for 38 girls between 1-15 years compared to 55 boys of the same age. Michels et al. (120), in a study of 460 children aged 5-10 years observed lower values for both time- and frequency- domain indices (SDNN, RMSSD, pNN50, LF, HF) among girls. Jarrin et al. (130) support these findings in a population based sample of 1,036 children between 9-11 years of age, with the exception of LF/HF-Ratio, which appears to be higher in girls.

1.2.3 Sexual Maturity

Gender differences appear to be dependent on age, suggesting a possible relationship between HRV and sexual maturation. Compared with younger children, VLF and LF differ by gender from the age of 11 years while SDNN, RMSSD and HF differences are observed from the age 12 years (122).

Sex hormones modulate the regulation of cardiac autonomic activity and might partly explain both gender and age differences observed in pubertal HRV recordings. As supported by scientific evidence, testosterone increases sympathetic activity and estrogen decreases sympathetic activity (131-134). With this in mind, differences in the hormonal profile might plausibly explain why the sympathovagal balance is higher in pubertal boys compared to their female peers. Finally, it may be important to consider that girls typically experience an earlier onset of puberty than do boys (135).

1.2.4 Physical Activity

Physical activity is associated with favorable HRV parameters (136-140). Veijalainen et al. (141) observed higher levels of physical activity, lower sedentary time, and greater cardiorespiratory fitness to be associated with better cardiac autonomic function in children aged 6-9 years. Prado et al. (142) evaluated two 4-month weight loss intervention programs for children with obesity. Despite similar weight loss between groups, aerobic exercise in combination with restricted diet resulted in significantly lower LF/HF-Ratios compared to hypocaloric diet alone. Similarly, Gutin et al. (143) reported an increase in RMSSD after 4 month of physical training. However, the favourable parasympathetic modulation diminished 4 months post intervention.

In their systematic review, Oliveira et al. (144) reaffirm the link between RMSSD and moderate-to-vigorous physical activity (MVPA) in children and adolescents. Overall, despite numerous studies investigating the association between cardiorespiratory fitness and HRV, the evidence remains weak and inconsistent.

All evidence considered, exercise appears to improve parasympathetic modulation and overall HRV, with some researchers suggesting that exercise may even reduce the predisposition for cardiovascular disease by improving autonomic imbalance (10).

1.3 Assessment of Adiposity

1.3.1 BMI z-Score

Most studies investigating associations between HRV and adiposity in pediatric samples, used BMI to assess weight status (35). Even though BMI percentiles are usually calculated, there is a vast heterogeneity among definitions of obesity due to differences in national age- and sex-specific cut-offs. The most common internationally accepted BMI references include BMI z-scores published by the Centre for Disease Control and Prevention (CDC) and the World Health Organization (WHO) (145). The practicability and its widespread application in pediatrics make BMI z-score a useful and internationally comparable objective measure of weight status.

1.3.2 Android-to-Gynoid-Ratio

By its very nature, BMI does not assess body composition and body fat distribution. Accumulating evidence emphasises the importance of central adiposity in ANS

modulation. In adults, the strong influence of central adiposity on autonomic functioning is widely accepted (146, 147). Alterations in HRV have also been shown to be amplified in the presence of increased central adiposity in both adults (148, 149) and children (35, 36, 150-152). Over the past decades it has also become evident that obesity is associated with chronic systematic low-grade inflammation (153). Animal models provide further evidence, with administered pro-inflammatory cytokines provoking an increase in sympathetic activity (154, 155) and a decrease in overall HRV (156). As the pro-inflammatory nature of obesity is especially prominent in visceral body fat (157), it is plausible that the sympathovagal imbalance is aggravated by abdominal adiposity (151, 158, 159). In addition, central adiposity is more strongly associated than BMI with cardiovascular and metabolic abnormalities of the metabolic syndrome (160-162).

Together with other imaging techniques like MRI and CT, d-energy-X-ray absorptiometry (DXA) is considered the most accurate instrument available to quantify body composition (163). To date, only a handful of studies have investigated the relationship between HRV and body composition measured directly with DXA in a pediatric population (43, 143, 151, 152, 164). Since the Android-to-Gynoid-Ratio is associated with cardiometabolic risks in both adults (165, 166) and children (167-169), an association with HRV seems plausible. However, to our knowledge no study has investigated in this relationship so far.

1.3.3 Waist-to-Height-Ratio

Waist-to-Height-Ratio (WHtR, measures as waist circumference in centimeter divided by height in centimeter) is an anthropometric indicator of central adiposity and visceral fat tissue (170); an independent predictor of metabolic and cardiovascular disease (159, 161). Elevated inflammatory biomarkers such as CRP can be observed in children with high waist circumference (171). Walter et al. (172) report that waist circumference and WHtR in children aged 3-17 years are more strongly associated with impaired HRV than BMI z-score; reinforcing the idea that waist circumference may be more sensitive to autonomic modulations than simple measures of weight status. Most recently, WHtR has been suggested as a useful tool to assess central adiposity and to screen children for related cardiometabolic risk (173). Findings in regards of WHtR might help us to identify whether WHtR is a reliable proxy for central adiposity measured with DXA.

2 Methods and Material

2.1 Participants

Data originate from the Quebec Adipose and Lifestyle Investigation in Youth study (QUALITY), an ongoing prospective cohort study of 630 participants, who were aged 8-10 years at the time of recruitment. The overarching goal of the QUALITY study is to describe the natural history, determinants and consequences of childhood obesity.

Families were recruited through a school-based sampling strategy; all schools located within 75 km of Montreal, Quebec City and Sherbrooke in the province of Quebec, Canada, between 2005 and 2008 were contacted. Eighty percent of the 1,040 contacted schools agreed to participate. Flyers outlining purpose and structure of the study were distributed to all students attending grades 2 to 5 from participating schools. Interested parents were asked to contact the research team.

Inclusion criteria specified that eligible children be aged 8–10 years at baseline, and that at least one biological parent be obese (i.e. body mass index (BMI) ≥30 kg/m^2 or waist circumference >102 cm in men and >88 cm in women, based on self-reported measurements of height, weight and waist circumference collected at the time of the telephone recruitment interview). Only Caucasian children of Western European ancestry were included.

Children were excluded if they were previously diagnosed with type 1 or 2 diabetes, were treated with anti-hypertensive medication or steroids, suffered from a serious illness or cognitive disorder that prevented participation, restricted their diet to less than 600 kcal per day or the family intended to leave Quebec in the near future.

All parents provided informed consent and children provided assent. The study was approved by the ethical review boards of the Centre Hospitalier Universitaire (CHU) Sainte Justine, McGill University, and Laval University.

Baseline data collection (visit 1) took place between September 2005 and December 2008 and was conducted for 634 children aged 8-10 years and their families. Four families were removed following the completion of data collection because most or all of the data was missing although consent was provided initially. Of the original cohort, 564 children aged

10-12 years and their families were followed up between September 2008 and March 2011 (visit 2). A recruitment and participation chart is presented in the associated cohort profile (174).

In comparison with a representative sample of the Quebec population, children of the QUALITY cohort are of higher socio-economic status, more likely to be overweight or obese and have a worse lipid profile. More details on the QUALITY study and its measurements have been described elsewhere (174).

2.2 Data Collection

Families were invited to a full day visit at the Unité de recherche clinique du CHU Sainte-Justine in Montreal and the Institut universitaire de cardiologie et de pneumologie de Québec (IUCPQ) du Hôpital Laval in Quebec City. At each visit, biological, genetic, behavioral, psychological, and environmental determinants of obesity and cardiometabolic risk factors were collected. Participants were asked to arrive after an overnight fasting and underwent a complete assessment including blood sampling, oral glucose tolerance testing, ECG recordings, assessment of anthropometrics and sexual maturity. Interviewer-administered questionnaires were completed from children and their parents. Accelerometers and dietary assessment kits were provided, along with instructions for completion and return.

2.3 Measures

2.3.1 Anthropometric Measurements

At each visit, children's weight was measured using an electronic scale (CHU Sainte-Justine: Cardinal Detecto, 758C Series, Cardinal Scale Manufacturing Co., Webb City, Missouri, USA; IUCPQ: Tanita, model TBF-300A, Arlington Heights, Illinois, USA) dressed in light indoor clothing without shoes; height was measured with a stadiometer (CHU Sainte-Justine: Ibiom, model 600, Ibiom Instruments Ltée, Sherbrooke, Quebec, Canada; IUCPQ: Measuring Devices Seca Corp., Hanover, Maryland, USA) according to standardised protocols (174-176). Measurements were done in duplicate; if they differed by 0.5 cm or more, or by 0.2 kg or more, a third measurement was taken. The average of the two closest measurements was used for analysis. Body mass index was calculated based on these measures (kg/m^2) and CDC-based age-/sex-specific z-scores were computed using growth charts (https://www.cdc.gov/growthcharts/cdc_charts.htm).

According to the CDC reference standards, “underweight” was defined as BMI <5th percentile, “normal weight” as ≥5th percentile and <85th percentile, “overweight” as ≥85th percentile and <95th percentile, and “obese” as ≥95th percentile of the CDC growth chart. BMI z-score was chosen as a main outcome as BMI is the most commonly studied measure in HRV studies (35). Waist circumference, i.e. the mid-distance between the last floating rib and the iliac crest at the end of a normal expiration, was determined with a standard measurement tape. WHtR was calculated by dividing waist circumference by height. WHtR is thought to reflect central adiposity and is easy to obtain in clinical practice.

2.3.2 Body Composition Indicators

Fat mass, fat-free mass, percent body fat and fat distribution (i.e. android and gynoid region) were measured with dual energy X-ray absorptiometry (DXA, Prodigy Bone Densitometer System, DF+14664, GE Lunar Corporation, Madison, WI, USA). This imaging technique utilizes low-intensity X-rays (approximately 0.94 mrem) to assess bone mass density and body composition. Android-to-Gynoid-Ratio was computed by dividing fat mass of the android region by fat mass of the gynoid region. Android-to-Gynoid-Ratio is included in the analysis as it has recently been associated with cardiometabolic risk in children (167-169). As DXA is one of the most accurate measures to quantify body composition (163) and studies linking body fat distribution with HRV indices are scarce, we decided to include Android-to-Gynoid-Ratio in our models.

2.3.3 Heart Rate Variability

Heart rate variability was assessed by analysing time- and frequency-domains of the electrocardiographic recordings (Hardware: Marquette 8500 Series Holter Recorders; GE Marquette Medical System, Milwaukee, WI, USA). The electrocardiographic monitoring was conducted for 20 minutes in supine position during the 3-hour period of the oral glucose tolerance test. Children wore pre-gelled silver chloride ECG electrodes in a modified Lead II configuration (Table 2.1).

Channel	Lead	Placement
CH 1 (-)	mV5 (-)	Right clavicle at the right sternal edge over the first rib
CH 2 (-)	mV1 (-)	Left clavicle at the left sternal edge over the first rib
CH 3 (-)	aVF (-)	Left clavicle at the mid-clavicular line
CH 1 (+)	mV5 (+)	5^{th} intercostal space at the left axillary line
CH 3 (+)	aVF (+)	6^{th} rib at the left mid-clavicular line
---	Grounding	Near the lowest possible right rib cage on the abdomen
CH 2 (+)	mV1 (+)	4^{th} intercostal space at the right edge border

Table 2.1 Placement of Leads: Modified Lead II configuration for ECG recordings

The definition of QRS complex was based on standard Marquette algorithms for QRS labeling and verified by a board-certified cardiologist at a single site (Hôpital Laval). Artifacts were removed and cubic spline interpolation method was used to replace data points where artifacts were identified.

Standardized time-domain indices were calculated to quantify the amount of variability in measurements of the IBIs. The standard deviation of the NN intervals (SDNN), the square root of the mean of the differences of the successive NN intervals (RMSSD) and the proportion of NN intervals that differ by more than 50 ms from the previous interval (pNN50) were chosen as they are standard in the literature.

Fast Fourier Transformation spectral analyses was conducted to transform beat-to-beat intervals to frequency-domain bands. According to the standards set by the Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology (14), frequency-domains were classified as very low frequencies (VLF, 0.0033-0.04 Hz), low frequencies (LF, 0.04-0.15 Hz) and high frequencies (HF, 0.015-0.4

Hz). However, only LF and HF were considered in our analysis as the physiological meaning and interpretation of VLF is still vague. LF/HF-Ratio and normalized units of LF and HF (LFnu and HFnu) derive from the standardized frequency-domain parameters and were calculated as follows:

- LF/HF-Ratio = LF/HF
- LFnu = LF/(LF+HF)
- HFnu = HF/(LF+HF)

Parameter	Definition	Unit	Interpretation
Time-domain			
SDNN	Standard deviation of the NN intervals	ms	overall variability
RMSSD	Square root of the mean of the differences of the successive NN intervals	ms	PNS activity
pNN50	Proportion of NN intervals that differ by more than 50 ms from the previous interval	%	PNS activity
Frequency-domain			
LF	Low frequencies (0.04-0.15 Hz)	ms^2	SNS and PNS activity
HF	High frequencies (0.015-0.4 Hz)	ms^2	PNS activity
LF/HF	Low frequencies divided by high frequencies	/	SNS/PNS balance
LFnu	Low frequencies divided by the total power	nu	SNS and PNS activity
HFnu	High frequencies divided by the total power	nu	PNS activity

Table 2.2 Summary of Time- and Frequency-Domain Parameters

2.3.4 Physical Activity

Accelerometry data (assessed with Actigraph LS 7164 activity monitor, Actigraph LLC, Pensacola, FL, USA) was recorded on 7 consecutive days in the week following both visit 1 and visit 2 respectively. A minimum wear time of 10 hours per day was required, for at least 4 of the 7 days, including one weekend day (177). The accelerometer was worn at hip height and was only detached before going to bed, or when children were bathing, showering or swimming. Moderate to vigorous physical activity (MVPA) was computed by averaging the total minutes spent daily in moderate and in vigorous physical activity over the total wear time. Minutes recording at least 2,296 counts were considered to be MVPA.

2.3.5 Sexual Maturity

Stage of sexual maturity was scored by trained nurses according to Tanner (178, 179). Sex-specific criteria that served as a basis for staging are outlined in Table 2.3 and Table 2.4.

Stage	Pubic Hair	Penis	Testes and Scrotum
1	Very thin, similar to those on the abdominal lining	Preadolescent	Preadolescent
2	Scattered, long, lightly pigmented	Slightly increased in size	Enlargement, change in the skin texture
3	Darker, stronger, more curly, and extending sparsely to the pubic junction	Increased in length	Increase in volume
4	Adult, but the area covered is smaller than of adult as it doesn't extend over the inner thigh	Increase in length and width; enlargement of the glans	Increase of the volume and darker in colour
5	Adult distribution extending over the inner thighs	Adult size	Adult size

Table 2.3 Tanner Staging Criteria for Boys

Stage	Pubic Hair	Breasts
1	Preadolescent, similar to those on the abdomen	Preadolescent
2	Scattered, lightly pigmented, straight, along the inner labia majora	Appearance of a mammary bud, enlargement of the areola
3	Darker, stronger, more, ± curly	Further breast enlargement without contour or separation of breast and areola
4	Strong and curly, adult looking but less abundant	The contour of the areola is elevated relative to the mammary gland; increased volume of the mammary gland
5	Adult texture and quantity extending over the inner thighs	Adult breast; nipple prominent, areola no longer appears raised

Table 2.4 Tanner Staging Criteria for Girls

2.4 Data Analytic Strategy

A complete case analysis, comprising participants with complete data at both visit 1 and visit 2, was undertaken, to ensure comparability between the two cross-lagged models proposed. Table 3.1 gives the descriptive statistics for full and complete case samples at both time points. Comparing explanatory variables and other characteristics that might influence the results, no substantial differences between full and analytic samples were identified. On these grounds, we decided to forego procedures to adjust for missing data such as multiple imputation, as any biases, if present, would likely be minor.

HRV parameters were tested for normality through numeric and graphic methods and natural log transformation was conducted as needed to satisfy conditions for parametric analysis.

Correlation analyses were performed to examine association between adiposity measures, HRV and the corresponding heart rate. Univariate and multiple linear regression models were calculated bi-directionally to assess the associations between adiposity and cardiac autonomic function. Two different approaches were undertaken to address our initial hypotheses (see Figure 1.1):

i. To analyze our first cross-lagged relation, HRV indices at visit 2 were the primary outcome variables. In separate models Android-to-Gynoid-Ratio, BMI z-score and WHtR at visit 1 were included as continuous explanatory variables.
ii. In an analogous manner, the second cross-lagged relation was examined by defining adiposity measurements at visit 2 as primary outcomes and HRV indices at visit 1 as continuous explanatory variables. In separate models Android-to-Gynoid-Ratio, BMI z-score and WHtR at visit 2 were considered as primary outcomes.

Models were estimated for the different adiposity measurement to help elucidate physiological processes.

Clinically relevant covariates were included in the multiple linear regression models. The final models were controlled for the difference in body fat (%) between visit 1 and 2, sex (male, female), sexual maturity (Tanner stage) at visit 2, age (years) at visit 2 and MVPA (minutes per day) at visit 1.

Sexual maturity and age at visit 2 (rather than at visit 1) were included as confounders because physiological and developmental changes due to puberty and age itself influence both the cardiac autonomic function and body composition in a developing body at the time the outcome is measured. On the other hand, physical activity is considered a cumulative lifestyle behavior that influences adiposity and HRV in the long run. Therefore prior physical activity behaviour was considered to be potentially more influential than concurrent physical activity.

2.4.1 Secondary and Sensitivity Analyses

We performed sensitivity analyses to examine the extent to which our results might be affected by various methodological decisions and assumptions (180).

Marginal Approaches Using Propensity Scores

In our multiple linear regression models we jointly modeled our main outcome variables together with a selection of influential variables as covariates. However, there is no way of knowing whether the effects of the covariates are linear or non-linear and whether interrelationships between exposure and other influential covariates are additive, multiplicative or otherwise linked. To challenge the assumption of independent linear covariates, marginal approaches were introduced. The idea is to balance the sample with respect to potential confounders that affect both exposure and outcome before estimating the effects of the exposure. This approach allows us to compare the outcome between two groups that differ by exposure status but are otherwise very similar. Potential confounders would therefore be less likely to interfere with the relationship between the exposure of interest and the outcome. To balance the study sample according to potential confounders, the same selection of observed influential covariates as used in the main analyses were utilized to calculate the predicted probability (or propensity) of being overweight (i.e. propensity score). With the propensity scores developed and balance established, two common methods were used to examine the balanced sample (181):

- **Propensity Score Matching**

  In a first approach, confounding adjustment was achieved by matching the 20 percent of the most extreme values of adiposity measures with controls of similar propensity. Optimal matching was conducted using the R package '*MatchIt'* (182) and its add-on '*optmatch'* (183) to find matched samples with the smallest average absolute distance in propensity scores across all the matched pairs. In doing propensity score matching we intended to select controls that resembled the top quintile comprising the most extreme values of adiposity measurements (highest Android-to-Gynoid-Ratio, highest BMI z-score, highest WHtR) based on sex, age, sexual maturity, physical activity and changes in percent body fat. Hence, comparing matched samples will help determine risk factors with the greatest potential for adiposity development. To evaluate the potential significance of central adiposity, differences in means in HRV parameters by subgroups of adiposity measure were compared, and t-tests were performed.

- **Re-Weighting With Bootstrapping**

  In a second approach, the inverses of the propensity scores were added as weights to the initial univariate linear regression models (184-186). Hence, each participant received a weight inversely proportional to the estimated covariate balanced probability of being in the overweight subgroup. Subgroups that are expected to be balanced in the weighed population were defined by median split. Weighted subgroups were additionally analysed by calculating differences in means to categorically estimate causal effects of the exposure variable. The main advantage of the re-weighting method is that the entire sample is represented in the analyses. Bootstrapping was incorporated for both the weighted regression models and the differences in means to construct confidence intervals by resampling the original dataset with replacement many thousands of times to create many simulated samples. Bootstrapping approaches are particularly helpful to test new hypotheses as they generate cut-offs so that the probability of erroneously rejecting the null hypothesis (i.e. type 1 error) remains low (187). Further bootstraps estimate the standard error as they test the reproducibility of the results (188).

Analyses were performed using R (R Core Team, 2014).

3 Results

3.1 Characteristics

Selected characteristics of the children are presented in Table 3.1. Only participants who completed both visits were retained for our final analysis. Thus, a sample of 406 children (229 boys, 177 girls) comprised the analytic sample. They had an average age of 9.6 years (SD = 0.9) and 11.7 years (SD = 1.0) at visit 1 and visit 2 respectively. 80 % of the sample was prepubertal at visit 1, whereas the majority of children (67 %) had initiated puberty at visit 2. At visit 1, 42 % of the children were considered overweight or obese. While the proportion of overweight or obese children remained constant over time, the proportions of body composition parameters changed slightly. On average, the percentage of total body fat increased and android fat became more prominent.

3.2 Correlation Analyses for Corresponding Heart Rate

A closer examination of correlations between adiposity measures, heart rate and SDNN, as a surrogate for overall HRV, revealed no significant correlations between both heart rate and SDNN with adiposity measures. This holds for both cross-sectional and 2-year prospective associations. Further, relationships between HRV and heart rate were confirmed. Correlation plots depict an expected negative exponential relation between heart rate and SDNN. The same relation is observed when heart rate is plotted against heart period. Further, the association between heart period and SDNN depicts a positive quasi linear behavior.

3.3 Main Analyses

Initial unadjusted linear regression analyses showed positive associations between adiposity measures and LF/HF-Ratio and LFnu and negative associations between adiposity measures and HFnu in either direction.

i. BMI z-score at visit 1 additionally resulted in an increase of LF and SDNN at visit 2; this effect could not be shown for Android-to-Gynoid-Ratio.
ii. A decrease in RMSSD and pNN50 at visit 1 was associated with greater Android-to-Gynoid-Ratio and BMI z-score at visit 2.

Univariate linear regression models are enclosed in the supplementary material.

Tables 4.2 to 4.5 show results of multiple linear regression models in both directions. Results for Android-to-Gynoid-Ratio and BMI z-score are presented in separate tables.

i. After multivariable adjustment, greater adiposity at visit 1 was associated with specific short-term HRV indices two years later. These included an increase in LF, LF/HF-Ratio and LFnu as well as a decrease in HFnu.
ii. When HRV measures at visit 1 were modelled as explanatory variables, lower RMSSD ($p<0.1$) and pNN50 ($p<0.05$) were significantly associated with greater adiposity two years later. Moreover, a greater LF/HF-Ratio and greater LFnu at age 8-10 years predicted greater adiposity at age 10-12 years. HFnu was inversely associated with adiposity two years later.

Findings were consistent for all adiposity outcomes. No significant associations between adiposity and HF and SDNN were observed in either direction. Full multiple linear regression models including all covariates are included in the supplementary material.

3.4 Secondary and Sensitivity Analyses

Secondary analyses were introduced to examine the importance of central adiposity more closely. Sensitivity analyses were performed to check the robustness and reproducibility of our results. In general, results of additional analyses supported overall findings from main analyses. Details regarding secondary and sensitivity analyses are enclosed in the supplementary material.

Propensity Score Matching

i. Comparisons of participants with the top quintile comprising the most extreme values of adiposity measurements at visit 1 with propensity score matched controls, revealed similar results except of LF that did not differ between subgroups.
ii. When comparing different adiposity measurements, higher means of RMSSD and pNN50 at visit 1 in the android group but not in the high BMI z-score group indicate substantial effects of RMSSD and pNN50 on the development of central adiposity two years later.

Re-Weighting Models With Bootstrapping

i. Subgroups described by greater adiposity at visit 1 present with similar results with the exception of the effects of adiposity at visit 1 in LF two years later that diminish in those models questioning the reliability of LF predictions based on adiposity.

ii. After bootstrapping was applied, the influence of parasympathetically-driven time-domain parameters, RMSSD and pNN50, at visit 1 between median split groups of adiposity at visit 2 became even more apparent reinforcing the reliability of these estimates.

3.5 Ancillary Analyses

Results were not appreciably altered in models using WHtR as exposure and outcome. Notably, no difference in pNN50 and RMSSD at visit 1 in high WHtR group were observed when compared with propensity score matched controls. Analyses including WHtR are also enclosed in the supplementary material.

Characteristics	Visit 2		Visit 2	
	Full sample	Complete case sample	Full sample	Complete case sample
General characteristics	**n = 630***	**n = 406**	**n = 564***	**n = 406**
Age, mean (SD), y	9.6 (0.9)	9.6 (0.9)	11.7 (0.9)	11.7 (1.0)
Male, n (%)	343 (54)	229 (56)	313 (56)	229 (56)
Sexual Maturity, n (%), Tanner stage				
Stage 1	494 (79)	324 (80)	186 (33)	135 (33)
Stage 2	117 (19)	72 (18)	181 (32)	128 (31)
Stage 3	16 (2)	9 (2)	135 (24)	97 (24)
Stage 4	2 (0)	1 (0)	48 (9)	39 (10)
Stage 5	0 (0)	0 (0)	10 (2)	7 (2)
Anthropometrics				
BMI categories, n (%)				
Underweight	12 (2)	8 (2)	13(2)	9 (2)
Normal weight	354 (56)	228 (56)	327 (58)	238 (59)
Overweight	121 (19)	85 (21)	98 (18)	70 (17)
Obese	143 (23)	85 (21)	126 (22)	89 (22)
BMI z-score, mean (SD)	0.71 (1.08)	0.71 (1.03)	0.68 (1.09)	0.71 (1.07)
Waist-Height-Ratio, mean (SD)	0.49 (0.07)	0.48 (0.07)	0.48 (0.08)	0.48 (0.08)
Body composition (DEXA)				
Android-Gynoid-Ratio, mean (SD)	0.31 (0.12)	0.31 (0.11)	0.33 (0.12)	0.33 (0.12)
Total fat mass, mean (SD), %	26.55 (10.93)	26.33 (10.65)	28.42 (10.91)	28.49 (10.80)
Heart rate variability indices median (IQR)	**n = 575**	**n = 406**	**n = 503**	**n = 406**
LF, ms²	1 078 (935)	1 046 (947)	1 178 (1 063)	1 144 (1 053)
HF, ms²	745 (765)	742 (772)	748 (833)	727 (835)
LF/HF-Ratio	1.560 (0.795)	1.570 (0.755)	1.670 (0.875)	1.650 (0.818)
LFnu, normalized units	0.610 (0.118)	0.611 (0.114)	0.626 (0.121)	0.623 (0.115)
HFnu, normalized units	0.390 (0.118)	0.390 (0.114)	0.375 (0.121)	0.378 (0.115)
SDNN, ms	82 (29)	81 (28)	87 (34)	86 (33)
RMSSD, ms	47.0 (23.0)	47.5 (24.0)	49.0 (24.5)	48.5 (24.8)
pNN50, %	25.3 (22.0)	25.0 (21.8)	27.1 (22.0)	26.9 (22.7)
Average heart period (NN interval), ms	697 (90)	696 (86)	733 (110)	733 (112)
Average heart rate, bpm	86 (11)	86 (11)	81 (13)	81 (13)
Physical activity	**n = 550**	**n = 406**	**n = 445**	**n = 320**
Moderate to vigorous physical activity, mean (SD), min/day	51.3 (25.9)	50.9 (24.3)	42.9 (23.3)	41.9 (23.2)
Parental/household characteristics	**n = 630***	**n = 406***	**n = 564***	**n = 406***
BMI of mothers, mean (SD), kg/m²	29.5 (6.6)	29.3 (6.4)	29.7 (6.2)	29.7 (5.9)
BMI of fathers, mean (SD), kg/m²	30.7 (5.5)	30.6 (5.6)	31.2 (5.5)	31.2 (5.6)
Number of parents with the metabolic syndrome, n (%)				
0	217 (35)	141 (35)	82 (36)	65 (38)
1	327 (53)	212 (53)	121 (53)	86 (50)
2	73 (12)	47 (12)	26 (11)	21 (12)
Parental education, n (%)				
2 parents with high school degree or less	49 (8)	30 (7)	38 (7)	26 (7)
1 or 2 parents with technical/ vocational/trade school degree	237 (38)	154 (38)	227 (43)	167 (44)
1 or 2 parents with university degree	341 (54)	221 (55)	264 (50)	188 (49)
Annual household income, mean (SD), $	42 360 (18 574)	42 689 (18 147)	48 644 (22 191)	48 366 (21 966)

Table 3.1 Descriptive Statistics for Full Cohort and Complete Case Sample at Visit 1 and Visit 2

*Sample includes occasional missing values for some variables.

AndGyn V1 HRV V2	β	Standard Error	CI 95%	t-value	Sig
LF (ln)	0.490	0.292	-0.084; 1.063	1.679	0.09
HF (ln)	-0.013	0.364	-0.728; 0.702	-0.036	0.97
LF/HF (ln)	0.502	0.181	0.147; 0.857	2.778	<0.01
LFnu	0.108	0.041	0.028; 0.188	2.645	<0.01
HFnu	-0.108	0.041	-0.188; -0.028	-2.645	<0.01
SDNN (ln)	0.076	0.129	-0.178; 0.330	0.587	0.56
RMSSD	-1.117	7.731	-16.316; 14.082	-0.144	0.89
pNN50	-5.260	6.676	-18.385; 7.865	-0.788	0.43

Table 3.2 Multiple Linear Regression With Android-Gynoid-Ratio at Visit 1 and HRV Indices at Visit 2

HRV V1 AndGyn V2	β	Standard Error	CI 95%	t-value	Sig
LF	8.971e-06	6.083e-06	-2.987e-06; 2.092e-05	1.475	0.14
HF	-9.985e-08	8.108e-06	-1.604e-05; 1.584e-05	4.588	0.99
LF/HF	0.032	0.008	0.016; 0.048	3.920	<0.001
LFnu	0.242	0.065	0.115; 0.369	3.754	<0.001
HFnu	-0.242	0.065	-0.369; -0.115	-3.754	<0.001
SDNN	1.602e-04	2.431e-04	-3.177e-04; 6.381e-04	0.659	0.51
RMSSD	-6.546e-04	3.743e-04	-1.391e-03; 8.129e-05	-1.749	0.08
pNN50	-1.002e-03	4.239e-04	-1.836e-03; -1.689e-04	-2.364	0.02

Table 3.3 Multiple Linear Regression With HRV Indices at Visit 1 and Android-Gynoid-Ratio at Visit 2

BMIz V1 HRV V2	β	Standard Error	CI 95%	t-value	Sig
LF (ln)	0.075	0.031	0.013; 0.137	2.394	0.02
HF (ln)	0.031	0.039	0.047; 0.107	0.765	0.44
LF/HF (ln)	0.045	0.020	0.007; 0.084	2.302	0.02
LFnu	0.010	0.004	0.001; 0.018	2.172	0.03
HFnu	-0.010	0.004	-0.018; -0.001	-2.172	0.03
SDNN (ln)	0.025	0.014	-0.002; 0.052	1.798	0.07
RMSSD	0.803	0.835	-0.838; 2.443	0.961	0.34
pNN50	0.214	11.467	-1.205; 1.634	1.382	0.77

Table 3.4 Multiple Linear Regression With BMI z-Score at Visit 1 and HRV Indices at Visit 2

HRV V1 BMIz V2	β	Standard Error	CI 95%	t-value	Sig
LF	8.895e-05	5.289e-05	-1.503e-05; 1.929e-04	1.682	0.09
HF	6.101e-06	7.056e-05	-1.326e-04; 1.448e-04	0.086	0.93
LF/HF	0.328	0.070	0.190; 0.466	4.683	<0.001
LFnu	2.431	0.558	1.334; 3.528	4.356	<0.001
HFnu	-2.431	0.558	-3.528; -1.334	-4.356	<0.001
SDNN	0.003	0.002	-0.002; 0.007	1.269	0.21
RMSSD	-0.006	0.003	-0.012; 0.001	-1.706	0.09
pNN50	-0.009	0.004	-0.016; -0.002	-2.430	0.02

Table 3.5 Multiple Linear Regression With HRV Indices at Visit 1 and BMI z-Score at Visit 2

4 Discussion

To our knowledge, no longitudinal study investigating HRV in healthy children has been published so far. In order to better understand how impairments in HRV and the development of obesity are associated, we examined 2-year bi-directional associations in pre-adolescents between 8 and 12 years of age. In doing so, we investigated in both the potential impact of obesity on subsequent HRV, as well as the reverse relation, i.e. the potential impact of HRV on subsequent obesity (compare with the cross-lagged panel proposed in the introduction).

We identified meaningful albeit different patterns for the two cross-lagged relations. We found a consistent sympathovagal imbalance in terms of a sympathetic predominance in either direction. In addition to bi-directionally consistent findings, we further discovered that a greater adiposity at age 8-10 years predicted higher levels of LF two years later. In response to our second cross-lagged relation, we observed that lower RMSSD and pNN50 at age 8-10 years were associated with greater adiposity at age 10-12 years.

Full multiple linear regression models elicited that the associations between HRV in 8-10-year-olds and Android-to-Gynoid-Ratio in 10-12-year-olds are further influenced by the difference in percent body fat, sexual maturity and physical activity. Interestingly, results appear to be independent of sex and age. To predict BMI z-score at age 10-12 years, however, all added covariates showed a significant influence.

For the reverse cross-lagged relation, sex seemed to be the only influential covariate to predict HRV at the age of 10-12 years; a consistent finding for all measures of adiposity.

Based on propensity score matching, we confirmed an aggravated development of central adiposity at age 10-12 years in children who exhibited lower values of RMSSD and pNN50 two years prior.

Marginal sensitivity analyses that enabled us to observe differences in a propensity score balanced sample, reinforced findings of the main analyses. Bootstrapping ensured the reproducibility of significant associations. Notably, the prediction of LF at age 10-12 years was the only association that could not be replicated in our sensitivity analyses.

In the following sections, results are discussed in more detail and contextualised in lights of the existing literature.

4.1 Impact of Adiposity at Age 8-10 Years on Heart Rate Variability at Age 10-12 Years

4.1.1 Frequency-Domain Indices

In regards of relationships between adiposity measures at age 8-10 years and HRV at age 10-12 years, patterns for frequency-domain indices were consistent across all adiposity measures. Greater adiposity in 8-10-year-olds were associated with higher levels of LF at age 10-12 years. No associations in regards of HF were observed.

Higher LF values in children with greater adiposity two years prior may be due to an increase of SNS activity related to pre-existing adiposity. SNS augmentation may represent a reactive compensation for expected reductions in SNS reactivity and adrenoceptor sensitivity in an overweight body (11). However, the observed LF effect diminishes in propensity score matching and re-weighting analyses. Inconsistent findings on whether LF is influenced by pre-existing adiposity may be explained by the wide confidence interval of our LF values. After randomly resampling our observed data multiple times via bootstrapping, we cannot reliably predict the direction of the association between adiposity at the age of 8-10 years and LF values two years later. Wide ranges of HF were probably also why we did not observe an association between adiposity and HF in our regression models.

Wide ranges of both LF and HF may indicate fluctuations of total power rather than ANS modulation (80, 81), as suggested by correlational analyses (Figure 4.1).

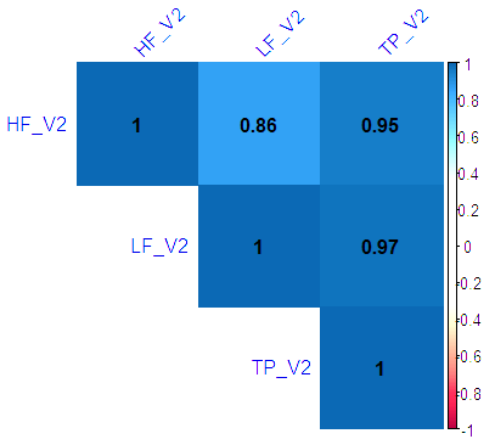
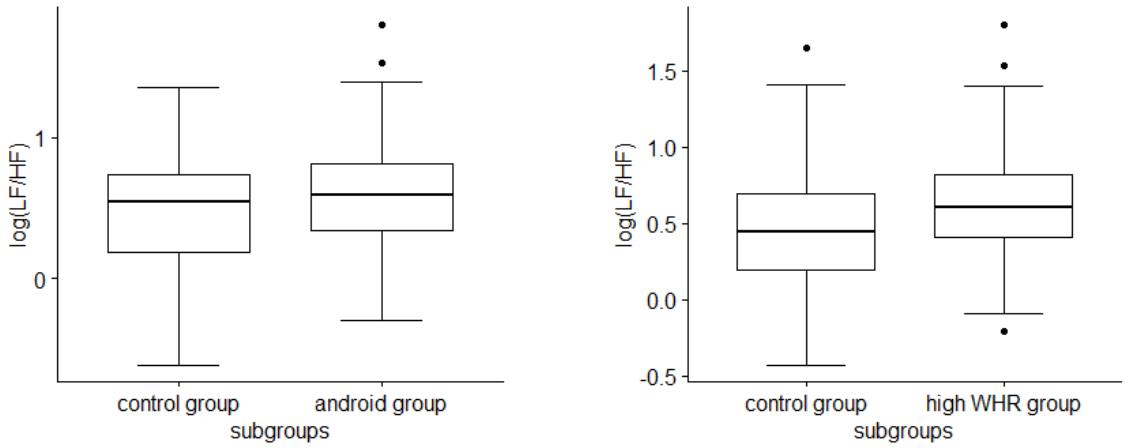


Figure 4.1 Correlation Matrix of Frequency-Domain Indices and Their Corresponding Total Power at Visit 2

Therefore, as recommended by the Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology (14), LF/HF-Ratio as well as the normalized units were computed. These parameters are thought to be less prone to changes in total power.

In regards of the impact of adiposity on LF/HF-Ratio and normalized units, we observe a distinct behavior. An increase of LFnu and LF/HF-Ratio as well as a decrease of HFnu imply a sympathovagal imbalance, in terms of sympathetic dominance. Comparison of propensity score matched groups further revealed aggravated effects of central adiposity; even though mean changes in percent total body fat (Δ %BF) tended to be higher in controls (Figure 4.2). These findings replicate previous research suggesting that elevated visceral adiposity is associated with higher sympathetic and lower parasympathetic activity, independent of total body fat (151).



t(161.26) = -2.16, **p = 0.03**, d = -0.36				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	2.013	0.916	1.12
Control group	82	1.731	0.643	1.40

t(162) = -2.92, **p = 0.004**, d = -0.39				
Subgroup	n	mean	SD	Δ%BF
High WHtR group	82	2.052	0.921	0.94
Control group	82	1.717	0.799	1.33

Figure 4.2 Differences in Means of LF/HF-Ratio Between Android/High WHtR Subgroup and Propensity Score Matched Controls: Higher LF/HF-Ratios were observed for measures of central adiposity, independent of changes in percent total body fat.

However, we do acknowledge that the interpretation of LF and its computed derivatives like LF/HF-Ratio and LFnu is complex. Since they are not mere surrogates for sympathetic modulation (80-82) but also partly influenced by PNS activity (70, 71), the interpretability of LF remains contested. On these grounds, the accuracy of LF/HF-Ratio to quantify sympathovagal balance remains uncertain (79). Nonetheless, the majority of studies

investigating in frequency-domain analyses of HRV, consider LF/HF-Ratio as a measure of sympathovagal balance.

Longitudinal HRV studies are generally scarce. Although Nagai et al. (44) conducted a cross-sectional study, they plotted the timing of obesity by collecting information about the onset of obesity retrospectively. Results of 42 children with obesity aged 6-12 years and another 42 matched controls of normal weight illustrate an overall autonomic depression in the obese group. Reduced LF and HF were accentuated when participants were obese for more than 3 years. We identified opposite patterns for LF. This contradictory finding might be due to our lack of information about the preceded duration of obesity. In addition, Nagai et al. (44) used national BMI cut-offs to define obesity in their relatively small sample and their controls were only matched for age, sex and height and did not consider sexual maturity and physical activity as we did.

Results of a similar study by Rabbia et al. (43) are consistent with our findings. They retrospectively reviewed the duration of obesity in 50 children with obesity with a mean age of 14.9 years and compared them with 12 normal-weight peers. In contrast to Nagai et al. (44), all obese participants exhibited normal values of LF. Furthermore, only children with a recent onset of obesity (< 4 years) presented with increased values of LFnu and LF/HF-Ratio as well as decreased HFnu. Hence, our findings of a marked sympathovagal imbalance may be indicative of a shorter exposure window for obesity in our participants. In fact, animal models confirm an increase in SNS and a decrease in PNS in the dynamic phase of weight gain. After feeding dogs with a high-fat diet, Verwaerde et al. (189) reported increased LF and decreased HF values. The resulting sympathovagal imbalance was further validated by changes in the dogs' catecholamine plasma levels. After the dynamic weight gain period, SNS activity returned to normal. Differences in the duration of obesity might also be a plausible explanation of the wide range of LF observed in our sample.

The majority of traditional cross-sectional studies assessing frequency-domain HRV report an increase of LF/HF-Ratio in obese children (35). Results vary by age groups, recording times and sample sizes. In addition, there are only a few studies that use accurate measures of body composition and, at the same time, consider physical activity. In a smaller sample of 50 Caucasian prepubertal children aged 6-10 years, Santos-Magalhaes et al. (150) observed a similar relation between LF/HF-Ratio and adiposity measured via DXA.

They adjusted for age, Tanner stage and MVPA. Their results reveal identical patterns, i.e. greater adiposity was associated with a sympathovagal imbalance in terms of a sympathetic dominance. In a study of 304 adolescents aged 14-18 years, higher LF/HF-Ratio was also associated with both higher levels of visceral adiposity tissue and subcutaneous adiposity tissue measured via MRI (152).

4.1.2 Time-Domain Indices

In terms of time-domain parameters, we did not observe any significant effects, which is consistent with Santos-Magalhaes et al. (150). In contrast, Gutin et al. (152) and Rabbia et al. (43) reported significant inverse effects for parasympathetically-driven time-domain parameters; however, they used 24h recordings, which may compromise comparability with our short-term recordings. In one of the only prospective HRV studies, Cho et al. (190) also reported, that higher BMI and WHtR were significant predictors of lower SDNN and RMSSD in short-term ECG recording of adolescents followed over 7 years. However, their sample was restricted to older adolescents with type 1 diabetes.

4.2 Impact of Heart Rate Variability at Age 8-10 years on Adiposity at Age 10-12 Years

To our knowledge there are no longitudinal studies that have investigated the potential influence of HRV on changes in adiposity. While existing literature offers enough evidence to justify ANS impairments as a potential cause of excessive weight gains, the present study provides a new hypothesis that should stimulate further research.

4.2.1 Frequency-Domain Indices

We observed a positive association between LF/HF-Ratio at age 8-10 years and measures of adiposity at age 10-12 years. Increased LFnu and decreased HFnu were associated with greater adiposity two years later.

4.2.2 Time-Domain Indices

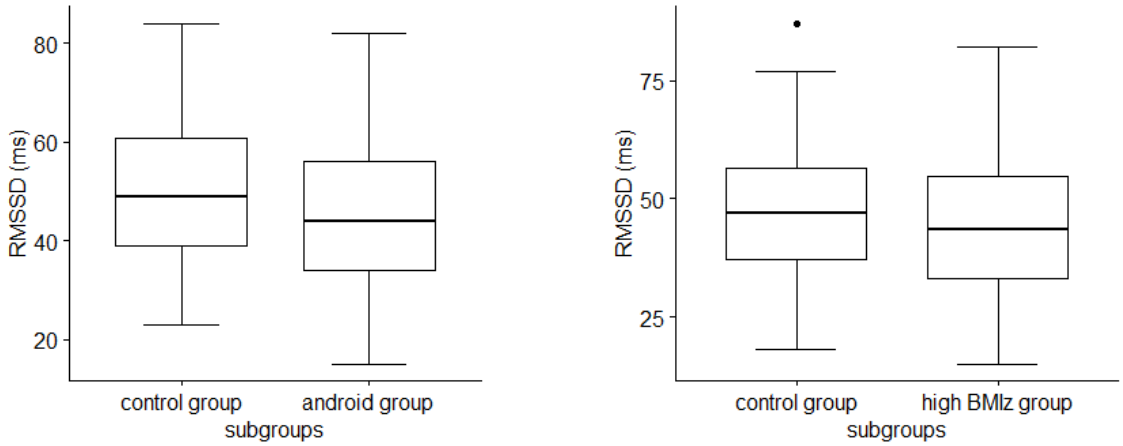
The most striking difference between our two opposing models, i.e. whether HRV impairments are the cause or the consequence of pediatric obesity, emerge in parasympathetically-driven time-domain parameters. While no differences were observed in the reverse direction (see Section 4.1.2), lower levels of RMSSD and pNN50 at age 8-10 years appeared to predict greater adiposity at age 10-12 years. These finding might imply

that a decrease in PNS activity indicate or aggravate the establishment of early-onset adiposity. From a physiological point of view, a prior reduction in PNS modulation is plausible. Impaired PNS activity might blunt the sense of satiety and simultaneously promote pathological eating behavior like impulsive uncontrolled food intake.

Eyre et al. (35) reviewed 13 cross-sectional studies examining the influence of weight status and body composition on time-domain indices. He concluded that the majority of studies reported that lower RMSSD (8 out of 13 included studies) and pNN50 (7 out of 9 included studies) were associated with greater adiposity. Finding in regards of RMSSD and pNN50 are only partly in line with our findings, as we only observe lower levels in one direction. We propose that our dissimilar patterns represent dynamic ANS changes in the development of childhood obesity.

Building on work by Soares-Miranda et al. (151) we investigated HRV and its association with body fat distribution in a larger sample. With the present study we were able to observe changes in HRV indices, independent of changes in percent body fat. Compared to propensity score matched controls we observed significantly lower means of RMSSD and pNN50 at age 8-10 years in the android group but not in the high BMI z-score group (Figure 4.3 and Figure 4.4). These findings reinforce the idea of the substantial effects of the PNS in the development of central adiposity two years later.

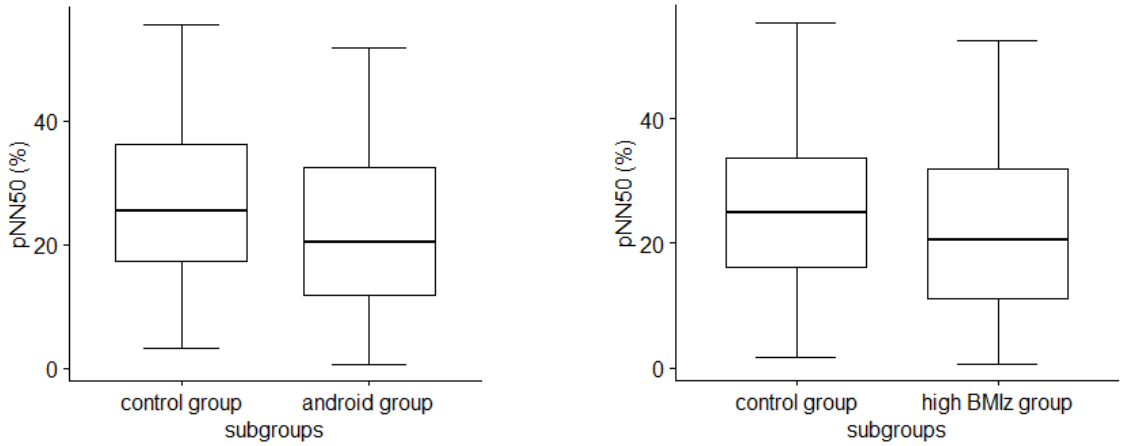
There were also no differences in means of RMSSD and pNN50 at age 8-10 years between high and low WHtR groups, indicating that WHtR is not equivalent to DXA measures in these regards. Our findings suggest that WHtR does not appear to be superior to BMI z-score. However, considering that results between Android-to-Gynoid-Ratio and WHtR and BMI z-score were similar in all regression models and corresponding bootstrapping procedures, we conclude that both WHtR and BMI z-score are reasonable alternatives for a resource-friendly assessment of adiposity in clinical practice.



t(162) = 2.03, **p = 0.04**, d = 0.27				
Subgroup	n	mean	SD	Δ%BF
Android group	82	45.4	16.4	2.27
Control group	82	49.6	14.8	3.03

t(162) = 1.26, p = 0.21, d = 0.20				
Subgroup	N	mean	SD	Δ%BF
High BMIz group	82	44.5	15.9	2.98
Control group	82	47.5	14.1	2.61

Figure 4.3 Differences in Means of RMSSD Between Android/High BMI z-Score Subgroup and Propensity Score Matched Controls: When subgroups are divided according to Android-to-Gynoid-Ratio, differences in RMSSD are evident. This difference is not observed when groups are grouped by BMI z-score.



t(162) = 2.52, **p = 0.01**, d = 0.33				
Subgroup	n	mean	SD	Δ%BF
Android group	82	22.5	13.8	2.27
Control group	82	27.0	13.1	3.03

t(162) = -1.72, p = 0.09, d = 0.27				
Subgroup	n	mean	SD	Δ%BF
High BMIz group	82	21.8	13.5	2.98
Control group	82	25.3	12.5	2.61

Figure 4.4 Differences in Means of pNN50 Between Android/High BMI z-Score Subgroup and Propensity Score Matched Controls: When subgroups are divided according to Android-to-Gynoid-Ratio, differences in pNN50 are evident. This difference is not observed when groups are grouped by BMI z-score.

4.3 The Relationship Between Heart Rate Variability and Its Corresponding Heart Rate

Thirty-five years ago, Akselrod et al. (191) were the first to identify a relationship between HRV and its corresponding heart rate. Consistent with more recent reports by de Geus (192), we also observed a negative exponential relation between heart rate and SDNN (a surrogate for overall HRV) (Figure 4.5, left). This relationship can predictably be converted to a close-to linear one by replacing heart rate with heart period (Figure 4.5, right), given the converting equation from heart rate to heart period (i.e., heart rate = 60,000/heart period).

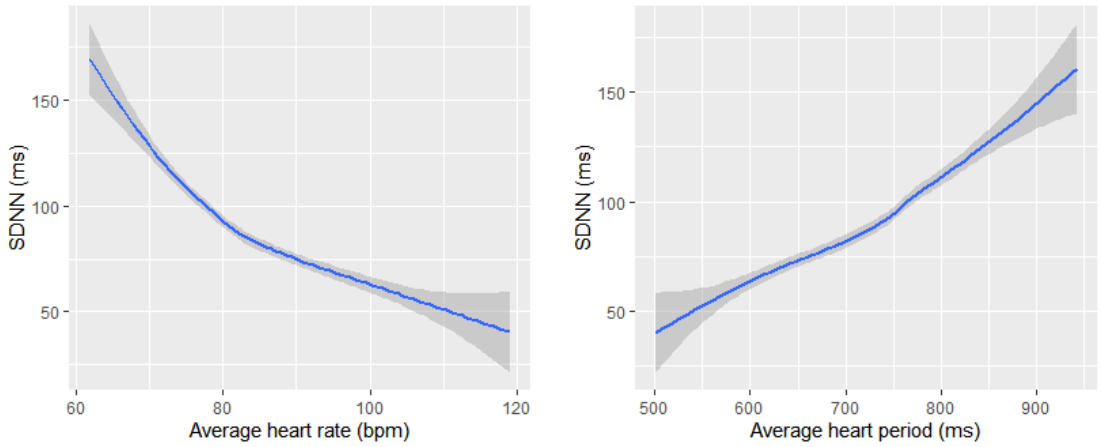


Figure 4.5 Relationship Between SDNN and Heart Rate/Heart Period: A negative exponential relation was observed between SDNN and heart rate at visit 1. When SDNN is plotted against heart period, a predictable conversion into a close-to linear relation can be observed.

Due to this non-linear cycle-length-dependence, identical heart rate fluctuations result in different heart period changes. As indicated in Figure 4.6, oscillations of a slow heart rate lead to a much broader variation of the heart period than the same oscillations of a fast heart rate. This phenomenon is extensively addressed by a working group led by Sacha (193-195). Whether or not this predictable relationship should be considered in HRV interpretations continues to be vigorously contested.

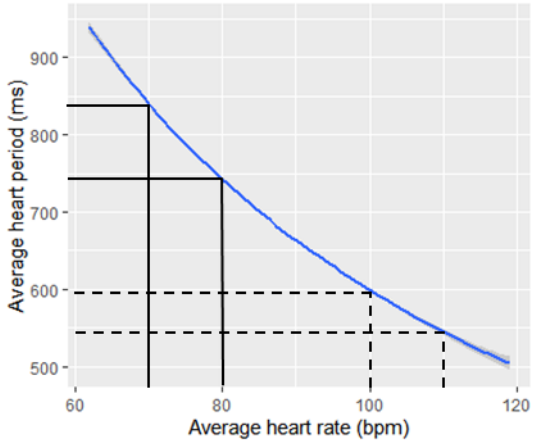


Figure 4.6 Non-Linear Cycle Length-Dependence Between Heart Rate and Heart Period: Oscillations of a slow heart rate lead to a much broader variation of the heart period than the same oscillations of a fast heart rate.

Some authors raise concerns about mathematical bias when it comes to traditional HRV interpretations (194-197). On these grounds, various heart rate adjustment approaches have been promoted to account for this "restriction-of-range effect" (194, 197-200). For example, Gąsior et al. (123) applied a heart rate correction procedure on ECG recordings of 346 children aged 6-13 years to provide normative values for corrected HRV parameters for different age groups. Monfredi et al. (197) even argue that findings of altered HRV are substantially attributable to changes in heart rate and therefore HRV studies that did not adjust for heart rate should be re-evaluated.

However, advocates of the traditional uncorrected approach disagree arguing that heart rate and its variability represent two different entities. Simulated regression models by de Geus et al. (192) suggest that a semi-partial correlation of HRV and heart rate with a third variable would underestimate the contribution of both HRV and heart rate. Moreover they report that using HRV parameters adjusted for heart rate would strongly underestimate the contribution of HRV and further compromise the amount of explained variance in the calculated model.

In light of these recommendations, we opted not to "regress out" heart rate effects in our covariate analyses. Our decision is also supported by additional sensitivity analyses. When we plotted heart rate against Android-to-Gynoid-Ratio and BMI z-score, the average heart rate did not appear to change with the degree of adiposity. In fact, a correlation analysis also suggested that there are no significant correlations between heart rate and adiposity measures in our analytic sample (Figure 4.7).

In addition, neither cross-sectional nor 2-year-prospective analyses revealed significant correlations between SDNN, as a marker for overall HRV, and adiposity. These findings suggest that observed changes in our sample stem from shifts between SNS and PNS activity. On these grounds, it seems likely that alterations in HRV parameters are not solely attributable to the corresponding heart rate and hence a correction process would not be justified. While we appreciate the interdependence of heart rate and its variability, our analyses emphasise that HRV alterations should be interpreted as a separate entity.

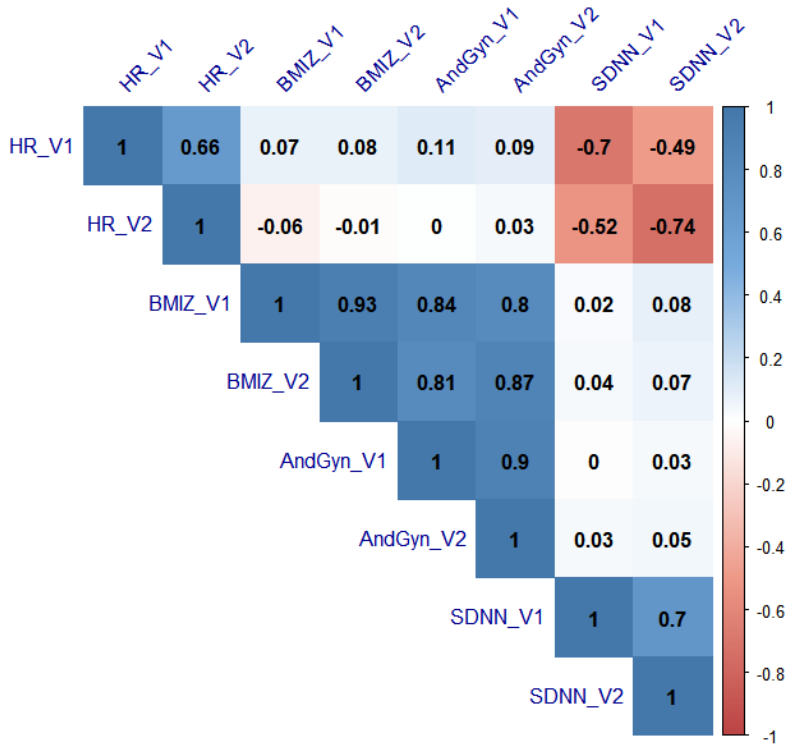


Figure 4.7 Correlation Matrix Depicting Cross-Sectional and 2-Year-Prospective Correlation for Heart Rate, SDNN, Android-to-Gynoid-Ratio and BMI z-Score: The average heart rate and SDNN do not correlate with any of our analyzed adiposity measures. Identical results are observed for cross-sectional and 2-year-prospective correlations.

4.4 Conclusion

Causes and consequences of pediatric obesity remain complex. Considering the leading role of the ANS in directly regulating both energy expenditure and energy intake, the assessment of SNS and PNS activity appears to be an appealing diagnostic tool for the clinical evaluation of adaptive processes in the development of obesity.

In the present study meaningful albeit different patterns for the two proposed cross-lagged relations emerged. The illustrated association between low PNS activity at age 8-10 years and adiposity at age 10-12 years contributes to better understand the pathogenesis of pediatric obesity. Impaired PNS activity might promote weight gain in children aged 8-10 years. This could be further aggravated by a sympathovagal imbalance in terms of a sympathetic predominance. Due to the lack of reliability of HRV analyses to quantify SNS activity, we cannot discern whether the imbalance stems from a mere decrease in PNS activity or if an additional increase in SNS exacerbates the imbalance. Reflecting upon the opposite cross-lagged relation, greater measures of adiposity at age 8-10 years were also associated with a sympathovagal imbalance but did not appear to influence parasympathetically-driven time-domain parameters, RMSSD and pNN50, two years later. Bi-directional findings of a sympathovagal imbalance indicate that the development of obesity is accompanied by a general disruption of the children's normal ANS maturation. This conclusion is challenged by findings suggesting that the response of HRV to the development of obesity changes over time.

Having said this, we have to acknowledge that our study is limited by the lack of information about the history of obesity prior to the beginning of our data collection. Inconsistent findings in regards of SNS activity might arise from our exposure window. Whether SNS activity, expressed by LF, changes depending on the duration of obesity remains unsolved. The hypothesis of an early, but transient, increase in SNS activity might explain these inconsistent finding but further research is needed to investigate in the exposure-dependent behaviour of the SNS in the development of obesity.

The informative value of LF/HF-Ratio and normalized units remains another subject of active debate. Further investigations considering other measurement techniques are required to better understand SNS contributions in the development of obesity and to enhance the interpretability of frequency-domain parameters (i.e. LF and HF) and derived indices (i.e. LF/HF-Ratio, LFnu and HFnu).

Results in terms of PNS activity are more elucidated. It is broadly accepted that the PNS plays a key role in children's health. Low PNS activity is an independent risk factor for cardiovascular disease indicating that the PNS is a plausible link between obesity and adverse cardiovascular outcomes. Converging evidence suggests that blunted PNS activity promotes weight gain but that it is modifiable through caloric-restricting weight loss interventions (including hypocaloric diets and bariatric surgeries) and, above all, exercise. Accordingly, the level of physical activity should always be considered in HRV analyses. Although we controlled for physical activity at baseline using objective accelerometry data, future studies should be stimulated to investigate in changes in physical activity over time and see how this might impact HRV assessments and future weight gains. In a next step, adding measures of aerobic fitness, such as peak oxygen consumption during exercise, would be another aspect worth examining as MVPA is considered a current snapshot of physical activity while measures of aerobic fitness are thought to be better proxies for the overall fitness state.

Associations between Android-to-Gynoid-Ratio and HRV in obese but otherwise healthy children seemed plausible but have not been subject to any studies so far. Findings of the present study should encourage researchers to use this relatively new measure to evaluate central adiposity. Our secondary analyses elicited that subjects with lower levels of RMSSD and pNN50 at age 8-10 year are more likely to establish central adiposity measured by Android-to-Gynoid-Ratio two years later. By comparing different adiposity measures we replicated previous findings suggesting to consider fat distribution rather than weight status or total body fat in the association between the cardiac ANS and pediatric obesity. According to our findings, we conclude that WHtR and BMI z-score cannot be considered as surrogates for more sophisticated methods to evaluate body fat distribution such as DXA. Given that WHtR and BMI z-scores and Android-to-Gynoid-Ratio showed similar results in our main analyses, both WHtR and BMI z-score can be considered reasonable resource-friendly alternatives for the assessment of adiposity in the context of HRV analyses.

To our knowledge, no longitudinal study investigating HRV in healthy children has been published so far. By employing a cross-lagged-panel design we aimed to examine longitudinal associations. While this approach helped us to generate new hypotheses, at least three waves of data collection would be needed to infer causality and reliably talk

about predictions. Further studies will have to observe changes in HRV over a longer period to better understand the role of the ANS in the development of obesity.

Although our sample was considerably large in comparison with existing HRV studies in children, generalizability is limited as participation was restricted to children with at least one obese parent. When compared to a representative sample of the Quebec population, subjects of the present study were more likely to be overweight or obese and had a worse lipid profile. Since we endeavoured to unmask HRV patterns that are indicative of future weight gains, investigating in children at risk of obesity appears to be reasonable. It should also be acknowledged that our sample was restricted to Caucasian children. Hence, the generalizability to other ethnicities is likely but needs to be confirmed. The short exposure window of two years observing pre-adolescents during their sexual maturation is another limiting factor compromising generalizability. By incorporating Tanner stage in our models, we strived to account for physiological influences due to puberty.

To conclude, this study provides valuable insight, as reduced RMSSD and pNN50 in otherwise healthy 8-10 year olds may be a conceivable early sign indicating pathophysiological processes before excess weight is gained. In the future, this could be used as a clinical tool for risk stratification to counteract the problem of obesity before it even develops. Whether routine HRV surveillance during childhood would be beneficial for an early detection of children developing obesity or whether modulation of ANS will decrease the risk of future weight gains requires further investigation.

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Appendices

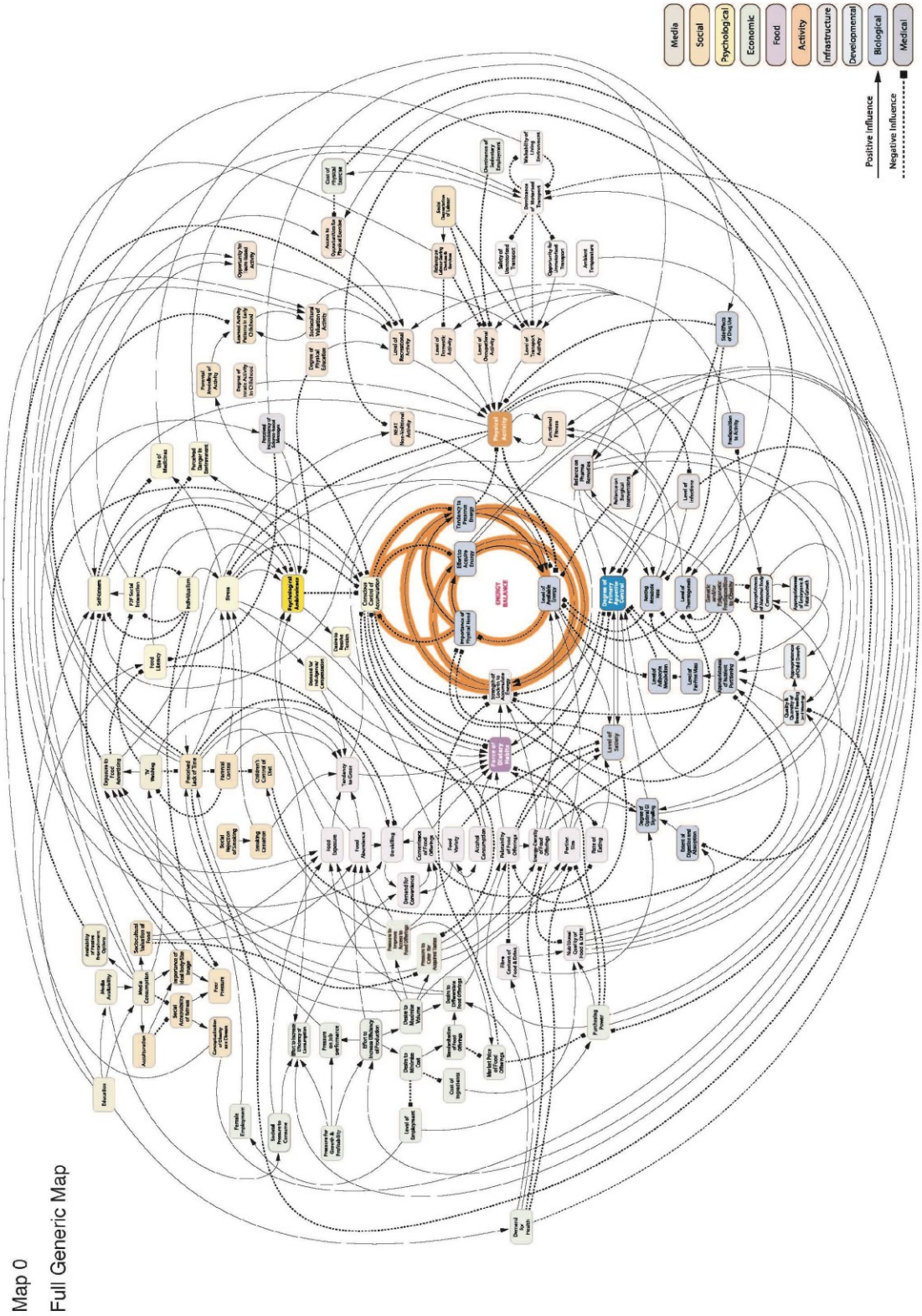


Figure 0.1 UK Foresight Obesity System Map extracted from Butland B, Jebb S, Kopelman P, McPherson K, Thomas S, Mardell J, et al., editors. Foresight. Tackling obesities: future choices. Project report 2007.

I. Univariate and Multivariate Linear Regression Models

	HRV V1	Parameters of the Univariate Linear Regression Analysis				
		β	Standard Error	CI 95%	t-value	Sig
AndGyn V2	LF	7.217e-06	6.214e-06	-4.999e-06; 1.943e-05	1.16	0.25
	HF	-1.083e-06	8.342e-06	-1.748e-05; 1.532e-05	-0.13	0.90
	LF/HF	0.032	0.008	0.016; 0.049	3.94	<0.001
	LFnu	0.248	0.066	0.118; 0.378	3.74	<0.001
	HFnu	-0.248	0.066	-0.378; -0.118	-3.74	<0.001
	SDNN	1.821e-04	2.494e-04	-3.081e-04; 6.723e-04	0.73	0.47
	RMSSD	-7.519e-04	3.819e-04	-1.503e-03; -1.035e-06	-1.97	<0.05
	pNN50	-1.117e-03	4.325e-04	-1.967e-03; -2.663e-04	-2.58	0.01

Table 0.1 Univariate Linear Regression Model With Android-Gynoid-Ratio at Visit 2 Defined as Outcome

	HRV V2	Parameters of the Univariate Linear Regression Analysis				
		β	Standard Error	CI 95%	t-value	Sig
AndGyn V1	LF (ln)	0.486	0.279	-0.063; 1.036	1.74	0.08
	HF (ln)	-0.080	0.346	-0.760; 0.600	-0.23	0.82
	LF/HF (ln)	0.565	0.174	0.222; 0.907	3.24	<0.01
	LFnu	0.121	0.039	0.044; 0.198	3.08	<0.01
	HFnu	-0.121	0.039	-0.198; -0.044	-3.08	<0.01
	SDNN (ln)	0.107	0.124	-0.137; 0.351	0.86	0.39
	RMSSD	-1.487	7.386	-16.006; 13.032	-0.20	0.84
	pNN50	-5.249	6.372	-17.777; 7.278	-0.82	0.41

Table 0.2 Univariate Linear Regression Model With Android-Gynoid-Ratio at Visit 1 Defined as Exposure

	HRV V1	Parameters of the Univariate Linear Regression Analysis				
		β	Standard Error	CI 95%	t-value	Sig
BMI z-Score V2	LF	7.262e-05	5.566e-05	-3.679e-05; 1.820e-04	1.31	0.19
	HF	-8.950e-06	7.475e-05	-1.559e-04; 1.380e-04	-0.12	0.91
	LF/HF	0.342	0.074	0.196; 0.487	4.62	<0.001
	LFnu	2.512	0.590	1.352; 3.672	4.26	<0.001
	HFnu	-2.512	0.590	-3.672; -1.352	-4.26	<0.001
	SDNN	0.003	0.002	-0.001; 0.008	1.45	0.15
	RMSSD	-0.007	0.003	-0.013; 2.693e-04	-1.89	0.06
	pNN50	-0.010	0.004	-0.018; -0.003	-2.62	<0.01

Table 0.3 Univariate Linear Regression Model With BMI z-Score at Visit 2 Defined as Outcome

	HRV V2	Parameters of the Univariate Linear Regression Analysis				
		β	Standard Error	CI 95%	t-value	Sig
BMI z-Score V1	LF (ln)	0.076	0.030	0.016; 0.135	2.50	0.01
	HF (ln)	0.021	0.038	-0.053; 0.095	0.57	0.57
	LF/HF (ln)	0.054	0.019	0.017; 0.092	2.85	<0.01
	LFnu	0.012	0.004	0.003; 0.020	2.69	<0.01
	HFnu	-0.012	0.004	-0.020; -0.003	-2.69	<0.01
	SDNN (ln)	0.029	0.013	0.003; 0.056	2.18	0.03
	RMSSD	0.712	0.803	-0.865; 2.290	0.89	0.38
	pNN50	0.147	0.694	-1.216; 1.511	0.21	0.83

Table 0.4 Univariate Linear Regression Model With BMI z-Score at Visit 1 Defined as Exposure

	Determinant	Parameters of Multiple Linear Regression Analysis					
		β	CI 95%	Sig	R^2	F-test	Sig
AndGyn V2	LF V1	8.971e-06	-2.987e-06; 2.092e-05	0.14	0.086	6.275	<0.001
	Δ % body fat	0.006	0.004; 0.009	<0.001			
	Sex	-0.020	-0.046; 0.005	0.12			
	Tanner V2	0.022	0.007; 0.037	<0.01			
	Age V2	0.004	-0.011; 0.019	0.59			
	MVPA	-7.583e-04	-1.258e-03; 2.580e-04	<0.01			
	HF V1	-9.985e-08	-1.604e-05; 1.584e-05	0.99	0.081	5.880	<0.001
	Δ % body fat	0.006	0.004; 0.009	<0.001			
	Sex	-0.021	-0.046: 0.005	0.11			
	Tanner V2	0.022	0.007; 0.037	<0.01			
	Age V2	0.005	-0.010; 0.020	0.51			
	MVPA	-7.075e-04	-1.207e-03; 2.078e-04	<0.01			
	LF/HF V1	0.032	0.015; 0.0477	<0.001	0.115	8.668	<0.001
	Δ % body fat	0.006	0.004; 0.009	<0.001			
	Sex	-0.015	-0.041; 0.010	0.24			
	Tanner V2	0.021	0.007; 0.035	<0.01			
	Age V2	0.004	-0.011: 0.019	0.58			
	MVPA	-6.485e-04	-1.136e-03; -1.598e-04	<0.01			
	LFnu V1	0.242	0.115; 0.369	<0.001	0.113	8.437	<0.001
	Δ % body fat	0.006	0.004; 0.009	<0.001			
	Sex	-0.016	-0.041; 0.010	0.23			
	Tanner V2	0.021	0.007; 0.036	<0.01			
	Age V2	0.004	-0.011; 0.019	0.59			
	MVPA	-6.646e-04	1.154e-03; -1.755e-04	<0.01			
	HFnu V1	-0.242	-0.369; -0.115	<0.001	0.113	8.437	<0.001
	Δ % body fat	0.006	0.004; 0.008	<0.001			
	Sex	-0.016	-0.041; 0.010	0.23			
	Tanner V2	0.021	0.007; 0.036	<0.01			
	Age V2	0.004	-0.011; 0.019	0.59			
	MVPA	-6.646e-04	-1.154e-03; -1.755e-04	<0.01			
	SDNN V1	1.602e-04	-3.177e-04; 6.381e-04	0.51	0.082	5.959	<0.001
	Δ % body fat	0.006	0.004; 0.009	<0.001			
	Sex	-0.021	-0.046; 0.005	0.12			
	Tanner V2	0.022	0.007; 0.036	<0.01			
	Age V2	0.005	-0.010; 0.020	0.53			
	MVPA	-7.219e-04	-1.221e-03; -2.233e-04	<0.01			
	RMSSD V1	-6.546e-04	-1.391e-03; 8.129e-05	0.08	0.088	6.435	<0.001
	Δ % body fat	0.006	0.004; 0.009	<0.001			
	Sex	-0.021	-0.046; 0.005	0.11			
	Tanner V2	0.022	0.007; 0.036	<0.01			
	Age V2	0.006	-0.009; 0.020	0.46			
	MVPA	-6.397e-04	-1.141e-03; -1.386e-04	0.01			
	pNN50 V1	-1.002e-03	-1.836e-03; -1.689e-04	0.02	0.094	6.894	<0.001
	Δ % body fat	0.006	0.004; 0.009	<0.001			
	Sex	-0.020	-0.046; 0.005	0.12			
	Tanner V2	0.021	0.007; 0.036	<0.01			
	Age V2	0.006	-0.009; 0.021	0.45			
	MVPA	-6.172e-04	-1.117e-03; -1.177e-04	0.02			

Table 0.5 Multiple Linear Regression Model With Android-Gynoid-Ratio at Visit 2 Defined as Outcome

HRV V2	Determinant	Parameters of Multiple Linear Regression Analysis					
		β	CI 95%	Sig	R^2	F-test	Sig
LF (ln)	AndGyn V1	0.490	-0.084; 1.063	0.09	0.023	1.560	0.16
	Δ % body fat	-0.004	-0.018; 0.010	0.57			
	Sex	-0.092	-0.232; 0.047	0.19			
	Tanner V2	0.005	-0.077; 0.086	0.91			
	Age V2	0.035	-0.046; 0.117	0.40			
	MVPA	0.002	-0.001; 0.004	0.30			
HF (ln)	AndGyn V1	-0.013	-0.728; 0.702	0.97	0.003	0.214	0.97
	Δ % body fat	0.003	-0.015; 0.021	0.76			
	Sex	0.018	-0.156; 0.192	0.83			
	Tanner V2	-0.007	-0.108; 0.095	0.90			
	Age V2	0.018	-0.083; 0.120	0.73			
	MVPA	0.002	-0.002; 0.005	0.32			
LF/HF (ln)	AndGyn V1	0.502	0.147; 0.857	<0.01	0.055	3.833	<0.001
	Δ % body fat	-0.007	-0.016; 0.002	0.13			
	Sex	-0.111	-0.197; -0.024	0.01			
	Tanner V2	0.012	-0.039; 0.062	0.65			
	Age V2	0.017	-0.034; 0.067	0.51			
	MVPA	-2.610e-04	-1.956e-03; 1.434e-03	0.76			
LFnu	AndGyn V1	0.108	0.028; 0.189	<0.01	0.051	3.597	<0.01
	Δ % body fat	-0.002	-0.004; 0.001	0.14			
	Sex	-0.024	-0.044; -0.005	0.01			
	Tanner V2	0.002	-0.010; 0.013	0.75			
	Age V2	0.004	-0.007; 0.016	0.45			
	MVPA	-6.457e-05	-4.466e-04; 3.175e-04	0.74			
HFnu	AndGyn V1	-0.108	-0.188; -0.028	<0.01	0.051	3.597	<0.01
	Δ % body fat	0.002	-0.001; 0.004	0.14			
	Sex	0.024	0.005; 0.044	0.01			
	Tanner V2	-0.002	-0.013; 0.010	0.75			
	Age V2	-0.004	-0.016; 0.007	0.45			
	MVPA	6.457e-05	-3.175e-04; 4.466e-04	0.74			
SDNN (ln)	AndGyn V1	0.076	-0.178; 0.330	0.56	0.022	1.513	0.17
	Δ % body fat	-0.003	-0.009; 0.004	0.43			
	Sex	-0.052	-0.114; 0.010	0.10			
	Tanner V2	0.023	-0.013; 0.059	0.22			
	Age V2	0.002	-0.034; 0.038	0.93			
	MVPA	5.979e-04	-6.156e-04: 1.811e-03	0.33			
RMSSD	AndGyn V1	-1.117	-16.316; 14.082	0.89	0.011	0.743	0.62
	Δ % body fat	-0.099	-0.475; 0.278	0.61			
	Sex	-1.327	-5.034; 2.380	0.48			
	Tanner V2	-0.235	-2.390; 1.920	0.83			
	Age V2	1.106	-1.052; 3.264	0.31			
	MVPA	0.040	-0.033; 0.112	0.28			
pNN50	AndGyn V1	-5.260	-18.385; 7.865	0.43	0.011	0.737	0.62
	Δ % body fat	-0.099	-0.424; 0.226	0.55			
	Sex	-0.600	-3.800; 2.602	0.71			
	Tanner V2	-0.160	-2.021; 1.701	0.87			
	Age V2	0.918	-0.945; 2.782	0.33			
	MVPA	0.035	-0.027; 0.098	0.27			

Table 0.6 Multiple Linear Regression Model With Android-Gynoid-Ratio at Visit 1 Defined as Exposure

	Determinant	Parameters of Multiple Linear Regression Analysis					
		β	CI 95%	Sig	R^2	F-test	Sig
BMI z-Score V2	LF V1	8.895e-05	-1.503e-05; 1.929e-04	0.09	0.140	10.790	<0.001
	Δ % body fat	0.061	0.038; 0.084	<0.001			
	Sex	-0.330	-0.552; -0.108	<0.01			
	Tanner V2	0.420	0.292; 0.547	<0.001			
	Age V2	-0.132	-0.262; -0.003	<0.05			
	MVPA	-0.006	-0.010; -0.001	0.01			
	HF V1	6.101e-06	-1.326e-04; 1.448e-04	0.93	0.134	10.250	<0.001
	Δ % body fat	0.061	0.038; 0.084	<0.001			
	Sex	-0.336	-0.559; -0.113	<0.01			
	Tanner V2	0.418	0.290; 0.546	<0.001			
	Age V2	-0.125	-0.254; 0.005	0.06			
	MVPA	-0.005	-0.009; -0.001	0.02			
	LF/HF V1	0.328	0.190; 0.466	<0.001	0.179	14.460	<0.001
	Δ % body fat	0.06	0.042; 0.086	<0.001			
	Sex	-0.278	-0.496; -0.059	0.01			
	Tanner V2	0.407	0.283; 0.532	<0.001			
	Age V2	-0.133	-0.259; -0.007	0.04			
	MVPA	-0.004	-0.009; -0.000	0.04			
	LFnu V1	2.431	1.33; 3.528	<0.001	0.173	13.900	<0.001
	Δ % body fat	0.063	0.041; 0.085	<0.001			
	Sex	-0.283	-0.502; -0.064	0.01			
	Tanner V2	0.411	0.286; 0.536	<0.001			
	Age V2	-0.133	-0.260; -0.006	0.04			
	MVPA	-0.005	-0.009; -0.000	0.03			
	HFnu V1	-2.431	-3.528; -1.334	<0.001	0.173	13.900	<0.001
	Δ % body fat	0.063	0.041; 0.085	<0.001			
	Sex	-0.283	-0.502; -0.064	0.01			
	Tanner V2	0.411	0.286; 0.536	<0.001			
	Age V2	-0.133	-0.260; -0.006	0.04			
	MVPA	-0.005	-0.009; -0.000	0.03			
	SDNN V1	0.003	-0.002; 0.007	0.21	0.137	10.560	<0.001
	Δ % body fat	0.061	0.038; 0.083	<0.001			
	Sex	-0.330	-0.553; -0.108	<0.01			
	Tanner V2	0.414	0.286; 0.542	<0.001			
	Age V2	-0.128	-0.258; 0.002	0.05			
	MVPA	-0.005	-0.010; -0.001	0.02			
	RMSSD V1	-0.006	-0.012; 0.001	0.09	0.140	10.800	<0.001
	Δ % body fat	0.062	0.039; 0.084	<0.001			
	Sex	-0.335	-0.557; -0.113	<0.01			
	Tanner V2	0.416	0.289; 0.544	<0.001			
	Age V2	-0.119	-0.248; 0.011	0.07			
	MVPA	-0.004	-0.009; -0.000	<0.05			
	pNN50 V1	-0.009	-0.016; -0.002	0.02	0.146	11.380	<0.001
	Δ % body fat	0.062	0.040; 0.084	<0.001			
	Sex	-0.332	-0.553; -0.111	<0.01			
	Tanner V2	0.413	0.286; 0.540	<0.001			
	Age V2	-0.117	-0.246; 0.012	0.08			
	MVPA	-0.004	-0.009; 0.000	0.06			

Table 0.7 Multiple Linear Regression Model With BMI z-Score at Visit 2 Defined as Outcome

HRV V2	Determinant	Parameters of Multiple Linear Regression Analysis					
		β	CI 95%	Sig	R^2	F-test	Sig
LF (ln)	BMIz V1	0.075	0.013; 0.137	0.02	0.030	2.052	0.06
	Δ % body fat	-0.004	-0.018; 0.010	0.57			
	Sex	-0.070	-0.210; 0.071	0.33			
	Tanner V2	-0.007	-0.089; 0.076	0.88			
	Age V2	0.049	-0.033; 0.130	0.25			
	MVPA	0.002	-0.001; 0.004	0.28			
HF (ln)	BMIz V1	0.030	-0.047; 0.107	0.44	0.005	0.312	0.93
	Δ % body fat	0.003	-0.015; 0.021	0.74			
	Sex	0.028	-0.148; 0.204	0.76			
	Tanner V2	-0.016	-0.119; 0.087	0.76			
	Age V2	0.023	-0.079; 0.125	0.66			
	MVPA	0.003	-0.002; 0.005	0.28			
LF/HF (ln)	BMIz V1	0.045	0.007; 0.084	0.02	0.049	3.414	<0.01
	Δ % body fat	-0.007	-0.016; 0.002	0.11			
	Sex	-0.097	-0.185; -0.010	0.03			
	Tanner V2	0.009	-0.042; 0.061	0.72			
	Age V2	0.025	-0.026; 0.076	0.33			
	MVPA	-3.548e-04	-0.002; 0.001	0.68			
LFnu	BMIz V1	0.010	0.001; 0.018	0.03	0.046	3.204	<0.01
	Δ % body fat	-0.002	-0.004; 0.000	0.12			
	Sex	-0.022	-0.041; -0.002	0.03			
	Tanner V2	0.001	-0.010; 0.013	0.81			
	Age V2	0.006	-0.005; 0.018	0.30			
	MVPA	-8.510e-05	-4.6733-04; 2.971e-04	0.66			
HFnu	BMIz V1	-0.010	-0.018; -0.001	0.03	0.046	3.204	<0.01
	Δ % body fat	0.002	-0.000; 0.004	0.12			
	Sex	0.022	0.002; 0.041	0.03			
	Tanner V2	-0.001	-0.013; 0.010	0.81			
	Age V2	-0.006	-0.018; 0.005	0.30			
	MVPA	8.510e-05	-2.971e-04; 4.673e-04	0.66			
SDNN (ln)	BMIz V1	0.025	-0.002; 0.052	0.07	0.029	2.005	0.06
	Δ % body fat	-0.002	-0.009; 0.004	0.45			
	Sex	-0.044	-0.107; 0.018	0.16			
	Tanner V2	0.017	-0.019; 0.053	0.36			
	Age V2	0.006	-0.030; 0.042	0.75			
	MVPA	6.663e-04	-5.398e-04; 1.872e-03	0.28			
RMSSD	BMIz V1	0.803	-0.838; 2.443	0.34	0.013	0.895	0.50
	Δ % body fat	-0.090	-0.467; 0.286	0.64			
	Sex	-1.067	-4.807; 2.673	0.58			
	Tanner V2	-0.500	-2.676; 1.684	0.66			
	Age V2	1.235	-0.937; 3.407	0.26			
	MVPA	0.044	-0.028; 0.116	0.23			
pNN50	BMIz V1	0.214	-1.205; 1.634	0.77	0.010	0.647	0.69
	Δ % body fat	-0.090	-0.416; 0.235	0.59			
	Sex	-0.517	-3.753; 2.718	0.75			
	Tanner V2	-0.339	-2.225; 1.547	0.72			
	Age V2	0.943	-0.936; 2.822	0.32			
	MVPA	0.039	-0.023; 0.102	0.22			

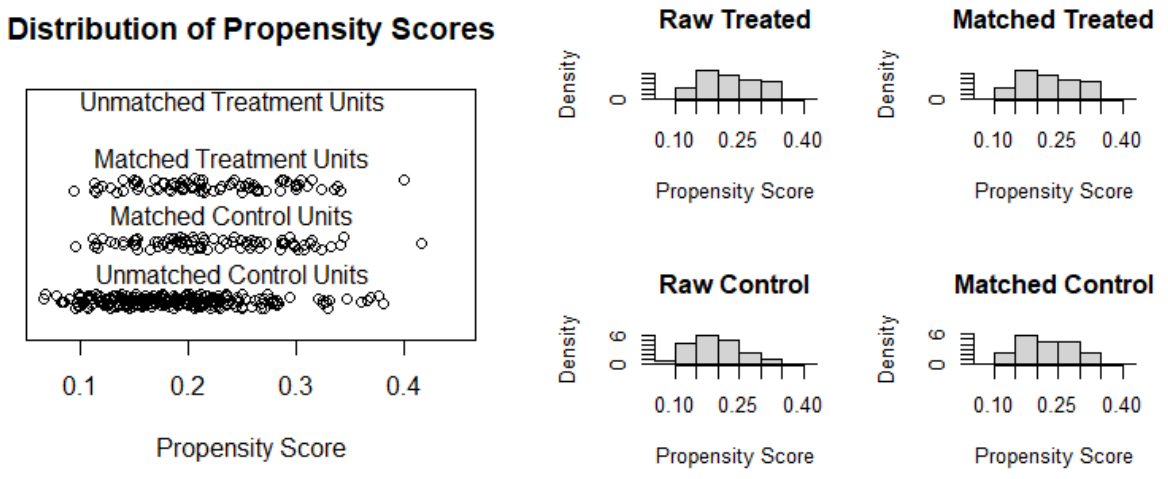
Table 0.8 Multiple Linear Regression Model With BMI z-Score at Visit 1 Defined as Exposure

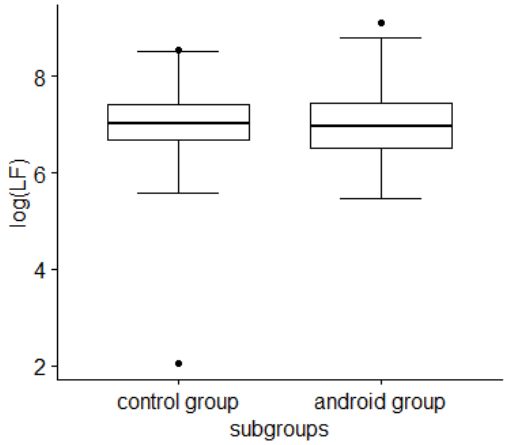
II. Propensity Score Matching

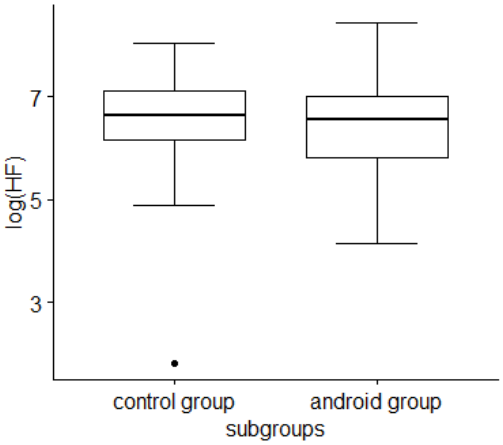
a. HRV at Visit 1 and Android-to-Gynoid-Ratio at Visit 2

```
Call:
matchit(formula = subgroup ~ delta_bodyfat + SEX + TANNER_V2 +
    AGE_V2 + MVPA_V1, data = df, method = "optimal")

Summary of balance for all data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2230        0.1967     0.0646    0.0263  0.0266   0.0272  0.0507
delta_bodyfat       2.6738        2.0206     4.9014    0.6532  0.7085   0.8515  3.8632
SEX                 1.3902        1.4475     0.4980   -0.0573  0.0000   0.0610  1.0000
TANNER_V2           2.2439        2.1265     1.0466    0.1174  0.0000   0.1341  1.0000
AGE_V2             11.7920       11.6446     0.9607    0.1473  0.1650   0.1668  0.3700
MVPA_V1            46.3934       52.0582    24.8077   -5.6648  7.5357   6.6682 14.0000


Summary of balance for matched data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2230        0.2231     0.0666   -0.0001  0.0006   0.0011  0.0158
delta_bodyfat       2.6738        3.0285     4.7816   -0.3548  0.3211   0.5435  3.4496
SEX                 1.3902        1.4024     0.4934   -0.0122  0.0000   0.0122  1.0000
TANNER_V2           2.2439        2.1585     0.9872    0.0854  0.0000   0.0854  1.0000
AGE_V2             11.7920       11.6985     0.9553    0.0934  0.1150   0.1322  0.3300
MVPA_V1            46.3934       45.4695    20.6318    0.9239  2.6190   3.7128 49.5000

Percent Balance Improvement:
             Mean Diff. eQQ Med eQQ Mean   eQQ Max
distance         99.5859 97.7781  95.9761   68.8035
delta_bodyfat    45.6855 54.6794  36.1791   10.7059
SEX              78.7122  0.0000  80.0000    0.0000
TANNER_V2        27.2611  0.0000  36.3636    0.0000
AGE_V2           36.5913 30.3030  20.7602   10.8108
MVPA_V1          83.6904 65.2449  44.3205 -253.5714

Sample sizes:
          Control Treated
All           324      82
Matched        82      82
Unmatched     242       0
Discarded       0       0
```

Subgroup	AndGyn V2	Δ % Body fat	% Male	% Prepubertal V2	Age V2	MVPA V1
Android group	0.511	2.27	61.0	25.6	11.8	46.4
Control group	0.294	3.03	59.8	29.3	11.7	45.5

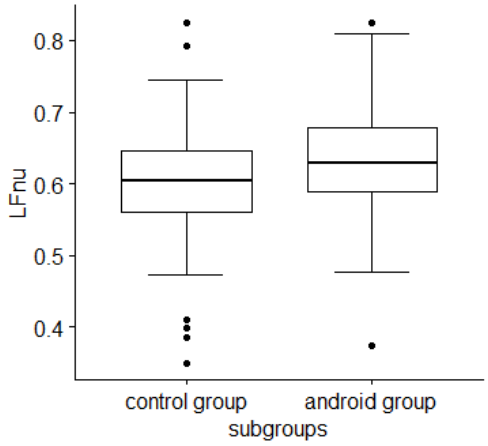


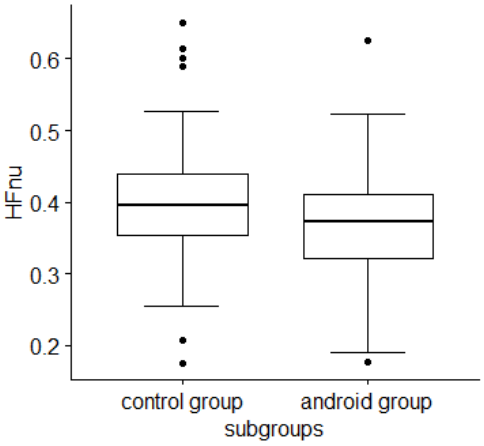




t(160.44) = -0.08, p = 0.93, d = -0.07				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	1454	1364	2.27
Control group	82	1376	906	3.03

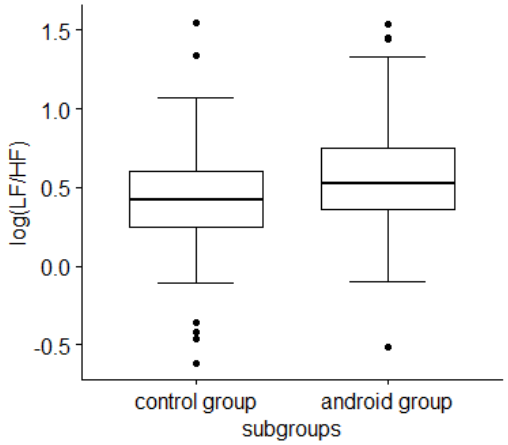
t(162) = 0.99, p = 0.32, d = 0.06				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	930	885	2.27
Control group	82	974	742	3.03



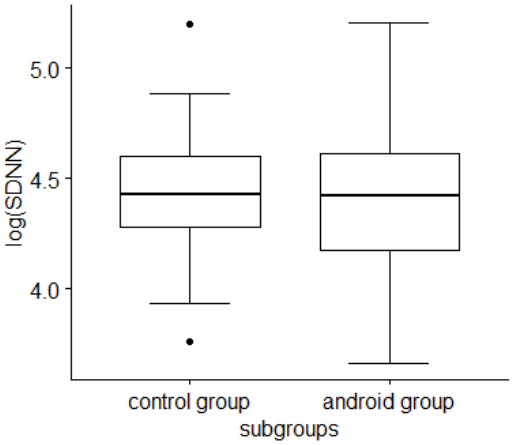


t(162) = -2.26, **p = 0.03**, d = -0.35				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	0.634	0.083	2.27
Control group	82	0.604	0.084	3.03

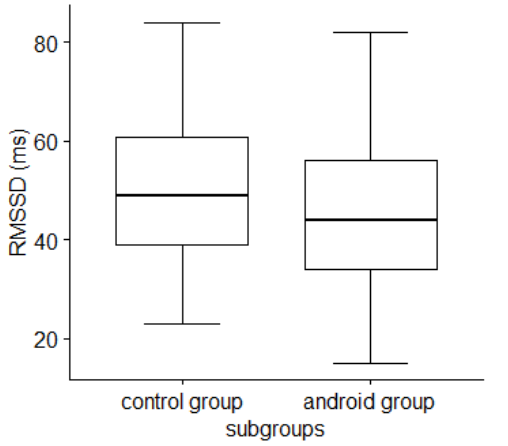
t(162) = 2.26, **p = 0.03**, d = 0.35				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	0.366	0.398	2.27
Control group	82	0.398	0.084	3.03



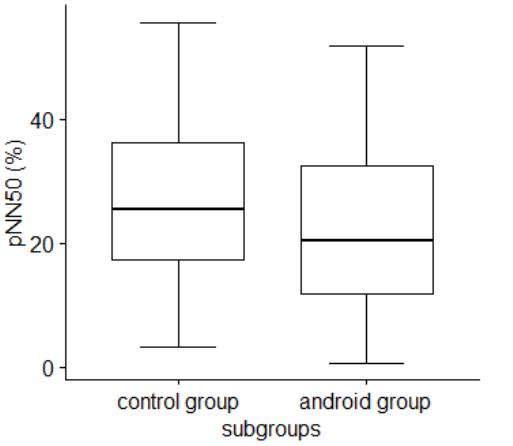
t(162) = -2.26, **p = 0.03**, d = -0.34				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	1.898	0.790	2.27
Control group	82	1.654	0.653	3.03



t(156.31) = 0.33, p = 0.74, d = -0.01				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	86.3	28.9	2.27
Control group	82	86.1	23.2	3.03



t(162) = 2.03, **p = 0.04**, d = 0.27				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	45.4	16.4	2.27
Control group	82	49.6	14.8	3.03

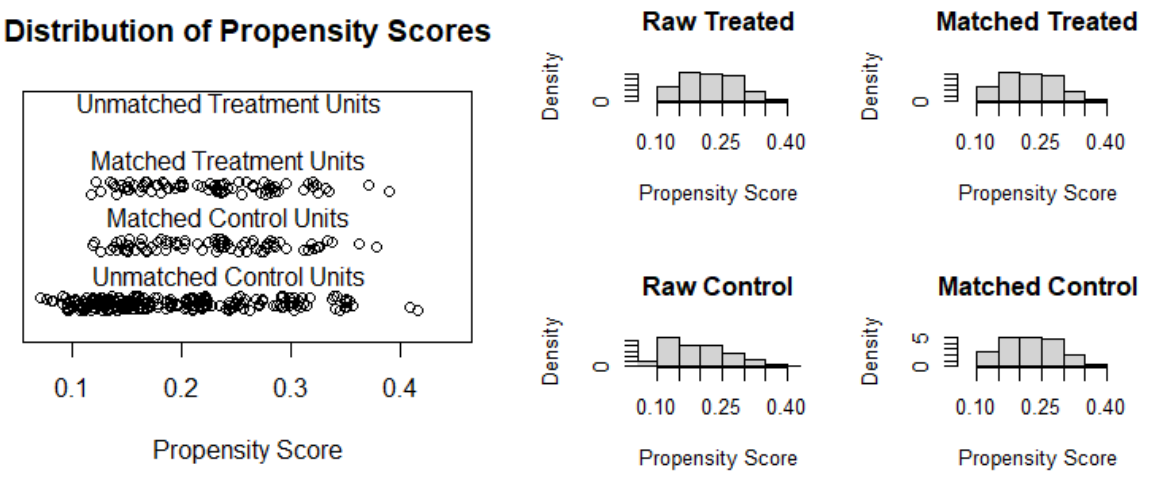


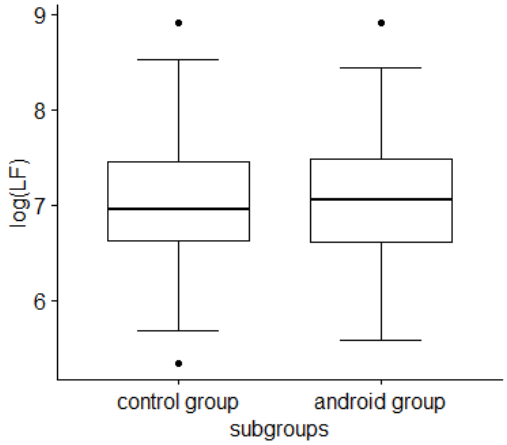
t(162) = 2.52, **p = 0.01**, d = 0.33				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	22.5	13.8	2.27
Control group	82	27.0	13.1	3.03

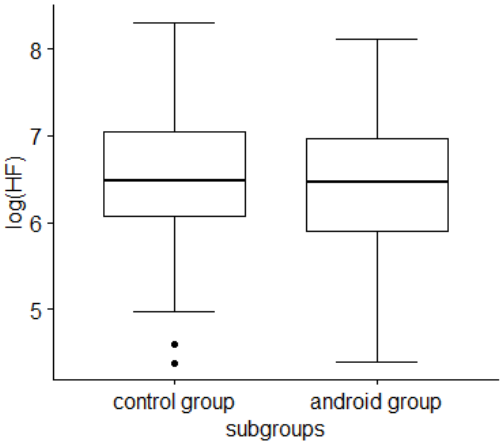
b. Android-to-Gynoid-Ratio at Visit 1 and HRV at Visit 2

```
Call:
matchit(formula = subgroup ~ delta_bodyfat + SEX + TANNER_V2 +
    AGE_V2 + MVPA_V1, data = df, method = "optimal")

Summary of balance for all data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2252        0.1961     0.0734    0.0291  0.0323   0.0305  0.0561
delta_bodyfat       1.1194        2.4140     4.9650   -1.2945  1.1899   1.4484  8.1854
SEX                 1.4512        1.4321     0.4961    0.0191  0.0000   0.0244  1.0000
TANNER_V2           2.4146        2.0833     1.0331    0.3313  0.0000   0.3293  1.0000
AGE_V2             11.9477       11.6052     0.9582    0.3425  0.3900   0.3663  0.6700
MVPA_V1            46.5585       52.0164    24.7021   -5.4579  7.3929   6.5416 12.2857


Summary of balance for matched data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2252        0.2251     0.0630    0.0001  0.0007   0.0010  0.0128
delta_bodyfat       1.1194        1.3975     5.0120   -0.2780  0.4643   0.8118  5.1211
SEX                 1.4512        1.4268     0.4977    0.0244  0.0000   0.0244  1.0000
TANNER_V2           2.4146        2.2927     1.0828    0.1220  0.0000   0.1707  1.0000
AGE_V2             11.9477       11.9627     0.8662   -0.0150  0.0500   0.0626  0.2800
MVPA_V1            46.5585       45.2954    19.6024    1.2631  2.2857   3.8802 48.1667

Percent Balance Improvement:
             Mean Diff. eQQ Med eQQ Mean   eQQ Max
distance         99.6077 97.9808  96.7419   77.1057
delta_bodyfat    78.5235 60.9791  43.9554   37.4354
SEX             -27.5591  0.0000   0.0000    0.0000
TANNER_V2        63.1902  0.0000  48.1481    0.0000
AGE_V2           95.6200 87.1795  82.9228   58.2090
MVPA_V1          76.8575 69.0821  40.6839 -292.0543

Sample sizes:
          Control Treated
All           324      82
Matched        82      82
Unmatched     242       0
Discarded       0       0
```

Subgroup	AndGyn V1	Δ % Body fat	% Male	% Prepubertal V2	Age V2	MVPA V1
Android group	0.482	1.12	54.9	20.7	11.9	46.6
Control group	0.269	1.40	57.3	28.1	12.0	45.3

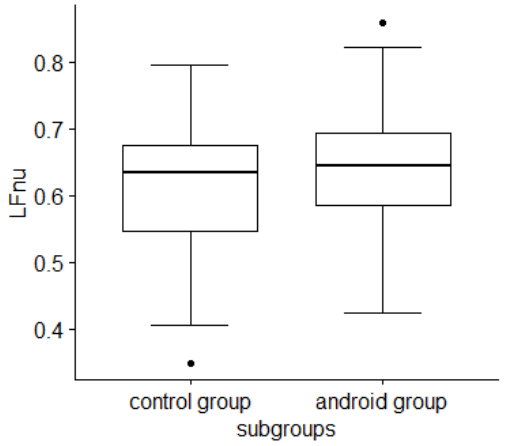


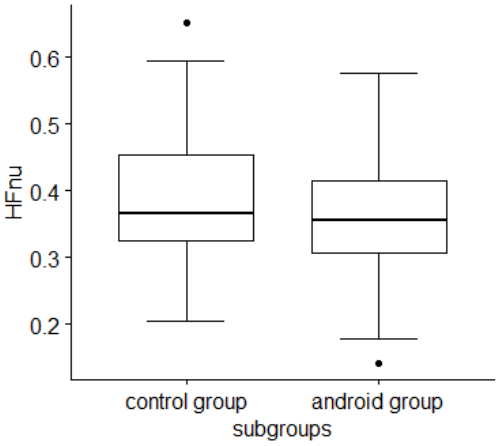




t(162) = -0.62, p = 0.54, d = -0.09				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	1476	1144	1.12
Control group	82	1379	1083	1.40

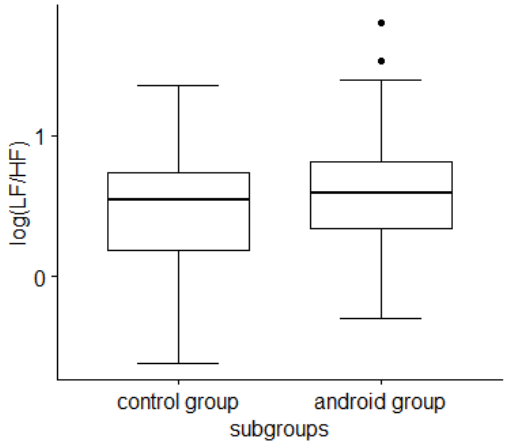
t(162) = 0.58, p = 0.56, d = 0.07				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	863	682	1.12
Control group	82	910	727	1.40



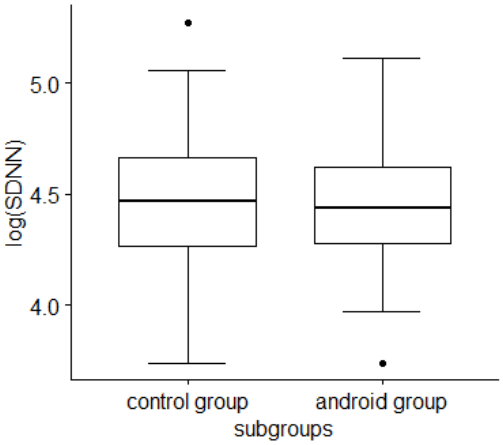


t(162) = -2.08, **p = 0.04**, d = -0.33				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	0.643	0.090	1.12
Control group	82	0.614	0.090	1.40

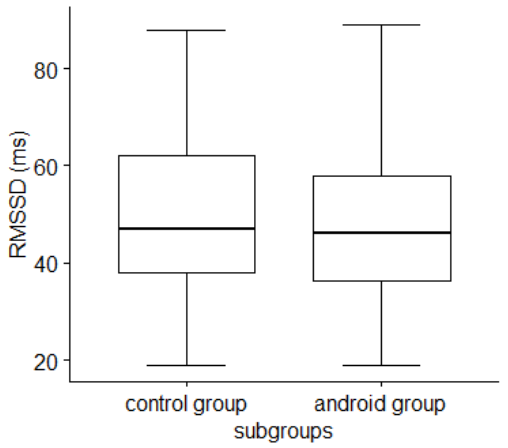
t(162) = 2.08, **p = 0.04**, d = 0.33				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	0.357	0.090	1.12
Control group	82	0.386	0.090	1.40



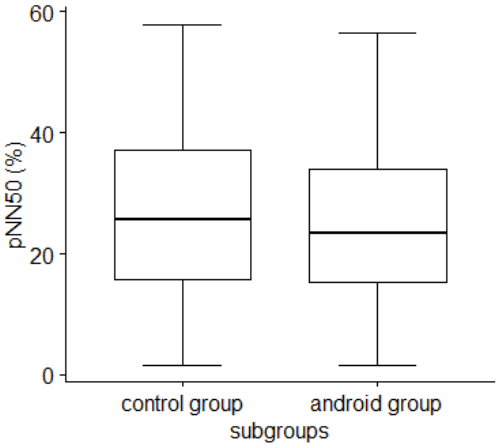
t(161.26) = -2.16, **p = 0.03**, d = -0.36				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	2.013	0.916	1.12
Control group	82	1.731	0.643	1.40



t(162) = -0.06, p = 0.95, d = 0.01				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	90.2	26.7	1.12
Control group	82	90-34	27.9	1.40



t(162) = 0.70, p = 0.49, d = 0.11				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	48.3	16.1	1.12
Control group	82	50.1	16.9	1.40

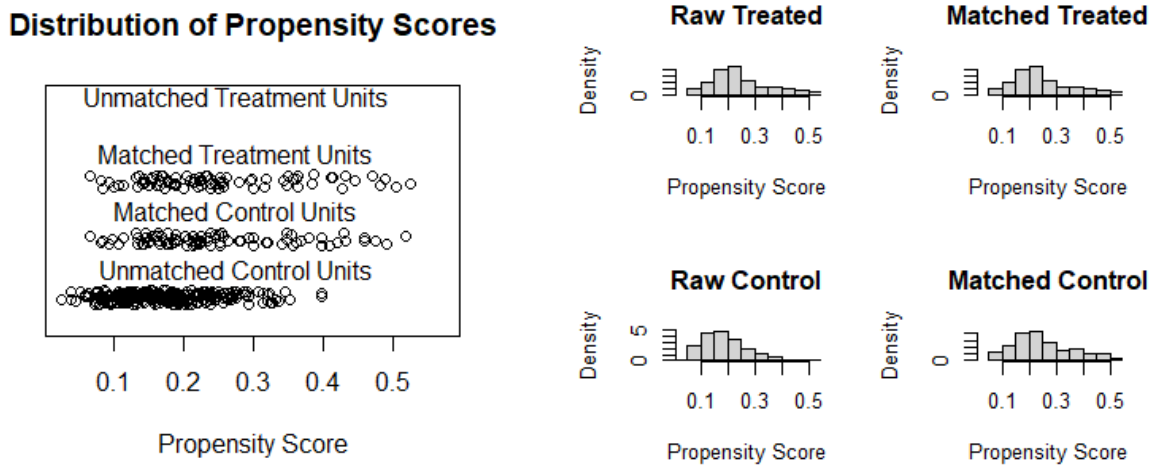


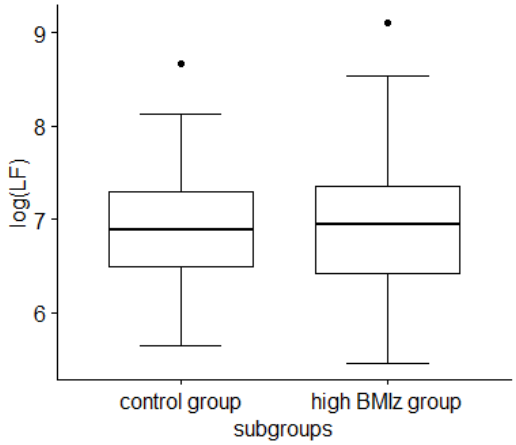
t(162) = -0.95, p = 0.34, d = 0.15				
Subgroup	n	Mean	SD	Δ%BF
Android group	82	25.1	13.2	1.12
Control group	82	27.2	14.5	1.40

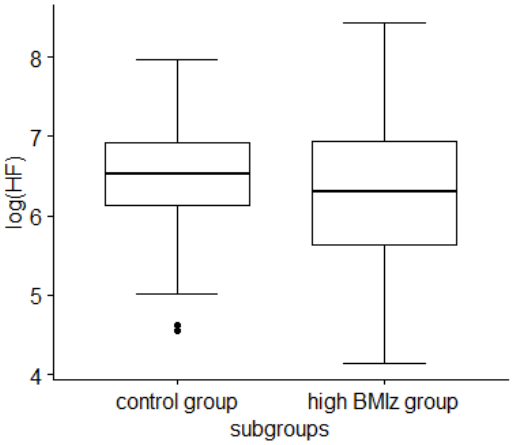
c. HRV at Visit 1 and BMI z-Score at Visit 2

```
Call:
matchit(formula = subgroup ~ delta_bodyfat + SEX + TANNER_V2 +
    AGE_V2 + MVPA_V1, data = df, method = "optimal")

Summary of balance for all data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2478        0.1904     0.0891    0.0575  0.0479   0.0569  0.1151
delta_bodyfat       2.9805        1.9430     4.9491    1.0376  1.1894   1.3900  3.8632
SEX                 1.3902        1.4475     0.4980   -0.0573  0.0000   0.0610  1.0000
TANNER_V2           2.4024        2.0864     1.0071    0.3160  0.0000   0.3049  1.0000
AGE_V2             11.8356       11.6336     0.9541    0.2020  0.2300   0.2110  0.3800
MVPA_V1            46.9036       51.9290    24.6170   -5.0254  5.9286   5.7042 11.3333


Summary of balance for matched data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2478        0.2465     0.1068    0.0013  0.0006   0.0022  0.0209
delta_bodyfat       2.9805        2.6085     5.4457    0.3721  0.8167   1.1716  4.8511
SEX                 1.3902        1.3415     0.4771    0.0488  0.0000   0.0488  1.0000
TANNER_V2           2.4024        2.4512     1.1456   -0.0488  0.0000   0.1951  1.0000
AGE_V2             11.8356       11.8533     0.9715   -0.0177  0.0650   0.0730  0.2900
MVPA_V1            46.9036       49.3366    24.9142   -2.4330  2.8571   3.6760  9.8000

Percent Balance Improvement:
             Mean Diff. eQQ Med eQQ Mean  eQQ Max
distance         97.7165 98.6628  96.1534  81.8567
delta_bodyfat    64.1386 31.3364  15.7114 -25.5713
SEX              14.8489  0.0000  20.0000   0.0000
TANNER_V2        84.5641  0.0000  36.0000   0.0000
AGE_V2           91.2474 71.7391  65.3757  23.6842
MVPA_V1          51.5866 51.8072  35.5554  13.5294

Sample sizes:
          Control Treated
All           324      82
Matched        82      82
Unmatched     242       0
Discarded       0       0
```

Subgroup	BMIz V2	Δ % Body fat	% Male	% Prepubertal V2	Age V2	MVPA V1
High BMIz group	2.090	2.98	61.0	24.4	11.8	46.9
Control group	0.530	2.61	65.9	26.8	11.9	49.3

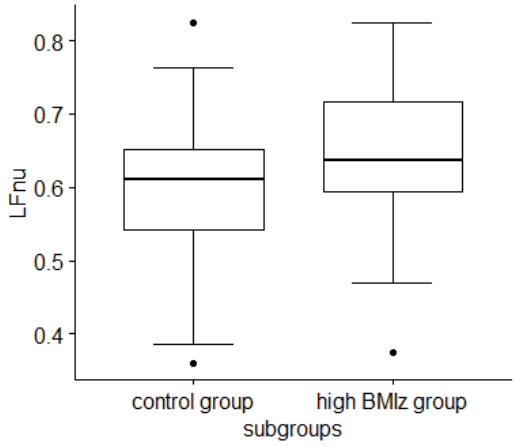


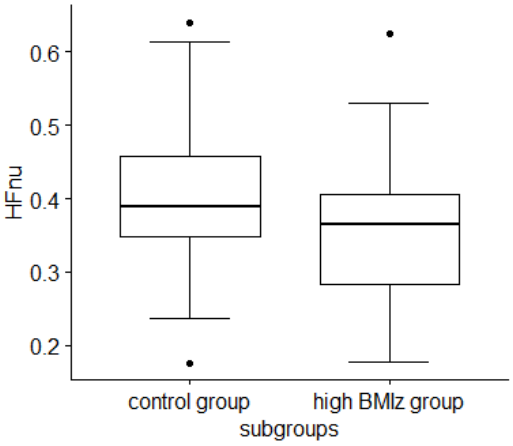




t(160.54) = -0.31, p = 0.76, d = -0.11				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	1327	1221	2.98
Control group	82	1214	856	2.61

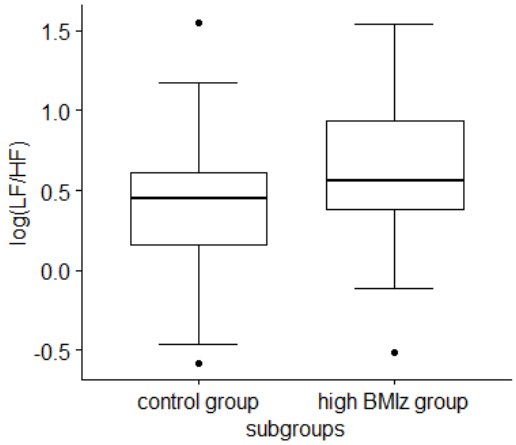
t(155.06) = 1.20, p = 0.23, d = 0.01				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	829	824	2.98
Control group	82	834	595	2.61



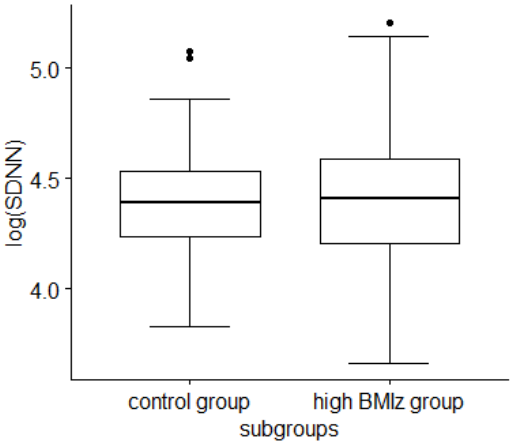


t(162) = -2.94, **p = 0.004**, d = -0.46				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	0.643	0.092	2.98
Control group	82	0.601	0.089	2.61

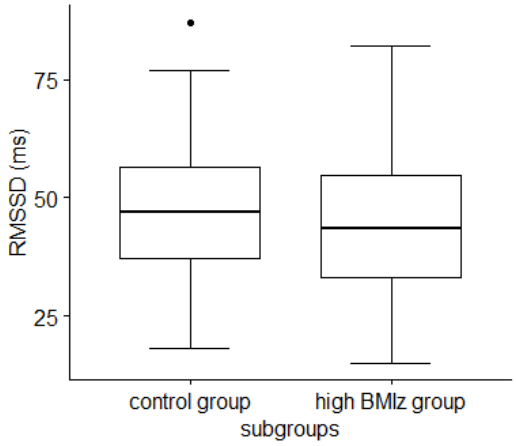
t(162) = 2.94, **p = 0.004**, d = 0.46				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	0.357	0.092	2.98
Control group	82	0.399	0.089	2.61



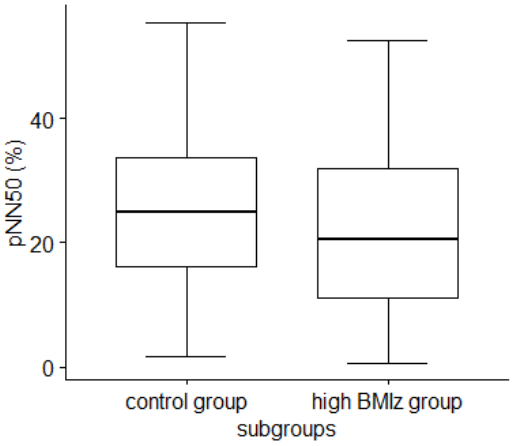
t(161.54) = -3.13, **p = 0.002**, d = -0.48				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	2.097	0.879	2.98
Control group	82	1.634	0.660	2.61



t(162) = -0.38, p = 0.71, d = -0.06				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	84.7	27.2	2.98
Control group	82	83.3	22.1	2.61



t(162) = 1.26, p = 0.21, d = 0.20				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	44.5	15.9	2.98
Control group	82	47.5	14.1	2.61

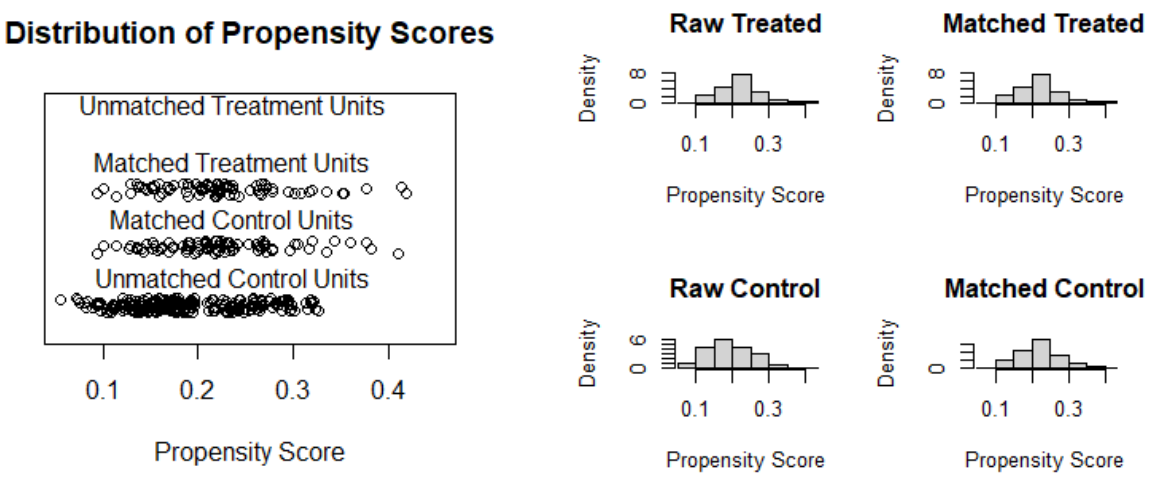


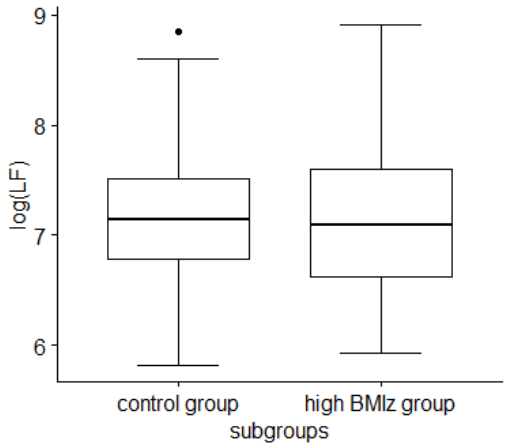
t(162) = 1.72, p = 0.09, d = 0.27				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	21.8	1364	13.5
Control group	82	25.3	906	12.5

d. BMI z-Score at Visit 1 and HRV at Visit 2

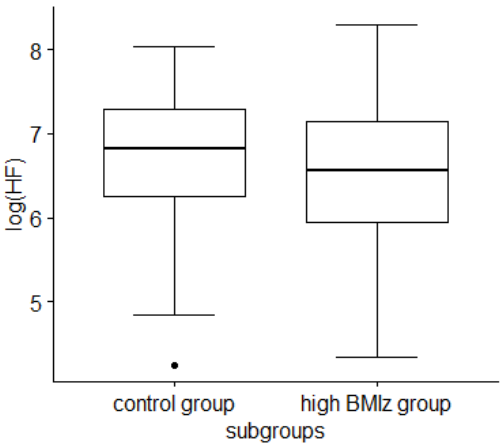
```
Call:
matchit(formula = subgroup ~ delta_bodyfat + SEX + TANNER_V2 +
    AGE_V2 + MVPA_V1, data = df, method = "optimal")

Summary of balance for all data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2224        0.1968     0.0645    0.0256  0.0263   0.0257  0.0708
delta_bodyfat       1.3596        2.3532     4.8620   -0.9936  0.6761   0.9991  7.7805
SEX                 1.4390        1.4352     0.4965    0.0038  0.0000   0.0000  0.0000
TANNER_V2           2.3415        2.1019     1.0163    0.2396  0.0000   0.2317  1.0000
AGE_V2             11.7912       11.6448     0.9585    0.1464  0.1600   0.1554  0.2900
MVPA_V1            44.9164       52.4320    24.7246   -7.5156  8.1964   7.8396 17.0000


Summary of balance for matched data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2224        0.2218     0.0644    0.0006  0.0005   0.0013  0.0314
delta_bodyfat       1.3596        1.0052     4.7149    0.3544  0.5711   0.6561  4.9103
SEX                 1.4390        1.4756     0.5025   -0.0366  0.0000   0.0366  1.0000
TANNER_V2           2.3415        2.3537     1.1152   -0.0122  0.0000   0.0854  1.0000
AGE_V2             11.7912       11.7522     1.0155    0.0390  0.1000   0.1273  0.3400
MVPA_V1            44.9164       45.1313    20.4047   -0.2149  2.9667   3.8209 28.8333

Percent Balance Improvement:
             Mean Diff. eQQ Med eQQ Mean  eQQ Max
distance         97.5302 97.9213  95.0064  55.6481
delta_bodyfat    64.3287 15.5247  34.3330  36.8894
SEX            -852.9412  0.0000     -Inf     -Inf
TANNER_V2        94.9105  0.0000  63.1579   0.0000
AGE_V2           73.3449 37.5000  18.0534 -17.2414
MVPA_V1          97.1403 63.8054  51.2617 -69.6078

Sample sizes:
          Control Treated
All           324      82
Matched        82      82
Unmatched     242       0
Discarded       0       0
```

Subgroup	BMIz V1	Δ % Body fat	% Male	% Prepubertal V2	Age V2	MVPA V1
High BMIz group	2.080	1.36	56.1	26.8	11.8	44.9
Control group	0.427	1.01	52.4	28.1	11.8	45.1

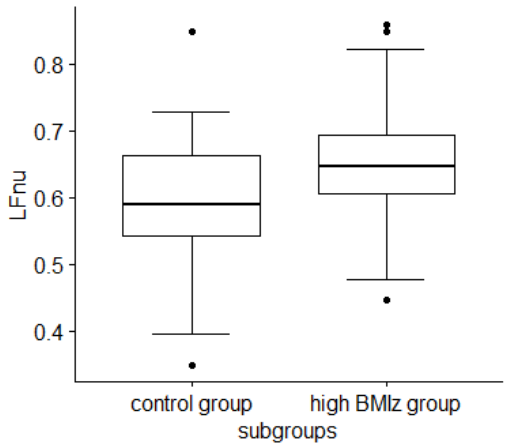




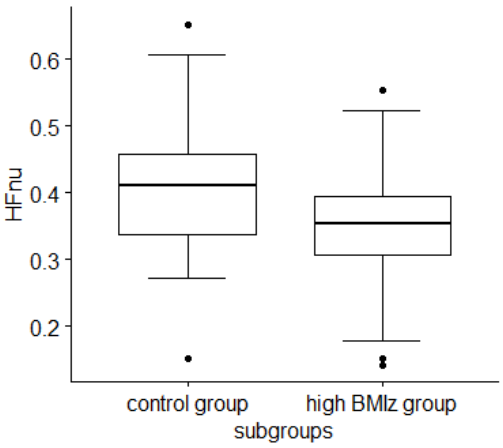
t(162) = -0.09, p = 0.93, d = -0.08				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	1649	1345	1.36
Control group	82	1557	1114	1.01



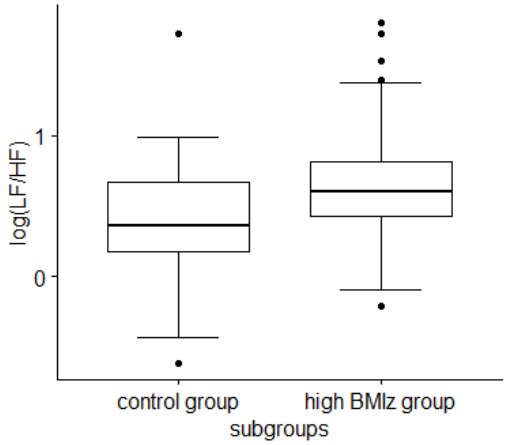
t(162) = 1.94, p = 0.05, d = 0.19				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	940	777	1.36
Control group	82	1081	702	1.01



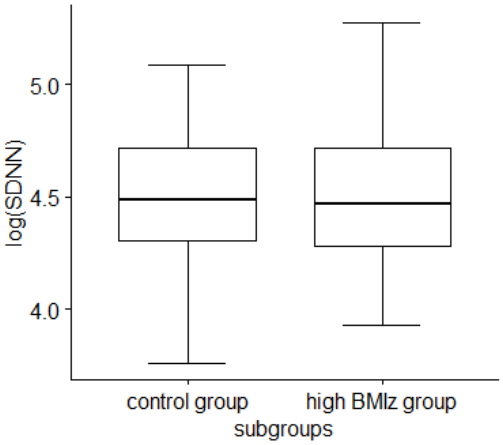
t(162) = -4.09, **p = <0.001**, d = -0.64				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	0.649	0.087	1.36
Control group	82	0.595	0.084	1.01



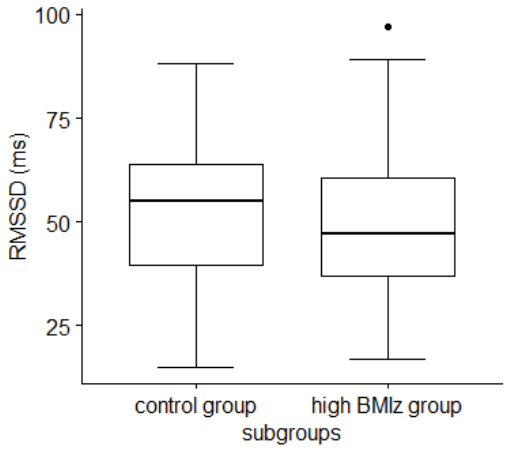
t(162) = 4.09, **p = <0.001**, d = 0.64				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	0.351	0.871	1.36
Control group	82	0.405	0.084	1.01



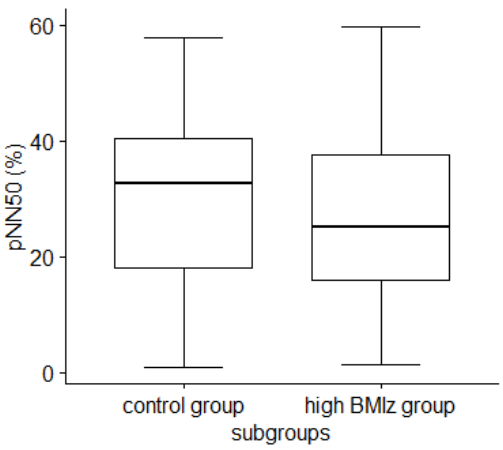
t(160.03) = -4.06, **p = <0.001**, d = -0.57				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	2.076	0.985	1.36
Control group	82	1.593	0.677	1.01



t(162) = -0.12, p = 0.91, d = -0.02				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	94.1	30.5	1.36
Control group	82	93.6	25.9	1.01



t(162) = 1.37, p = 0.17, d = 0.21				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	50.0	17.5	1.36
Control group	82	53.6	15.8	1.01



t(162) = 1.82, p = 0.07, d = 0.28				
Subgroup	n	Mean	SD	Δ%BF
High BMIz	82	26.4	14.3	1.36
Control group	82	30.3	13.5	1.01

III. Re-Weighting

a. Inverse Probability Weighting for HRV at Visit 1 Grouped by Median Split of Android-to-Gynoid-Ratio at Visit 2

HRV V1	Mean Difference Between Subgroups			Subgroup Coefficient for Regression Models		
	Mean	Bootstrap		β	Bootstrap	
		Mean	CI 95%		Mean	CI 95%
LF	82.420	76.393	-152.115; 310.309	0.028 ^{L}	0.018^{L}	-0.108^{L} ;0.156^{L}
HF	-59.306	-56.708	-230.983; 120.666	-0.141 ^{L}	-0.143^{L}	-0.305^{L}; 0.024^{L}
LF/HF	0.292	0.360	0.202; 0.527	0.176 ^{L}	0.165^{L}	0.092^{L}; 0.239^{L}
LFnu	0.023	0.038	0.017; 0.059	0.038	0.036	0.019; 0.054
HFnu	-0.048	-0.043	-0.064; -0.022	-0.038	-0.036	-0.054; -0.019
SDNN	-1.352	0.873	-4.978; 6.716	-0.005 ^{L}	0.002^{L}	-0.055^{L}; 0.058^{L}
RMSSD	-4.160	-4.168	-8.080; -0.456	-2.948	-3.396	-6.673; -0.172
pNN50	-3.975	-4.380	-7.877; -1.133	-3.328*	-3.689	-6.582; -0.969

Table 0.9 Inverse Probability Weighting for HRV at Visit 1 Grouped by Median Split of Android–to-Gynoid-Ratio at Visit 2; ^{L} log transformed values

b. Inverse Probability Weighting for Android-to-Gynoid-Ratio at Visit 1 Grouped by Median Split of HRV at Visit 2

HRV V2	Mean Difference Between Subgroups			Subgroup Coefficient for Regression Models		
	Mean	Bootstrap		β	Bootstrap	
		Mean	CI 95%		Mean	CI 95%
LF	0.015	0.015	-0.007; 0.037	0.016	0.015	-0.006; 0.038
HF	0.006	0.004	-0.020; 0.026	0.006	0.004	-0.020; 0.026
LF/HF	0.027	0.030	0.005; 0.052	0.028	0.034	0.011; 0.054
LFnu	0.029	0.031	0.006; 0.054	0.029	0.035	0.011; 0.056
HFnu	-0.029	-0.036	-0.060; -0.013	-0.029	-0.035	-0.057; -0.013
SDNN	0.002	0.001	-0.021; 0.023	0.003	0.002	-0.020; 0.025
RMSSD	-0.009	-0.011	-0.032; 0.012	-0.009	-0.012	-0.032; 0.012
pNN50	-0.010	-0.012	-0.035; 0.009	-0.010	-0.013	-0.035; 0.008

Table 0.10 Inverse Probability Weighting for Android–to-Gynoid-Ratio at Visit 1 Grouped by Median Split of HRV at Visit 2

c. Inverse Probability Weighting for HRV at Visit 1 Grouped by Median Split of BMI z-Score at Visit 2

HRV V1	Mean Difference Between Subgroups			Subgroup Coefficient for Regression Models		
	Mean	Bootstrap		β	Bootstrap	
		Mean	CI 95%		Mean	CI 95%
LF	119.828	127.417	-123.797; 376.126	0.023^{L}	0.018^{L}	-0.111^{L}; 0.155^{L}
HF	-21.618	-27.457	-211.903; 158.311	-0.132^{L}	-0.135^{L}	-0.306^{L}; 0.031^{L}
LF/HF	0.294	0.375	0.206; 0.575	0.161^{L}	0.157^{L}	0.084^{L}; 0.235^{L}
LFnu	0.040	0.058	0.036; 0.081	0.036	0.035	0.018; 0.052
HFnu	-0.032	-0.031	-0.053; -0.008	-0.036	-0.035	-0.052; -0.018
SDNN	-2.142	4.512	-1.105; 10.971	0.003^{L}	0.005^{L}	-0.049^{L}; 0.063^{L}
RMSSD	-2.633	-2.556	-6.754; 1.199	-3.016	-3.293	-6.738; -0.271
pNN50	-3.348	-3.725	-7.395; -0.367	-3.558	-3.770	-6.803; -1.222

Table 0.11 Table 0.9 Inverse Probability Weighting for HRV at Visit 1 Grouped by Median Split of BMI z-Score at Visit 2; ^{L} log transformed values

d. Inverse Probability Weighting for BMI z-Score at Visit 1 Grouped by Median Split of HRV at Visit 2

HRV V2	Mean Difference Between Subgroups			Subgroup Coefficient for Regression Models		
	Mean	Bootstrap		β	Bootstrap	
		Mean	CI 95%		Mean	CI 95%
LF	0.152	0.147	-0.055; 0.352	0.156	0.147	-0.050; 0.352
HF	0.110	0.094	-0.127; 0.302	0.110	0.093	-0.127; 0.293
LF/HF	0.267	0.321	0.096; 0.532	0.268	0.320	0.108; 0.523
LFnu	0.266	0.319	0.104; 0.533	0.266	0.316	0.121; 0.511
HFnu	-0.266	-0.331	-0.545; -0.126	-0.266	-0.321	-0.521; -0.132
SDNN	0.120	0.142	-0.056; 0.338	0.122	0.141	-0.056 ;0.336
RMSSD	0.011	-0.006	-0.214; 0.209	0.012	-0.007	-0.214; 0.202
pNN50	-0.001	-0.022	-0.224; 0.181	-0.001	-0.023	-0.226; 0.174

Table 0.12 Inverse Probability Weighting for BMI z-Score at Visit 1 Grouped by Median Split of HRV at Visit 2

IV. Ancillary Analyses Including Waist-to-Height-Ratio

a. Regression Analyses Including Waist-to-Height-Ratio

	HRV V1	Parameters of the Univariate Linear Regression Analysis				
		β	Standard Error	CI 95%	t-value	Sig
WHtR V2	LF	5.246e-06	4.056e-06	-2.727e-06; 1.322e-05	1.29	0.20
	HF	-1.189e-06	5.446e-06	-1.190e-05; 9.518e-06	-0.22	0.83
	LF/HF	0.026	0.005	0.015; 0.036	4.77	<0.001
	LFnu	0.189	0.043	0.105; 0.274	4.40	<0.001
	HFnu	-0.189	0.043	-0.274; -0.105	-4.40	<0.001
	SDNN	9.386e-05	1.629e-04	-2.2633-04; 4.140e-04	0.58	0.57
	RMSSD	-6.113e-04	2.487e-04	-1.100e-03; -1.224e-04	-2.46	0.01
	pNN50	-8.845e-04	2.813e-04	-1.438e-03; -3.316e-04	-3.15	<0.01

Table 0.13 Univariate Linear Regression Model With WHtR at Visit 2 Defined as Outcome

	HRV V2	Parameters of the Univariate Linear Regression Analysis				
		β	Standard Error	CI 95%	t-value	Sig
WHtR V1	LF (ln)	0.981	0.431	0.134; 1.828	2.28	0.02
	HF (ln)	0.212	0.535	-0.839; 1.263	0.40	0.69
	LF/HF (ln)	0.767	0.270	0.236; 1.298	2.84	<0.01
	LFnu	0.165	0.061	0.045; 0.284	2.70	<0.01
	HFnu	-0.165	0.061	-0.284; -0.045	-2.70	<0.01
	SDNN (ln)	0.274	0.192	-0.103; 0.650	1.43	0.15
	RMSSD	5.018	11.418	-17.428; 27.465	0.44	0.66
	pNN50	-1.652	9.862	-21.039; 17.734	-0.17	0.87

Table 0.14 Univariate Linear Regression Model With WHtR at Visit 1 Defined as Exposure

	HRV V1	Parameters of the Multiple Linear Regression Analysis				
		β	Standard Error	CI 95%	t-value	Sig
WHtR V2	LF	6.100e-06	3.971e-06	-1.707e-06; 1.391e-05	1.54	0.13
	HF	-8.318e-07	5.294e-06	-1.124e-05; 9.576e-06	-0.16	0.88
	LF/HF	0.025	0.005	0.015; 0.036	4.83	<0.001
	LFnu	0.187	0.042	0.104; 0.269	4.46	<0.001
	HFnu	-0.187	0.042	-0.269; -0.104	-4.46	<0.001
	SDNN	7.994e-05	1.588e-04	-2.322e-04; 3.920e-04	0.50	0.62
	RMSSD	-5.767e-04	2.436e-04	1.056e-03; -9.774e-05	-2.37	0.02
	pNN50	-8.462e-04	2.755e-04	-1.388e-03; -3.046e-04	-3.07	<0.01

Table 0.15 Multiple Linear Regression With HRV Indices at Visit 1 and WHtR at Visit 2

	HRV V2	Parameters of the Multiple Linear Regression Analysis				
		β	Standard Error	CI 95%	t-value	Sig
WHtR V1	LF (ln)	0.966	0.443	0.095; 1.837	2.18	0.03
	HF (ln)	0.334	0.553	-0.754; 1.421	0.60	0.55
	LF/HF (ln)	0.631	0.276	0.089; 1.174	2.29	0.02
	LFnu	0.135	0.062	0.013; 0.258	2.18	0.03
	HFnu	-0.135	0.062	-0.258; -0.013	-2.18	0.03
	SDNN (ln)	0.224	0.197	-0.163; 0.611	1.14	0.26
	RMSSD	5.765	11.766	-17.366; 28.896	0.49	0.62
	pNN50	-1.040	10.171	-21.036; 18.955	-0.10	0.92

Table 0.16 Multiple Linear Regression With WHtR at Visit 1 and HRV Indices at Visit 2

	Determinant	Parameters of Multiple Linear Regression Analysis					
		β	CI 95%	Sig	R^2	F-test	Sig
WHtR V2	LF V1	6.100e-06	-1.707e-06; 1.391e-05	0.13	0.087	6.298	<0.001
	Δ % body fat	0.004	0.003; 0.006	<0.001			
	Sex	-0.020	-0.037; 0.003	0.02			
	Tanner V2	0.014	0.004; 0.023	<0.01			
	Age V2	-1.346e-04	-9.863e-03; 9.594e-03	0.98			
	MVPA	-4.592e-04	-7.858e-04; -1.325e-04	<0.01			
	HF V1	-8.318e-07	-1.124e-05; 9.576e-06	0.88	0.081	5.874	<0.001
	Δ % body fat	0.004	0.003; 0.006	<0.001			
	Sex	-0.020	-0.037; -0.004	0.02			
	Tanner V2	0.014	0.004; 0.023	<0.01			
	Age V2	4.616e-04	-9.285e-03; 1.020e-02	0.93			
	MVPA	-4.222e-04	-7.485e-04 -9.595e-05	0.01			
	LF/HF V1	0.025	0.015; 0.036	<0.001	0.132	10.100	<0.001
	Δ % body fat	0.004	0.003; 0.006	<0.001			
	Sex	-0.016	-0.032; 0.000	0.06			
	Tanner V2	0.013	0.004; 0.022	<0.01			
	Age V2	-2.776e-04	-9.741e-03; 9.185e-03	0.95			
	MVPA	-3.775e-04	-6.936e-04; -6.143e-05	0.02			
	LFnu V1	0.187	0.104; 0.269	<0.001	0.125	9.478	<0.001
	Δ % body fat	0.004	0.003; 0.006	<0.001			
	Sex	-1.640e-02	-3.281e-02; 1.573e-05	0.05			
	Tanner V2	0.013	0.004; 0.023	<0.01			
	Age V2	-2.773e-04	-9.780; 9.225e-03	0.95			
	MVPA	-3.915e-04	-7.086e-04; -7.434e-05	0.02			
	HFnu V1	-0.187	-0.269; -0.104	<0.001	0.125	9.478	<0.001
	Δ % body fat	0.004	0.003; 0.006	<0.001			
	Sex	-1.640e-02	-3.281e-02; 1.573e-05	0.05			
	Tanner V2	0.013	0.004; 0.023	<0.01			
	Age V2	-2.773e-04	-9.780e-03; 9.225e-03	0.95			
	MVPA	-3.915e-04	-7.086e-04; -7.434e-05	0.02			
	SDNN V1	7.994e-05	-2.322e-04; 3.920e-04	0.62	0.082	5.916	<0.001
	Δ % body fat	0.004	0.003; 0.006	<0.001			
	Sex	-0.020	-0.037; -0.004	0.02			
	Tanner V2	0.014	0.004; 0.023	<0.01			
	Age V2	3.030e-04	-9.436e-03; 1.004e-02	0.95			
	MVPA	-4.319e-04	-7.575e-04; -1.062e-04	<0.01			
	RMSSD V1	-5.767e-04	1.056e-03; -9.774e-05	0.02	0.094	6.886	<0.001
	Δ % body fat	0.004	0.003; 0.006	<0.001			
	Sex	-0.020	-0.037; -0.004	0.02			
	Tanner V2	0.014	0.004; 0.023	<0.01			
	Age V2	9.726e-04	-8.702e-03; 1.065e-02	0.84			
	MVPA	-3.648e-04	-6.910e-04; -3.861e-05	0.03			
	pNN50 V1	-8.462e-04	-1.388e-03; -3.046e-04	<0.01	0.102	7.581	<0.001
	Δ % body fat	0.004	0.003; 0.006	<0.001			
	Sex	-0.020	-0.037; -0.004	0.02			
	Tanner V2	0.014	0.004; 0.023	<0.01			
	Age V2	0.001	-0.009; 0.011	0.83			
	MVPA	-3.483e-04	-6.728e-04; -2.370e-05	0.04			

Table 0.17 Multiple Linear Regression Model With WHtR at Visit 2 Defined as Outcome

HRV V2	Determinant	Parameters of Multiple Linear Regression Analysis					
		β	CI 95%	Sig	R^2	F-test	Sig
LF (ln)	WHtR V1	0.966	0.095; 1.837	0.03	0.028	1.887	0.08
	Δ % body fat	-0.004	-0.018; 0.010	0.59			
	Sex	-0.078	-0.218; 0.062	0.27			
	Tanner V2	0.003	-0.078; 0.084	0.94			
	Age V2	0.040	-0.042; 0.121	0.34			
	MVPA	0.002	-0.001; 0.004	0.25			
HF (ln)	WHtR V1	0.334	-0.754; 1.421	0.55	0.004	0.275	0.95
	Δ % body fat	0.003	-0.015; 0.021	0.73			
	Sex	0.024	-0.152; 0.199	0.79			
	Tanner V2	-0.011	-0.112; 0.090	0.82			
	Age V2	0.019	-0.082; 0.121	0.71			
	MVPA	0.002	-0.002; 0.005	0.28			
LF/HF (ln)	WHtR V1	0.631	0.089; 1.174	0.02	0.049	3.404	<0.01
	Δ % body fat	-0.007	-0.016; 0.002	0.12			
	Sex	-0.102	-0.189; -0.014	0.02			
	Tanner V2	0.015	-0.036; 0.065	0.57			
	Age V2	0.020	-0.031; 0.071	0.43			
	MVPA	-2.869e-04	-1.990e-03; 1.417e-03	0.74			
LFnu	WHtR V1	0.135	0.013; 0.258	0.03	0.046	3.208	<0.01
	Δ % body fat	-0.002	-0.004; 0.001	0.13			
	Sex	-0.023	-0.042; -0.003	0.03			
	Tanner V2	0.003	-0.009; 0.014	0.66			
	Age V2	0.005	-0.006; 0.017	0.39			
	MVPA	-7.014e-05	-4.539e-04; 3.137e-04	0.72			
HFnu	WHtR V1	-0.135	-0.258; -0.013	0.03	0.046	3.208	<0.01
	Δ % body fat	0.002	-0.001; 0.004	0.13			
	Sex	0.023	0.003; 0.042	0.03			
	Tanner V2	-0.003	-0.014; 0.009	0.66			
	Age V2	-0.005	-0.017; 0.006	0.39			
	MVPA	7.014e-05	-3.137e-04; 4.539e-04	0.72			
SDNN (ln)	WHtR V1	0.224	-0.163; 0.611	0.26	0.025	1.676	0.13
	Δ % body fat	-0.002	-0.009; 0.004	0.45			
	Sex	-0.049	-0.111; 0.014	0.13			
	Tanner V2	0.021	-0.015; 0.057	0.24			
	Age V2	0.003	-0.034; 0.039	0.89			
	MVPA	6.494e-04	-5.647e-04; 1.864e-03	0.29			
RMSSD	WHtR V1	5.765	-17.366; 28.896	0.62	0.012	0.780	0.59
	Δ % body fat	-0.092	-0.469; 0.284	0.63			
	Sex	-1.232	-4.956; 2.493	0.52			
	Tanner V2	-0.334	-2.483; 1.815	0.76			
	Age V2	1.125	-1.034; 3.284	0.31			
	MVPA	0.043	-0.030; 0.115	0.25			
pNN50	WHtR V1	-1.040	-21.036; 18.955	0.92	0.010	0.634	0.70
	Δ % body fat	-0.093	-0.419; 0.233	0.58			
	Sex	-0.603	-3.822; 2.617	0.71			
	Tanner V2	-0.263	-2.120; 1.594	0.78			
	Age V2	0.904	-0.962; 2.771	0.34			
	MVPA	0.038	-0.025; 0.101	0.24			

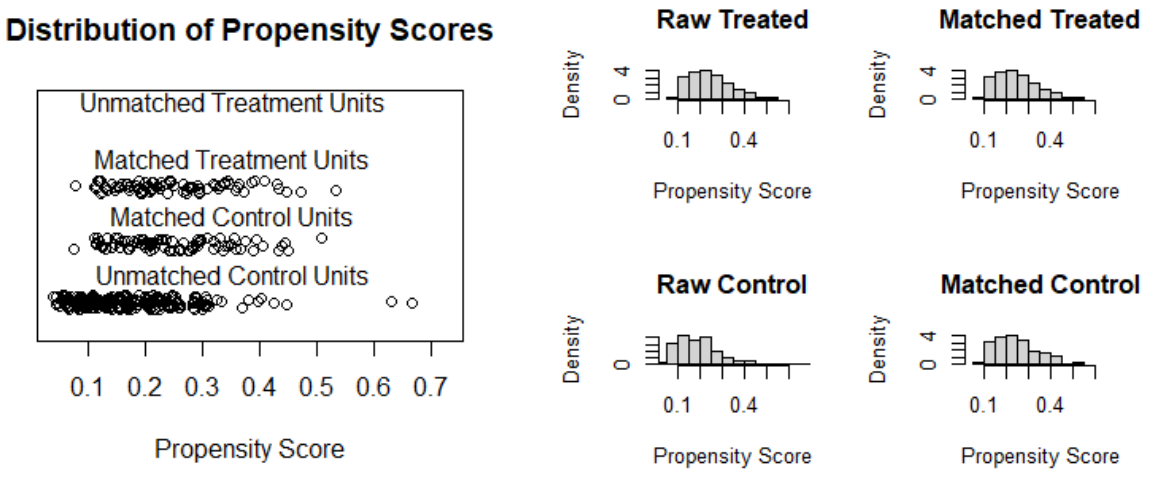
Table 0.18 Multiple Linear Regression Model With WHtR at Visit 1 Defined as Exposure

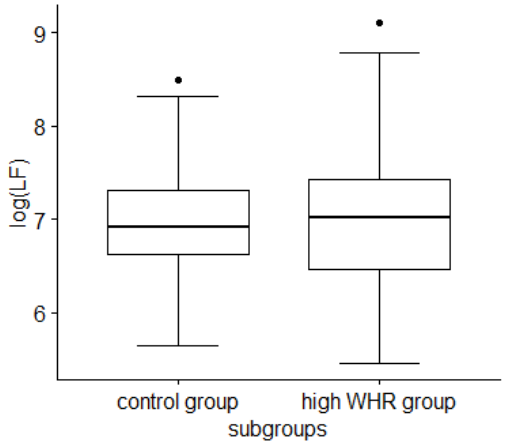
b. Propensity Score Matching Including Waist-to-Height-Ratio

i. HRV at Visit 1 and Waist-to-Height-Ratio at Visit 2

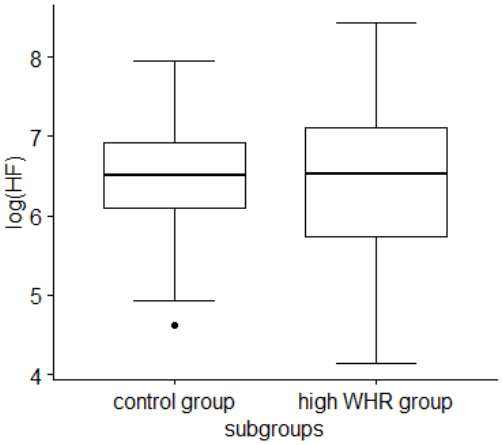
```
Call:
matchit(formula = subgroup ~ delta_bodyfat + SEX + TANNER_V2 +
    AGE_V2 + MVPA_V1, data = df, method = "optimal")

Summary of balance for all data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2472        0.1905     0.0969    0.0567  0.0587   0.0587  0.1324
delta_bodyfat       3.6993        1.7611     4.9394    1.9383  1.8518   2.0477  7.9149
SEX                 1.3780        1.4506     0.4983   -0.0726  0.0000   0.0732  1.0000
TANNER_V2           2.1585        2.1481     1.0482    0.0104  0.0000   0.1463  1.0000
AGE_V2             11.8241       11.6365     0.9604    0.1877  0.2100   0.2112  0.3800
MVPA_V1            46.7343       51.9719    25.3734   -5.2376  5.4690   6.9300 30.5714


Summary of balance for matched data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2472        0.2466     0.0952    0.0007  0.0008   0.0018  0.0250
delta_bodyfat       3.6993        3.6755     4.2978    0.0238  0.4394   0.5127  1.5447
SEX                 1.3780        1.3537     0.4810    0.0244  0.0000   0.0244  1.0000
TANNER_V2           2.1585        2.2195     1.1114   -0.0610  0.0000   0.1829  1.0000
AGE_V2             11.8241       11.6918     0.9927    0.1323  0.1500   0.1548  0.3800
MVPA_V1            46.7343       44.9222    24.0346    1.8121  5.6762   6.0972 14.2143

Percent Balance Improvement:
             Mean Diff. eQQ Med eQQ Mean eQQ Max
distance         98.8385 98.5560  96.8992 81.1204
delta_bodyfat    98.7725 76.2694  74.9644 80.4841
SEX              66.3900  0.0000  66.6667  0.0000
TANNER_V2      -486.9565  0.0000 -25.0000  0.0000
AGE_V2           29.4929 28.5714  26.7321  0.0000
MVPA_V1          65.4011 -3.7875  12.0174 53.5047

Sample sizes:
          Control Treated
All           324      82
Matched        82      82
Unmatched     242       0
Discarded       0       0
```

Subgroup	WHtR V2	Δ % Body fat	% Male	% Prepubertal V2	Age V2	MVPA V1
High WHtR group	0.605	3.70	62.2	29.3	11.8	46.7
Control group	0.456	3.68	64.6	32.9	11.7	44.9

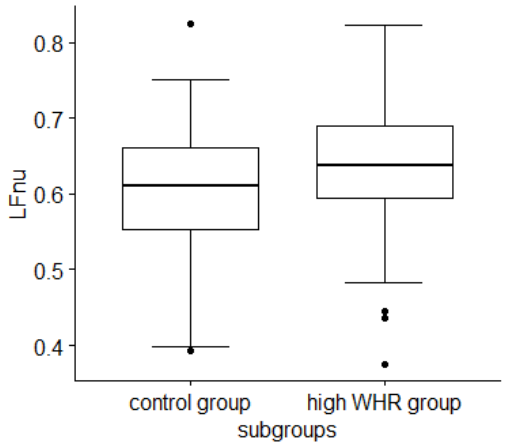




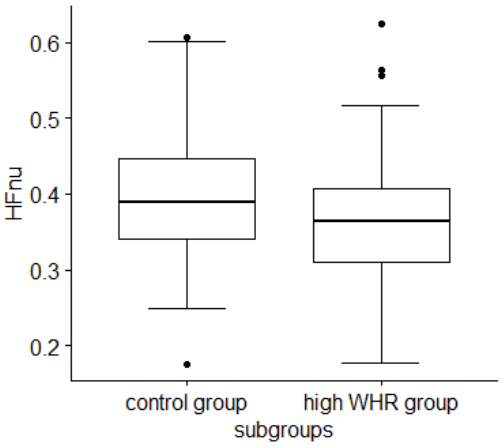
t(153.59) = -0.50, p = 0.62, d = -0.20				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	1477	1374	3.70
Control group	82	1255	835	3.68



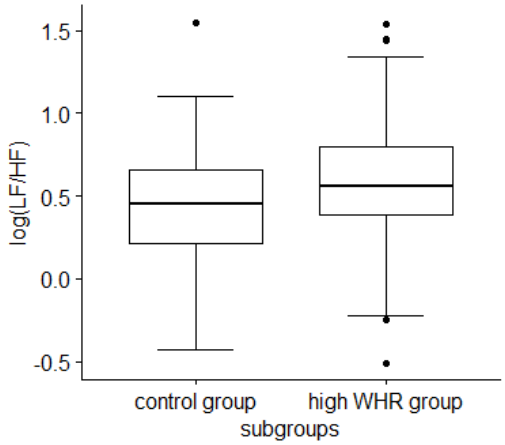
t(151.55) = 0.63, p = 0.53, d = -0.08				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	937	882	3.70
Control group	82	873	655	3.68



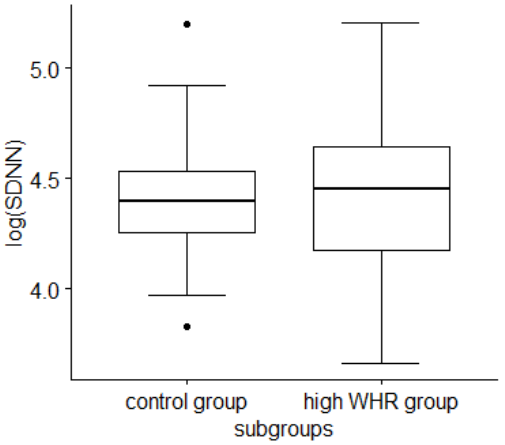
t(162) = -2.20, **p = 0.03**, d = -0.34				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	0.637	0.091	3.70
Control group	82	0.606	0.086	3.68



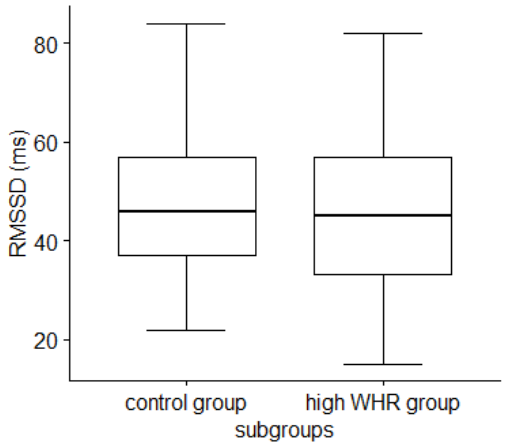
t(162) = 2.20, **p = 0.03**, d = 0.34				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	0.364	0.091	3.70
Control group	82	0.394	0.086	3.68



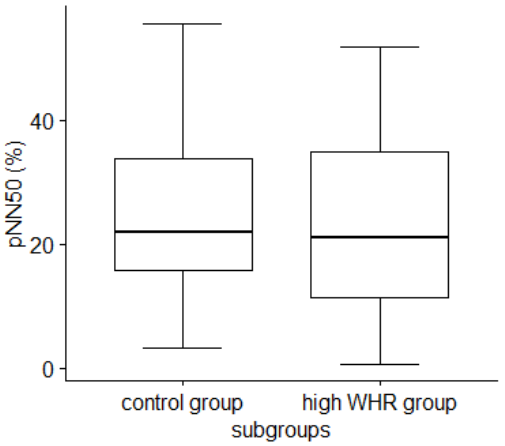
t(160.73) = -2.24, **p = 0.03**, d = -0.36				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	1.945	0.838	3.70
Control group	82	1.675	0.667	3.68



t(150.07) = -0.21, p = 0.84, d = -0.11				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	87.0	29.6	3.70
Control group	82	84.2	22.2	3.68



t(162) = 0.33, p = 0.74, d = 0.05				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	46.2	16.8	3.70
Control group	82	47.0	14.5	3.68

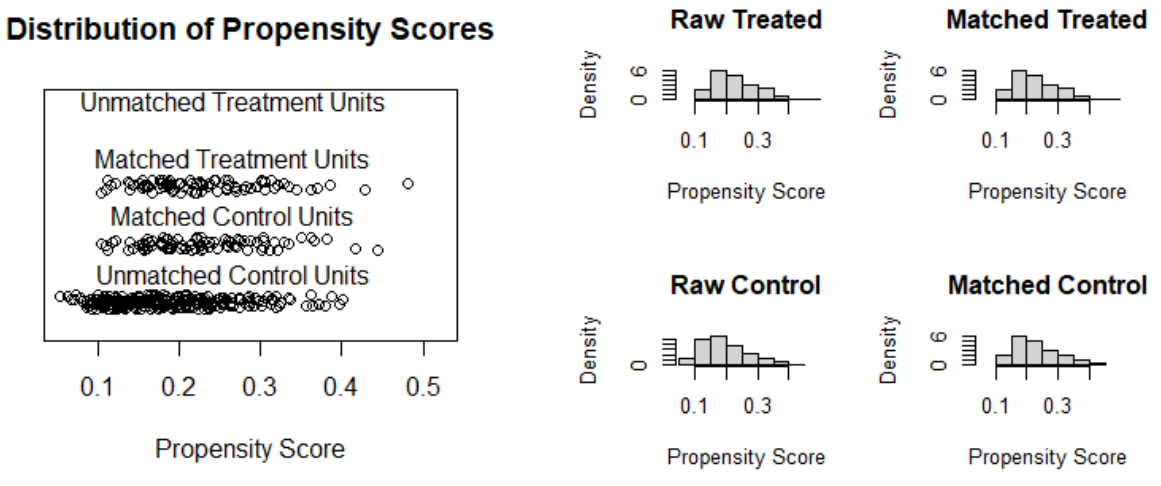


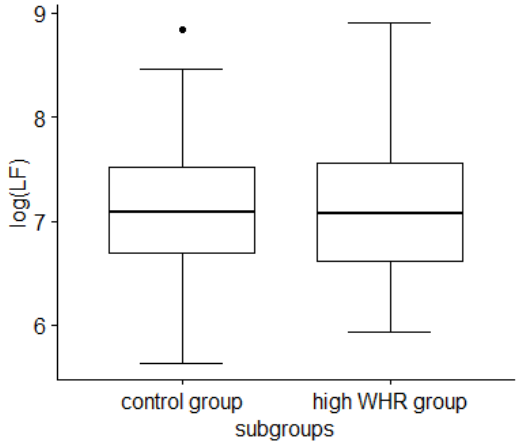
t(162) = 0.49, p = 0.63, d = 0.08				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	23.3	14.2	3.70
Control group	82	24.3	12.7	3.68

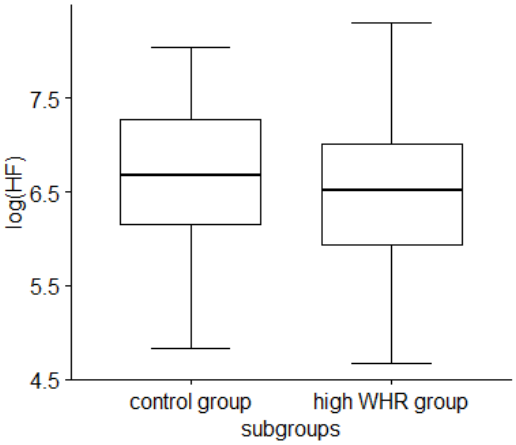
c. Waist-to-Height-Ratio at Visit 1 and HRV at Visit 2

```
Call:
matchit(formula = subgroup ~ delta_bodyfat + SEX + TANNER_V2 +
    AGE_V2 + MVPA_V1, data = df, method = "optimal")

Summary of balance for all data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2284        0.1953     0.0748    0.0331  0.0341   0.0329  0.0516
delta_bodyfat       0.9457        2.4580     4.9038   -1.5123  1.3626   1.5156  8.0631
SEX                 1.4268        1.4383     0.4969   -0.0114  0.0000   0.0122  1.0000
TANNER_V2           2.3659        2.0957     1.0200    0.2702  0.0000   0.2683  1.0000
AGE_V2             11.8654       11.6260     0.9645    0.2393  0.2650   0.2632  0.4800
MVPA_V1            45.2496       52.3477    24.7514   -7.0981  7.8810   7.5334 15.7143


Summary of balance for matched data:
             Means Treated Means Control SD Control Mean Diff eQQ Med eQQ Mean eQQ Max
distance            0.2284        0.2278     0.0727    0.0006  0.0006   0.0013  0.0360
delta_bodyfat       0.9457        1.3291     4.8464   -0.3834  0.3771   0.6013  6.6800
SEX                 1.4268        1.3902     0.4908    0.0366  0.0000   0.0366  1.0000
TANNER_V2           2.3659        2.2927     1.0828    0.0732  0.0000   0.0976  1.0000
AGE_V2             11.8654       11.9220     0.9417   -0.0566  0.0700   0.1107  0.3800
MVPA_V1            45.2496       45.0063    20.9516    0.2433  3.1571   4.2035 25.1429

Percent Balance Improvement:
             Mean Diff. eQQ Med  eQQ Mean  eQQ Max
distance         98.2970 98.3450   96.0310  30.2782
delta_bodyfat    74.6493 72.3258   60.3273  17.1530
SEX            -219.7368  0.0000 -200.0000   0.0000
TANNER_V2        72.9172  0.0000   63.6364   0.0000
AGE_V2           76.3554 73.5849   57.9240  20.8333
MVPA_V1          96.5728 59.9396   44.2018 -60.0000

Sample sizes:
          Control Treated
All           324      82
Matched        82      82
Unmatched     242       0
Discarded       0       0
```

Subgroup	WHtR V1	Δ % Body fat	% Male	% Prepubertal V2	Age V2	MVPA V1
High WHtR group	0.602	0.94	57.3	25.6	11.9	45.2
Control group	0.459	1.33	61.0	29.3	11.9	45.0

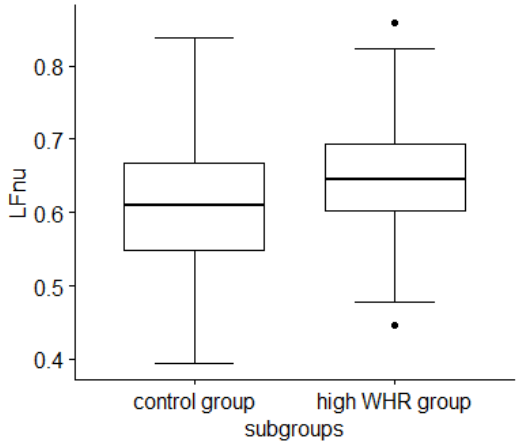


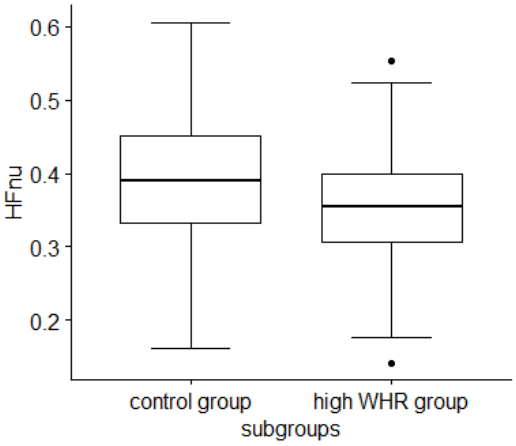




t(162) = -0.55, p = 0.58, d = -0.11				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	1480	1099	0.94
Control group	82	1617	1354	1.33

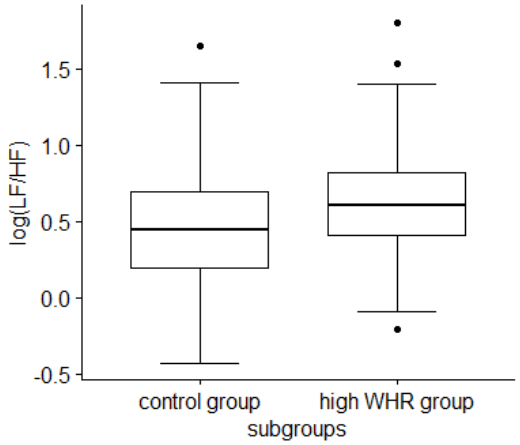
t(162) = 1.04, p = 0.30, d = 0.09				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	915	771	0.94
Control group	82	983	708	1.33



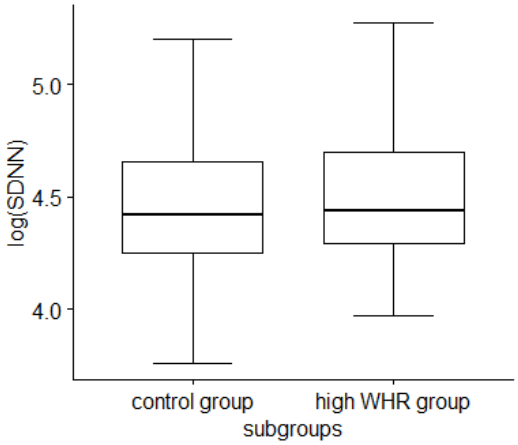


t(162) = -2.98, **p = 0.003**, d = -0.47				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	0.649	0.086	0.94
Control group	82	0.606	0.097	1.33

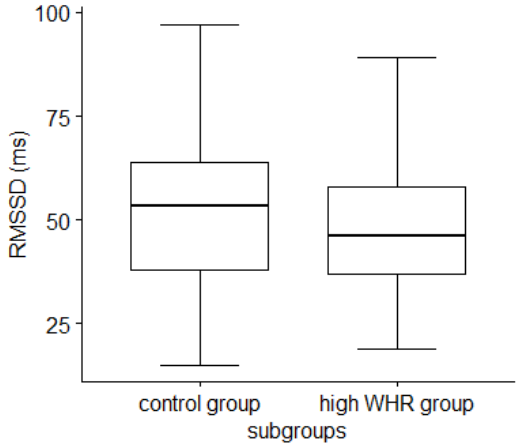
t(162) = 2.98, **p = 0.003**, d = 0.47				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	0.351	0.086	0.94
Control group	82	0.394	0.097	1.33



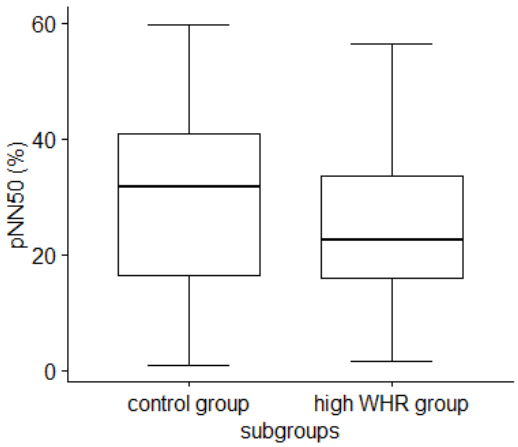
t(162) = -2.92, **p = 0.004**, d = -0.39				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	2.052	0.921	0.94
Control group	82	1.717	0.799	1.33



t(162) = -0.38, p = 0.70, d = -0.06				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	93.0	29.6	0.94
Control group	82	91.3	28.5	1.33



t(162) = 1.47, p = 0.14, d = 0.23				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	48.5	16.6	0.94
Control group	82	52.4	17.6	1.33



t(162) = 1.81, p = 0.07, d = 0.28				
Subgroup	n	Mean	SD	Δ%BF
High WHtR	82	25.1	13.5	0.94
Control group	82	29.1	14.9	1.33

d. Re-Weighting Including Waist-to-Height-Ratio

i. Inverse Probability Weighting for HRV at Visit 1 Grouped by Median Split of Waist-to-Height-Ratio at Visit 2

HRV V1	Mean Difference Between Subgroups			Subgroup Coefficient for Regression Models		
	Mean	Bootstrap		β	Bootstrap	
		Mean	CI 95%		Mean	CI 95%
LF	109.13	142.250	-103.503; 410.595	0.067^{L}	0.059^{L}	-0.075^{L}; 0.188^{L}
HF	-14.595	11.033	-170.526; 206.502	-0.085^{L}	-0.086^{L}	-0.245^{L}; 0.087^{L}
LF/HF	0.252	0.347	0.172; 0.537	0.150^{L}	0.141^{L}	0.059^{L};0.215^{L}
LFnu	0.020	0.046	0.024; 0.069	0.034	0.032	0.014; 0.050
HFnu	-0.043	-0.032	-0.055; -0.010	-0.034	-0.032	-0.050; -0.014
SDNN	-0.128	3.421	-2.771; 9.723	0.154^{L}	0.014^{L}	-0.045^{L}; 0.067^{L}
RMSSD	-3.701	-2.575	-6.604; 1.459	-2.565	-2.725	-5.920; 0.244
pNN50	-3.722	-3.414	-6.810; 0.058	-3.111	-3.185	-5.973; -0.505

Table 0.19 Inverse Probability Weighting for HRV at Visit 1 Grouped by Median Split of Waist-to-Height-Ratio at Visit 2; ^{L} log transformed values

ii. Inverse Probability Weighting for Waist-to-Height-Ratio at Visit 1 Grouped by Median Split of HRV at Visit 2

HRV V2	Mean Difference Between Subgroups			Subgroup Coefficient for Regression Models		
	Mean	Bootstrap		β	Bootstrap	
		Mean	CI 95%		Mean	CI 95%
LF	0.008	0.009	-0.005; 0.023	0.010	0.010	-0.004; 0.023
HF	0.004	0.003	-0.014; 0.018	0.004	0.003	-0.014; 0.017
LF/HF	0.016	0.013	-0.002; 0.027	0.017	0.021	0.006; 0.034
LFnu	0.017	0.014	-0.002; 0.029	0.017	0.021	0.006; 0.035
HFnu	-0.020	-0.022	-0.037; -0.007	-0.017	-0.021	-0.036; -0.007
SDNN	0.005	0.005	-0.010; 0.019	0.006	0.006	-0.008; 0.020
RMSSD	-0.004	-0.004	-0.018; 0.011	-0.003	-0.004	-0.018; 0.010
pNN50	-0.003	-0.004	-0.019; 0.010	-0.003	-0.005	-0.019; 0.009

Table 0.20 Inverse Probability Weighting for Waist-to-Height-Ratio at Visit 1 Grouped by Median Split of HRV at Visit 2